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Anticoagulant Pharmacotherapy in Obese Patients

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Obesity, defined as a body mass index (BMI) of greater than 30 kg/m^2, is a major issue in modern health care whose prevalence has increased exponentially over the past few decades[1,2]. In 2005, the World Health Organization (WHO) estimated the worldwide prevalence of overweight and obese adults to be 1.6 billion and 400 million respectively[3]. Obesity is a chief risk factor that is closely associated with the development of diabetes, cardiovascular disease, osteoarthritis, cancer, and numerous other ailments that create unparalleled burdens for both patients and the healthcare system.[4,5] A recent projection indicates that if the current trend continues, approximately 60% of the world's population will be considered either overweight or obese by the year 2030[6]. Obesity is an independent risk factor for the development of venous thromboembolism (VTE) and ischemic heart disease, both of which can be devastating in terms of cost and quality of life deficiencies[1,7,8,9]. This may be partly attributed to the development of a pro-inflammatory and pro-thrombotic state in obese patients, which is thought to favor the progression of atherosclerotic disease[10]. For VTE prevention, the current standard of care involves the use of various anticoagulants in hospitalized patients who are non-ambulatory for extended periods of time. This approach is also used in patients undergoing various surgical procedures, where the risk of thrombus formation is particularly elevated[11]. Many of these same agents are also utilized for the treatment of patients who experience a VTE and acute coronary syndromes (ACS) that occur secondary to thrombus formation[11,12]. With an increasing prevalence of obesity, VTE, and ACS, more obese patients are being initiated on anticoagulant pharmacotherapy than ever before.

Table 1 | Criteria for diagnosis of obesity based on BMI as recommended by the World Health Organization[1,5]

Body Mass Index (BMI; kg/m^2)	Classification
< 18.5	Underweight
≥ 18.5 and < 25.0	Normal weight
≥ 25.0 and < 30.0	Overweight
≥ 30.0 and < 35.0	Obese class I
≥ 35.0 and < 40.0	Obese class II
≥ 40.0	Obese class III

Bariatric surgery, an effective method for facilitating significant weight loss, has been shown to help resolve type 2 diabetes in 73-90% of patients, as well as reduce the incidence of coronary artery disease by approximately 50%[13]. Furthermore, it has been documented as being one of the few treatment strategies for morbid obesity to produce a long-term, sustained, loss of weight[14]. There are various bariatric surgical techniques, including those that are purely restrictive including gastric banding, and those that are both restrictive and malabsorptive, such as gastric bypass[14,15]. Each type of surgical procedure may affect various pharmacokinetic parame-

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ters differently, while data pertaining to pharmacokinetic changes in this patient population is quite limited.

With the aforementioned considerations in mind, clinicians have a dilemma when prescribing anticoagulants to obese patients who often may have unpredictable pharmacokinetics. These agents exhibit an inherently narrow therapeutic index where doses that are too low can permit thrombus formation and where doses too high can facilitate life-threatening hemorrhage. One major issue is that obese patients are often excluded from clinical trials during the drug development process[16]. Data pertaining to alterations in various pharmacokinetic parameters remains limited in this particular patient population[16]. In general, the absorption of oral agents appears to be minimally affected by obesity, whereas distinct differences in both the distribution and clearance of various medications have been documented consistently in the biomedical literature.[17-20]

The goal of this article is to review the various documented changes in both the pharmacokinetics and pharmacodynamics in obese patients, and review the literature pertaining to the use of anticoagulants in obese patients in order to shed light on how they can be effectively and safely used in this growing patient population. Consideration will also be given to patients undergoing bariatric surgery.

Pharmacokinetic Implications

There are clear changes in both the distribution and clearance of medications in obesity, whereas alterations in oral drug absorption appear to be minimal[17-20]. The volume of distribution ($V_{d,}$) describes the relationship of the total amount of drug in the body to the various compartments where the drug may or may not be present. The V_d is highly dependent on the intrinsic properties of the drug in question, namely, the size of the compound, ionization state, and lipophilicity[16]. Compounds that are smaller with a lipophilic profile generally have a higher volume of distribution as they are able to more readily cross membranes and partition into the extravascular space. In comparison to non-obese individuals, obese persons have a larger volume of adipose tissue. Drugs that are lipophilic have the potential to distribute further, but the degree to which the drug's distribution is affected is agent dependent[16]. Volume of distribution is also affected by both intravascular protein binding and extravascular tissue protein binding. While obesity does not affect a drug's ability to bind to albumin, studies pertaining to α_1-acid glycoprotein in this patient population have been contradictory[21-25].

