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Impact of body mass index on 90-day warfarin requirements: a retrospective chart review

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Abstract

Background: Rates of obesity continue to rise worldwide as evidenced in the 2017 *Centers for* Disease Control and Prevention (CDC) report that indicated over 35% of United States (US) citizens are obese, with Louisiana ranked as the fifth most obese state in America. Since large clinical trials tend to exclude obese patients, health care providers are faced with concerns of under- or overdosing these patients on warfarin.

Methods: This retrospective chart review evaluated patients who reported to a community anticoagulation clinic for warfarin management between 1 June 2017 and 30 September 2017. Along with baseline demographics, chronic use of drugs that have clinically significant interactions with warfarin, social activity such as tobacco use and alcohol consumption, were collected. Body mass indexes (BMI) were collected and categorized according to the World Health Organization definitions as follows: Normal (BMI 18–24.9 kg/m^2), Overweight (25–29.9 kg/m^2), Obesity Class I (30–34.9 kg/m^2), Obesity Class II (35–39.9 kg/m^2), Obesity Class III ($\geq$40 kg/m^2). The primary outcome was the mean 90-day warfarin dose required to maintain "intermediate control" or "good control" of international normalized ratio (INR), stratified by BMI classifications. The secondary outcome was the time in therapeutic range (TTR) stratified by BMI classifications.

Results: A total of 433 patient encounters were included in this study. There was a total of 43 encounters in the Normal BMI category, 111 Overweight encounters, 135 Obesity Class I encounters, 45 Obesity Class II encounters, and 99 Obesity Class III encounters. Approximately 63% of the study population were male, and over 90% the patients were African American. The Obesity Class I and Obesity Class II class required an average of 11.47 mg and 17.10 mg more warfarin, respectively, to maintain a therapeutic INR when compared with the Normal BMI category. These findings were statistically significant with p values of 0.007 and $<$0.001, respectively. Additionally, upon comparing the Overweight BMI category with the Obesity Class II category, there was a mean warfarin dose difference of 11.22 mg (p = 0.010) more in Obesity Class II encounters to maintain a therapeutic INR. In the secondary analysis of TTR, Overweight category encounters had the highest TTR, whereas encounters in the Normal BMI category had the lowest TTR.

Conclusion: As BMI increases, there is an increased chronic warfarin requirement to maintain "intermediate control" or "good control" of INR between 2 and 3 in an ambulatory care setting.

Keywords: warfarin, obesity, coumadin, INR, therapeutic, vitamin K, smoking, NSAIDs

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Introduction

Warfarin, a vitamin K antagonist, is among the most commonly prescribed and highly effective anticoagulants for millions of patients.[1] Warfarin has proven efficacy for numerous conditions, including atrial fibrillation, prevention of systemic

embolism in patients with heart valve replacements, and prevention of recurrent venous thromboembolism.[1] A balance between achieving clinical efficacy and minimizing the risk of bleeding is evaluated through the international normalized ratio (INR). The INR often must be maintained in a targeted therapeutic range, typically between 2 and 3.[1,2]

Brudasca demonstrated that interpatient and intrapatient variability in the initial response to warfarin therapy and warfarin dose requirements may complicate the achievement of attaining an INR within therapeutic range.[3] The mechanism of underlying variability in warfarin dose requirements has been investigated but is as yet not fully understood. Patient factors such as age, sex, comorbid conditions, nutritional status, concomitant medications, adherence, and influence of genetic polymorphisms have been previously identified in clinical trials as barriers to achieving appropriate therapeutic range.[2] Currently, guidelines recommend against routine pharmacogenetic testing to guide warfarin dosing.[1] However, it is important to highlight the testing protocol as it incorporates race, gender, smoking, and body surface area, yet it does not account for the patients' weight or body mass index (BMI).[1,2]

Wallace and colleagues highlighted that, compared with normal BMI category patients, newly initiated hospitalized patients on warfarin therapy who were obese and morbidly obese had a decreased initial response to warfarin and were less likely to achieve therapeutic INR in the same time frame before discharge.[4] Based on the results of this study, clinicians are expected to anticipate the need for 40–50% higher initial warfarin doses in the obese and morbidly obese populations compared with patients of normal BMI in order to effectively achieve a therapeutic INR within the same time to discharge.[4]

