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REVIEW ARTICLE

Factor Five Leiden:
the case for global screening

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Abstract
In 1994 Dr. Bertina et al. discovered Factor Five Leiden, the most common cause of the thrombophilias, occurring in 5% of the Caucasian population. Since then, hundreds of thousands of individuals have experienced venous thromboembolic events and many have died as a consequence of this mutation. Currently global screening for this mutation has not been advocated. A review of the Factor Five Leiden pathophysiology, prevalence, and impact on a variety of common conditions such as oral contraception, pregnancy, and surgery helps establish the case for global screening. In this era of patient-centric medicine, the contention is that patients deserve the right to know their Factor Five Leiden status in order to make informed decisions about not only birth control choices, but also management during high-risk circumstances. This editorial is meant to be thought provoking and hypothesis generating. Should we or should we not screen the public for this common and life-threatening disorder?

Keywords
Factor Five Leiden, thrombophilias, oral contraception, pulmonary embolism, deep vein thrombosis, venous thromboembolic disease

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«Even one preventable death from heart disease and stroke is too many», asserted Tom Frieden, MD, MPH, and Director of the *Centers for Disease Control and Prevention* in a motivational plea to prevent an estimated 200,000 deaths in people under the age of seventy-five [1]. No one would dare dispute the Director's proclamation; it would be heartless to do so. Diminishing mortality and morbidity is the prime agenda for physicians. This is the lens through which I will present a history of Factor Five Leiden and propose a simple strategy to save many thousands of lives.

Homeostasis is essential in countless aspects of human biology and physiology, but perhaps its failure is most obvious in the thrombophilias, disorders leading to excess and inappropriate clotting. Although several genetic mutations have been identified as etiologies of the thrombophilias, the most prevalent is Factor Five Leiden, a mutation described by Professor Bertina *et al*. in 1994 [2]. Factor five is one of our vitamin K-dependent hepatic-derived clotting factors. In the setting of vascular injury, thrombin activates factor five on the surface of endothelial cells so it may participate in forming a robust and ostensibly protective clot [3]. Activated factor five binds negatively charged phospholipids on the surface of platelets to then function as a receptor site for activated factors nine and ten [4]. Homeostasis always demands mechanisms to control the volume of biologic processes; in this case, there needs to be an off-switch so that the budding clot does not grow out of control. Protein C is this switch. Also a vitamin K-dependent plasma protein, Protein C undergoes activation to degrade factor five, damp its efficacy, and limit progression of the nascent thrombus. A number of disorders can result in activated protein C (APC) resistance. Autoantibodies against protein C, anti-phospholipid antibodies, and functional protein S deficiency are a few culprits [4]. These disorders are rare, however, accounting for very few cases of venous thrombosis. Yet, we know that APC resistance is present in 40% of patients with venous thrombosis, but only 7% of the general population [3]. In 1994 Professor Bertina described the prime cause of resistance to Activated Protein C (APC), a mutation in factor five. Being discovered in Leiden, the mutation was appropriately dubbed Factor Five Leiden. We now know this mutation's identity; R506Q, a substitution of glutamine for arginine at position 506, and DNA testing can easily and accurately identify it [5,6]. We also know its prevalence. The mutation occurs in a heterozygous form in 5% of the Caucasian population, while the homozygous prevalence is 1/1,600 [7]. Clearly the Factor Five Leiden mutation prevalence is extraordinarily high, but that does not necessarily translate into morbidity and mortality. To understand the consequences of the mutation we require more information. Before addressing this question though, I will bring the disorder to light by painting the image of a real patient — me.

