

Antithrombotic therapy in obesity

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Summary

Clinical management of obese subjects to reduce their risk of suffering cardiovascular events is complex. Obese patients typically require preventive strategies, life-style modifications, and multi-drug therapy to address obesity-induced co-morbidities. Data regarding the effects of excess weight on the pharmacokinetics of most drugs is scarce as these individuals are often excluded from clinical trials. However, the physiological alterations observed in obese patients and their lower response to some antiplatelet agents and anticoagulants have sug-

gested that dosage regimes need to be adjusted for these subjects. In this review we will briefly discuss platelet alterations that can contribute to increased thrombotic risk, analyse existing data regarding the effects of obesity on drug pharmacokinetics focusing on antiplatelet agents and anticoagulants, and we will describe the beneficial effects of weight loss on thrombosis.

Keywords

Obesity, antiplatelets, anticoagulants

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Introduction

Obesity has been shown to play a central role in the metabolic syndrome, which increases the risk of developing cardiovascular disease 1.5- to 3-fold (1-3). In fact, evidence for a link between obesity and coronary artery disease (CAD) development has been repeatedly reported, possibly in part due to the development of a pro-inflammatory and pro-thrombotic state in obese subjects which favours atherosclerosis progression. Indeed, obesity, mainly through hyperlipidaemia and inflammation, contributes to increase plaque formation and vulnerability (4) as biologically active molecules produced by adipose tissue promote endothelial function impairment, disturb the haemostatic and fibrinolytic systems, and produce alterations in platelet function that affect the initiation, progression, and stabilization of intra-luminal thrombi (5) (► Figure 1). Moreover, obese patients show a lower response to some antithrombotic agents which has suggested that dosage regimes should be adjusted for these subjects.

Platelet alterations in obesity

Platelet hyperactivity occurs early in subjects with abdominal obesity and plays a key role in the pathology of atherothrombosis of these subjects (6, 7). Under normal conditions, platelet activation is counteracted by endothelial-derived nitric oxide (NO) and prostaglandin I₂ (PGI₂) through the increase of intra-platelet cGMP and cAMP levels, respectively. However, it has been shown

that platelets from obese subjects have a reduced response to PGI₂ and NO-donors [glyceryl trinitrate (GTN) and sodium nitropruside (SNP)] (8) which was associated with reduced cGMP and cAMP intra-platelet levels, respectively (9, 10). Obese subjects also show increased plasmatic concentrations of *in vivo* activation markers such as soluble P-selectin (sP-sel) and soluble CD40L (a pro-inflammatory mediator mainly released from activated platelets) (11, 12). Indeed, even though no differences have been observed in intra-platelet CD40L, platelets from obese subjects have been described to release more sCD40L than those from non-obese subjects when stimulated with thrombin (13).

Mean platelet volume (MPV) has also been found to be increased in obese subjects independently of other cardiovascular risk factors (14). MPV is clinically considered as an index of platelet activity as large platelets have been shown to be more reactive and aggregable and increased MPV has been linked to increased cardiovascular risk (15, 16). In obesity, increased MPV might be a consequence of the existing chronic inflammatory state, as increased platelet size has been associated with the presence of low-grade inflammation (17), and several inflammatory proteins have been proven to influence megakaryocyte maturation and platelet formation (18, 19). Moreover, interleukin (IL) 6 has been shown to be increased in obese subjects (20-23) and to alter the morphology and reactivity of platelets released from the bone marrow (24). Indeed, we have recently described that obese-diabetic rats have an altered megakaryopoiesis that contributes to increase thrombosis (25). Zucker diabetic fatty (ZDF) rats have an increased megakaryopoiesis (reflected by increased platelet counts and an increased

MPV). Indeed, ZDF rats showed an increased platelet turnover as a result of accelerated platelet death that was confirmed by the observation of an increased number of reticulated platelets (the youngest, more immature, and more reactive platelets) in these animals. Importantly, all these alterations were associated with an increased thrombotic risk analyzed *in vivo* by real-time intravital microscopy in both wild-type ZDF animals as well as in lean normoglycemic controls transplanted with ZDF-bone marrow (25). Moreover, we have also described that obese non-diabetic Zucker rats (ZF) also show increased platelet counts and increased MPV which were associated with an increased thrombotic risk (similar to that observed in ZDF rats) (26). Indeed, we have shown that platelet number, MPV, and thrombotic risk are directly correlated with weight and that a reduction of peripheral insulin resistance could contribute to reduce thrombotic risk in obese subjects (26).