Similarly, in 2018, Tellor and colleagues concluded that data from their institutional setting evaluation may suggest that BMI, especially 40 kg/m^2 and over, in addition to other traditional factors affecting warfarin requirements, should be taken into account when determining warfarin doses in hospitalized patients.[5,6]

Finally, in 2014, Mueller and colleagues performed a study to determine the association between BMI and the total weekly dose of warfarin over 30 days. The researchers found that BMI is positively correlated with the total weekly warfarin dose, and showed that for each 1-point increase in BMI, the weekly warfarin dose increased by 0.69 mg.[7] However, several factors, such as significantly interacting medications and vitamin K intake, that may alter the warfarin requirement were not taken into account.

Despite its increasing prevalence and correlation with cardiovascular disease and risk of recurrent venous thromboembolism, the effect of BMI on warfarin therapy has been minimally evaluated. Based on the limited information available, data have demonstrated that obesity is associated with higher warfarin requirements to achieve a therapeutic INR due to a higher volume of distribution related to fat solubility and increased clearance in an institutional setting.[5,7] This study evaluated the impact that BMI, with respect to pertinent clinical factors, has on warfarin dosing requirements for patients in an ambulatory care setting.

Methods

This study was a single-center retrospective chart review conducted at University Medical Center New Orleans (UMCNO) Coumadin clinic. Ethics approval was obtained for the present study by Xavier University of Louisiana Institutional Review Board (approval number 711). Participants of the study were not solicited, contacted or provided with informed consent due to the retrospective nature of this study. The study proposed involves no more than minimal risk to subjects. Lastly, there were no changes to the proposal that may affect the wellbeing of the participants.

The patients included in this study spanned BMI categories that were established according to World Health Organization (WHO) categories: Normal (BMI 18–24.9 kg/m^2), Overweight (25–29.9 kg/m^2), Obesity class I (30–34.9 kg/m^2), Obesity class II (35–39.9 kg/m^2), and Obesity class III ($\geq$40 kg/m^2). The patients included in this study were patients who were seen and received warfarin therapy management from the clinicians at UMCNO outpatient anticoagulation clinic between June 2017 and September 2017.

Patients that were included in this study were those age 18 years and older, required warfarin for

an indication that has a therapeutic INR range 2–3 as defined in the American College of Chest Physicians guidelines. Such indications include atrial fibrillation, venous thromboembolism, mechanical aortic valve replacements, cardioembolic stroke history, peripheral vascular disease, and hypercoagulable states such as protein C and S deficiency or antiphospholipid syndrome. All patients included in this study also required warfarin therapy for a minimum of 3 months. For this study, patients who took warfarin for an indication that required an INR goal outside of the range 2–3 were excluded. The following exclusion criteria were used for this study: those who initiated warfarin and/or a significantly interacting medication with warfarin within 30 days of 1 June 2017, those who stopped warfarin for an elective or emergency procedure, those who missed appointments in the anticoagulation clinic, those who had an emergency department (ED) visit between June and September 2017, and pregnant patients.

Data collection

The information collected include baseline patient demographics, weekly warfarin dose, INR, social activity, and concurrent medication use with significant drug interactions with warfarin. Baseline demographics included patient's age, gender, height, and weight. BMI was calculated for each patient and further categorized using the WHO categories. Social activity included tobacco use, marijuana use, alcohol consumption, and changes in vitamin K foods. Finally, drugs/drug classes that have a known clinically significant interaction with warfarin that were evaluated in this study are as follows: amiodarone, anticonvulsants, antiplatelets, azole antifungals, metronidazole, nonsteroidal anti-inflammatory drugs (NSAIDs), fluoroquinolones, steroids, tetracyclines, and trimethoprim/sulfamethoxazole. All information was collected from electronic health records.

