Venous thromboembolism (VTE) affects more than 300,000 people in the United States each year. However, it has been estimated that current diagnostic testing fails to identify pro-thrombotic risk in 50% of VTE patients. This article examines the relationship between levels of the pro-coagulant proteins factor VIII (FVIII), von Willebrand factor (VWF), and fibrinogen and risk of VTE in order to assess the impact of these novel risk factors. Data were collected from patients enrolled in the matched case-control Genetic Attributes and Thrombosis Epidemiology study. Crude and adjusted conditional logistic regression models were used to assess the impact of FVIII, VWF, and fibrinogen on risk of VTE. Before adjustment for independent predictors of VTE risk, high levels of FVIII, VWF, and fibrinogen were significantly associated with increased risk of VTE in both Blacks and Whites. After adjustment for ABO type, factor VII levels, hypertension, renal disease, recent surgery, diabetes, annual household income, alcohol use, and the other proteins of interest (FVIII, VWF, and/or fibrinogen), high FVIII and VWF levels were associated with increased risk of VTE in Blacks (OR: 1.97 [1.01–3.84] and 3.39 [1.58–7.27], respectively). High FVIII only was significantly associated with risk of VTE in Whites (OR: 2.35 [1.16–4.75]). Future research into the inclusion of these protein levels in risk models for VTE could help identify persons at highest risk.

**Key Words:** Venous Thromboembolism, Fibrinogen, Factor VIII, Von Willebrand Factor

**INTRODUCTION**

Venous thromboembolism (VTE) is estimated to affect 300,000–600,000 people in the United States each year; it is the third leading cause of cardiovascular death, and disproportionately affects Blacks. Because current diagnostic testing for VTE fails to identify underlying pro-thrombotic tendency in about 50% of patients, identification of novel risk factors for VTE is essential. Furthermore, several risk factors known to be associated with risk of VTE in Whites have been shown to have little impact on VTE risk in Blacks. Identification of risk factors that may explain these racial differences could prove important in preventing VTE and reducing associated health disparities.

Several reports have indicated that high levels of pro-coagulant proteins may be independent risk factors for VTE. Factor VIII (FVIII) circulates in plasma bound to von Willebrand factor (VWF) and is proteolytically cleaved during clot formation to yield activated FVIII which serves as a cofactor for the activation of Factor X (FX). Subsequently, activated FX serves as a cofactor for the conversion of prothrombin to thrombin, which acts on fibrinogen to form a fibrin clot. VWF stabilizes FVIII and provides an adhesive linkage between platelets and the subendothelium at sites of vascular injury. Elevated levels of FVIII have consistently been shown to be associated with risk of VTE, while elevated levels of VWF and fibrinogen have not been consistently associated with an increased risk of VTE. Furthermore, ethnic differences in mean steady-state levels of these proteins have been reported, with Blacks having higher average levels of both FVIII and VWF. Factor VIII, VWF, and fibrinogen, however, are acute phase reactants and are elevated in some conditions known to be risk factors for VTE. Our study examines the relationship between pro-coagulant protein levels measured after VTE events in a group of VTE cases compared to protein levels measured after TVE events in a group of control patients and risk of VTE in both Blacks and Whites after adjustment for covariates.