

**CME Perioperative Venous Thromboembolism: A Review**

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Venous thromboembolism (VTE) is a significant problem in the perioperative period, increasing patient morbidity, mortality, and health care costs. It is also considered the most preventable of the major postoperative complications. Despite widespread adoption of prophylaxis guidelines, it appears that morbidity from the disease has not substantially changed within the past 2 decades. It is becoming clear that current prophylaxis efforts are not sufficient. Using more potent anticoagulants may decrease the incidence of VTE, but increase the risk for bleeding and infection. Much has been learned about the pathophysiology of venous thrombogenesis in recent years. Beyond the “traditional coagulation cascade,” which anticoagulants modulate, there is a growing appreciation for the roles of tissue factor, monocytes, neutrophils, neutrophil extracellular traps, microvesicles, and platelets in thrombus initiation and propagation. These recent studies explain to some degree why aspirin appears to be remarkably effective in preventing thrombus propagation. Endothelial dysfunction, traditionally thought of as a risk factor for arterial thrombosis, plays an important role within the cusps of venous valves, a unique environment where the majority of venous thrombi originate. This suggests a role for newer treatment modalities such as statins. Not all patients have an equal likelihood of experiencing a VTE, even when undergoing high-risk procedures, and better tools are required to accurately predict VTE risk. Only then will we be able to effectively individualize prophylaxis by balancing the risks for VTE against the risks associated with treatment. Given the different cell types and pathways involved in thrombogenesis, it is likely that multimodal treatment regimens will be more effective, enabling the use of lower and safer doses of hemostatic modulating therapies such as anticoagulants, antithrombotics, and antiplatelet medications. (Anesth Analg 2017;125:403–12)

Few health problems rival deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively known as venous thromboembolism (VTE), in terms of morbidity and mortality.<sup>1–4</sup> Yet according to statements issued by the Surgeon General and the National Institutes of Health in 2008, these conditions continue to receive little attention.<sup>1</sup> **In fact, it is estimated that VTE may be responsible for up to 10% of all hospital-related deaths.**<sup>1,5</sup> Some estimates of VTE mortality rates place these above those for breast cancer,<sup>1</sup> myocardial infarction,<sup>6</sup> and stroke.<sup>6</sup> Both hospitalization and surgical interventions dramatically increase the risk for VTE.<sup>7</sup> In fact, major surgery may be the single most important risk factor.<sup>7</sup> In 1 study of almost a million women, those having an inpatient surgical procedure were 70 times more likely to be readmitted for a VTE within 6 weeks of surgery compared to those women not having surgery.<sup>3</sup>

**Perioperative VTE is also considered the most preventable cause of death in hospitalized patients.**<sup>2,8–10</sup> In the United States, the Centers for Medicare and Medicaid Services (CMS) and the Joint Commission mandate and track thromboprophylaxis compliance through Surgical Care Improvement Project measures.<sup>11</sup> Health care institutions

are rated on how well they perform in complying with these measures.<sup>11</sup> While current thromboprophylaxis consensus statements such as the ninth and most recent guidelines published by the American College of Chest Physicians (AT9)<sup>12</sup> help to decrease the incidence of VTE, VTE remains a major perioperative complication. In fact, it appears that morbidity from VTE may not have changed substantially within the past 2 decades.<sup>6</sup> Part of the challenge is that VTE prophylaxis is associated with significant risks, most notably the risk for perioperative bleeding due to anticoagulants.<sup>13–15</sup> Current guidelines therefore allow significant leeway to facilitate some degree of tailoring to each patient and surgical procedure, balancing the risk for VTE against the risk for bleeding.<sup>12</sup> As such, there is substantial interdisciplinary and institutional variability in how the guidelines are interpreted and applied.

Anesthesiologists have a detailed understanding of physiology, pharmacology, and each patient’s medical history. Furthermore, they have a unique perspective on the dynamic interactions between patient comorbidities, surgical, and anesthetic risk factors. Anesthesiology as a specialty is therefore well placed to assume a leading role in optimizing each patient’s perioperative management with the aim to safely minimize VTE risk. The goal of this article is not to review current evidence-based prophylaxis guidelines, but rather to examine emerging concepts in deep venous thrombus formation and use them as a framework to better evaluate the different treatment options for rational optimum prophylaxis. A second goal is to further heighten awareness of the ever-present risk for this often silent but potentially lethal disease. By being acutely aware of VTE risk, we will be able to identify more opportunities to favorably influence patient outcome.

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## VTE AND SURGERY—THE SCOPE OF THE PROBLEM

The true incidence of VTE is a matter of considerable uncertainty, but VTE may affect up to 25% of in-hospital surgical patients.<sup>2</sup> While major surgery is likely the single most important risk factor for VTE,<sup>7</sup> the postoperative risk for VTE varies considerably by surgery type, with the highest incidence reported in hip and knee arthroplasty and cancer surgery.<sup>16,17</sup> The reported increase in risk for VTE following surgery compared to spontaneous VTE varies significantly, however, with values ranging from 8- to 70-fold.<sup>7,8,17</sup> Estimates of the annual fatal PE events vary from as low as 100,000 to as high as 300,000,<sup>6,18,19</sup> and wide estimates of the number of VTE events ranging from 350,000 to 2,000,000 may also be found.<sup>6,20,21</sup> The fraction of these associated with surgery and anesthesia is not known precisely, but is estimated to be between 20% and 30%.<sup>10</sup>

An important reason for this substantial degree of uncertainty is that studies generally report symptomatic DVTs only, even though VTE is predominantly an easily overlooked silent disease.<sup>5,10,19,22</sup> In fact, in 70% to 80% of in-hospital deaths due to PE, this diagnosis was not even considered prior to the patient's death.<sup>5</sup> Also, VTE may occur several weeks out following surgery, causing the reported incidence of VTE to increase when patients are followed up for longer periods postoperatively.<sup>17</sup> Regardless of the true incidence of VTE, however, morbidity from the disease has not substantially changed within the past 2 decades, and it is increasingly clear that current prophylaxis efforts are not sufficient.<sup>6,10,23</sup>

## HISTOLOGICAL OBSERVATIONS

In contrast to arterial thrombosis, the precise mechanisms leading to VTE are not well understood.<sup>20</sup> However, the histological appearance of venous thrombi throughout the various stages of the disease has been carefully documented and should be accounted for by any proposed model.