Study outcomes

The primary outcome was the mean 90-day warfarin dose required to maintain "intermediate control" or "good control" of INR, stratified by BMI classifications. Intermediate control is defined as a time in therapeutic range (TTR) 50–70% of all clinic appointments between June 2017 and September 2017 for the purpose of this study. Good control requires the TTR to be greater than 70% of all clinic appointments within the specified time frame, in this case between June 2017 and September 2017.[8] These definitions allow providers to assess the success of warfarin therapy, both in efficacy and safety, while also maximizing benefits.[8] The secondary outcome was the TTR stratified by BMI classifications.

Statistical analysis

All significance testing was set at $\alpha < 0.05$. A population analysis proved that the target sample size for this study is 256 patient encounters to detect 80% power. Descriptive statistics were used to analyze baseline demographics among groups. Furthermore, a Fisher exact test was used for statistical comparisons of categorical variables of patient demographics. To evaluate the primary endpoint, a one-way ANOVA was conducted for differences among mean warfarin dose stratified by BMI classifications. A Tukey *post hoc* analysis was performed to determine which BMI classifications had significant differences in warfarin dose. A Pearson correlation coefficient was calculated to assess whether there is an association between BMI and weekly warfarin dose. To evaluate the secondary endpoint, a multinomial linear regression was used to assess whether there is an association between BMI and weekly warfarin dose. All analyses will be considered significant with $p < 0.05$. All analyses will be performed using IBM SPSS Statistics Version 24.

Results

A total of 83 patients met the inclusion criteria in this study, which yielded a total of 433 qualified patient encounters between 1 June 2017 and 30 September 2017. Power was met based on the number of patient encounters reviewed in this study. A sample selection flow chart can be found in Figure 1. There was a total of 43 encounters in the Normal BMI category, 111 Overweight encounters, 135 Obesity class I encounters, 45 Obesity class II encounters, and 99 Obesity class III encounters. Approximately 63% of the study population were male, and over 90% of the patients were African American. A detailed examination of the patient demographics can be found in Table 1.

Of the data collected regarding significant drug interactions with warfarin, 43.6% of patient

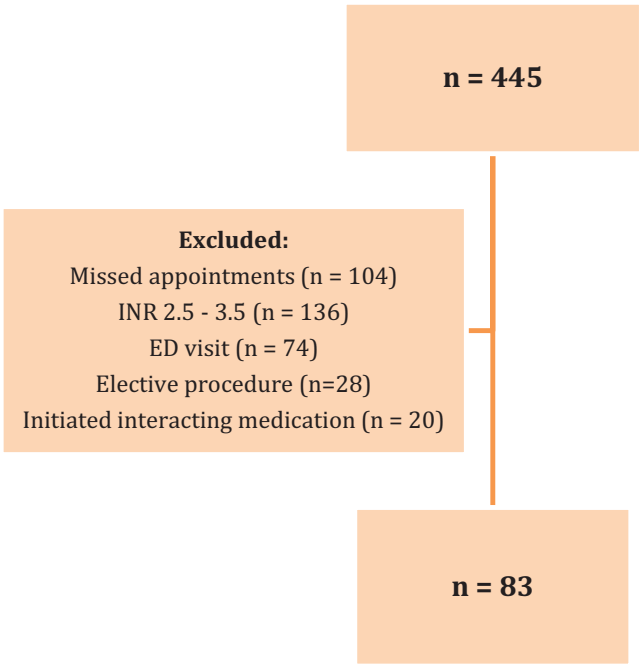

Figure 1. Detailed exclusion criteria. Each exclusion reason is followed by number of patients excluded. A total of 83 patients were included for this study.
ED, emergency department; INR, international normalized ratio.

Table 1. Patient demographics.

	(*n* = 83 patients)
Age in years, mean (range)	60 (34–85)
Sex, *n* (%)	
Male	52 (62.7)
Female	31 (37.3)
Race, *n* (%)	
African American	67 (80.7)
Caucasian	11 (13.3)
Hispanic	5 (6)
BMI in kg/m^2, mean (SD)	32.7 (8.04)

BMI, body mass index; SD, standard deviation.

encounters had an antiplatelet, such as clopidogrel, aspirin, and ticagrelor, on their reconciled medication list, as depicted in Table 2. Regarding social aspects that may affect INR and warfarin dosing, nearly 20% of patient encounters had documented positive alcohol use.