C-reactive protein (CRP) is a powerful inflammatory marker of increased atherothrombotic events that has also shown to positively correlate with body mass index (BMI) and visceral fat accumulation (27). CRP may contribute to thrombosis via several mechanisms (i.e. increasing endothelial adhesion molecule ex-

pression; stimulating macrophage production of inflammatory cytokines which may render the atherosclerotic plaque vulnerable to rupture; and/or inducing monocyte tissue factor production). Interestingly, we have recently reported that not all CRP conformations confer platelets a prothrombotic phenotype (28, 29). Classically, studied serum native CRP (natCRP) is a pentamer formed by five non-covalently bound globular subunits arranged as a cyclic annular disk. However, natCRP can undergo subunit dissociation into individual monomeric units that undergo a conformational change that significantly modifies their structure, solubility, and antigenicity. Indeed, this monomeric or modified CRP (mCRP), which dissociates from natCRP on the surface of activated platelets (29), is the form that displays a prothrombotic effect contributing to platelet activation, enhancing platelet deposition, and increasing thrombus growth under arterial flow conditions (28, 29).

Platelet-derived microparticles (PMP) are submicron membrane vesicles released from activated platelets that provide an additional procoagulant phospholipid surface that enables the assembly of the clotting enzyme complexes and thrombin gener-