In 2007, at the age of forty-seven, I, a preventive cardiologist but formerly an interventional cardiologist, became a victim of my genes. After a particularly difficult weekend of planting trees in the sweltering sun I entered my house and announced to my wife (also a physician) that I had developed severe left-sided, localized chest pain. My ribs were tender to palpation and so I assumed I had either fractured them or strained an intercostal muscle. That night I slept very little, finding it difficult to escape the pain. The following morning I went to the gym to perform my daily exercise routine, an hour on the elliptical and thirty minutes of resistance training. Feeling subpar, I simply walked on the treadmill. My workout partner, a Harvard-trained interventional cardiologist, and I discussed the differential diagnosis. Musculoskeletal pain topped the list; the pain was too severe, localized, and reproducible with palpation for us to feel I had experienced a pulmonary embolism. In fact, we even concluded there was no reason for me to have experienced a clot; I was devoid of predisposing risks. I went to work as usual, suffered through the day, and returned home for another failed attempt to sleep. At four AM, unable to continue my relentless tossing and turning, I went to my office to do paperwork. I had developed weakness and shortness of breath and could no longer evade the inevitable conclusion that this might in fact be a pulmonary embolism (PE). At seven AM I contacted a radiologist colleague to arrange a lunchtime chest CT angiogram. Wisely he had me cancel my patients so I could expeditiously come to his centre for the study. The scan was easy; the results were not. My colleague and friend rested his hand on my shoulder and declared, «It's a miracle you're alive.» Disbelieving and embarrassed, I responded, «Come on. Just tell me I have something wrong and I'm not just being a baby.» My fear of humiliation had definitely clouded my senses. The scan was correct. I had a large clot burden bilaterally involving central and peripheral pulmonary arteries. I had also infarcted my left lower lung (Figures 1–5). During the requisite lower extremity venous ultrasound (which did detect a large right proximal deep vein thrombosis (DVT)) I began to shower more emboli, desaturated and dropped my blood pressure, and was therefore

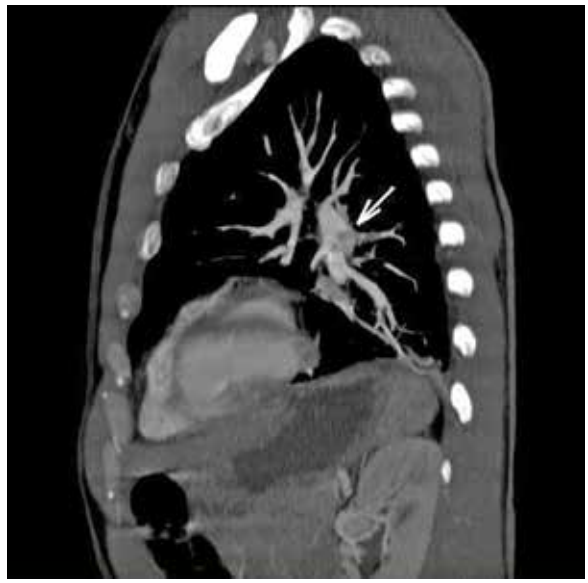

Figure 1. Computed tomographic (CT) sagittal slice: large thrombus in the proximal left pulmonary artery (arrow)

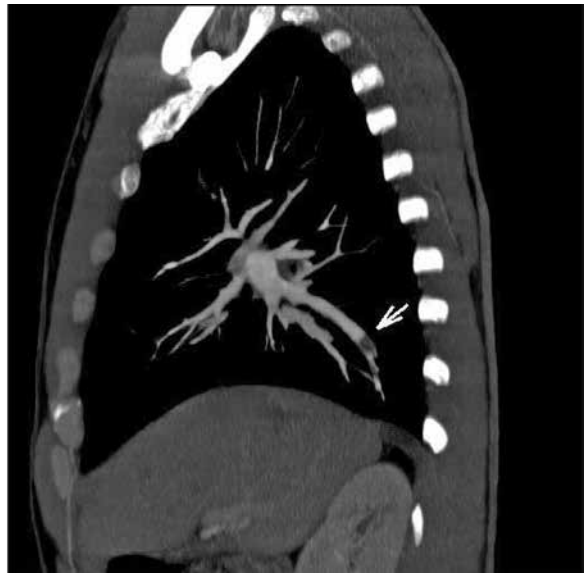

Figure 2. Computed tomographic (CT) sagittal slice: thrombus in the pulmonary artery to the right lower lobe (arrow)

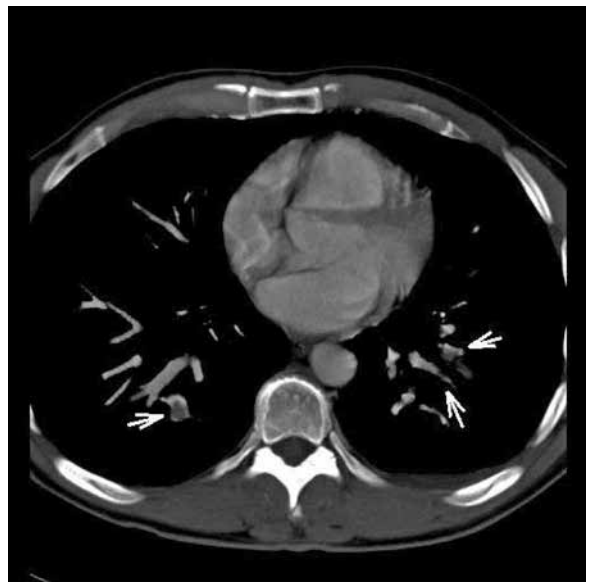

Figure 3. Computed tomographic (CT) axial slice: bilateral lower lobe pulmonary arterial thrombi (arrows)

