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REVIEW ARTICLE

The treatment of venous thromboembolism in special populations

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Abstract Anticoagulant therapy for the typical venous thromboembolism patient is straightforward with predictably favorable outcomes. However, for certain patients with venous thromboembolism, there remains uncertainty and controversy about optimal treatment. These controversial areas include venous thromboembolism patients with: heparin resistance, renal insufficiency, morbid obesity, cancer, antiphospholipid antibody syndrome, recurrent thrombosis despite appropriate anticoagulation, and patients with unprovoked VTE who may or may not benefit from thrombophilia testing. This review summarizes the current data for these special patient populations with venous thromboembolism and provides our recommendations for management.

Abbreviations: UFH, Unfractionated Heparin; LMWH, Low-Molecular Weight Heparin; HIT, Heparin-Induced Thrombocytopenia; APLA, Antiphospholipid Antibodies; VTE, Venous Thromboembolism; PE, Pulmonary Embolism; DVT, Deep Vein Thrombosis; INR, International Normalized Ratio; ESRD, End-Stage Renal Disease; CrCl, Creatinine Clearance; ABW, Actual Body Weight; IBW, Ideal Body Weight; DW, Dosing Weight; BMI, Body Mass Index; BID, Twice Daily; OAC, Oral Anticoagulation; LA, Lupus Anticoagulant; FVL, Factor V Leiden; AT, Antithrombin; PC, Protein C; PS, Protein S; aPTT, Activated Partial Thromboplastin Time; APS, Antiphospholipid Antibody Syndrome.

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Introduction

Approximately 250,000 people are diagnosed and treated for venous thromboembolism (VTE) in the United States annually [1,2]. For most, management is straightforward and involves the prompt initiation of a parenteral anticoagulant such as unfractionated heparin (UFH), low-molecular weight heparin (LMWH) or fondaparinux. Of the parenteral anticoagulants, LMWH and fondaparinux have become preferable to UFH in the management of VTE due to their ease of administration, more predictable pharmacology, equivalent or superior clinical outcomes, lower incidence of heparin-induced thrombocytopenia (HIT), and cost effectiveness [3,4]. In general, these parenteral anticoagulants are continued for at least 5 days as a bridge to long-term therapy with warfarin, dosed to achieve an international normalized ratio (INR) of 2.0 to 3.0. Subsequent duration of warfarin therapy is dependent on the clinical evaluation of an individual patient's risk of recurrence and bleeding complications. This routine treatment for patients with VTE has been reviewed extensively elsewhere [3—6].

Yet, despite tremendous advances in our knowledge and understanding of optimal anticoagulation management for these patients, there remain numerous areas of controversy and uncertainty. These areas of controversy include patients with heparin resistance, renal insufficiency, morbid obesity, underlying cancer, antiphospholipid antibody syndrome (APS), recurrent thrombosis despite adequate anticoagulation, and patients with unprovoked VTE who may or may not benefit from thrombophilia testing to predict recurrence and guide warfarin duration decisions. The purpose of this paper is to review the literature and discuss management options for these "special patient populations" with VTE.

What is heparin resistance and is it clinically important?

Unfractionated heparin (UFH) is a large repeating disaccharide polyanion with heterogeneous molecular weight that binds to and causes a conformational change in antithrombin. This conformational change results in the potentiation of antithrombin's inhibition of activated coagulation enzymes. The heterogeneity in molecular weight and negative charge of UFH leads to significant variation in bioavailability and clearance that results in inter-individual variation in dose response [7,8]. Because of this unpredictability in pharmacokinetics, it is recommended to monitor and adjust heparin based upon the aPTT. But, due to inherent problems in standardizing the aPTT, institutional target aPTT ranges should correspond to heparin anti-Xa activity levels of 0.3—0.7 IU/ml [8]. In general, the aPTT does correlate with clinical efficacy, but this correlation becomes less certain in patients receiving at least 35,000 units of heparin daily, as these patients have a low risk of recurrent VTE independent of the aPTT [4,8]. These patients who require daily doses of heparin exceeding 35,000 units/day are labeled as having "heparin resistance".

Management of these patients is problematic given that the association of heparin-induced