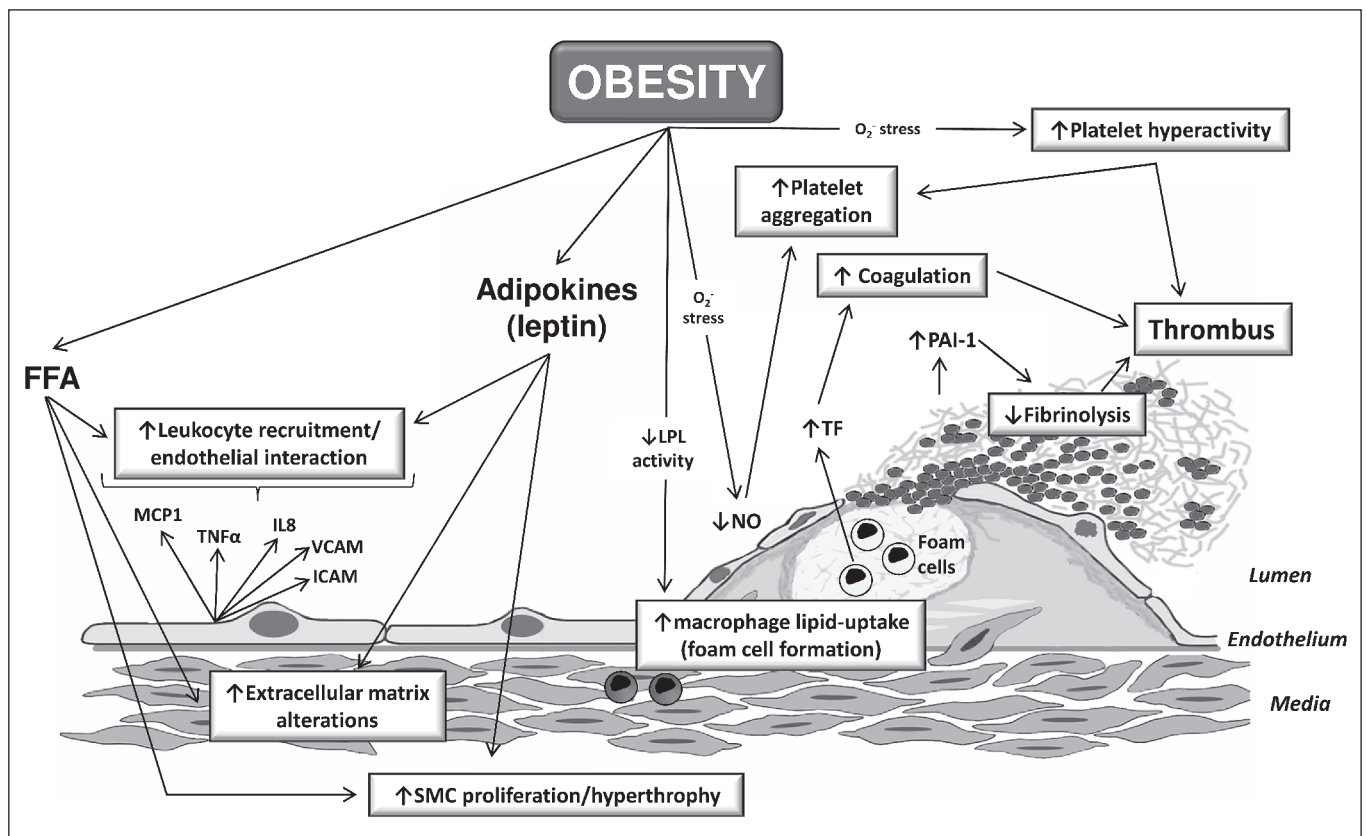


Figure 1: Effect of obesity on the pathophysiology of the atherothrombotic process. Obesity mediators interfere in different pathways and mechanisms associated to thrombosis. Increased amounts of free fatty acids (FFA) can induce endothelial expression of proinflammatory and adhesion molecules that favour monocyte recruitment and monocyte-endothelium interaction, stimulate smooth muscle cell (SMC) proliferation, and modify extracellular matrix components increasing lipid retention. Altered adipokine levels can also contribute to atherosclerotic plaque growth by increasing sys-

temic inflammation, promoting the recruitment of inflammatory cells, and favouring macrophage-to-foam cell transformation. Platelets from obese patients seem to show increased adhesiveness and aggregability; and the oxidative stress can reduce endothelial nitric oxide (NO) production. Finally, obese subjects may have increased tissue factor (TF)-mediated coagulation, higher levels of other components of the coagulation cascade, and a reduced fibrinolysis. ICAM: intercellular adhesion molecule 1, IL-8: interleukin 8, MCP1: monocyte chemoattractant protein 1, PAI-1: plasminogen activator in-

ation. Recent studies have demonstrated that PMP number is positively correlated with both BMI and waist circumference and inversely with weight reduction (30).

Finally, oxidative stress has also been linked to the increased platelet activation observed in obesity, as obese women have shown increased urinary excretion of 8-iso-prostaglandin F_{2α} (iso-PGF_{2α}; an *in vivo* marker of oxidative stress) and 11-dehydrothromboxane (Tx)-B₂ [the major enzymatic metabolite of thromboxane A₂ (TxA₂), an index of *in vivo* platelet activation] compared to age-matched non-obese women (31, 32).

Effects of obesity on drug pharmacokinetics

One of the major problems currently found in the clinical management of obese patients is the lack of guidelines on how to adjust drug doses for these individuals, as obese subjects are often excluded from clinical trials during drug development, limiting the amount of available data regarding the influence of obesity over pharmacokinetics of most drugs.

Obese patients differ from non-obese individuals in numerous physiologic characteristics that can alter drug absorption, distribution, and metabolism creating a need to adjust dosage regimes for these subjects as they typically receive multi-drug therapy to address obesity-related co-morbidities (e.g. cardiovascular disease, diabetes, hypertension, etc.). Indeed, significant differences have been described in obese subjects in regional blood flow, cardiac output, and body composition (fat mass vs lean mass) (33, 34), as well as in pro-inflammatory cytokine production and hormone release (22, 35-37).