Intravascular thrombi are classified into 2 histological types: (1) so-called white clots, which form under conditions of high shear and consist primarily of platelets, and (2) "red clots," which form under conditions of low shear and contain significant quantities of red blood cells and fibrin.<sup>24</sup> Arterial white clots trigger myocardial infarction and stroke, whereas venous red clots are the hallmark of VTE.<sup>24</sup> In dissection of red clots at necropsy, certain features are evident.

Thrombi almost always originate within a venous valve pocket or region of reduced flow.<sup>18,22,25,26</sup> Consistent with this, the thrombi are most organized and loosely tethered to the venous or valvular endothelium at its origin.<sup>18,22,25-27</sup> Within the thrombus, laminations of alternating (fibrin-red blood cell) "red" and (platelet-neutrophil) "white" areas are present.<sup>18,22,26</sup> These laminations are known as Lines of Zahn and are always present in propagating thrombi.<sup>18,22</sup> More proximally, away from the oldest portion of the thrombus, these white areas consisting of platelets and leukocytes with surrounding fibrin borders become increasingly prevalent and also grow in size. As a result, platelet masses are usually large and numerous in the propagating head, but may be small and less prominent elsewhere.<sup>22,26</sup> Red areas appear

to play the major role with respect to thrombus origination, whereas white areas play the major role with respect to thrombus propagation. Thrombus growth therefore occurs by mechanisms involving platelets in addition to the coagulation cascade.<sup>22,26</sup>

In arterial thrombi, platelets make up the core, as well as the cellular components closest to the vessel wall. In contrast to this, fibrin appears to be the substance attaching the thrombus to the vessel wall in venous thrombi, with platelets attaching to fibrin downstream.<sup>22,24,26-28</sup> In recent years, studies have demonstrated that the red areas are interspersed not only with fibrin threads but also with neutrophil extracellular traps (NETs), essentially extracellular DNA trabeculae that promote clot stabilization and propagation.<sup>6,8</sup> Indeed, fibrin, NETs, and ultralarge von Willebrand factor (ul-vWF) provide the required scaffolding that facilitates thrombus growth.<sup>6,8,29</sup>

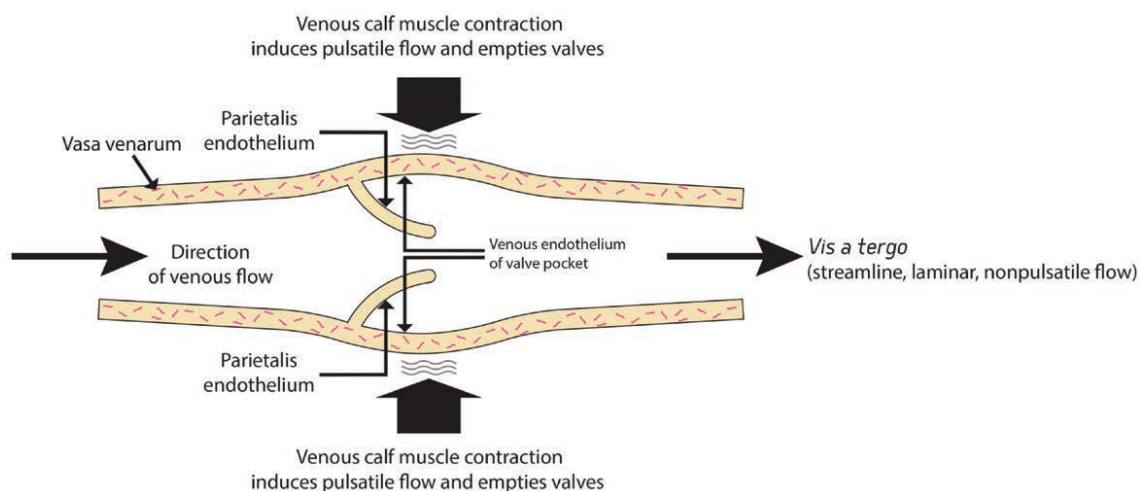
## VENOUS THROMBOGENESIS

As noted, the exact mechanisms of DVT formation are not completely understood, but it is important to appreciate and understand a number of critical events in venous thrombogenesis.

### Venous Stasis

Normal peripheral venous flow is required to prevent the accumulation of procoagulants such as thrombin, which could overcome local anticoagulant defense mechanisms under conditions of stasis.<sup>29</sup> Normal peripheral venous flow is the sum total of 2 complementary components. The first is continuous venous flow, also referred to as laminar or streamline flow,<sup>18,27,28,30,31</sup> which occurs in the supine, still individual. This type of flow relies on vis a tergo, the pressure generated by left ventricular contraction and elastic recoil of the arterial tree, which pushes blood through the capillary beds back to the atria.<sup>30,31</sup> While vis a tergo acts as the primary driving pressure, streamline venous flow is also affected by changes in microvascular resistance and increases in venous pressure.<sup>18,27,28,30</sup> As such, streamline flow is sensitive to sympathetic mediated changes in microvascular tone, and particularly vulnerable to venous obstruction due to positioning or tissue edema, as observed in knee and hip arthroplasty surgery. The second contribution to peripheral venous blood flow occurs during muscle contraction, when the deep veins are compressed to force blood back to the heart. This is known as pulsatile flow, and it is facilitated by venous valves that prevent reflux secondary to gravity (Figure 1). Pulsatile flow is significantly decreased during bed rest and abolished by general anesthesia.

Continuous venous flow helps to maintain the pro- and antithrombotic balance by preventing local accumulation of thrombin, but is insufficient to prevent thrombus formation in the venous valve pockets in the absence of pulsatile flow. Only pulsatile flow is effective in emptying the venous valve pockets where DVTs are known to originate.<sup>18,22,26-33</sup> Further, in the absence of pulsatile flow, the parietalis endothelium (Figure 1) of the valve cusp is rendered hypoxic within a matter of 2 hours in spite of normal continuous venous flow,<sup>18,27-29,31</sup> a consequence of the cusp's avascular



**Figure 1.** Venous flow consists of contributions from continuous venous flow and pulsatile flow from the calf muscle pump.

anatomy, and sole dependence on oxygen diffusion from deoxygenated venous blood for its viability.<sup>28,31,33</sup>

### Venous Valve Hypoxia and Endothelial Dysfunction

The histological findings described above suggest that DVTs almost always originate in venous sinuses. Interestingly, not all individuals have the same number of venous valves, and the risk for developing DVT increases with an increase in the number of venous valves.<sup>34,35</sup> Furthermore, compared to regular venous endothelial cells, venous valve endothelial cell surfaces express significantly higher levels of anticoagulant proteins such as thrombomodulin and endothelial cell protein C receptor, and at the same time lower levels of the procoagulant ul-vWF.<sup>34</sup> Similar to the arterial circulation, it therefore appears that normal vascular endothelial function, in particular in the at-risk venous pockets, may play a pivotal role in preventing thrombosis.<sup>24,34,36</sup>