Results show that weekly warfarin requirements increased as the patient's BMI increased. A weak, but statistically significant, Pearson correlation coefficient was found at 0.131 ($p = 0.006$). A depiction of mean warfarin requirement across all BMI categories can be found in Figure 2.

Upon further comparisons of BMI status with warfarin requirement, Obesity Class I and Obesity Class II class required an average of 11.5 mg and 17.1 mg more, respectively, to maintain a therapeutic INR when compared with the Normal BMI category. These findings were statistically significant with p values of 0.007 and <0.001, respectively. Additionally, upon comparing the overweight BMI class with the Obesity class II, there was a mean warfarin dose difference of over 11.2 mg ($p = 0.01$) more in the Obesity II class to maintain a therapeutic INR. The collective data comparisons across BMI classes can be found in Table 3.

In the secondary analysis of TTR, Overweight encounters had the highest TTR whereas encounters in the Normal BMI category had the lowest TTR. There were no statistically significant differences among BMI categories and TTR. A detailed comparison of the TTR is found in Figure 3.

The effects of well-established social predictors on warfarin dosing were also evaluated, as depicted in Table 4. There were statistically significant predictors on weekly warfarin dose for patients who were taking NSAIDs and/or antiplatelets, and patients who reported "yes" to using tobacco products and/or drinking alcohol (Table 5).

Discussion

In this retrospective chart review, warfarin requirements were compared across five different BMI categories. There were statistically significant differences among the race and BMI classifications that were included in this study. Of the patients included, there was a statistically significant difference among the warfarin requirements to maintain a therapeutic INR across all BMI categories ($p = 0.006$). Additionally, a correlation coefficient of 0.131, indicates that BMI, on its own, accounted for 1.7% of weekly warfarin doses. The findings of the study indicate that there is an association between BMI status and

chronic warfarin dosing needed to maintain a therapeutic INR between 2 and 3.

Unexpectedly, the encounters in the Obesity Class III category had a lower average warfarin (mg) dose when compared with Obesity Class I and Obesity Class II categories. After running a *post hoc* analysis of clinically significant warfarin interactions among all the BMI categories, it was noted that the encounters in the Obesity Class III category reported significantly higher rates of NSAIDs and antiplatelet use. A detailed breakdown of those who reported using these classes of medications can be found in Figure 4. Studies have shown how NSAIDs positively impact INR, which in turn influences a change in warfarin requirement. Choi and colleagues performed a study in Korean patients to evaluate the risk factors of the drug interaction between warfarin and NSAIDs. This study further evaluated management strategies for these patients and found that, of the 39.7% of patients in their cohort who experienced an increase in INR, over 48% of patients were told to decrease the weekly dose of warfarin to achieve a therapeutic INR.[9] The study evaluators went on to conclude that patients who are receiving >40 mg of warfarin per week and taking NSAIDs along with other significantly interacting medications, will require a decrease in warfarin dose to maintain an adequate TTR.[1]

Table 2. Baseline characteristics.

History	Yes (n = 433 encounters)	Percentage
Alcohol use	86	19.9
Anticonvulsants	93	21.5
Antiplatelets	189	43.6
Marijuana status	13	3
NSAIDs	32	7.4
Steroids	63	14.5
Tobacco status	61	14.1
Change in vitamin K intake	51	13.2

NSAIDS, nonsteroidal anti-inflammatory drugs.

Obesity is a well-recognized risk factor for the development of cardiovascular disease including ischemic stroke. Dickerson and colleagues highlighted key lifestyle modifications needed to reduce the risk of recurrent stroke that include management of obesity.[9] The patients in the Obesity Class III category were likely taking antiplatelets to reduce the recurrence of cardiovascular complications, thereby decreasing their warfarin requirements. Similar to NSAIDs, it has been clinically proven that antiplatelets may alter