Absorption

Obesity has been associated with a significant increase of subcutaneous adipose tissue that could potentially interfere with the absorption of drugs administered subcutaneously, transdermally, or intramuscularly. However, the few studies published up to date analysing the effects of obesity on extravascular drug absorption (38, 39) have found no significant differences between obese and non-obese subjects. Likewise, no significant differences have been found in oral drug absorption despite that an accelerated gastric emptying rate, a higher cardiac output, and an increased gut perfusion have been observed in obese patients (33, 40).

Distribution

Drug distribution is determined by the physicochemical properties of the drug (i.e. lipophilicity, molecular weight, degree of ionisation, and ability to cross biological membranes) and the chemical and physical properties of tissues (34, 41, 42). Nevertheless, tissue distribution is primarily dependent on the lipophilicity of the compound (43).

The volume of distribution (V_d) is an estimate of the extent to which a drug is distributed to extravascular tissues. Therefore, understanding the effects of obesity on V_d is critical to determine

the optimal loading dose of drugs where maximum concentration and/or rapid achievement of maximum concentration is needed (42). Comparison of the weight-normalised V_d [V_d /total body weight (TBW)] between obese and non-obese subjects is a useful tool to identify the best weight descriptor to adjust loading drug doses, as it reflects the ability of the drug to penetrate into the excess tissue. Thus, drugs whose weight-normalised V_d is similar in obese and non-obese subjects exhibit a marked uptake into adipose tissue, and therefore their weight-based loading dose should be adjusted by their TBW in order to obtain the same maximum plasma concentrations as in non-obese subjects. Conversely, drugs whose weight-normalised V_d is significantly lower in obese patients are incompletely distributed into excess bodyweight and therefore lean bodyweight (LBW; a weight descriptor devoid of most adipose tissue) is a better metric for estimating the loading dose of these compounds (41). Therefore, TBW is a good weight descriptor to determine loading doses of lipophilic drugs, while LBW is better to establish those of hydrophilic drugs that are mainly distributed in plasma or lean tissue (42).

Metabolism

Clearance is another important pharmacokinetic parameter potentially influenced by the presence of obesity. Clearance is inversely correlated to the steady-state plasma concentration of drugs and is therefore critical to establish maintenance doses. However, unlike V_d , clearance is mainly controlled by physiology, the liver and kidneys being the main organs involved in the elimination of drugs and their metabolites (41, 42). In fact, clearance can be defined as the volume of blood from which a drug is completely removed in a given amount of time. Thus, clearance mainly depends on organ blood flow and the organ's capacity to extract the drug from blood (41).

Clearance of most drugs is mediated by the liver. However, the effects of obesity on liver drug metabolism still remain unclear. Indeed, it has been observed that while the clearance of some drugs with high hepatic extraction remains unaltered in obese subjects (42), there is also clear evidence of an increased hepatic clearance of others (44-46). Increased liver fat content has been associated with obesity (47) and it has also been shown that fat accumulation in the liver of these subjects may alter hepatic blood flow (48), suggesting that this might influence hepatic drug clearance. Nevertheless, there is still a lack of experimental data regarding the impact of obesity-induced liver damage on drug clearance.

Cytochrome P450 enzymes are responsible for the oxidative metabolism of exogenous substances including many antiplatelet compounds (e.g. thienopyridines). However, the effects of obesity on them is still unclear and seems isozyme-specific, as an increase in the activity of CYP2E1 has been observed in obese subjects, while at the same time data regarding other members of this family is inconsistent and inconclusive (34).

Similarly to what occurs with liver metabolism, the effects of obesity on renal function and consequently their impact on drug excretion are still under debate. Obesity could affect renal drug clearance by altering glomerular filtration, tubular secretion, and/

or tubular reabsorption. However, the effects of obesity on these processes are still unclear. Indeed, studies analysing drug renal clearance have found increased, decreased, or similar glomerular filtration rates when comparing obese and non-obese subjects.