Unfortunately, because of the tenuous oxygen supply outlined above, endothelial cells in venous valves are remarkably at risk for hypoxia in the absence of pulsatile flow.<sup>18,24,27–29,31</sup> Hypoxia and subsequent inflammation activate endothelial cells to downregulate the expression of the anticoagulant proteins and upregulate the expression of procoagulant proteins such as tissue factor (TF) and vWF, disrupting the delicate balance between local pro- and anticoagulant mechanisms.<sup>24,34,36–40</sup> It is important to understand that this endothelial phenotypic change occurs quite rapidly. In fact, within 30 minutes of hypoxia, endothelial Weibel-Palade bodies begin to release ul-vWF, P-selectin, and E-selectin,<sup>37,39</sup> thereby activating endothelial cells to promote thrombogenesis.

### Thrombus Initiation: TF Dependent

The selectins expressed on activated endothelial cells attract monocytes, neutrophils, and highly procoagulant TF-releasing circulating microvesicles (MVs).<sup>18,41–43</sup> P-selectin, in particular, recruits and activates additional monocytes, which then release additional TF-releasing MVs,<sup>8,20,42,43</sup> greatly amplifying the response.<sup>18</sup> Simultaneously, ul-vWF, which is stickier and more thrombophilic than vWF found in blood,<sup>29</sup> recruits and activates platelets and

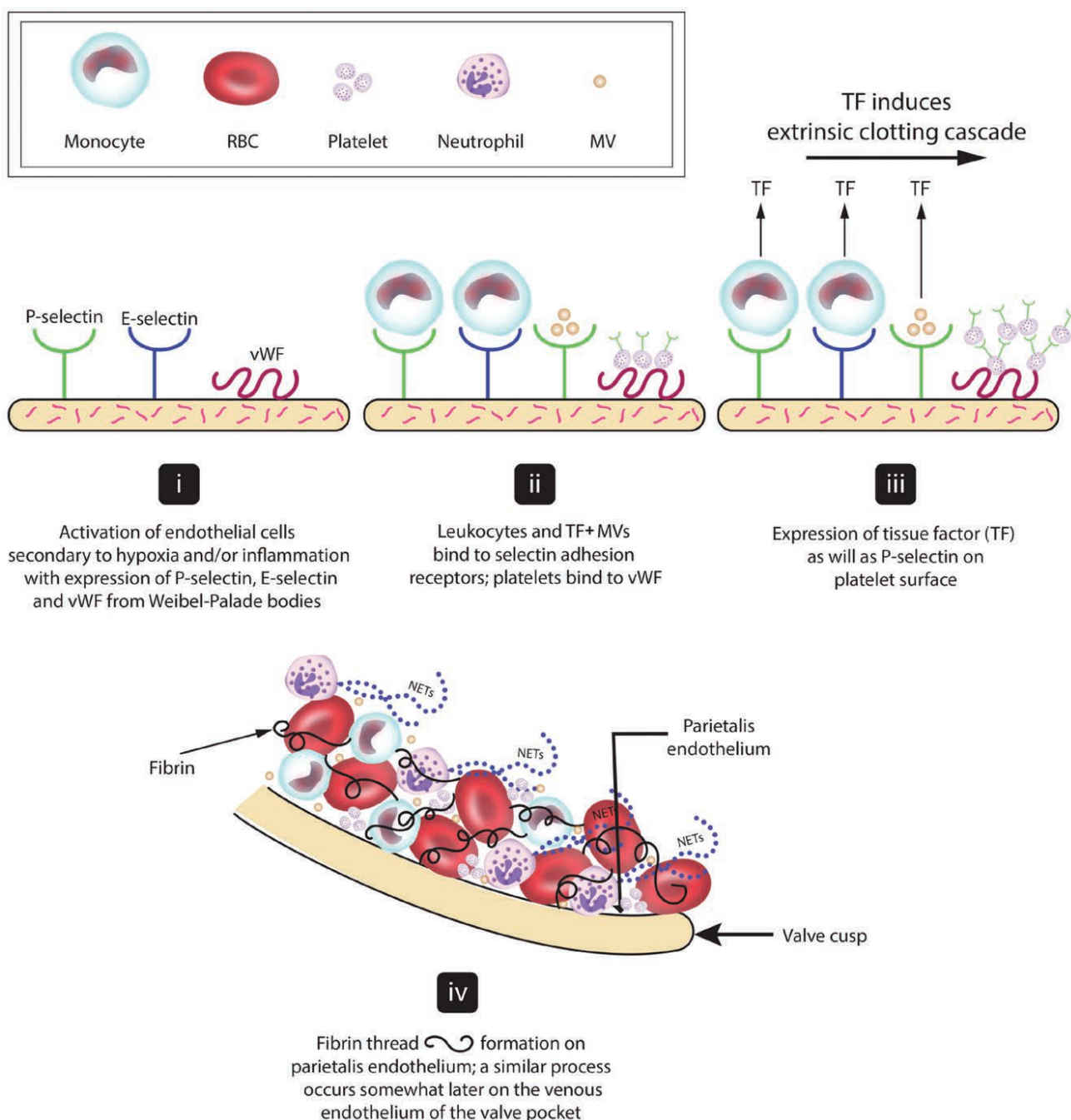
neutrophils, inducing expression of more P-selectin on platelet surfaces,<sup>41–43</sup> promoting platelet adhesion and formation of NETs.<sup>6,41</sup> As illustrated in Figure 2, TF triggers the extrinsic cascade, which leads to thrombin generation and conversion of fibrinogen to fibrin.

An accumulating body of evidence indicates that MVs play a key role in venous thrombus formation, in particular, in patients with malignancies.<sup>8,18,20,24,29</sup> Also, in patients undergoing total knee arthroplasty, a surgical procedure associated with a significant risk for VTE, TF expression by circulating monocytes is significantly increased.<sup>44,45</sup> While TF derived from MVs and monocytes triggers the extrinsic clotting cascade, platelets simultaneously trigger the contact cascade, augmenting thrombin formation and conversion of fibrinogen to fibrin. Fibrin threads and NETs then ensnare red blood cells, platelets, and additional neutrophils.<sup>18,24,29,41</sup> This coagulum of fibrin, NETs, red blood cells, platelets, and neutrophils, as illustrated in Figure 2iv, forms the initial thrombotic nidus outlined above, originally described by Sevitt<sup>26</sup> in his groundbreaking histological study.