The clearance (CL), is defined as the volume of blood from which a drug can be completely removed in a given time period[16]. This parameter is heavily dependent on the blood flow to the organ that is responsible for the extraction of the respective drug[16]. For most agents, this organ is the liver, which houses numerous enzymes that are responsible for making modifications to various endogenous and exogenous molecular entities that are delivered via the portal system. Obesity is heavily correlated with nonalcoholic fatty liver disease, which has the potential to alter hepatic blood flow and thus affect drug delivery to the liver[26,27]. Data suggests that there is an increase in the cytochrome P450 isoenzyme 2E1, however, there are few known drug substrates that are metabolized by this particular enzyme so its clinical significance is still debatable[28,29]. For conjugative enzymes, there are proportional increases in both sulfonation and glucuronidation in relation to total body weight[30,31].

The renal system, which is responsible for the elimination of drugs in the urine, is also affected by changes in body weight. Studies have found both increased and decreased creatinine clearance in obese patients[16].

In general, it is thought that pharmacokinetic changes in obesity can be summarized by three major observations: obese persons exhibit higher absolute clearance than non-obese individuals, clearance does not increase linearly with total body weight, and clearance and lean body weight are more linearly correlated[32].

As mentioned above, the two main classes of bariatric surgery include solely restrictive surgery or a surgery that involves both restriction and malabsorption[14,15]. A given bariatric surgical procedure may have varying effects on a patient's intrinsic pharmacokinetics. For example, restriction surgeries involve changes in the gastric environment that subsequently alter the pH, gastric emptying, and gastric mixing[15,33,34]. This can lead to changes in absorption in medications that are administered orally, especially agents that are controlled release preparations[34]. In malabsorptive surgeries, the drug dissolution rate may be lessened, leading to a potential decrease in drug absorption for orally administered medications[33]. Drugs that are lipophilic are potentially affected by less bile salt emulsification and less enterohepatic recirculation[34]. Due to the significant reduction in the size of the stomach, drug absorption may be further reduced. However, it is possible that an intestinal adaptation may occur where an increase in intestinal absorption due to mucosal hypertrophy may counterbalance this effect[34].

Table 2 | Pharmacokinetic changes in obese patients and bariatric surgery patients [17-34]

Pharmacokinetic Parameter	Changes Observed in Obese Patients	Changes Observed in Bariatric Surgery Patients
Absorption	Presumably not affected	Increased or decreased
Distribution	Potentially increased for lipophilic drugs; agent specific	May decrease as weight is rapidly lost for lipophilic drugs; agent specific
Metabolism	Increased overall clearance	Unknown
Elimination	Under debate	Unknown

CLINICAL STUDIES

VTE PROPHYLACTIC DOSING

Low Molecular Weight Heparin (LMWH)

Since introduction into clinical practice in the 1990's, LMWH has been preferred vs. heparin for its immediate onset of action and more predictable pharmacokinetic profile secondary to an improved bioavailability, dose-independent clearance, and lower affinity for heparin binding proteins[35-37]. Three agents are available in the United States: enoxaparin, tinzaparin, and dalteparin. Their pharmacokinetic profiles are individually described in Table 3. These agents are almost entirely confined to the intravascular space, with the Vd corresponding to the volume of plasma, and the clearance being primarily renal[38]. Dose-dependent anti-Xa activity has been observed with LMWH use, and the peak effect occurs between 3-4 hours after subcutaneous injection, with anti-Xa activity occurring 12 hours after administration[38]. Due to this more predictable pharmacokinetic and pharmacodynamic profile, routine monitoring of LMWH effectiveness is not typically undertaken[16]. However, both the American College of Pathology and the ACCP Guidelines recommend consideration of routine anti-Xa monitoring in certain patient populations, including the obese. They suggest a target peak concentration range of 0.5-1.0 U/ml or > 1.0 U/ml four hours after administration for twice daily and once daily treatment dosing respectively[39,40]. While neither of the above-mentioned organizations have concrete recommendations for prophylaxis dosing, some have recommended a peak anti-Xa range of 0.2-0.5 U/m[41,42].

