CLINICAL RESEARCH STUDY

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Impact of Body Mass Index and Genetics on Warfarin Major Bleeding Outcomes in a Community Setting

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ABSTRACT

BACKGROUND: Several studies have demonstrated an association between body mass index (BMI) and warfarin therapeutic dose, but none evaluated the association of BMI with the clinically important outcome of major bleeding in a community setting. To address this evidence gap, we conducted a case–control study to evaluate the association between BMI and major bleeding risk among patients receiving warfarin.

METHODS: We used a case–control study design to evaluate the association between obesity (BMI >30.0 kg/m^2) and major bleeding risk among 265 cases and 305 controls receiving warfarin at Group Health, an integrated healthcare system in Washington State. Multivariate logistic regression was used to adjust for potential confounders derived from health plan records and a self-report survey. In exploratory analyses we evaluated the interaction between genetic variants potentially associated with warfarin bleeding (*CYP2C9*, *VKORC1*, and *CYP4F2*) and obesity on the risk of major bleeding.

RESULTS: Overall, the sample was 55% male, 94% Caucasian, and mean age was 70 years. Cases and controls had an average of 3.4 and 3.7 years of warfarin use, respectively. Obese patients had significantly lower major bleeding risk relative to non-obese patients (odds ratio [OR] 0.60, 95% confidence interval [CI] 0.39-0.92). The OR was 0.56 (95% CI 0.35-0.90) in patients with ≥1 year of warfarin use, and 0.78 (95% CI 0.40-1.54) in patients with <1 year of warfarin use. An exploratory analysis indicated a statistically significant interaction between *CYP4F2*3* genetic status and obesity ($P = .049$), suggesting a protective effect of obesity on the risk of major bleeding among those wild type for *CYP4F2*3*, but not among variants.

CONCLUSIONS: Our findings suggest that BMI is an important clinical factor in assessing and managing warfarin therapy. Future studies should confirm the major bleeding associations, including the interaction between obesity and *CYP4F2*3* status identified in this study, and evaluate potential mechanisms.

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KEYWORDS: Body mass index; *CYP2C9*; *CYP4F2*; Gene–environment interaction; Major bleeding; *VKORC1*; Warfarin

Warfarin (Bristol-Myers Squibb Company, Princeton, NJ) is a commonly prescribed anticoagulant that is highly effective in reducing blood clotting events in patients with medical conditions that confer increased risk (eg, atrial fibrillation, myocardial infarction, and heart valve replacement).[1-6] However, warfarin management is difficult because giving

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too high a dose can result in increased risk of major bleeding (eg, cerebral hemorrhage), giving too low a dose can increase risk of serious clots (eg, stroke), and dose requirements are highly variable. For example, dose requirements are impacted by concomitant drug use, diet, alcohol use, and genetic status.[4,7,8] Collectively these factors create a significant barrier to appropriate use of this otherwise effective and inexpensive drug that prevents potentially serious clotting events. This is important at a population level because an estimated 2 million Americans currently use warfarin, despite the availability of newer anticoagulant medications.[2,4,9] Accordingly, it is critical to continue to identify warfarin major bleeding risk factors to improve warfarin outcomes, enhance patient and provider confidence, and provide high value anticoagulation care.

CLINICAL SIGNIFICANCE

- The influence of body mass index on bleeding risk among patients receiving the anticoagulant warfarin is poorly understood.
- Obese patients receiving warfarin had a 40% lower risk of major bleeding compared with non-obese patients.
- The protective effect of obesity was observed in wild-type *CYP4F2*3* patients but not patients with variant type *CYP4F2*3*, which itself has been shown to be protective.

Studies have shown that body mass index (BMI) impacts warfarin volume of distribution and clearance and is positively correlated with coagulation factor levels (VII, VIIIc, fibrinogen)[10,11]—suggesting potential mechanisms for BMI to impact clinical outcomes. For example, Mueller et al[12] demonstrated that for each 1-point increase in BMI, the average weekly therapeutic dose of warfarin increased by 0.69 mg. Because a typical weekly warfarin dose is 30-40 mg, not accounting for BMI can result in clinically important deviations in dose. No studies to date have evaluated whether this relationship extends to the clinically important warfarin outcome of major bleeding risk.[10-14]

Genetics also play an important role in warfarin outcomes. Recent studies have identified 3 genes that impact warfarin dose requirements and major bleeding risk: *CYP2C9*, *VKORC1*, and *CYP4F2*.[4,7,15-18] *CYP2C9* is primarily responsible for the metabolism of warfarin, *VKORC1* is the warfarin drug target, and *CYP4F2* is associated with enzymatic activity in the vitamin K/warfarin pathway and may also be associated with vitamin K metabolism.[4,13,16,17] Variants of *CYP2C9* (*CYP2C9*2*, rs17998523 or *3, rs1057910) and *VKORC1* (1173G>A, rs9934438) have been associated with increased major bleeding risk,[19,20] whereas a variant of *CYP4F2* (*3, rs2108622) has been associated with decreased risk.[6,18] However, no studies have evaluated gene−obesity interactions and major bleeding risk.

The primary objective of this analysis is to evaluate the association between BMI and warfarin major bleeding risk. We also conducted exploratory analyses to evaluate interactions between *CYP2C9*, *VKORC1*, and *CYP4F2* variants, obesity, and major bleeding risk. The results have the potential to enhance understanding about the clinical significance of BMI in warfarin therapy and inform clinical strategies to mitigate major bleeding risk.

METHODS

Study Design

This retrospective case−control study was conducted using data from an existing case−control study among patients receiving warfarin therapy. The parent study (Warfarin Investigation for Safety and Health, or WISH) was designed to evaluate the association between genetic variants that influence warfarin dose requirements and major bleeding risk.[6] Study participants were recruited from Group Health (GH), a nonprofit integrated healthcare system that insures and provides medical care to approximately 600,000 patients in Washington State.[6] The sample included 265 cases who experienced a major bleeding event while receiving warfarin and 305 similar controls who did not have major bleeding. For this analysis the primary exposure was obesity, and the outcome of interest was major bleeding. Analyses were adjusted for a variety of factors derived from GH automated databases and a 44-item mailed survey that collected supplemental clinical, behavioral, and demographic information.[6] Additional details regarding cases, controls, warfarin use, genetic testing, and covariate information were included in previous publications.[6,21]

Cases

Cases were GH patients 18 years of age or older who had an inpatient diagnosis of a major bleeding event (index date) between January 1, 2005 and April 1, 2011. A validated International Classification of Diseases, 9th revision algorithm was used to identify major bleeding events.[22] Events were classified as "major bleeding" if they were clinically apparent and resulted in hospitalization, hemoglobin decreased >2 mg/dL, and/or more than 2 U of packed red blood cells were transfused.[22,23] We required cases to be continuously enrolled in GH for at least 1 year before index with no evidence of major bleeding events in the year before the index date. The date of the bleeding event was set as the index date. Using GH pharmacy records, we required cases to be using warfarin within 3 days of the bleeding event.

Controls

Controls were selected using a risk set sampling approach in which patients who met all eligibility criteria above (except major bleeding) were assigned a random index date (date of