Published in final edited form as:
Arterioscler Thromb Vasc Biol. 2008 March ; 28(3): 367–369. doi:10.1161/ATVBAHA.108.163097.

Venous Thromboembolism: A Need for More Public Awareness and Research Into Mechanisms

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In 2005, the US Senate declared March as deep vein thrombosis (DVT) awareness month in the United States to increase the American public's understanding of deep vein thrombosis.1 This was triggered by the death of 39-yr-old David Bloom, a National Broadcasting Company (NBC) reporter who died on April 6, 2003 from a massive pulmonary embolism (PE), and the activities of his widow, Melanie Bloom.2 Two days before his death David Bloom had developed cramping leg pain that was not recognized as a DVT2—leg DVT was only found postmortem. He had several risk factors for DVT and PE (collectively called venous thromboembolism [VTE)]): (1) prolonged immobility (working and sleeping in a cramped position in a tank in the war in Iraq); (2) long distance flights between the US and Kuwait, (3) dehydration, and (4) postmortem the discovery that he was heterozygous for the prothrombotic variant of factor V called factor V Leiden.2 Melanie Bloom made it a mission to make the American public aware of the symptoms of DVT.

This March edition of *Arteriosclerosis, Thrombosis, and Vascular Biology* contains 8 articles focused on VTE, to highlight the efforts that are being devoted to understanding this disease. Although the exact incidence of VTE is not clear and a variety of different incidence numbers are used in medical and lay publications—VTE incidences in the United States per year between 300 000 to more than 2 million are quoted by different sources[3,4]—it is clear that the problem is substantial. Modeling suggests that more than 900 000 episodes of VTE occur in the United States annually and nearly 300 000 deaths per year.[5] Clearly, there is a need for the various medial and public health communities to use more consistent presentations of incidence data when communicating with the public and health policy makers to avoid confusion. An effort should be undertaken in the near future to come to a consensus on what data to use.

In the first article, Dr Heit discusses the epidemiology and risk factors of VTE. It is striking that the initial clinical presentation of PE in 25% of patients is sudden death. Noteworthy is that the incidence of VTE increases dramatically over 45 yr of age. In light of the increase in life expectancy in the US population, one can predict that the burden of this disease will rise significantly in the future. Next, Dr Moll, a practicing hematologist, provides us with a clinical perspective of VTE with examples of the clinical presentations of DVT and PE, diagnostic approaches, and, finally, treatment. As he points out, every patient's VTE event is unique, although there are a number of commonalities that contribute to the high incidence of mortality and morbidity from VTE. These include (1) a lack of VTE prophylaxis or inappropriate prophylaxis in risk situations, (2) missed or delayed diagnosis because of a lack of physicians'

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Disclosures
Dr Moll is a consultant for Bristol Myers Squibb, Bayer, and Roche Diagnostics. Dr Mackman is a consultant for Daiichi Sankyo.

consideration of DVT and PE as possible diagnoses in patients presenting with extremity or respiratory symptoms, (3) unawareness by the patient and the public in general of the risk factors and symptoms of DVT and PE, and (4) suboptimal anticoagulation management in the person with established VTE. The third article is written by Dr Gross and Dr Weitz and discusses the anticoagulant drugs that are available for the treatment of VTE. Somewhat surprisingly the present choices are limited to only 2 major drug classes: (1) unfractionated heparin, low molecular weight heparin, and pentasaccharides that are used for short-term anticoagulant therapy and are delivered intravenously or by subcutaneous injection. These drugs enhance the ability of antithrombin to inhibit coagulation proteases; (2) oral vitamin K antagonists that are used for long-term anticoagulation and act by reducing the activity of several coagulation proteases. The major disadvantage of vitamin K antagonists is the need for frequent coagulation monitoring to maintain a therapeutic level. The exciting development of new anticoagulants, foremost the oral anticoagulants, is discussed. Recent data from the RECORD 1 clinical study showed that the orally-available Factor Xa inhibitor rivaroxaban reduced venous thromboembolic events from 3.7% to 1.1% compared with the low molecular weight heparin enoxaparin in patients undergoing total hip replacement.[6] In the future, these new drugs may be used in place of both heparins and vitamin K antagonists and, if so, can be expected to have a huge impact on the treatment of VTE. The final scientific article is by Dr Wakefield and colleagues and discusses the mechanisms of venous thrombosis and resolution. In contrast to arterial thrombosis that is most often triggered by rupture of atherosclerotic plaques, the triggering events that lead to venous thrombosis are not clear. Virchow proposed that thrombosis could be triggered by changes in the blood (thrombophilia), changes in the vessel wall, and changes in blood flow, such as turbulent flow and stasis. Dr Wakefield and colleagues present data supporting a role for inflammation in venous thrombosis, including the idea that docking of P-Selectin Gly-coprotein Ligand-positive microparticles to P-selectin may be a critical step in the process. In general, venous thrombosis has been thought to occur without damage to the vessel wall. However, inflammatory mediators can activate the endothelium and convert it from an anticoagulant surface to a procoagulant surface. The Figure shows a diagram of the different factors that may conspire to initiate venous thrombosis.