Antiplatelet agents in obesity

Platelets have a central role in the pathophysiology of arterial thrombosis and subsequent clinical events and hence antiplatelet agents have become a mainstay of cardiovascular therapy. Despite a large body of clinical evidence supporting the efficacy and safety of aspirin and/or clopidogrel therapy in reducing ischaemic events, questions remain concerning their optimal use in obese patients, especially taking into consideration that obesity is associated with a pro-thrombotic condition and a lower platelet suppression upon aspirin and clopidogrel administration.

Obesity and acetylsalicylic acid (aspirin)

Bordeaux et al. (49) evaluated the impact of obesity on platelet-responsiveness to low-dose aspirin in a total of 2,014 apparently healthy subjects from families with premature CAD. They found that platelets from obese individuals had greater native platelet reactivity and retained higher residual platelet function despite aspirin treatment as compared to non-obese individuals supporting the aforementioned innate hyperaggregable state in obesity (49). Smaller studies have suggested that insulin-resistance may contribute to blunt aspirin inhibitory effect (50, 51). Indeed, insulin inhibits platelet aggregation by mechanisms which appear to involve stimulation of NO production, a potent platelet inhibitor (52). Moreover, platelets of obese are known to have reduced levels of cAMP and cGMP which may lower their threshold for activation (53). All together, these observations may contribute to explain the ineffectiveness of aspirin treatment detected in obese subjects. However, the clinical impact of reduced platelet suppression by aspirin detected in obese as compared to non-obese individuals remains to be determined and whether obese subjects might benefit from aspirin at higher doses.

P2Y₁₂ receptor blockers

The first family of adenosine diphosphate (ADP) P2Y₁₂ receptors inhibiting drugs is represented by thienopyridines. Thienopyridines are orally administered pro-drugs that suffer liver metabolism leading to the formation of active metabolites capable of irreversibly blocking the P2Y₁₂ receptor. Ticlopidine was the first thienopyridine approved by the U.S. Food and Drug Administration (FDA), but its potential side effects (neutropenia, anaemia, gastrointestinal distress and thrombotic thrombocytopenic purpura) discouraged its use. The second generation of thienopyridines is represented by clopidogrel, which has replaced ticlopidine as a therapeutic antiplatelet agent, used alone or in combination with aspirin. In fact, clopidogrel co-administered with aspirin, is considered the treatment of choice for prevention of atherothrombotic

complications. The relationship between BMI and the efficacy of clopidogrel, however, remains a topic of debate. Evidence supports an association between elevated BMI, higher platelet aggregation, and diminished response to clopidogrel (54). Angiolillo et al. found in a small study of 48 patients undergoing elective percutaneous coronary intervention (PCI) that inhibition of platelet aggregation during treatment with clopidogrel (300 mg) and aspirin was found to be significantly less in overweight patients (defined by BMI >25 kg/m²) both at baseline and at 24 hours when compared with normal weight (BMI <25 kg/m²) patients. The study concluded that obese patients may therefore require a higher clopidogrel dose at the time of PCI (54, 55). An accompanying editorial suggested that a higher loading dose of 600 mg should be considered for overweight patients undergoing elective PCI (56). These clinical findings contrast with clinical data of Kelly et al. (57) who in a post-hoc observational analysis of the CREDO study including over 2,000 PCI patients showed that as BMI increased, the relative benefit of clopidogrel was actually greater. Of note, obese PCI patients in general have shown a better short- and long-term outcome compared with thinner patients. Indeed, during PCI, patients with lower BMI have a trend towards more bleeding complications compared with higher BMI patients. Some studies have reported that obesity favours a hypercoagulable state and that this may lower bleeding risks for obese patients. Others attribute these observations to lesion characteristics, co-medications in obese and/or unadjusted dosing in non-obese patients. Further studies are required to assess whether clopidogrel should be dose- and weight-adjusted.