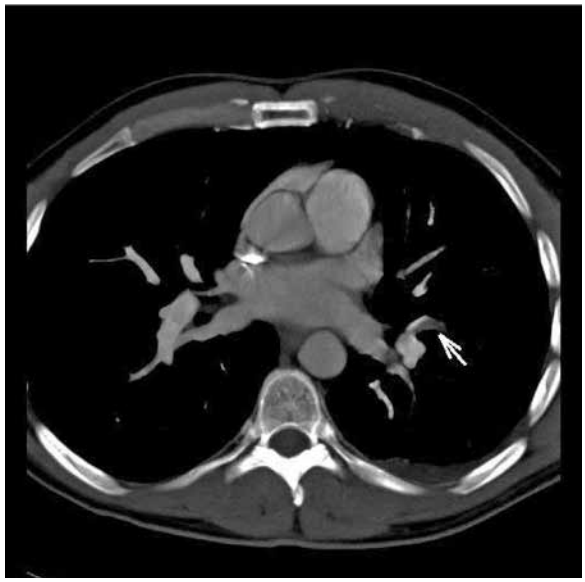

Figure 4. Computed tomographic (CT) axial slice: thrombus in a branch of the pulmonary artery to the left lower lobe (arrow)

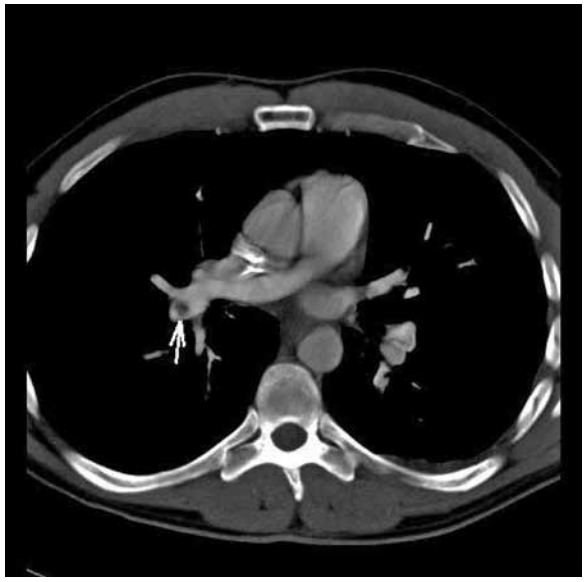

Figure 5. Computed tomographic (CT) axial slice: thrombus in the proximal right pulmonary artery (arrow)

whisked to the lab for an inferior vena cava (IVC) filter followed by nine days in the intensive care unit (ICU). I survived the event but am now left with residual issues as a consequence of my delay in diagnosis and treatment. Had I suspected a PE, I would surely have been treated early and avoided the impact of such a large burden of clot.

Virchow's triad — hypercoagulability, venous stasis, and venous injury — are the three elements that predispose to thrombogenesis. At the time, I believed I had none of the three. My workup however revealed my being heterozygous for the Factor Five Leiden mutation. I was in fact hypercoagulable, which combined with significant volume depletion from planting trees in the hot Florida sun had put me at risk for venous thromboembolic disorders (VTE). Again, had I known my genetic state I would have averted a great deal of damage. I survived the PE, but each year many thousands do not. In fact, the majority of PEs are discovered postmortem, not the way most physicians like to make their diagnoses [7]. Retrospective reviews have shown that although most patients' charts documented evidence of their impending fate, the PEs remained undiagnosed until after death. Fatal PEs are also far more frequent than most imagine; some estimates claim PE to be the third leading cause of death in the US, accounting for 650,000 deaths per year [8]. Venous thromboembolism with or without death is also far more common than most physicians believe. It occurs in 1 per 1,000 people annually and its inci-

dence increases significantly with age [4]. Thus, VTE represents a significant threat, one that merits preventive strategies if possible. Let's return specifically to Factor Five Leiden in order to understand its part in the genesis of both VTE and PE.

Rosendaal *et al*. evaluated 471 consecutive patients under the age of 70 with their first documented DVT and compared them with 474 healthy adults [9]. They found a seven-fold increased relative risk for heterozygous Factor Five Leiden patients and an eighty-fold increased relative risk for homozygous patients. As the risk of venous thrombosis increases with age, the absolute risk is highest in the elderly. The authors estimated a 2% per year risk of venous thrombotic disease in homozygous individuals over the age of 50. This translates into a near certainty of an event during every homozygous patient's lifetime. Although heterozygous individuals experience a lower lifetime risk of clotting, they too are at much greater risk than the general population.