Governmental activities in several countries have started to support activities raising awareness among the public and health care providers about VTE, with the goal to decrease mortality and morbidity. In the United States, the US Surgeon General held a workshop on DVT in May 2006, with participation of patients, clinicians and scientists, and government agencies.[7] At the meeting's conclusion the Surgeon General highlighted that “DVT and PE are critical public health problems” and that he, therefore, authorized “the development of a Surgeon General Call to Action on DVT.” He explained that “the goal of this effort will be not only to reach all health professionals, including physicians, nurses, paramedics, EMTs (emergency medical technicians), and others involved in treating this multifactorial disease, but also to reach the public at large, so as to create greater awareness of and demand for appropriate prevention and treatment of DVT.”[7] The formal launch of this Call to Action is eagerly being awaited by patients and the medical-scientific community.

In this edition of *Arteriosclerosis, Thrombosis, and Vascular Biology* representatives from the National Institutes of Health (NIH) and the Centers for Disease Control (CDC) present an overview of US governmental activities that are designed to foster thrombosis research and improve prevention of VTE and its long-term complications. A number of organizations, societies, coalitions, foundations, networks, consortia, and interest groups exist that have a focus on thrombosis (Table). Their goals are to educate the public, patients, and health care providers about thrombosis, improve health care delivery, research, public policy, and advocacy. Although there are clear differences between the goals of some of these groups, there is also much overlap in what they are trying to achieve. To optimize resources and avoid duplication of efforts, future discussions about collaborations, partnerships, or mergers appear

very appropriate. Patient advocacy can be a powerful tool in shaping health policy, as Randy Fenninger discusses in his article. With 900 000 individuals in the US affected by VTE and 300 000 dying from PE every year, as well as 300 000 affected by postthrombotic syndrome, the creation of a national patient advocacy group for thrombosis in the United States (NATT; National Alliance for Thrombosis and Thrombophilia) in 2003 had been long overdue. Fenninger joined NATT as a Board member in 2004 and was elected president in 2007. In the United Kingdom, an "All Party Parliamentary Thrombosis Group" has been formed "to promote awareness among parliamentarians about the risk and management of venous thromboembolism (VTE); to increase knowledge of its causes, effects, treatments; and to monitor the implementation of government initiatives and other research being undertaken."[8] Furthermore, an independent expert working group was set up to develop a national strategy on the prevention and treatment of VTE.9 The UK now has an annual "National Thrombosis Week," with the next one occurring May 12th to 16th, 2008. In this edition of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Dr Beverly Hunt, one of the founders and the present Medical Director of the U.K. nonprofit organization "Lifeblood - a Thrombosis Charity" reports on the activities in the UK to raise awareness about VTE.

Finally, however, the best research, science, treatment guidelines, and training of health care professionals may not translate to better health outcomes, if health care delivery is compromised. A recent study showed that the United States had the highest death rates from treatable conditions of 19 industrialized countries studied. The authors conclude that the reasons for this observation are unclear, but state that it is "difficult to disregard the observation that the slow decline in US amenable mortality has coincided with an increase in the uninsured population."[10] In 2004 there were 45.8 million uninsured individuals in the United States, ie, approximately 1/6 of the US population.[11] It is tempting to speculate that improvement in health care access would lead to a significant improvement in the prevention and treatment of VTE.

A number of activities are on the way to address the health threat that VTE poses. We welcome March DVT Awareness month as one of these activities.

Acknowledgments

Dr Moll receives support from the Centers for Disease Control via a grant (1 UO1 DD000292-01) and a cooperative agreement (U27 DD00326). Dr Mackman acknowledges support from the National Institutes of Health. and colleagues Drs Key and Kasthori for helpful discussions.