Prasugrel represents the third generation of thienopyridines, and, in contrast to clopidogrel, only one hepatic metabolism step is necessary for its conversion to its active form, inducing a more rapid, potent and predictable platelet inhibition than clopidogrel (58). In fact, prasugrel has been shown to lead to a greater reduction of ischaemic events as compared to clopidogrel, yet, with an increased risk of major bleeding, including fatal bleeding (59). A recent study in acute coronary syndrome patients receiving maintenance prasugrel treatment reported that, similar to clopidogrel (54), obesity appears to be independently associated with insufficient platelet inhibition (a 3-fold higher platelet reactivity) (60).

Finally, so far, little data is available regarding the effect of obesity on non-thienopyridine derivatives (i.e. ticagrelor, cangrelor and elinogrel) which, in contrast to thienopyridines, do not require metabolic activation and lead to a reversible P2Y₁₂ receptor inhibition. For instance, the PLATO study (61) showed that ticagrelor reduced the primary endpoint compared to clopidogrel in patients with BMI ≥30 kg/m² in a similar way to those with BMI <30 kg/m² whereas there was a borderline interaction regarding major bleeding and BMI. In addition, Storey et al. (62) characterised dyspnoea in PLATO study patients and reported that a tendency for higher susceptibility to ticagrelor-related dyspnoea appears in patients with a higher body weight. This did not apply to patients under clopidogrel.

GPIIb/IIIa receptor inhibitors

Glycoprotein (GP)IIb/IIIa inhibitors are effectively used in unstable angina, myocardial infarction, and high-risk PCI with and without intracoronary stenting. GPIIb/IIIa inhibitors are administered based on weight-adjusted regimens and therefore their efficacy should not differ in obese vs non-obese individuals. A sub-study of the TARGET trial (63) - aimed at evaluating the routine use of GP IIb/IIIa inhibition in patients undergoing planned coronary bare-metal stent placement- examined the relationship of obesity to the short- and long-term outcomes including the incidence of target vessel revascularisation. The study found that long-term and short-term ischaemic events were similar in obese and non-obese patients; obese patients had less major bleeding, but extreme obesity was associated with an increase in target vessel revascularisation especially in patients less than 65 years of age. The authors suggested that such an effect was mainly due to the continuous inflammatory state found in obese patients rather than a platelet-driven effect.

Anticoagulants and obesity

Obesity has been demonstrated to be an independent risk factor for venous thromboembolism (VTE) in both men and women (64). Ageno et al. (65) found in a meta-analysis combining eight case-control and one cohort study that subjects with a BMI above 30 kg/m² had twice the risk of suffering VTE as compared to those overweight (BMI 25-30 kg/m²). Moreover, this association became stronger as BMI increased and morbidly obese subjects (BMI >40 kg/m²) were at even higher risk than those with BMI 30-40 kg/m² (66). Yet, not only had the incidence of VTE increased with obesity but also the recurrence of events (67). On the other hand, bariatric surgery has been acknowledged as the most effective weight loss strategy in the morbidly obese (National Institute of Health and Clinical Excellence 2006) emphasising the need for VTE thromboprophylaxis during hospitalisation and/or the postoperative period (68). Unfortunately, outside of bariatric surgery groups, the information regarding the efficacy and safety of anticoagulants in obese subjects is scarce and inconclusive, since severely obese patients have been consistently under-represented in clinical trials (69).

Warfarin and heparins

Warfarin dosing is dependent on age, concurrent disease states, nutritional status, other medications, and the presence of genetic polymorphisms, making it difficult to establish the influence that obesity may have. However, as warfarin is monitored, under- and over-coagulation can be prevented with appropriate monitoring for dose-adjustment.