For the prevention of VTE, fixed doses of agents are typically given despite significant variation in total body weight. There remains very little guidance from the various manufacturers pertaining to appropriately dosing of these drugs in obese patients. There is an inverse relationship between anti-Xa levels and total body weight during the first 10 hours after administration of a 40 mg prophylactic dose of enoxaparin[43]. This data has been extrapolated to suggest that conventional doses of LMWH may be insufficient as total body weight increases beyond a certain threshold.

The majority of data pertaining to the dosing of LMWH in obese patients for VTE prophylaxis has been collected from patients undergoing bariatric surgery, with enoxaparin being the most common agent assessed. In 2002, Scholten et al compared enoxaparin 30 mg twice daily vs enoxaparin 40 mg twice daily in a population consisting of 481 patients who were undergoing primary or revisional bariatric surgery. They reported a lower incidence of post-operative VTE in the 40 mg group and concluded that this dosing scheme was more effective[44]. Rowan et al conducted a study in 2008 where they compared the same enoxaparin dosing regimens in 52 obese patients undergoing gastric banding or gastric bypass. They found that anti-Xa levels, measured after the first and third dose, were closer to therapeutic goal in the 40 mg cohort but over 50% of this group failed to attain these target levels[45]. Borkgren-Okonek, et.al. assessed both the safety and efficacy of an extended duration, BMI-stratified enoxaparin VTE prophylaxis regimen in gastric bypass surgery patients. They monitored anti-Xa levels in the 223 patients, 124 of which had a BMI < 50 kg/m^2 and 99 of which had a BMI > 50 kg/m^2. The patients in the more obese group were given 60 mg enoxaparin twice daily whereas the patients in the less obese group were given 40 mg enoxaparin twice daily for 10 days after discharge. They reported that 74% of patients in the BMI > 50 kg/m^2 group achieved target anti-Xa levels of 0.2-0.4 units/ml and that this regimen was more effective in the prophylaxis of VTE[46]. In 2010, Rondina et al studied a weight-based

Table 3 | Data regarding route of administration, FDA approved indications, and pharmacokinetics of heparin, LMWH, and fondaparinux

Agent(s)	Route of administration	FDA Approved Indications	Mechanism of Action	Half-life	Elimination	Antidote
Heparin	Subcuteaneous Intravenous	VTE Prophylaxis and Treatment Acute coronary syndromes	Antithrombin III mediated inhibition of factors II, VII, IX, X, XI, XII	0.5-2hr	Reticuloendothelial degradation; some renal elimination at higher doses	Protamine sulfate
Enoxaparin Dalteparin Tinzaparin	Subcutaneous Intravenous	VTE prophylaxis and treatment Acute coronary syndromes	Antithrombin III mediated inhibition of factors II and X	6 hr	Renal	Protamine sulfate
Fondaparinux	Subcutaneous Intravenous	VTE prophylaxis and treatment	Antithrombin mediated inhibition of factor X	17-21 hr	Renal	None

prophylactic regimen of enoxaparin 0.5 mg/kg once daily in 28 morbidly obese patients at an inpatient facility. The average weight of these patients was 135.6 kg and the average BMI was 48.1 kg/m^2. The average daily dose of enoxaparin in these patients was 67 mg which corresponded to an average peak anti-Xa level of 0.25 units/ml when taken 4-6 hours after the first dose. They reported no incidence of either VTE or bleeding events and concluded that this weight-based regimen was both effective and feasible[47].

