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THROMBOPROPHYLAXIS IN IMMOBILIZED MEDICAL PATIENTS

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Abstract: Venous thromboembolism accounts for a large number of preventable deaths. The majority of these events occur in medical patients, but medical thromboprophylaxis remains underutilised in this population. The purpose of this review is to examine the results of recent clinical trials of low molecular weight heparins in the prevention of venous thromboembolic disease in medical patients. The available data make a compelling case in favor of widespread use of low molecular weight heparin in medical patients.

Key words: venous thromboembolism; deep vein thrombosis; pulmonary embolism; prophylaxis; low molecular weight heparin; dalteparin; enoxaparin

INTRODUCTION

Venous thromboembolic (VTE) disease in immobilized acutely ill medical patients confronts clinicians with unique challenges, related to the facts that it is deadly, clinically underdiagnosed, and associated with limited opportunities for meaningful treatment when it arises. Furthermore, while it is one of the leading causes of serious morbidity and mortality in hospitalized medical patients, it is also relatively infrequent when considered from an individual patient's risk. Taken in totality, these considerations lead us to the position that safe and effective prevention is of paramount importance and, indeed, is the only rational strategy to pursue in acutely ill, immobilized patients. This review will examine each of the issues outlined above and will provide an update on the most recent data for medical thromboprohylaxis.

DEADLY, COMMON, AND UNDERDIAGNOSED

The fundamental dilemma confronting physicians in the management of pulmonary embolism is that once it has occurred, the opportunity to intervene has already been lost [1]. Most pulmonary emboli destined for a fatal outcome lead to death within a short time after occurrence [1]. Effective strategies for treating pulmonary embolism certainly exist, starting with the seminal clinical trial of systemic anticoagulation published forty years ago [2] and evolving into contemporary practice including thrombolytic [3, 4] or mechanical approaches to resolve the embolism [5]. In examining any of these approaches we must ackowledge an undeniable preexisting "survivor bias": most patients who will die have already died before any of these time-proven or novel approaches can be administered.

There are seemingly contradictory but accurate statements about the frequency and magnitude of risk of VTE in actutely ill, immobilized patients. VTE, as a whole, continues to be a disturbingly frequent source of mortality, particularly in hospitalized patients. The number of deaths from VTE in the United States, for example, numbers in the hundreds of thousands per year [6]. It is estimated that 75% of those VTE events occur in medical, not surgical, patients [7, 8]. Hence, any effort directed at reducing the number of VTE deaths has to encompass medical, as well as surgical cases.

The apparent rates of VTE deaths, however, do appear to be declining [6]. This is in spite of an increasingly aging population who disproportionately suffer from diseases associated with increased VTE risk and whose older age is in and of itself an important risk factor. The cause of this decline is uncertain, but factors which could explain this include earlier mobilization of patients from bedrest than was the case in past decades, and broader use of thromboprophylaxis. The latter is still substantially underutilized, however [9].

Viewed from other perspectives, the frequency of VTE appears less dramatic. First, deaths attributable to VTE constitute only a small portion of overall death rates [7]. The relevance of this observation is twofold: even if we successfully eliminate all VTE-related deaths, overall mortality rates are not likely to change. Consequently, designing and conducting a clinical trial of thromboprophylaxis which will definitively demonstrate a reduction in total mortality is essentially impossible. The sample-size calculations are staggering and the likelihood of success is very low. Consequently, modern VTE prevention studies have focused on the totality of VTE burden, rather than a simple mortality endpoint as in other arenas of medicine [10, 11]. One older controlled clinical trial had reported a significant mortality reduction with heparin prophylaxis [12], but this was in the context of an era in which antithrombotic therapy for other indications, such as myocardial infarction and acute coronary syndromes, had not yet become established therapy and it is

therefore likely that a large part of the mortality benefit was attributable to the favorable impact of heparin on coronary events.

The perspective of the individual patient, and the physician caring for the patient, is the most important. The absolute risk of a fatal or serious VTE event during a given hospitalization is small. In the two recent large controlled trials of medical thromboprophylxis, in which morbid and mortal VTE events were systematically sought and collected, fatal events attributable to VTE were reported in 0 placebo-treated patients in MEDENOX [10] and 0.28% in PREVENT [13]. These findings in turn lead to several considerations. First, this may lead to a certain degree of complacency which may be one of the contributing factors to the underutilization of thromboprohylaxis. Second, because the absolute risk is small, and the benefits of thromboprophylaxis are commensurate, safety of any prophylactic approach is of paramount importance. Clinical trials of pharmacologic prophylaxis not only need to demonstrate efficacy, but a favorable ratio of the risk of hemorrhage as compared to the benefit of preventing VTE.