As for unfractionated heparin (UFH), although it also requires monitoring, Raschke et al. (70) demonstrated a clear relationship between an individual's weight and their UFH requirements to maintain anticoagulation at the desired level. However, further studies demonstrated that patients weighing over 100 kg required

a lower dose than anticipated to achieve the target level. In fact, clinical outcome data of obese patients from the ESSENCE (71) and TIMI11B (72) trials suggest that obese patients do not present higher recurrence of bleeding events as compared to non-obese subjects. Moreover, the RIETE registry (73) has provided evidence that obese patients with acute VTE have less than half the rate of mortality when compared with normal BMI patients, confirming the existence of the so-called "obesity paradox" (i.e. among patients with a number of chronic diseases excess weight is paradoxically associated with a decreased risk of adverse outcomes) (74, 75). Further research is needed to elucidate the pathophysiological mechanisms responsible for the more favourable outcome in the obese. RIETE registry, however, supports the reported increase in mortality and major bleeding associated with being underweight, suggesting that these patients should be closely monitored in order to reduce the risk of bleeding during therapy. Though low-molecular-weight heparins (LMWH) have a more predictable pharmacokinetic profile, the dosing question in the obese sub-population applies more to LMWH than to UFH or warfarin, as efficacy monitoring is not routinely conducted. Obese subjects have a lower proportion of highly vascular and lean body mass as a percentage of total body weight (41). It is therefore possible that in obese subjects treatment with LMWH could lead to an overdose, since LMWH treatment is based on body weight. Conversely, arbitrary dose reduction or capping could lead to sub-therapeutic anticoagulation and increased risk of recurrent vein thrombosis. Therefore, there is an on-going debate whether the dose should be increased linearly, adjusted for weight or capped at some point at a maximum allowable dose. Nevertheless, close monitoring of their therapeutic effects with the classical methods allow adjusting the dose according to the response.

Fondaparinux

Fondaparinux is a synthetic pentasaccharide that works by potentiating factor (F)Xa inhibition through binding to antithrombin. A subgroup analysis of a meta-analysis including four randomised controlled trials comparing fondaparinux with enoxaparin (LMWH) in major orthopaedic surgery demonstrated a greater than 50% risk reduction of total VTE at hospital day 11 in obese patients (BMI >45 kg/m²) receiving 2.5 mg of fondaparinux daily without an increase in major bleeding (76). Further studies suggested that in extreme-weight patients (BMI >51 kg/m²) higher levels seemed required to achieve target anti-FXa levels. These observations suggest that increasing the dose with increasing weight might be required for fondaparinux in the management of VTE (77).

Oral direct thrombin and FXa inhibitors

Oral direct thrombin inhibitors (dabigatran) and direct FXa inhibitors (rivaroxaban and apixaban) have the combined advantages of warfarin and LMWH in that they are orally active, have a rapid onset and offset of action, and have a predictable dose-response curve. However, their fixed dosing schedule does once

again raise the question of appropriate dosing in the obese sub-population. In fact, studies evaluating these drugs in the obese population are presently limited and although the manufacturers of currently licensed agents suggest that no dosing alterations are required in the obese population, small-scale studies demonstrate a lower drug exposure with increasing weight; further study and experience will determine whether the manufacturers' current dosing strategy of "one size fits all" is correct.

Effects of weight loss on thrombotic risk

Lifestyle modifications to promote weight loss are usually the first step in the management of patients with obesity or the metabolic syndrome. Weight loss has been shown to reduce cardiovascular risk factors and the development of co-morbidities such as type 2 diabetes, hypertension, and cardiovascular disease (6, 78-80). Indeed, intentional weight loss has been associated with a ~25% reduction of cardiovascular mortality in obese-diabetic subjects (81).

The mechanisms behind the reduction of cardiovascular risk produced by weight loss are numerous. In obese women, weight loss has been shown to exert atheroprotective effects by reducing circulating levels of free fatty acids (FFAs) and inflammatory cytokines (IL-6, IL-18, and CRP), and increasing adiponectin levels (82). Similarly, the combination of diet with exercise significantly reduced IL-6 and CRP plasmatic levels in obese postmenopausal women (83).

