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# A Systematic Review of Warfarin Use in Post-Bariatric Surgery Patients: Cases Compiled From a Literature Review

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## Abstract

**Objective:** The objective of this review was to provide dosing recommendations for percentage change in weekly warfarin dose and rates of thrombotic and bleeding events in patients requiring long-term warfarin therapy after bariatric surgery.

**Data Sources:** A comprehensive literature search of PubMed (through April 5, 2021), Cochrane Library, and Google Scholar (through April 5, 2021) databases was completed using the keywords warfarin OR vitamin k antagonist AND bariatric surgery.

**Study selection and data extraction:** Retrospective studies and matched-cohort studies evaluating preoperative and postoperative use of warfarin after bariatric surgery for obesity were considered. Weekly dose defined as sum of daily doses of warfarin for 7 consecutive days was a required outcome to be considered in this review. Patients were excluded from review if post-operative dosage change was not reported.

**Data synthesis:** Six studies were included with a total of 160 patients who met the criteria. A decrease in average warfarin dose was seen in all studies, with the largest decrease occurring at 1 month postsurgery followed by an upward trend toward baseline about 90 days postsurgery. While thrombotic events were observed in none of the patients, there was an increased risk of bleeding in patients, particularly in those who underwent roux-en-y gastric bypass (RYGB) surgery.

**Relevance to patient care and clinical practice:** The study provides a specific warfarin dosing titration regimen, as well as embolic and bleed risk in post-bariatric surgery population.

**Conclusions:** Clinicians may consider lowering warfarin weekly dose by about 25% immediately postsurgery, with doses approaching closer to baseline about 90 days postsurgery.

## Keywords

bariatric surgery, anticoagulation, warfarin, gastric bypass, systematic review, obesity

## Introduction

The prevalence of obesity in the United States in 2018 was about 42.4%. The annual health care costs for obese patients in 2008 were estimated to be US\$147 billion.<sup>1</sup> Patients who have morbid obesity are at higher risk of type 2 diabetes, heart disease, cancer, and thromboembolic events.<sup>1,2</sup> Bariatric surgery has been shown to reduce mortality rate, lower blood pressure, reverse metabolic syndrome, and increase the quality of life.<sup>3,4</sup> As the most effective method of weight loss in patients with moderate (body mass index [BMI]  $\geq 35$  kg/m<sup>2</sup>) and severe (BMI  $\geq 40$  kg/m<sup>2</sup>) obesity, there is an increase in the number of individuals undergoing bariatric surgery.<sup>5</sup> The different types of bariatric procedures available include roux-en-y gastric bypass (RYGB), sleeve gastrectomy (SG), and adjustable gastric banding (AGB). These procedures achieve weight loss by reducing the stomach volume and limiting caloric intake by promoting early satiety or reducing the number of calories absorbed

by bypassing pancreatic secretions, bile acids, or the proximal jejunum and duodenum.<sup>6</sup> While there are remarkable positive outcomes of bariatric surgery, there are some medical and surgical complications postoperatively. These include nutritional deficiencies, postsurgical thromboembolic risk, as well as bleeding risk.<sup>7</sup>

It is important to note that a sedentary lifestyle, immobility, and venous obstruction from obesity are risk factors for the development of venous thromboembolism (VTE).<sup>8</sup> In

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addition, patients undergoing bariatric surgery may have various indications for anticoagulation use, such as atrial fibrillation, prevention of VTE, genetic predisposition to coagulation, or presence of mechanical heart valves.<sup>9</sup> Clinicians must balance the risk of thromboembolism versus the risk of hemorrhaging from surgery. Warfarin is the most widely used anticoagulant in the world and is the recommended anticoagulant after bariatric surgery.<sup>6,10</sup>

Warfarin is a weak acid that is unionized at normal stomach pH. The drug is extensively absorbed through the stomach and proximal small intestine and boasts a high bioavailability. However, the absorption of warfarin is dependent on exposure of the drug to the gastrointestinal tract. RYGB and SG decrease the surface area in the stomach leading to a reduction in the absorption of warfarin.<sup>11,12</sup> Dose adjustments of warfarin are further complicated by the influence of dietary vitamin K. Warfarin's mechanism of action focuses on the antagonism of vitamin K-dependent clotting factors. Vitamin K deficiency after bariatric surgery leads to decreased vitamin k-dependent clotting factors and affects warfarin dosage requirements.<sup>11</sup> Finally, patients who have undergone bariatric surgery require significant lifestyle changes. Patients are encouraged to alter their diet and exercise to aid in their weight loss. Overall, weight loss can lead to an increase in international normalized ratio (INR) and can therefore cause the need for warfarin dose adjustments throughout the weight loss process.<sup>13,14</sup> While bariatric surgery alters drug absorption, weight, and diet—all factors that may affect therapeutic anticoagulation requirements—there is currently no formal guidance for dose adjustment in this patient population. Although there is a significant decrease in drug absorption after bariatric surgery, several studies have reported that warfarin may still be absorbed in varying amounts due to its high bioavailability.<sup>15</sup> This systematic review aims to compile case reports and identify percent change in weekly warfarin dose and rates of thrombotic and bleeding events in patients requiring long-term warfarin therapy after bariatric surgery.