The final element to consider in devising an effective strategy to address the VTE problem is that the clinical diagnosis of DVT in medical patients is fraught with difficulties. Conventional wisdom and extensive autopsy series both hold forth that most VTE goes clinically unrecognized. This notion is reinforced by MEDENOX and PREVENT. In both of these studies, the majority of deep vein thrombosis (DVT), including proximal DVT, was clinically unsuspected and was identified via systematic screening with venography or ultrasound. As this sort of screening is not feasible in general practice, there is no meaningful strategy that can be devised around the notion that we have effective treatment for DVT. The only rational conclusion is that if we wish to reduce the fatal events, we have to prevent VTE, and not merely attack those episodes of DVT or PE which come to our attention [10, 13].

Identifying the Patient at Risk

It is now well known that certain risk factors can identify medical patients at increased risk of VTE during episodes of hospitalization with immobilization. Critically ill patients in intensive care units are at very high risk and constitute a group in whom thromboprophylaxis should be routine in the absence of specific contraindications [14].

Patients admitted to medical services with acute illnesses are diverse in their underlying disease states, the treatments they receive, and in the types of physicians caring for them. Despite this seeming disparity, however, their potential risk of VTE is a shared characteristic and one which has been quantitated. The risk factors relevant to medical patients are summarized in Table 1. Consequently, MEDENOX and PREVENT focused on patients with these risk factors in defining the population in whom to examine the effects of low molecular weight heparins [10, 11].

Table 1. Risk Factors for Venous Thromboemblism in Medical Patients.

Risk Factor	Degree of Increased Risk
Central venous line	Moderate
Chemotherapy	Moderate
Congestive Heart Failure	Moderate
Respiratory Failure	Moderate
Hormone Replacement Therapy	Moderate
Cancer	Moderate
Oral Contraceptive Therapy	Moderate
Paralytic Stroke	Moderate
Prior venous thromboembolism	Moderate
Thrombophilia	Moderate
Immobilization	Mild
Increasing age	Mild
Obesity	Mild
Varicose veins	Mild

Medical Thromboprophylaxis with Heparins

A number of controlled clinical trials, each with methodological flaws, had examined the questions of whether unfractionaed heparin reduced the risk of VTE in medical patients. Taken in total, via a formal meta-analysis, these data strongly suggested a benefit [17], but the enhanced statistical power of a meta-analysis does not overcome the methodological shortcomings of the underlying studies. Thus, this continued uncertainty set the stage for the two modern clinical trials.

MEDENOX was the first of the two trials of low molecular weight heparins. MEDENOX compared two doses of enoxaparin (20 mg and 40 mg QD) to placebo in acutely ill, immobilized medical patients. The higher, but not the lower, enoxaparin dose successfully reduced the incidence of VTE. DVT's were systematically sought via bilateral venography. This venography-based approach proved to be both a strength and weakness of MEDENOX. The advantage of this approach was that it allowed MEDENOX to identify what no doubt was the vast majority of DVT's and thus demonstrate the benefit of a LMWH. However, most of the impact on thromboprophylaxis was in preventing small, asymptomatic distal (calf-vein) DVT's, a result of uncertain clinical significance. These distal DVT's would not have ever been identified in normal clinical practice and due to their lower propensity to propagate or embolize, are or limited clinical relevance. Nevertheless, MEDENOX had proven the principle that a LMWH could prevent VTE.

The PREVENT study was designed to build on the foundation established by MEDENOX. PREVENT chose to focus on clinically important endpoints – symptomatic, objectively verified DVT

and PE, sudden death, and proximal DVT. The latter were systematically screened via compression ultrasound (CUS), which was a departure from virtually all previous studies which had principally relied upon venography. CUS presents the advantages of being safer than venography, is well validated for proximal DVT [18], and to a large degree has supplanted venography in clinical practice [19]. Consequently, it was appropriate to move forward and replace venography with CUS in the clinical-trial setting [20].

PREVENT demonstrated a 45% risk reduction of clinically important VTE with 5000 IU. QD of dalteparin [13]. This reduction was consistent across the individual components of the primary , combined endpoint, across patient subgroups, and geographically [13]. Equally important, this clinical benefit was accomplished with a low risk of major hemorrhage (0.49%) or thrombocytopenia (0.54%) [13].