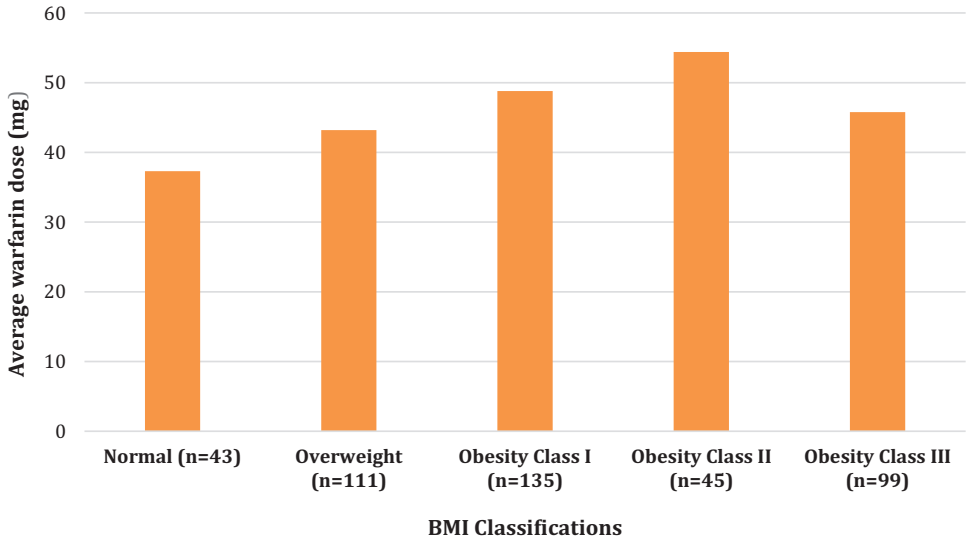

Figure 2. BMI *versus* average weekly warfarin dose in milligrams. Each BMI class is followed by the number of encounters collected for this study.
BMI, body mass index.

Table 3. Comparisons of warfarin requirements across BMI status.

BMI status 1	BMI status 2	Mean difference in mg	*p* value
Normal	Overweight	−5.88	0.444
	Obesity Class I	−11.47	0.007*
	Obesity Class II	−17.1	<0.001*
	Obesity Class III	−8.47	0.121
Overweight	Obesity Class I	−5.59	0.165
	Obesity Class II	−11.22	0.010*
	Obesity Class III	−2.58	0.872
Obesity Class I	Obesity Class II	−5.63	0.446
	Obesity Class III	3.01	0.769
Obesity Class II	Obesity Class III	8.63	0.099

*Statistically significant finding ($p < 0.05$).
BMI, body mass index.

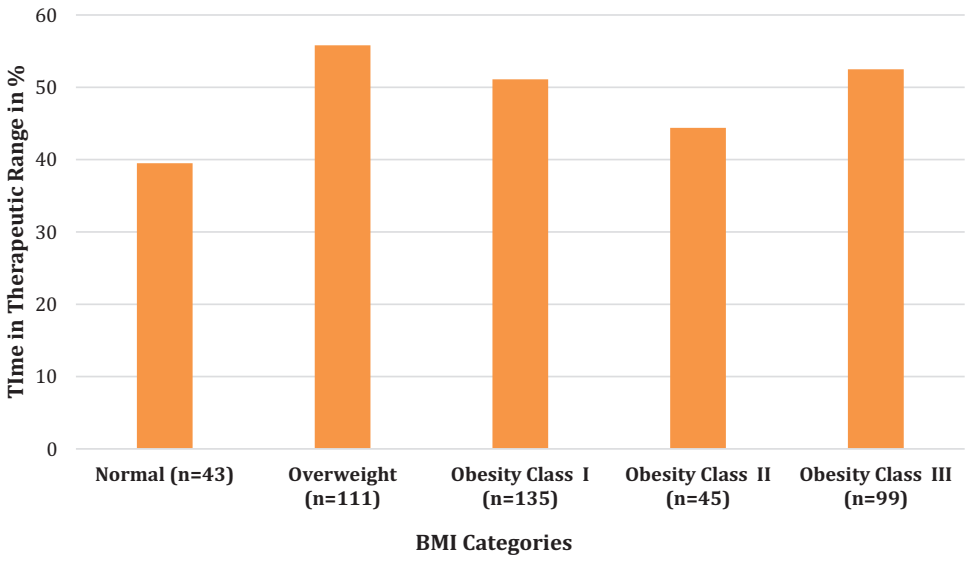

Figure 3. BMI categories *versus* TTR, measured in percentage.
BMI, body mass index; TTR, time in therapeutic range.