In 2012, a prospective study was conducted by Freeman et al to evaluate three different dosing regimens of enoxaparin in morbidly obese patients that were hospitalized and medically ill. In the 31 patients included in the study, peak anti-Xa levels were assessed in patients receiving fixed-dose enoxaparin of 40 mg daily, weight-based low dose enoxaparin of 0.4 mg/kg daily, and weight based high-dose enoxaparin of 0.5 mg/kg per day. The average weight of these patients was 176 kg and the average BMI was 62.1 kg/m^2 . There was no statistically significant difference in the study parameters between the three groups. They authors found a statistically significant difference in the patients who were able to achieve target peak anti-Xa levels when comparing the high-dose group to the fixed-dose and low-dose groups, with no adverse events occurring in any group[48].

Fondaparinux

Fondaparinux, a synthetic pentasaccharide with high affinity and specificity for antithrombin, was approved by the FDA in 2001, and is chemically similar to the LMWH[49] Fondaparinux is dosed in a weight-based fashion for the treatment of VTE, due to increased clearance with increases in total body weight, per the manufacturer. For the remaining indications, the drug is given in fixed doses.

In 2011, a retrospective chart review was conducted by Martinez et al in morbidly obese patients with a BMI > 45 kg/m^2. Anti-Xa values were obtained after ≥ 4 fondaparinux injections at a standard dose of 2.5 mg once daily for the prophylaxis of VTE. 45 patients were included in the study and of the 47 anti-Xa levels assessed, 22 (47%) were below the institution's target peak range of 0.3-0.5 mg/L. There were no documented thromboembolic complications. The authors emphasized that a direct relationship between anti-Xa levels and clinical outcomes has not been established. However, they concluded that BMI had a profound impact on anti-Xa levels[50].

In an unpublished, small, single-dose, cross over study Raftopoulos et al, evaluated 10 morbidly obese volunteers with a mean BMI of 51.5 kg/m^2 (range 35.1-76.6) and a mean total body weight of 145.1 kg (range 93.2-248.3) who were randomized to fondaparinux 2.5 or 5 mg separated by a two week washout. The authors found that the 5 mg dose achieved target drug exposures for C_{max}, time to C_{max}, and AUC_{0-24}, while the 2.5 mg dose did not. It was concluded that clearance of the drug increases with total body weight and that the 2.5 mg dose may be insufficient in morbidly obese patients[51].

VTE TREATMENT

Heparin

Unfractionated heparin (UFH) is physiologically cleared by two distinct mechanisms. The first involves binding of unfractionated receptors on the surface of endothelial cells and macrophages where it is subsequently degraded. This is a rapid and satu-

rable process[52]. A second slow and unsaturable mechanism involves renal clearance[52]. In general, the higher molecular weight constituents of UFH are cleared at a faster rate than the lower molecular constituents. At pharmacologically effective doses, UFH is cleared primarily through the rapid saturable, dose-dependent mechanism. This makes the metabolism of heparin a non-linear process. The half-life of the drug will vary depending on the dose administered[53-55].

While various dosing strategies have been utilized for dosing UFH, weight based dosing has been established as the most reliable. In 1993, Rachke et al compared a weight-based dosing nomogram to the conventional nomogram. He showed that a clear relationship existed between a patient's actual body weight and their respective UFH dosing requirement for maintaining a therapeutic PTT. Nine of the patients in the study weighed greater than 100 kg, and while those who were in the weight based dosing group received significantly higher doses when compared to the standard nomogram, all were therapeutic at the 24 hr time point. Since therapeutic monitoring is generally undertaken in patients receiving UFH, this observation may be merely academic as doses are adjusted based on the patient's response[56].

LMWH

While all three LMWH agents are dosed in a weight based fashion, data pertaining to both the safety and efficacy is limited in the obese population. Of these three agents, only the manufacturer of dalteparin recommends a daily dosing cap for the drug, which is set at 18,000 IU, for the treatment of VTE.

Enoxaparin—In 2002, Sanderink, et.al. studied the anti-Xa activity of enoxaparin 1.5 mg/kg once daily for 4 days in 24 obese volunteers (average weight = 99.6 kg) and 24 non-obese volunteers (average weight = 65.9 kg). They discovered that while the peak anti-Xa activity was similar in both groups, the time to target anti-Xa levels took an additional hour longer in the obese group. No adverse events occurred in either group and the authors concluded that no adjustments needed to be made to enoxaparin dosing in obese patients[57].