Weight loss has also been shown to improve endothelial function in obese subjects. Indeed, an improvement of endothelium dependent vasodilation of the brachial artery was observed in obese-insulin resistant patients (84), and a significant improvement of acetylcholine-stimulated vasodilation was observed in obese healthy subjects (85) after weight loss by combining caloric restriction and physical activity. The latter was also accompanied by a significant reduction of oxidative stress evaluated by intra-arterial infusion of vitamin C and indomethacin.

A reduction of platelet activation and aggregation has also been observed as a consequence of weight loss. Indeed, weight reduction produced a significant decrease of circulating sCD40L and sP-selectin (86). Weight loss has also been shown to produce a significant reduction of iso-PGF_{2α} and 11-dehydro-TxB₂ metabolites (31, 32) together with an increase in the anti-aggregating effects of sodium SNP, Iloprost, and the cyclic nucleotide analogs 8-bromoguanosine 3',5'-cyclic monophosphate and 8-bromoadenosine 3'-5'-cyclic monophosphate and an increase in cAMP and cGMP concentrations when treated with SNP and Iloprost, respectively (87). Moreover, weight reduction has also been associated with a reduction of the hypercoagulable state observed in obesity as a significant decrease of von Willebrand factor, activated FVII, and prothrombin fragment F1.2 have been observed after diet-induced weight loss (84). An improvement of fibrinolysis has also been observed in both children and adolescents (88, 89) after weight reduction with a low-calorie diet combined with exercise.

Clinical guidelines (90) recommend the use of pharmacological therapy as a part of a comprehensive weight loss program (includ-

ing diet and physical activity) for patients with a BMI over 30 kg/m² as well as for patients with a BMI ≥27 kg/m² with a major obesity-related co-morbidity (e.g. hypertension, diabetes, dyslipidaemia). Orlistat, an inhibitor of pancreatic lipase that decreases fat absorption in the intestine achieving a ~10% weight loss, has been shown to reduce plasmatic levels of inflammatory mediators CRP, IL-6, and tumour necrosis factor α and iso-PGF_{2α} (86). Moreover, orlistat has also been associated with a significant reduction of total and low-density lipoprotein (LDL) cholesterol and a reduction of systolic and diastolic blood pressure (80), altogether contributing to reducing cardiovascular risk. On the other hand, rimonabant (selective blocker of the cannabinoid receptor 1) has also been shown to reduce cardiovascular risk by reducing weight, waist circumference, blood pressure, and triglyceride levels and increasing adiponectin and high-density lipoprotein (HDL) in diabetic and non-diabetic obese subjects. Moreover, rimonabant also induced a reduction of inflammatory cytokines RANTES and MCP-1 in experimental models (91). However, rimonabant was withdrawn in 2007 as it increased the risk of depression, anxiety, and suicide.

Bariatric surgery is the last option to reduce weight in a limited number of obese patients (BMI ≥40 kg/m² or ≥35 kg/m² with co-morbid conditions). Surgical procedures (gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass, and biliopancreatic diversion) are highly effective at inducing weight loss and also resolve/improve other obesity-induced comorbidities (e.g. diabetes, hypertension, and dyslipidaemia), reducing by 40% the Framingham risk of these patients (92). In line with this, significant reductions of systemic inflammation (CRP, IL-6, and MCP-1), endothelial dysfunction, and oxidative stress and an increase in fibrinolysis have been observed after bariatric surgery (86).

Summarisation

Obese patients have an increased thrombotic risk and exhibit a low response to antithrombotic treatments. However, there is currently a lack of data regarding the effects of obesity on the pharmacokinetics of these drugs, as obese individuals are often excluded from clinical trials. Therefore, new clinical trials are needed in order to determine the effects of excess weight on the different antithrombotic agents as well as to determine the best weight descriptor/s to adjust dosage regimes in these subjects, as they often receive multidrug therapy to address obesity-induced co-morbidities.

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Conflicts of interest

None declared.

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