### Thrombus Propagation: Platelet and Leukocyte Accumulation

The exact pathophysiology of thrombus propagation remains somewhat uncertain, but likely involves cyclical thrombus organization and influx of fresh venous blood.<sup>28</sup> The process continues layer by layer as described histologically<sup>22,26</sup> (Figure 3), with organization diminishing farther away from the original nidus.<sup>18,26</sup> The ebb and flow of venous blood into and out of the valve pocket leads to the formation of a striated thrombus, which eventually fills the valve pocket and encroaches on the main venous channel (Figure 4).

As the thrombus enlarges, more ul-vWF and P-selectin are released during platelet activation and degranulation. Degradation of ul-vWF requires exposure of the protein to higher shear rates, which in turn leads to molecular extension and degradation by the enzyme ADAMTS 13.<sup>29</sup> Therefore, in contrast to initial thrombotic nidus formation, which occurs in the absence of pulsatile flow, thrombus propagation is more likely in the absence of continuous venous flow.



**Figure 2.** Activation of endothelium of valve cusp secondary to hypoxia and/or inflammation.<sup>6,8,18,24</sup> MVs indicates microvesicles; RBC, red blood cell; vWF, von Willebrand factor; NETs, neutrophil extracellular traps. i, valvular hypoxia initiates process; ii, binding of blood elements to endothelium; iii, tissue factor expression; iv, fibrin thread formation and NET scaffolding.

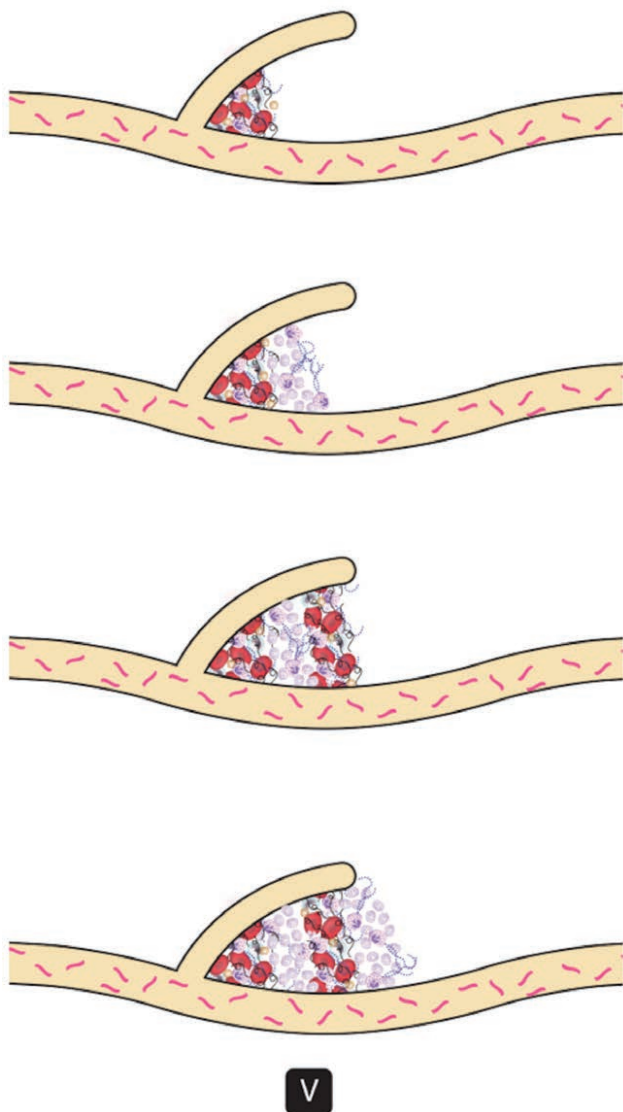
In summary, it is clear that multiple pathways and many different cells types, in addition to the traditional coagulation cascade, interact in a complex manner to promote thrombotic nidus formation and subsequent thrombus propagation. These mechanisms may offer many new molecular targets for intervention in addition to traditional anticoagulation and perhaps explain why anticoagulation on its own has largely failed to eliminate VTE.<sup>23,46-49</sup>

**PREDICTING PERIOPERATIVE VTE RISK**

While a blanket approach to prophylaxis can be adopted in high-risk surgical procedures, for some patients the risk

for bleeding and postoperative infection associated with prophylaxis may outweigh the risk for VTE.<sup>21</sup> Accurate preoperative VTE risk assessment is therefore essential for appropriate prophylaxis selection. However, as described above, accurate outcome data are lacking and risk prediction tools are not precise. Even the massive National Surgical Quality Improvement Program database, which is the basis for one of the risk prediction algorithms,<sup>50</sup> records only symptomatic VTE observed within 30 days of surgery. For these reasons, VTE risk is usually crudely assigned as low, moderate, high, or highest.<sup>5,21</sup> Swanson<sup>51</sup> points out that the Caprini Score, arguably the most widely used VTE

risk prediction tool, has no firm pathophysiologic footing, but rather is based on “logic, emotion, experience, and intuition.” To put the individual risk factors in the Caprini Score



**Figure 3.** Step V. Growth of the thrombus by alternating red and white layers, ultimately filling the valve pocket.<sup>22</sup>

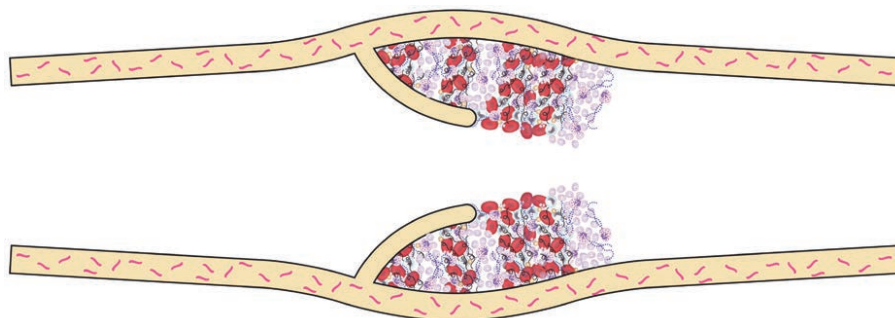
in better perspective, Swanson<sup>51</sup> compared each Caprini risk factor score with published levels of relative risk, as shown in Table 1, and found no correlation. Another recent study of surgical patients came essentially to the same conclusion that use of all but the highest Caprini scores ( $\geq 7$ ) led to overmedication of potent pharmacological agents.<sup>52</sup> Clearly, there is a need for more refined tools to predict perioperative VTE risk.