Bazinet et al compared anti-Xa activity in obese and non-obese patients receiving either enoxaparin 1.5 mg/kg daily or 1.0 mg/kg twice daily. They measured anti-Xa activity at 4 hours post administration on either day 2 or 3. The average anti-Xa was equivalent between the two cohorts. They did observe a linear increase in anti-Xa activity with BMI, the increase did not reach supratherapeutic levels. The authors concluded that no dosage adjustment was necessary in obese patients[58].

In 2003, Green and Duffull applied a population pharmacokinetic modeling in their study of 92 patients who were managed for either VTE or ACS with enoxaparin. One third of patients had a BMI < 24.9 kg/m^2, one third had a BMI between 25 and 29.9 kg/m^2, and one third had a BMI greater than 30 kg/m^2. They found that the clearance of enoxaparin was strongly correlated with lean body weight but the central volume compartment was best described by actual body weight. They suggested that the best dosing strategy in obese patients is 1 mg/kg every eight hours based on a patients lean body weight, though this has not been utilized in clinical practice[59].

Tinzaparin—In 2002, Hainer et al studied 37 obese volunteers with a weight range of 101-165 kg and a BMI range of 26-61 kg/m^2. They gave a single dose of 175 IU/kg tinzaparin followed by 75 IU/kg or vice versa with a washout period of 7 days. They observed anti-Xa activity over a 30 hour period after the initial dose and reported that anti-Xa activity was consistent over this weight and BMI range. Weight-adjusted tinzaparin showed a predictable response and dose capping was not necessary[60]. In contrast, Diepstraten et.al. reported successful management of a 252 kg patient with a BMI of 74 kg/m^2 with a pulmonary embolism with a dose capped at 28,000 IU/day. This correspondes to 175 IU/kg/day for a 160 kg patient and suggests that a dose cap may be appropriate[61].

Dalteparin—In 2000, Yee and Duffull studied 10 obese and 10 non-obese patients in an attempt to detect a difference in both the Vd and Cl between the two groups. They determined that lean body weight was less accurately correlated with both Vd and Cl than either total body weight or adjusted body weight in the obese group[62].

Wilson et al, in 2001, studied 37 patients with a weight range of 56-190 kg who were administered dalteparin 200 IU/kg/day for treatment of VTE with the dose calculated using total body weight. The authors observed no bleeding or thromboembolic complications and they concluded that a given patient's weight does not affect the pharmacokinetic or pharmacodynamic response in patients weighing up to 190 kg and with normal renal function[63].

A study conducted in 2005 by Al-Yaseen and colleagues retrospectively analyzed 193 patients that all weighed greater than 90 kg. They concluded that

dalteparin 200 IU/kg/day based on total body weight was safe[64].

Warfarin

While there is an overall lack of data pertaining to warfarin monitoring in hospitalized obese patients, a retrospective review was performed in 2013 that evaluated 211 patients on warfarin therapy with the following endpoints: initial warfarin response between obese and non-obese patients by estimating the average daily dose and mean discharge dose where these patients were stratified by BMI category. All patients were on warfarin for at least 4 consecutive days. Of the 211 patients, 10 were underweight, 45 were of normal weight, 48 were overweight, 71 were obese, and 37 were morbidly obese. When stratifying the amount of patients that had achieved a therapeutic INR at discharge by BMI categories, 71.1% of patients of normal weight were therapeutic compared to 42.3% of obese patients and 38% of morbidly obese patients ($p = 0.0004$). Furthermore, the obese and morbidly obese patients required a significantly longer time to attain therapeutic INR (8 and 10 days vs. 6 days), had a higher average daily dose (6.6 ± 0.3 and 7.6 ± 0.5 vs. 5 ± 0.3 mg) and mean discharge dose (6.7 ± 0.5 and 6.7 ± 0.7 vs. 4.4 ± 0.5 mg). The authors concluded that both obese and morbidly obese patients had a curbed early response to warfarin therapy[65].

