Letter to the Editor

The Food and Drug Administration recently approved two new classes of oral anticoagulants: direct thrombin inhibitors, dabigatran etexilate and factor Xa inhibitors, apixaban and rivaroxaban [1]. All three of these drugs are for the treatment of nonvalvular atrial fibrillation with rivaroxaban also gaining approval for venous thromboembolism. Absorption of each drug is regulated by P-glycoprotein efflux transporters and is variable. The bioavailability of dabigatran etexilate is 7% with peak effect within two hours after administration. Apixaban has a 50% bioavailability with peak effect occurring 3–4 hours after administration and rivaroxaban has a bioavailability greater than 80% with peak effect occurring 2–4 hours after administration [1].

A P-glycoprotein is located on the apical membrane of enterocytes, act by pumping substrates back into the intestinal lumen, thereby limiting drug absorption. Its concentration gradually increases from the stomach to the distal part of the intestine. Above a certain concentration, efflux outpaces influx preventing absorption. All three drugs have warnings against co-administration with medications that induce P-glycoprotein expression, resulting in increased P-glycoprotein concentration earlier in the gastrointestinal tract leading to decreased drug absorption [1, 2].

With the current obesity epidemic, an estimated 180,000 bariatric procedures are performed annually in the United States. The most common intestinal diversion procedure is the Roux-en-Y gastric bypass. The consequences of this procedure are a 95% reduction in gastric capacity as well as a reduction in the functional length of the gastrointestinal tract from bypass of the duodenum and proximal jejunum. These changes augment the effect of P-glycoprotein on limiting drug absorption, similar to the effect medications have on inducing P-glycoprotein expression. The surgery has been linked to nutritional deficiencies but has not been extensively studied for reductions in drug absorption [2, 3].

We report a 41-year-old male admitted to the cardiac care unit with chest pain while taking dabigatran etexilate 150 mg twice daily and dofetilide 500 μg twice daily for atrial fibrillation. Computed tomography (CT) scan revealed a saddle pulmonary embolus. His activated partial thromboplastin time (aPTT) was 25.2 seconds (normal 22.3–35.3 seconds), and he had no previous PTT results while on dabigatran etexilate. He started dofetilide for uncontrolled atrial fibrillation about 18 months ago and reported compliance with both dofetilide and dabigatran etexilate, taking them earlier that day. He underwent a Roux-en-Y gastric bypass for morbid obesity 21 years ago. After the pulmonary embolus was diagnosed, a heparin drip was started and was safely discharged home on enoxaparin.

This case raises an important issue related to the potential for impaired absorption of the novel oral anticoagulants (NOAC) after gastric bypass. In our case, the normal aPTT suggests no active dabigatran in his plasma since there should have been enough time from when he took his last dose to be reflected by an elevated aPTT [4]. We hypothesize that the normal aPTT while on dabigatran etexilate is explained by the loss of critical absorption necessary to achieve therapeutic plasma levels that normally occur in the stomach and duodenum, a low P-glycoprotein environment. There is the possibility...
that medication noncompliance led to the normal aPTT, and due to safety concerns, he was not re-challenged with dabigatran etexilate and aPTT monitoring to prove whether gastric bypass prevented his absorption. However, the patient mentioned that he was regularly taking his medications, a claim supported by the fact that he was in sinus rhythm on admission.

Despite the known effects of gastric bypass leading to malabsorption in the proximal small bowel, there are no warnings about the potential for decreased absorption of NOAC following gastric bypass surgery. There is a single case report of a bariatric surgery patient noted to achieve therapeutic anti-Xa levels after receiving rivaroxaban [5], although it is not clear, if this patient had a classic Roux-en-Y. This may suggest enough absorption can still occur with rivaroxaban and apixaban as they are not inhibited by the higher concentrations of P-glycoprotein that found earlier in the altered intestinal tract after gastric bypass surgery because absorption normally occurs more distally in a higher P-glycoprotein concentration compared to dabigatran etexilate.

Currently, there are no warnings or recommendations regarding the use of NOAC following gastric bypass surgery. This is a large group at risk for developing venous thromboembolism and atrial fibrillation and subsequently starting one of these NOAC, especially, if they have had difficulties on warfarin with its variable absorption after gastric bypass [4]. Unfortunately, we are unable either to prove or disprove whether the normal aPTT was from impaired absorption or noncompliance. With the lack of evidence at this time further studies are needed to assess whether post bypass patients are capable of obtaining a therapeutic level with the current dosing recommendations with the NOAC. Until assays are available to ensure adequate plasma levels are achieved, there remains the potential for sub-therapeutic dosing.

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Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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REFERENCES