**PREVENTING PERIOPERATIVE VTE**

Several guidelines have been published with the goal of preventing VTE. Unfortunately, adoption and adherence to these guidelines still provide a huge opportunity for health care improvement. Implementing strategies to improve compliance should be a primary focus point for all institutions.<sup>21</sup> Adopting simplified more universal protocols, a strategy to improve compliance, may not serve all patients well though. In the clinical practice of anesthesiology, patient management is routinely individualized, tailored to both patient and surgical factors. Anesthesiologists have an opportunity to make sure each and every patient receives individualized optimum prophylaxis, with the goal to prevent perioperative VTE. Similar to perioperative myocardial infarction, stroke, or kidney injury, anesthesiologists should also be acutely aware of VTE risk factors to individualize patient management within the context of the surgical procedure. This is especially relevant in light of the fact that many, if not most, VTEs begin their germination in the operating room, often at the outset of anesthetic induction.<sup>32,53,54</sup> Similar to acute and chronic postoperative pain, where several pathways are involved and a multimodal therapeutic approach is required, it is becoming evident that multiple pathways beyond the coagulation cascade are involved in perioperative VTE, and merely relying on anticoagulants is insufficient.<sup>55</sup>

**Intermittent Pneumatic Compression Devices**

Intermittent pneumatic compression devices (ICDs) should be the cornerstone in VTE prevention.<sup>10,21,56-60</sup> A recent large meta-analysis concluded that in hospitalized patients ICDs are more effective than thromboembolic deterrent stockings and may in fact be as effective as pharmacological prophylaxis, without the additional risk for bleeding.<sup>59</sup> Additionally, combining ICDs with pharmacological prophylaxis further



**Figure 4.** Encroachment.

Encroachment: the thrombus fills the valve pocket. At this point platelets and neutrophils play a more predominant role. Pulsatile flow no longer empties the valve pocket and venous flow *via vis a tergo* becomes the critical factor

**Table 1. Comparison of Caprini Scores With Relative Risk Factors**

Condition	Caprini Score	Relative Risk
Age >75 y	3	90
Postpartum	1	20
Major trauma	5	13
Hospitalization on a medical service	0	8
Cancer	3	6.5
Surgery	3	6
Pregnancy	1	5.5
Prolonged bed rest	1	5.5
Oral contraception	1	4
Factor V Leiden (heterozygous)	3	4
Hormone replacement therapy	1	3
Prothrombin 20210G (heterozygous)	3	2.5
Obesity (BMI >30)	1	2.5
Family history	3	2.5
Travel >4 h	0	2
Elevated homocysteine level	3	1.1

Data from Swanson.<sup>51</sup>

Abbreviation: BMI, body mass index, kg/m<sup>2</sup>.

reduced the risk for DVT.<sup>59</sup> Surprisingly, in AT9 the utilization of ICDs alone without additional pharmacological prophylaxis is designated as level 2C, defined as a “weak recommendation, low or very low-quality evidence.”<sup>12</sup> Similarly, in the second edition of the VTE guidelines for hip and knee arthroplasty from the American Academy of Orthopaedic Surgeons,<sup>21,61,62</sup> the evidence for ICDs alone is rated as moderate. A moderate recommendation means that the benefits exceed the potential harm, but the strength of the supporting evidence is not as strong. It would seem that, in the face of the almost universal acceptance of ICDs, and the numerous studies indicating their benefits, these guidelines are somewhat misleading. AT9 does note, “For general surgery patients with a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis with properly fitted graduated compression stockings.”<sup>12</sup>

It is our strong belief that the first line of defense in VTE prevention should always be minimization of the period of nonpulsatile flow, which may be accomplished by (i) preinduction and prolonged utilization of portable ICDs, (ii) early ambulation following surgery, and (iii) regularly scheduled foot and calf exercises, at least every 2 hours. Interestingly, in 1960 McLachlin et al<sup>32</sup> noted that intermittent positioning of the lower extremities in the nondependent (reverse Trendelenburg) position was sufficient to empty radiopaque dye from the venous valve pockets more effectively than vigorous calf contractions, a low-risk intervention. This has not been well studied.

Although there is widespread agreement regarding the effectiveness of ICDs in reducing the incidence of VTE following surgery, there is some uncertainty regarding the exact mechanisms by which they achieve this beneficial effect.<sup>63</sup> It has been suggested that ICDs derive their benefits not only from an increase in pulsatile flow, but also from increased fibrinolytic activity.<sup>63</sup> This theory originated with a 1976 *Lancet* publication by Knight and Dawson,<sup>64</sup> where the incidence of DVT was examined in 111 patients, 53 of whom had ICDs applied to the arms. The occurrence of DVT, as defined by <sup>125</sup>I fibrinogen leg scans, decreased from 32.7% to 13.2% and the expected postsurgical decrease in

euglobulin clot lysis time, a measure of fibrinolytic activity, was prevented for 2 days. A considerable number of subsequent studies, however, have failed to demonstrate any enhancement of fibrinolytic activity.<sup>28,65–67</sup> We therefore conclude that the prevention of nonpulsatile flow is the primary beneficial action of ICDs.

It is not clear if the type of ICD utilized is important. Maynard<sup>21</sup> advises that only portable, battery-powered ICDs capable of recording and reporting wear time on a daily basis are recommended for inpatient and extended use. Efforts should be made to achieve daily compliance of 18 hours or more.<sup>21</sup> Caprini<sup>10</sup> and Zhao et al<sup>68</sup> examined various ICDs for VTE prevention and found no significant difference in effectiveness. Since effectiveness appears to be a result of patient compliance, as well as when use was initiated, convenience may be the most important factor in device selection.

A recent study by Nunley et al<sup>56</sup> with approximately 3000 patients undergoing hip and knee arthroplasties found long-term portable ICD therapy (approximately 10 days) combined with aspirin equal in effectiveness to traditional anticoagulation with warfarin. Colwell et al<sup>57</sup> reported similar findings, again with a cohort of approximately 3000 patients, demonstrating that the effectiveness of long-term portable ICD therapy (minimum of 10 days) for VTE prevention was noninferior to warfarin, rivaroxaban, dabigatran, or enoxaparin. These clinical trials offer a strong argument in favor of long-term ICD usage. They also offer some reassurance that high VTE risk surgical procedures, such as hip and knee arthroplasties, can be safely performed without the use of potent anticoagulants, which may increase the risk for surgical bleeding and prohibit the use of neuraxial anesthetic techniques. To be clear, we are not advising against the use of anticoagulants for VTE prophylaxis, but merely questioning the role of potent anticoagulants as first-line therapy for a flow-induced complication. This is particularly true on the day of surgery when the risk for bleeding complications is at its greatest. In our opinion, mechanical ICD thromboprophylaxis should be routinely administered to all patients at risk for VTE unless contraindicated.