warfarin metabolism and lead to an unstable increase in INR, thereby decreasing the warfarin requirements.[10,11]

The Overweight BMI category had the highest TTR at 55.8% while the patients in the Normal BMI category had the lowest TTR at 39.4%. The findings of the TTR were not statistically significant among the BMI categories, likely due to the inequalities of patient encounters that were included in each category. Additionally, the Normal and Obesity Class II categories did not meet the criteria for intermediate control, likely due to their small sample size ($n = 43$, $n = 45$, respectively).

Table 4. Effects of social predictors on weekly warfarin dose.

Variable	Yes (*n*)	Mean dose (mg)	No (*n*)	Mean dose (mg)	*p* value
NSAIDs	32	48.67	401	45.91	0.002*
Antiplatelets	189	40.41	244	50.53	<0.001*
Tobacco use	61	60.19	372	43.81	<0.001*
Alcohol use	86	57.99	347	43.17	<0.001*
Marijuana use	13	68.08	420	45.44	0.221
Increase in vitamin K	44	45.36	376	46.13	0.275
Decrease in vitamin K	13	48.23	376	46.13	0.596

*Statistically significant finding ($p < 0.05$).

A detailed look at the statistical findings on the social predictors that affect warfarin dosing shows that those who reported the use of NSAIDs required more warfarin than those who reported "no" to use. This result may be due to positive use of combinations of other social factors that typically lower INR, which in turn increases warfarin requirement. An individual-based *post hoc* analysis would be beneficial to determine the true significance behind the patients who reported the use of NSAIDs but also had an increased warfarin requirement.

Of the remaining statistically significant social predictors on warfarin dosing, those who used any form of tobacco products had higher warfarin requirements (60.19 *versus* 43.81 mg), which coincide with previous data showing that tobacco use contributed to decreasing INRs.[12] On the other hand, positive alcohol use increased the warfarin requirements (57.99 *versus* 47.13 mg). From a mechanistic point of view, warfarin is 99% bound to plasma proteins, primarily human serum albumin (HSA).[13] Acute consumption of alcohol, specifically ethanol, tends to displace warfarin from HSA, thereby making more free warfarin available to exhibit its pharmacological effects and increase bleeding risk.[14] However, chronic consumption of alcohol activates cytochrome P450 and increases warfarin metabolism. As a result, higher warfarin doses are required to achieve the desired anticoagulant effect, as reflected in the patients in this study.[15]

Limitations

The limitations of this study include the retrospective nature of a single-center, which resulted in less than complete data on certain parameters such as the amount of alcohol and vitamin K foods consumed, along with weekly warfarin adherence rate. As expected, there was an imbalance on the patient population who qualified for inclusion due to the nature and location of the site chosen to conduct this study. This study had a small sample size as well. Lastly, the Underweight BMI classification was excluded from this study due to the lack of this patient population seen in the clinic.

Table 5. Breakdown of acute *versus* chronic alcohol ingestion.

Frequency	Number	Percent
0 times per week	347	80.1
1–3 times per week	60	13.9
4–6 times per week	14	3.2
⩾7 times per week	12	2.8

Future implications

This study solely evaluated patients with an INR goal 2–3 thereby excluding a significant part of the warfarin patient population with conditions that require a goal outside of this range. An evaluation of this subset of patients across all BMI categories would be beneficial to further establish BMI as a factor that affects chronic warfarin dosing. Future studies should also conduct a more in-depth evaluation of warfarin requirements long term as a