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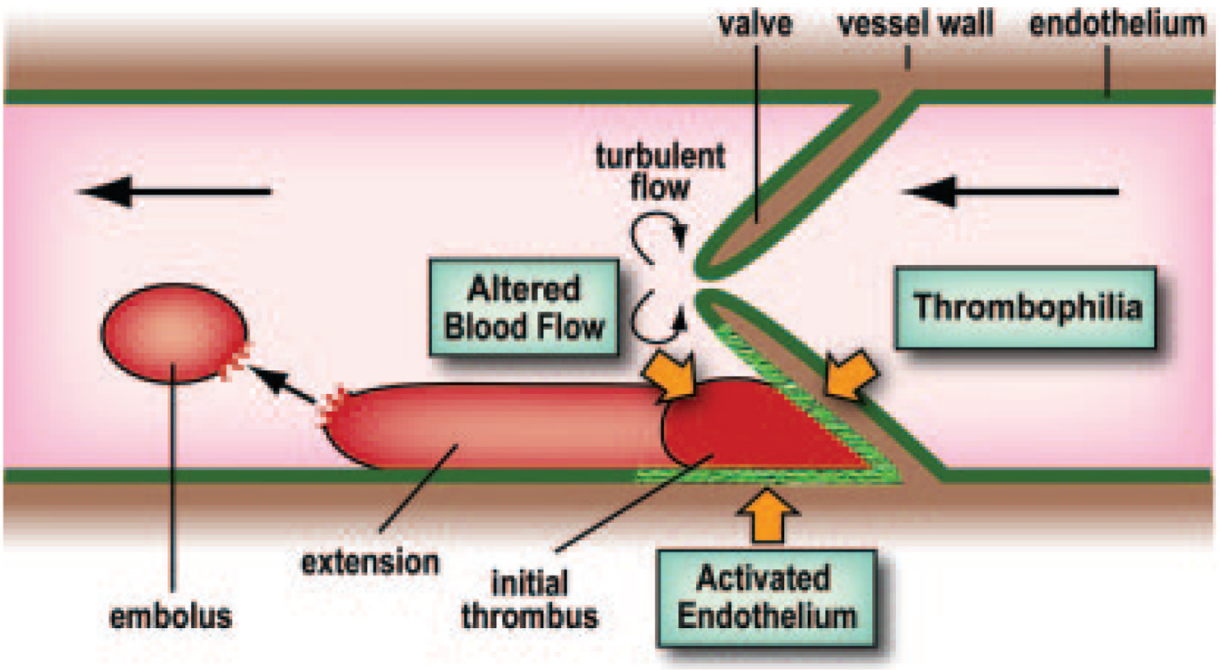

Figure.

Formation of a deep vein thrombus. The cartoon shows factors that may contribute to the formation of a thrombus in a large vein, such as thrombophilia, activated endothelium, and altered blood flow. The presence of valves in veins leads to turbulent flow and reduced oxygenation of the valve endothelium (light green) that may activate the endothelium and allow a thrombus to form. Once formed, the thrombus may extend along the vessel and embolize. Valve pocket thrombi have been analyzed in femoral veins[12]. Red areas containing mostly red cells and fibrin are the likely sites of origin of the thrombi, whereas the propagating thrombus consists of platelets with fibrin borders12. A recent study of saphenous veins indicated that the valvular endothelium has a thromboresistant phenotype compared with the endothelium of the non-valvular venous wall13, although this resistance may be lost under pathological conditions.

Table

Thrombosis-Interested Organizations, Listed in Order of the Year They Were Established (Other Organizations May Exist)

Abbreviated Name	Full Name	Website	Founded	Nonprofit[1]
ACP	American College of Phlebology	www.phlebology.org	1985	Yes
AVF	American Venous Forum	www.venous-info.com	1988	Yes
AC Forum	Anticoagulation Forum	www.acforum.org	1991	Yes
TIGC	Thrombosis Interest Group of Canada	www.tigc.org	1991	Yes
HTRS	Hemophilia and Thrombosis Research Society	www.htrs.org	1994	Yes
VDF	Vascular Disease Foundation	www.vdf.org	1998	Yes
NCBAP	Nat. Certification Board for Anticoagulation Providers	www.ncbap.org	1998	
ClotCare[2]	ClotCare	www.clotcare.com	2000	No
INATE	Investigators Against Thromboembolism	www.inate.org	2001	No
TAP[4]	Thrombophilia Awareness Project	www.fvleiden.org/tap	2002	Yes
Lifeblood	Lifeblood: The Thrombosis Charity	www.thrombosis-charity.org	2002	Yes
NATT[4]	National Alliance for Thrombosis and Thrombophilia	www.nattinfo.org	2003	Yes
DVT Coalition	DVT Coalition	www.preventdvt.org	2003	No
VDC	Venous Disease Coalition	www.venousdiseasecoalition.org	2006	Yes
ATHN	American Thrombosis and Hemostasis Network	www.athn.net	2006	Yes
NHF[4]	National Hemophilia Foundation	www.hemophilia.org	2006[3]	Yes
NATF	North American Thrombosis Forum	www.natfonline.org	2006	Yes

[1] Either 501c3 (=tax-exempt educational organization) or 501c6 (=tax-exempt professional organization).

[2] Education website only, not an organization.

[3] Founded in 1948 for patients with bleeding disorders; in 2006 expanded its focus to also cover some thrombosis/thrombophilia issues.

[4] Patient driven groups.