### Aspirin

As described earlier, immunological, hematological, and histological studies suggest a primary role for the TF-triggered extrinsic clotting cascade and factor VIIa in thrombus initiation within the venous valve cusp. Platelet activation and the intrinsic or contact cascade then assume a major role once propagation and encroachment occur. Therefore, maintenance of pulsatile flow and anticoagulants should play the major role in minimizing thrombus initiation, whereas maintenance of optimal venous flow (as, for example, via goal-directed fluid therapy) and antiplatelet drugs should be effective in preventing thrombus propagation.

Increasingly, studies are calling into question the effectiveness of potent anticoagulants as the primary means of VTE prevention in medical and surgical patients.<sup>23,47,49,69,70</sup> Indeed, it has even been suggested that all-cause mortality may be greater with their use.<sup>70</sup> Compared to anticoagulants, aspirin is believed to be associated with a lower incidence of bleeding and infectious complications,<sup>71</sup> the rationale behind

an increased adoption of aspirin in VTE prophylaxis. At least 5 studies in orthopedic surgery now suggest that aspirin combined with properly applied ICDs is as effective as warfarin or low-molecular-weight heparin.<sup>56,57,71–74</sup>

A recently published meta-analysis of data from the PeriOperative ISchemia Evaluation-2 (POISE-2), Pulmonary Embolism Prevention (PEP), and the Antiplatelet Trialists' Collaboration also showed that aspirin reduces the risk of symptomatic VTE in hospitalized surgical patients by about one-third.<sup>75</sup> Consistent with the hypothesis that antiplatelet agents should be effective against thrombus propagation, rather than thrombus initiation, exploratory analyses in this study found that aspirin was more effective in preventing large thrombi than smaller thrombi and may decrease the severity of PE.<sup>75</sup> Interestingly, the authors also reported that combining aspirin with anticoagulant prophylaxis did not modify the effect of aspirin on VTE or bleeding.<sup>75</sup> Therefore, in contrast to combining mechanical prophylaxis with either anticoagulants or aspirin,<sup>10,67</sup> the effects of aspirin and anticoagulants may not be additive.

### Novel Oral Anticoagulants

Novel oral anticoagulants that potently inhibit factor Xa (such as rivaroxaban and apixaban) or thrombin (dabigatran) without the need for blood level monitoring offer an extremely attractive alternative to current anticoagulants in perioperative VTE prophylaxis. A recent meta-analysis on the safety and efficacy of these drugs in preventing VTE after hip and knee arthroplasty showed that these drugs, compared to enoxaparin 40 mg once a day, do indeed lower VTE risk, but at the expense of increased postoperative bleeding.<sup>15</sup> At the dosing regimens tested, none of the oral agents were more effective than enoxaparin 30 mg twice daily. Predictably, the agents with the highest efficacy in preventing VTE also had the greatest risk for bleeding. The agent with the most favorable risk profile for bleeding was apixaban 2.5 mg twice daily, which appears to be a good alternative to enoxaparin 40 mg once daily.

Perioperative bleeding has associated risks beyond those of blood product transfusion and is far from being an innocuous event. It is important to note that bleeding typically occurs in the postoperative period when it is much more difficult to deal with. Furthermore, a much more sinister consequence of postoperative bleeding is the associated risk for infection, which can be devastating in the presence of prostheses. A recent single-center report of increased deep surgical site infections in patients who received rivaroxaban for thromboprophylaxis following knee or hip arthroplasty surgery is concerning.<sup>76</sup>

### Statins

A number of recently published studies observed a significant reduction in VTE risk in patients taking statin drugs.<sup>8,24,77–79</sup> The mechanism by which this group of drugs prevents VTE is unknown, but Mackman<sup>24</sup> has suggested their effect is possibly mediated through the inhibition of monocyte TF expression. Statins are also known to potently inhibit vascular inflammation, improve endothelial dysfunction, and prevent thrombogenesis, all of which may play a role in modifying VTE risk.<sup>77</sup> At this stage, prospective randomized data to suggest routine use of perioperative

statins for VTE prophylaxis are still lacking and cannot be recommended, unless required for an alternative indication.

### Lidocaine and Neuraxial Blockade

Blocking leukocyte and leukocyte-derived MVs binding to activated endothelium, predominantly through P-selectin coupling, may provide another novel method to prevent early venous thrombus formation, a hypothesis supported by several animal studies.<sup>24</sup> While clinical studies using P-selectin inhibitors are still lacking, a widely used anesthetic technique may be of benefit. Intravenous lidocaine, which is increasingly used as part of multimodal analgesic strategies, has been shown to significantly attenuate increases in plasma P-selectin and platelet-leukocyte aggregates.<sup>80</sup> The clinical significance of this finding is still unknown, and the effects of intravenous lidocaine on VTE have not been studied.

In contrast to intravenous lidocaine, the benefits of neuraxial anesthesia in preventing VTE are well documented.<sup>70,71,81–83</sup> Neuraxial anesthesia offers 2 advantages to the patient with respect to VTE: (1) the presence of neuraxial anesthesia prior to incision reduces the stress response and resulting cytokine release, ameliorating the increase in clotting kinetics; and (2) improvement in total venous blood flow.<sup>81</sup> If maintained into the postoperative period, epidural analgesia may improve washout of thrombin as encroachment occurs.