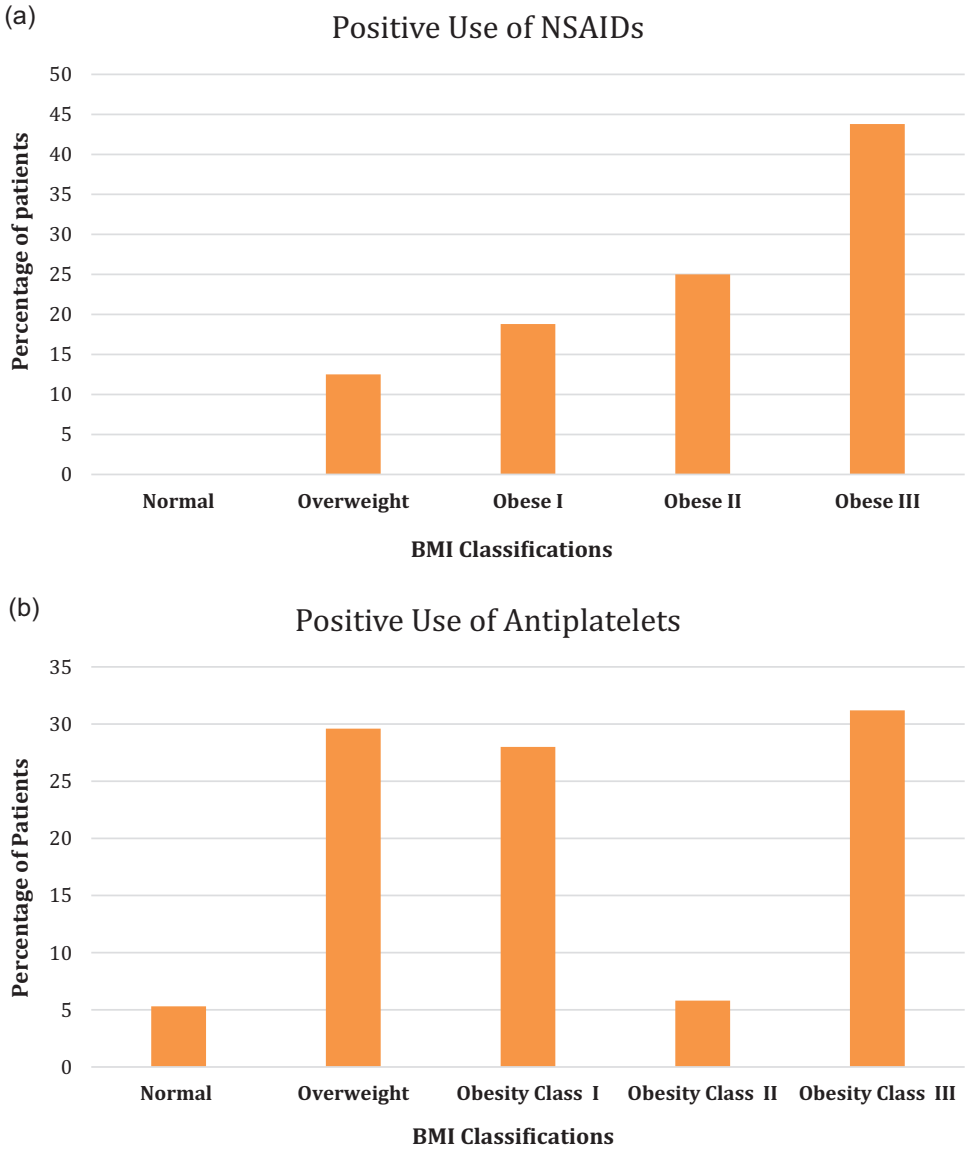

Figure 4. (a)Trends of encounters that reported "yes" to using NSAIDs; (b) trends of encounters that reported "yes" to use of antiplatelet medications. In both drug classes, encounters in Obesity Class III classifications had the highest reported use of medications in drug class that are considered NSAIDs or antiplatelets.
BMI, body mass index; NSAIDS, nonsteroidal anti-inflammatory drugs.

patient's BMI fluctuates between categories. The findings of this study suggest that clinicians should be more aggressive with warfarin dose adjustments in obese patients to maintain a therapeutic INR compared with non-obese patients.

Conclusion

Warfarin has a narrow therapeutic index and requires careful monitoring.[13] Warfarin has the potential to be influenced by factors both endogenous and exogenous. As BMI increases, there is an increased chronic warfarin requirement to maintain "intermediate control" or "good control" of INR between 2 and 3 in an ambulatory care setting, based on the findings of this study.

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Conflict of interest statement

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