## Methods

Two reviewers examined, collected, and extracted data from all relevant studies. This systematic review included a search of PubMed, the Cochrane Library, and Google Scholar databases with the following keywords: “warfarin” OR “vitamin K antagonist” and “bariatric surgery.” From this search, 23 articles were identified. Of these articles, 6 studies with 160 subjects that met review criteria were included in the review. Retrospective studies evaluating preoperative and postoperative use of warfarin after bariatric surgery for obesity were considered. Trials did not need an active comparator to be included in this review. Weekly dose must be an outcome measure to be considered in this review but was not restricted to being the primary outcome

measure. Weekly dose must be defined as the sum of daily doses of warfarin for 7 consecutive days. No limitations were applied for the year of publication. Participants of any age, treatment duration, indication, dosage, and type of bariatric surgery were included. Patients were excluded from review if postoperative dosage change was not reported. One article was excluded because the bariatric surgery was for an invasive adenocarcinoma of her gastric remnant. We extracted several components of the case reports, including age, sex, anticoagulation indication, percentage of dose change, and events of bleeding and thrombosis to determine whether there is need for warfarin dose adjustment following bariatric surgery.

## Results

Of the 160 subjects, 44% were male. Atrial fibrillation was the most common indication for anticoagulation followed by prior deep vein thrombosis (DVT)/pulmonary embolism (PE), artificial valve, and genetic predisposition. Mean weekly warfarin dose was between 37.08 and 58.4mg. All patients were severely obese, having a BMI > 40kg/m<sup>2</sup> (Table 1).<sup>7,16–20</sup>

A similar pattern of warfarin dose adjustment was observed across all studies. Weekly warfarin dose decreased immediately after surgery but returned close to baseline after 90 days (Figure 1). Interestingly, in the Steffen et al. study, weekly dose increased after 90 days. The investigators note that this comparison was not statistically significant due to small sample size. Increased risk of bleeding is a common complication after bariatric surgery. One study reports gastrointestinal bleeding (GIB) after bariatric surgery can occur between 1.1% and 4% of patients. This increased incidence can be due to bleeding at one of the staple lines or the overuse of anticoagulants.<sup>21</sup> Bleeding was reported in 17 patients. Of the 13 patients who experienced bleeding in the Bechtel et al. study, 11 occurred within 30 days of bariatric surgery. Six developed gastrointestinal tract hemorrhage and all underwent RYGB. Similarly in the Schullo et al. study, the 2 patients who experienced bleeding underwent RYGB and had GIB. One patient presented with bright red blood in her stool on postoperative day 8, had an INR of 2.9, and was using enoxaparin postoperatively. The second patient presented on day 21 with black stool and had an INR of 9.8. The reported incidence of DVT post bariatric surgery is between 0.12% and 3.8%. Thrombotic events were observed in 0 patients (Table 2).

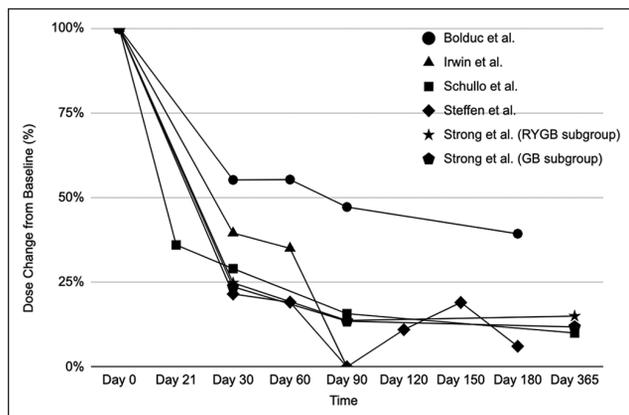
## Discussion

This is the largest compilation of case series summarizing several different published studies and providing clinical guidance to clinicians managing anticoagulation regimens for patients after bariatric surgery. In each of the studies mentioned above, the required warfarin dosage in order to