### PREOPERATIVE GENOMIC PROFILING

As we enter the era of precision medicine, preoperative genomic profiling will likely improve preoperative risk stratification and hopefully also lead to the development of newer therapeutic interventions. Inherited thrombophilias may be involved in up to 40% of VTE cases.<sup>1,84</sup> The relative risk associated with these conditions are outlined in Table 2. Unfortunately, unlike what is observed in preventative strategies where combination therapies are at best additive, the risk factors for VTE may enhance VTE risk in a synergistic way.<sup>24</sup> For example, the risk for VTE in patients on oral contraceptives is increased 4-fold, whereas the risk is increased 7-fold in patients with factor V Leiden deficiency. However, in a factor V Leiden patient on oral contraceptives, the risk is increased 36-fold.<sup>24,85</sup> Such patients are at risk for unprovoked VTE and could develop perioperative VTE even after minor surgery. Finally, genome-wide association studies have so far been of limited value in identifying further important polymorphisms. It is possible that

**Table 2. Increased Relative Risk of VTE for Various Thrombophilias**

Genetic Factor	Relative Risk of First VTE
Factor V Leiden (homozygous)	80
Antithrombin deficiency	50
Prothrombin G20210A (homozygous)	30
Protein C deficiency	15
Protein S deficiency	10
Factor V Leiden (heterozygous)	7
Prothrombin G20210A (heterozygous)	3–4
Non-O blood	2

Modified from Mannucci and Franchini.<sup>84</sup>  
Abbreviation: VTE, venous thromboembolism.

future studies may identify rare variants associated with a high risk for VTE.<sup>54</sup>

## CONCLUSIONS

VTE continues to be a serious problem after surgery, resulting in disabling morbidity and death. VTE is perhaps the most preventable of all the major perioperative complications, yet current prophylaxis guidelines have failed to eliminate the problem. This may be due to poor implementation of guidelines, and every effort should be made to increase awareness and provide each patient with optimum evidence-based prophylaxis. However, it is also likely that we are relying too much on anticoagulation as a primary modality for prophylaxis.

In recent years, great strides have been made in delineating the complex pathogenesis of VTE. With an understanding of the pathogenesis in hand, the anesthesiologist is ideally positioned to make a significant contribution in efforts to lower VTE incidence. Anticoagulant prophylaxis does not prevent venous stasis or venous valve endothelial activation. **We therefore advocate for mechanical prophylaxis in the form of ICDs in all patients at risk as a first line of defense against thrombotic nidus formation. Anesthetic and analgesic regimens should enable early and aggressive mobilization, and interventions (such as ICDs) should always start prior to the induction of general anesthesia or deep sedation where feasible.**<sup>53</sup> Research efforts should be directed at ways anesthetic techniques could attenuate TF and P-selectin release associated with major surgery and examine the impact of such interventions on VTE. **Platelet inhibition with aspirin can play an important role in preventing thrombus propagation and decrease PE risk, while associated with less surgical bleeding or infection. And although the jury is still out, evidence is accumulating that statin drugs may provide much needed additional protection against VTE.** Finally, preoperative genomic profiling, combined with standard preoperative evaluation, may help guide appropriate perioperative prophylaxis. ■

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## DISCLOSURES

**Name:** Ronald J. Gordon, MD, PhD.

**Contribution:** This author helped analyze the data and write the manuscript.

**Conflicts of Interest:** Dr Gordon is a consultant on perioperative genomics for Millennium Health.

**Name:** Frederick W. Lombard, MBChB, FANZCA.

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## REFERENCES

1. *The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism*. Rockville, MD: US Department of Health and Human Services; 2008.
2. Buesing KL, Mullapudi B, Flowers KA. Deep venous thrombosis and venous thromboembolism prophylaxis. *Surg Clin North Am*. 2015;95:285–300.
3. Caprini JA. Risk assessment as a guide to thrombosis prophylaxis. *Curr Opin Pulm Med*. 2010;16:448–452.

4. Raskob GE, Angchaisuksiri P, Blanco AN, et al; ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to global disease burden. *Arterioscler Thromb Vasc Biol*. 2014;34:2363–2371.
5. Caprini J. Thrombotic risk assessment: a hybrid approach. In: Bergan J, Bunke-Paquette N, eds. *The Vein Book*. 2nd ed. Oxford: Oxford University Press; 2014:295–305.
6. Fuchs TA, Brill A, Wagner DD. Neutrophil extracellular trap (NET) impact on deep vein thrombosis. *Arterioscler Thromb Vasc Biol*. 2012;32:1777–1783.
7. Heit JA, Silverstein MD, Mohr DN, et al. The epidemiology of venous thromboembolism in the community. *Thromb Haemost*. 2001;86:452–463.
8. Albayati MA, Grover SP, Saha P, Lwaleed BA, Modarai B, Smith A. Postsurgical inflammation as a causative mechanism of venous thromboembolism. *Semin Thromb Hemost*. 2015;41:615–620.
9. Bickdeli B, Sharif-Kashani B. Prophylaxis for venous thromboembolism: a great global divide between expert guidelines and clinical practice? *Semin Thromb Hemost*. 2012;38:144–155.
10. Caprini JA. Mechanical methods for thrombosis prophylaxis. *Clin Appl Thromb Hemost*. 2010;16:668–673.
11. Nakazawa KR, Egorova NN, Power JR, Faries PL, Vouyouka AG. The impact of Surgical Care Improvement Project measures on in-hospital outcomes following elective vascular procedures. *Ann Vasc Surg*. 2017;38:17–28.
12. MacLean S, Mulla S, Akl EA, et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e1S–e23S.
13. Doughtie CA, Priddy EE, Philips P, Martin RC, McMasters KM, Scoggins CR. Preoperative dosing of low-molecular-weight heparin in hepatopancreatobiliary surgery. *Am J Surg*. 2014;208:1009–1015.
14. Mohnike K, Sauerland H, Seidensticker M, et al. Haemorrhagic complications and symptomatic venous thromboembolism in interventional tumour ablations: the impact of peri-interventional thrombosis prophylaxis. *Cardiovasc Intervent Radiol*. 2016;39:1716–1721.
15. Venker BT, Ganti BR, Lin H, Lee ED, Nunley RM, Gage BF. Safety and efficacy of new anticoagulants for the prevention of venous thromboembolism after hip and knee arthroplasty: a meta-analysis. *J Arthroplasty*. 2017;32:645–652.
16. Rosendaal FR. Venous thrombosis: the role of genes, environment, and behavior. *Hematology Am Soc Hematol Educ Program*. 2005;2005:1–12.
17. Sweetland S, Green J, Liu B, et al; Million Women Study Collaborators. Duration and magnitude of the postoperative risk of venous thromboembolism in middle aged women: prospective cohort study. *BMJ*. 2009;339:b4583.
18. Bovill EG, van der Vliet A. Venous valvular stasis-associated hypoxia and thrombosis: what is the link? *Annu Rev Physiol*. 2011;73:527–545.
19. Line BR. Pathophysiology and diagnosis of deep venous thrombosis. *Semin Nucl Med*. 2001;31:90–101.
20. Lopez JA, Kearon C, Lee AY. Deep venous thrombosis. *Hematology Am Soc Hematol Educ Program*. 2004;2004:439–456.
21. Maynard G. *Preventing Hospital-Associated Venous Thromboembolism: A Guide for Effective Quality Improvement*. 2nd ed. Rockville, MD: Agency for Healthcare Research and Quality; 2016.
22. Hume M, Sevitt S, Thomas DP. *Venous Thrombosis and Pulmonary Embolism*. Cambridge: Harvard University Press; 1970.
23. Spencer A, Cawood T, Frampton C, Jardine D. Heparin-based treatment to prevent symptomatic deep venous thrombosis, pulmonary embolism or death in general medical inpatients is not supported by best evidence. *Intern Med J*. 2014;44:1054–1065.
24. Mackman N. New insights into the mechanisms of venous thrombosis. *J Clin Invest*. 2012;122:2331–2336.
25. Paterson JC, McLachlin J. Precipitating factors in venous thrombosis. *Surg Gynecol Obstet*. 1954;98:96–102.