Fondaparinux

In the treatment of VTE, fondaparinux was equally effective as enoxaparin in obese patients in the MATISSE trial. 11.4% of the patients weighed greater than 100 kg and 27% of patients had a BMI > 30 kg/m2 in the fondaparinux cohort. There were no statistically significant differences between the treatment groups for BMI or weight. The authors concluded that increasing dose to compensate for increasing weight is necessary when utilizing fondaparinux for VTE treatment[68].

Acute Coronary Syndromes (ACS) Treatment

LMWH

In 2003, a meta-analysis involving 7,081 patients was extrapolated from the TIMI 11B and ESSENCE trials with the goal of comparing the safety and efficacy of weight-adjusted enoxaparin and unfractionated heparin in obese patients. Of these patients 26% were obese. Analysis did not show a significant difference between weight groups in the primary end-points (mortality, myocardial infarction, urgent revascularization) or bleeding events[66].

Recently, a retrospective analysis was performed on members of the CRUSADE cohort with the objective of evaluating an association between enoxaparin dosing based on body weight[67]. An inverse relationship was found between enoxaparin dose and patient weight. Approximately 80% of patients that weighed greater than 150 kg received an initial dose that was lower than the recommended dose. Patients greater than 150 kg who received the recommended dose of enoxaparin were found to have a higher bleeding risk compared to the low-dose group. This suggests that the recommended dose of enoxaparin 1 mg/kg twice daily is associated with a higher bleeding risk in patients > 150 kg[67].

Fondaparinux

OASIS-5 was a randomized, double-blind study in 20,078 patients that sought to assess the effectiveness and safety of fondaparinux vs. enoxaparin in unstable angina and non-ST elevated myocardial infarction. In the fondaparinux arm, 591 patients (5.87%) weighed greater than 100 kg. Fondaparinux 2.5 mg subcutaneously daily showed similar efficacy to enoxaparin 1 mg/kg twice daily. The authors also found that the incidence of bleeding was reduced with increasing body weight in the fondaparinux arm[69]. The NICE guidelines on treatment of NSTEMI and unstable angina recommend the use of fondaparinux over enoxaparin due to a reduced incidence of bleeding events with fondaparinux. The ESC guidelines for ACS without STEMI also give fondaparinux a 1A recommendation, while the ACCF/AHA guidelines give a level B recommendation for fondaparinux in the treatment of NSTEMI or unstable angina in conservatively managed patients.

New Oral Agents

In the past few years, a new oral direct thrombin inhibitor and two direct Xa inhibitors have been introduced to the market. The agents currently available in the United States include the oral direct thrombin inhibitor Dabigatran (Pradaxa™) and two oral factor Xa inhibitors, Rivaroxaban (Xarelto™) and Apixaban (Eliquis™).

Dabigatran

While there is limited data pertaining to the

Table 4 | FDA approved indications and pharmacokinetic data for new oral anticoagulant agents [70-72]

Agent and Mechanism of Action	FDA Approved Indications	Protein Binding	Volume of Distribution	Half-life	Activation	Metabolism	Interactions	Renal excretion
Dabigatran Direct thrombin inhibitor (factor II)	Non-valvular atrial fibrillation	35%	50-70 L	12-17 hr	De-esterification and glucuronidation	Conjugation	P-glycoprotein	80%
Rivaroxaban Direct Xa Inhibitor	Non-valvular atrial fibrillation, VTE prophylaxis and Treatment	92-95%	50 L	5-9 hr	N/A	Oxidation via CYP3A4 and CYP2J2 and hydrolysis	P-glycoprotein and CYP3A4	36%
Apixaban Direct Xa Inhibitor	Non-valvular atrial fibrillation	87%	21 L	8-15 hr	N/A	Oxidation via CYP3A4 and conjugation	CYP3A4	25%

use of dabigatran in patients > 110 kg, the manufacturer states that no adjustment is necessary. The Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) trial, conducted in 2009[73] reported a mean weight of 82.6 kg (range of 32-222 kg). A subgroup analysis was conducted on the 17.1% of patients that weighed above 100 kg. They found that as total body weight increased, the serum levels of dabigatran decreased with normalized trough concentrations of 0.998, 0.824, and 0.652 ng/ml/mg in < 50, 50-100, and ≥ 100 kg patients, respectively[51].