**Table 1.** Baseline Characteristics of Study Patients.

Source	No. of patients	Percent of males (%)	Mean age (years)	Indications for anticoagulation	Mean baseline weekly warfarin dose (mg)	Type of gastric bypass surgery	Baseline BMI (kg/m <sup>2</sup> )
Bechtel et al. <sup>7</sup>	38	55.3	Age: 30-39 (4/38), 40-49 (11/38), 50-59 (7/38), 60+ (16/38)	Arrhythmia: 19/38 DVT/PE: 12/38 Genetic predisposition: 5/38 Artificial valve: 2/38	NR	NR	NR
Bolduc et al. <sup>16</sup>	20	65	54	AF: 14/20 Mechanical heart valve: 3/20 DVT/PE: 2/20 Unknown: 1/20	43.8	Standard BPD/DS: 14 Modified BPD/DS: 6	53
Irwin et al. <sup>17</sup>	27	18.5	56.9	AF: 3/27 Mechanical heart valve 9/27 History of DVT 11/27 History of PE 4/27	47.9	GB: 5 RYGB: 22	50.2
Schullo-Feulner et al. <sup>18</sup>	10	50	57	AF: 6/10 DVT/PE 2/10 DVT 1/10 Recurrent DVT 1/10	50.65	GB: 3 RYGB: 7	NR
Steffen et al. <sup>19</sup>	12	33.33	52	DVT prophylaxis (6/12) AF (6/12)	37.08	RYGB: 12	48.1
Strong et al. <sup>20</sup>	53	43.4	RYGB: 54.8 SG: 53.7	Prior VTE: 18 (34.0%) AF: 23 (43.4%) Mechanical heart valve: 3 (5.7%) Recurrent VTE: 58.5%	RYGB: 58.4 SG: 48.2	RYGB: 31 SG: 22	RYGB: 49.4 SG: 53.3

Abbreviations: BPD/DS, biliopancreatic diversion with duodenal switch; BMI, body mass index; DVT, deep vein thrombosis; GB, gastric banding; NR, not reported; PE, pulmonary embolism; RYGB, roux-en-y gastric bypass; SG, sleeve gastrectomy.



**Figure 1.** Percent decrease of warfarin dosing requirements after bariatric surgery.

remain in therapeutic range decreased after bariatric surgery with patients requiring lower doses than baseline prior to bariatric surgery. While the dosing did reduce significantly at first, the dose adjustments thereafter should require closer monitoring to allow for safer dose adjustments based on the INR. This review identified warfarin weekly dose to reach closer to prior baseline weekly dose about 90 days after surgery. Furthermore, information is available on the

**Table 2.** Embolic and Bleed Risk Post-Bariatric Surgery.

Source	Bleeding (no.)	Thrombosis (no.)
Bechtel et al. <sup>7</sup>	13	NR
Bolduc et al. <sup>16</sup>	NR	NR
Irwin et al. <sup>17</sup>	2	0
Schullo-Feulner et al. <sup>18</sup>	2	0
Steffen et al. <sup>19</sup>	0	0
Strong et al. <sup>20</sup>	N/A	N/A

INR readings of two patients who experienced bleeding after bariatric surgery while on warfarin, one of which was supratherapeutic. However, there are no data available for the other bleed events and hence unable to determine cause for bleeding.

This review identified that all postoperative bleeding episodes were reported in the patients who underwent RYGB surgery. However, these data are inconclusive since they are represented by a very small patient population. Further studies are needed to determine differences in bleed risk depending on the type of bariatric surgery. Three of the identified studies did not report embolic risk data, and the others reported no thrombotic events. Note, bariatric surgery had a high risk of VTE, especially for older patients. A

large population-based cohort study has reported bariatric surgery to have a high risk of VTEs, particularly in the older patient population.<sup>22</sup> Hence, further studies evaluating embolic risk of patients should be studied to further guide anticoagulation management strategies.

Our study did have some limitations. The retrospective nature of the studies resulted in incomplete collection of baseline characteristics, such as comorbidities, BMI, and concomitant medications. This is a drawback because many medications interact with warfarin, warranting a dosage change. In addition, some studies did not report bleeding or thromboembolism as noted above. The exclusion criteria and follow-up duration were not consistent in all studies, but follow-up did last at least 3 months in each case.

### Relevance to Patient Care and Clinical Practice

The study provides a specific warfarin dosing titration regimen, as well as embolic and bleed risk in post-bariatric surgery population.

### Conclusion

Our systematic review identified dose requirement decreased postoperatively. Clinicians may consider lowering warfarin weekly dose by about 25% immediately post surgery. This initial decrease was followed by an increase toward baseline dose seen about 90 days after the procedure. However, patients rarely need their prior baseline warfarin dose to remain therapeutic. Finally, due to increased bleed risk and unknown warfarin absorption in the studied population, patients on warfarin after bariatric surgery should be closely monitored to ensure the safety and efficacy of their anticoagulation therapy.

### Declaration of Conflicting Interests

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