The subgroup analyses are of important to clinicians confronting a variety of patients. It was thus reassuring to learn that the benefits of thromboprophylaxis extended equally to older and younger individuals [21], obese and lean individuals (particularly important considering that the dalteparin dose was fixed at 5000 U QD and was not adjusted for weight) [22], and amongst the major diagnoses (heart failure, respiratory diseases, and other medical illnesses) for which patients had been hospitalized (Fig. 1) [23, 24].

Remaining Questions

PREVENT and MEDENOX were not designed to address a number of relevant clinical questions and, indeed, it is likely that these questions will remain unanswered. As previously stated, it is unlikely that a clinical trial demonstrating a reduction in mortality, or for that matter, a reduction in pulmonary embolism, is feasible. The VTE-related death rate is small as compared to the overall mortality rate, and similarly the PE rate is too small to allow for realistic study design. It is also unlikely that a properly sized and designed study comparing the various LMWH's and/or UFH will ever take place. Sample size calculations quickly reach the tens of thousands when one considers appropriate definitions of "non inferiority" to compare the various antithrombotic regimens. Consequently physicians will need to make their decisions on the basis of the available evidence, taking into account which antithrombotics have been tested in rigorous clinical trials and the relevancy of the endpoints examined in the different trials.

Finally, it is unlikely that there will be any more placebo-controlled trials in this arena. Though the American College of Chest Physicians had issued a "Class I" recommendation for medical thromboprophylaxis several years ago, this was a somewhat unusual situation. Most "Class I" recommendations in cardiovascular medicine are issued only after the therapy in question has been demonstrated to impact mortality (e.g. thrombolysis in myocardial infarction) or a major morbid event (e.g. strokes in atrial fibrillation) and in more than one clinical trial. Though these conditions still have not been met, and as discussed above, it is unlikely that we will ever see definitive evidence that medical thromboprophylaxis impacts either mortality or pulmonary embolism, taken together, MEDENOX and PREVENT have established the benefit of VTE prophylaxis.

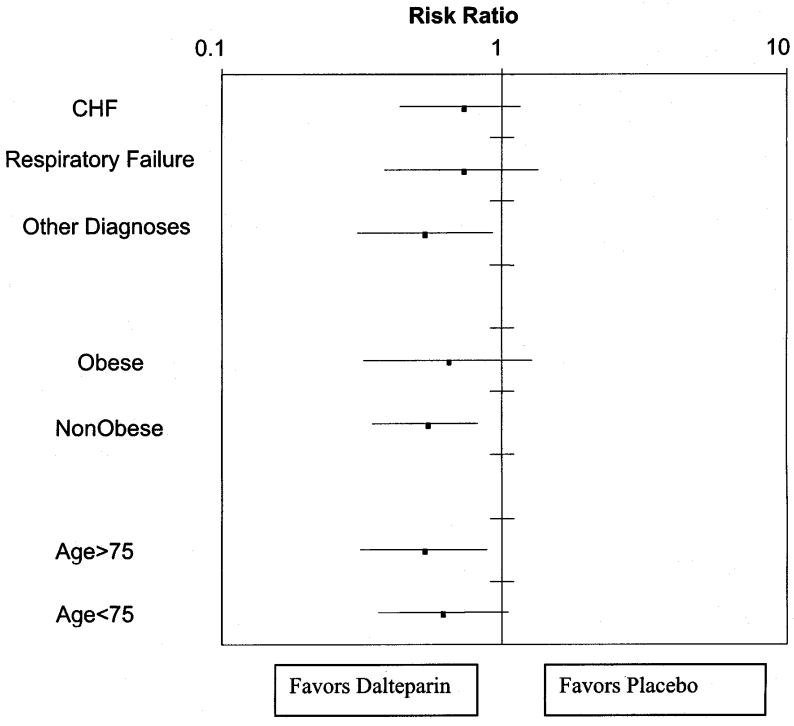

Fig. 1. The risk ratio of VTE in patient subgroups treated with dalteparin vs placebo in the PREVENT study are shown. All of the point estimates lie to the left of the line of unity, indicating a consistent benefit of dalteparin across patient subgroups.

Conclusions and Summary

The issue of VTE prophylaxis in medical patients remains an important problem due to the increasing age of the population, resulting in greater numbers of hospitalizations for acute medical illnesses which render patients immobile and at risk for VTE. VTE prophylaxis, however, remains underutilized. Consequently, the results of two large trials with the low-molecular weight heparins dalteparin and enoxaparin provide additional evidence on the benefits and safety of thromboprohylaxis and should spur physicians to more broadly use these agents in immobilized medical patients.

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