In 2012, a post-hoc pooled analysis of three phase III trials RE-MODEL, RE-NOVATE, and RE-NOVATE II was conducted by Eriksson et.al. to assess the safety and efficacy of dabigatran 220 mg daily versus enoxaparin 40 mg daily in prevention of VTE in patients undergoing total knee replacement or total hip replacement. Patients were grouped according to BMI indicating normal weight, overweight, or obese. The primary endpoint was major VTE, VTE-associated mortality, and clinically relevant bleeding. 1417 (24.9%) had a normal BMI, 2373 (41.7%) were overweight, and 1826 (32.1%) were obese. The authors found a significantly reduced incidence of the primary endpoint in normal weight patients in the dabigatran group compared to the enoxaparin group. No significant difference was found between dabigatran and enoxaparin in the remaining subgroups. Furthermore, they found no difference in bleeding events between groups. They concluded that dabigatran was effective and safe for normal, overweight, and obese patients[74].

RIVAROXABAN

The manufacturer states that a < 25% change in rivaroxaban concentrations was seen when the drug was administered to patients of varying weights and suggest that no dose adjustment is necessary for obese patients. A small study was conducted in 2007 with the goal of evaluating rivaroxaban pharmacokinetics in patients with extreme weights (≤ 50 kg and ≥150 kg) versus normal weight patients (80 kg). There were 12 patients in the obese group with a mean BMI 43.5 ± 4.2 kg/m^2 and a mean weight of 132.2 ± 9.9 kg. The peak concentrations were not found to be different in the obese group, whereas the peak was 24% greater in the ≤ 50 kg group. The authors concluded that rivaroxaban concentrations are not affected by body weight[75]. In 2008, a group conducted a population PK-PD modeling study of rivaroxaban in patients taking the drug for VTE prophylaxis after total hip replacement. They found that age and renal function significantly affected clearance whereas body surface area significantly affected the V_d of the drug[76].

APIXABAN

In 2010, Upreti et. al assessed the effect of body weight on the pharmacokinetics of apixaban. There were a total of 54 patients equally segregated

into three different weight groups: ≤ 50 kg, 65-85 kg, and ≥ 120 kg. The patients were given a single 10 mg dose of apixaban prior to PK-PD profiling. Patients in the high weight group had 30% lower peak concentration and a 20% lower AUC compared to those in the middle weight group, and patients in the smallest weight group were found to have a 30% increase in peak concentration and a 20% higher AUC compared to the middle weight group. Anti-Xa activity was well correlated with apixaban plasma concentrations, regardless of body weight. The authors concluded that body weight minimally affected apixaban exposure and did not recommend dosage adjustments for patients with very high or very low body weights[77].

SUMMARY

For heparin, LMWH, and fondaparinux, an inverse relationship between total body weight and anti-Xa activity has been consistently documented, suggesting that overall drug exposure may not be adequate in obese patients. It has been suggested that LMWH be dosed according to peak anti-Xa levels, with stronger recommendations for treatment monitoring as opposed to prophylaxis. However, this monitoring parameter merits further evaluation in tying its quantification to clinical outcomes. While most of the literature that exists for inadequacy of conventional LMWH dosing in obesity is related enoxaparin, smaller studies suggest that dalteparin and tinzaparin may be effective at conventional dosing. This statement must be taken with caution, however, due to the relative dearth of literature pertaining to the use of dalteparin and tinzaparin in this patient population. For dosing warfarin in obese patients, a longer time period may be required to titrate the dose to a given therapeutic INR. With the new oral anticoagulation agents dabigatran, rivaroxaban, and apixaban, there is a general lack of information in the biomedical literature. The currently available pharmacokinetic studies do not consistently suggest the same total drug exposure in obese patients and therefore further studies may be required to establish efficacy in this patient population.

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NEW GUIDELINE PUBLISHED

The update to ATP III has done away with LDL goals in favor of identifying 4 groups of patients at risk for events who warrant statin treatment. These new guidelines may greatly increase the number of patients eligible for treatment with statins. For more information please find the guidelines published at the citation below.

Stone NJ et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to reduce Atherosclerotic Cardiovascular Risk in Adults. Circulation. November 12, 2013

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