Simioni *et al*. also evaluated patients with their first episode of venous thrombosis to determine how both prothrombin and Factor Five Leiden mutations influenced future thrombotic events [10]. Not surprisingly they found a significantly increased risk of second events among carriers of either mutation. A relative risk of 2.4 was revealed, translating into a ten-year risk for future venous thromboembolism of 55%.

Recalling Virchow's triad we know that certain events increase our risk for VTE: surgery, immobilization, pregnancy, and oral contraception (OC) being some of the most common culprits. On top of the background of mutations that increase thrombosis — Factor Five Leiden being by far the most common — adding a second component of Virchow's triad greatly increases the risk of VTE. Thus, looking at specific and common circumstances that predispose us to venous thrombosis can elucidate the impact that Factor Five Leiden has on DVT and PE. Understanding Factor Five Leiden's magnitude of influence will enable us to establish appropriate approaches to diminish untoward events. As pregnancy and OC have been best studied they will be discussed.

Pregnancy brings with it hypercoagulability [11]. In fact, pregnant women are five times as likely to experience VTE as non-pregnant comparably-aged women [12]. Obvious physical changes such as an enlarging uterus will cause lower extremity venous stasis and compression of the venous system. There are other changes that have a major impact as well. Coagulation is increased through higher levels of factors two, seven, and ten [13]. Fibrin levels soar [14]. Protein S decreases, and the fibrinolytic system is down-regulated. These changes all conspire to increase venous clotting. Add to this an additional thrombophilia, the Factor Five Leiden mutation, and the risk of pregnancy-associated VTE increases an additional three-to-seven fold [11]. In addition to the mother's risk of VTE, there is also a significant risk to the unborn child. Fetal growth retardation, stillbirth, and placenta abruptio are all increased in women who bare at least one allele for the Factor Five Leiden mutation [15]. In the Kupferminc study, over 50% of women with the aforementioned complications of pregnancy bore a genetic mutation predisposing to thrombosis, about half of them possessing the Factor Five mutation. Pregnancy-associated complications tend to recur and therefore it has been suggested that women with such complications undergo testing for thrombophilias. Perhaps it would make more sense to test women prior to their initial event.

OC is another area of great concern for women with thrombophilias. The risk of VTE increases four-fold in normal women using OC [7]. Factor Five Leiden increases a woman's risk of VTE seven-fold. The combination of OC and Factor Five Leiden demonstrates an unfavourable synergy, increasing the risk 36 fold. It is important to note that the women we are now discussing are in the prime of their lives, working, raising children, and building a future. Their deaths from VTE disease can have dramatic repercussions impacting many others' lives. Even in 1995, just a year after Factor Five Leiden's discovery, Bridey *et al*. called for global screening in their Thrombosis and Haemostasis editorial [16]. So based upon this as well as aforementioned facts, the logical question arises, «Should we globally screen people for Factor Five Leiden?»

Here are the arguments opposing screening: the numbers needed to treat are too high. Although we would identify people at risk, how would their management change? Women with Factor Five Leiden might unnecessarily lose the opportunity to utilize OC, the «easiest» form of birth control. It is too costly to genetically screen our entire population. Knowledge of an abnormal result might adversely impact insurance.

In response to each of these arguments I would bring us back to Dr. Freiden's proclamation, «Even one preventable death from heart disease and stroke is too many». In medicine we are trained to save lives and the optimal way to do so is undeniably through prevention. In our newfound era of patient-centric medicine, nothing is more inviolable than candour in the doctor-patient relationship. It is disingenuous for practitioners to know the risk inherent in harbour-

ing a Factor Five Leiden mutation and yet withhold such information from our patients. Shouldn't every woman choosing her method of birth control be made aware of the VTE risk OC conveys, as well as the vastly enhanced risk Factor Five Leiden introduces? At the risk of being sentimental, how would any of us feel if our wives or daughters or granddaughters perished from an otherwise avoidable PE as a consequence of OC in the setting of undetected Factor Five Leiden? Truly the only valid argument against global screening is economic. There is no risk to this test, only benefit. Money alone must not be the deciding vote in any medical decision-making. In earnest, I cannot conceive of a solid and defensible reason not to screen everyone for Factor Five Leiden. After all, knowledge is always king.

Conflict of interest: None declared

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