26. Sevitt S. The structure and growth of valve-pocket thrombi in femoral veins. *J Clin Pathol.* 1974;27:517–528.
27. Malone PC, Agutter PS. The aetiology of deep venous thrombosis. *QJM.* 2006;99:581–593.
28. Malone PC, Agutter PS. *The Aetiology of Deep Venous Thrombosis: A Critical, Historical and Epistemological Survey.* Dordrecht: Springer; 2008.
29. López JA, Chen J. Pathophysiology of venous thrombosis. *Thromb Res.* 2009;123 (suppl 4):S30–S34.
30. Agutter PS, Malone PC, Silver IA. Experimental validation of methods for prophylaxis against deep venous thrombosis: a review and proposal. *Thrombosis.* 2012;2012:156397.
31. Hamer JD, Malone PC, Silver IA. The PO2 in venous valve pockets: its possible bearing on thrombogenesis. *Br J Surg.* 1981;68:166–170.
32. McLachlin AD, McLachlin JA, Jory TA, Rawling EG. Venous stasis in the lower extremities. *Ann Surg.* 1960;152:678–685.
33. Malone PC, Agutter PS. Deep venous thrombosis: the valve cusp hypoxia thesis and its incompatibility with modern orthodoxy. *Med Hypotheses.* 2016;86:60–66.
34. Brooks EG, Trotman W, Wadsworth MP, et al. Valves of the deep venous system: an overlooked risk factor. *Blood.* 2009;114:1276–1279.
35. Liu GC, Ferris EJ, Reifsteck JR, Baker ME. Effect of anatomic variations on deep venous thrombosis of the lower extremity. *AJR Am J Roentgenol.* 1986;146:845–848.
36. Watson SP. Platelet activation by extracellular matrix proteins in haemostasis and thrombosis. *Curr Pharm Des.* 2009;15:1358–1372.
37. Closse C, Seigneur M, Renard M, et al. Influence of hypoxia and hypoxia-reoxygenation on endothelial P-selectin expression. *Thromb Res.* 1997;85:159–164.
38. Ley K, Laudanna C, Cybulsky MI, Nourshargh S. Getting to the site of inflammation: the leukocyte adhesion cascade updated. *Nat Rev Immunol.* 2007;7:678–689.
39. Pinsky DJ, Naka Y, Liao H, et al. Hypoxia-induced exocytosis of endothelial cell Weibel-Palade bodies. A mechanism for rapid neutrophil recruitment after cardiac preservation. *J Clin Invest.* 1996;97:493–500.
40. Williams MR, Azcutia V, Newton G, Alcaide P, Luscinskas FW. Emerging mechanisms of neutrophil recruitment across endothelium. *Trends Immunol.* 2011;32:461–469.
41. Martinod K, Wagner DD. Thrombosis: tangled up in NETs. *Blood.* 2014;123:2768–2776.
42. Polgar J, Matuskova J, Wagner DD. The P-selectin, tissue factor, coagulation triad. *J Thromb Haemost.* 2005;3:1590–1596.
43. van der Meijden PE, Ozaki Y, Ruf W, et al. Theme 1: pathogenesis of venous thromboembolism (and post-thrombotic syndrome). *Thromb Res.* 2015;136(suppl 1):S3–S7.
44. Johnson GJ, Leis LA, Bach RR. Tissue factor activity of blood mononuclear cells is increased after total knee arthroplasty. *Thromb Haemost.* 2009;102:728–734.
45. Kageyama K, Nakajima Y, Shibasaki M, Hashimoto S, Mizobe T. Increased platelet, leukocyte, and endothelial cell activity are associated with increased coagulability in patients after total knee arthroplasty. *J Thromb Haemost.* 2007;5:738–745.
46. Becattini C, Rondelli F, Vedovati MC, et al. Incidence and risk factors for venous thromboembolism after laparoscopic surgery for colorectal cancer. *Haematologica.* 2015;100:e35–e38.
47. Colorectal Writing Group for Surgical C, Outcomes Assessment Program-Comparative Effectiveness Research Translation Network C, Nelson DW, Simianu VV, Bastawrous AL, et al. Thromboembolic complications and prophylaxis patterns in colorectal surgery. *JAMA Surg.* 2015;150:712–720.
48. Flanders SA, Greene MT, Grant P, et al. Hospital performance for pharmacologic venous thromboembolism prophylaxis and rate of venous thromboembolism: a cohort study. *JAMA Intern Med.* 2014;174:1577–1584.
49. van Adrichem RA, Nemeth B, Algra A, et al; POT-KAST and POT-CAST Group. Thromboprophylaxis after knee arthroscopy and lower-leg casting. *N Engl J Med.* 2017;376:515–525.
50. American College of Surgeons. ACS NSQIP Surgical Risk Calculator. ACS NSQIP Surgical Risk Calculator. Available at: <http://www.riskcalculator.facs.org>. Accessed March 2, 2017.
51. Swanson E. Caprini scores, risk stratification, and rivaroxaban in plastic surgery: time to reconsider our strategy. *Plast Reconstr Surg Glob Open.* 2016;4:e733.
52. Pannucci CJ, Swistun L, MacDonald JK, Henke PK, Brooke BS. Individualized venous thromboembolism risk stratification using the 2005 Caprini score to identify the benefits and harms of chemoprophylaxis in surgical patients: a meta-analysis *Ann Surg.* 2017;265:1094–1103.
53. Gordon RJ. Anesthesia dogmas and shibboleths: barriers to patient safety? *Anesth Analg.* 2012;114:694–699.
54. Makin GS. The effect of surgical operation on the velocity of venous return from the legs. *J Surg Res.* 1970;10:513–518.
55. Schnasser E, Gonzales DV, Sharrock NE. The rationale for the use of multimodal thromboprophylaxis with limited anticoagulation in patients undergoing total joint replacement: arguments against LMWHs being still the gold standard. In: Baldini A, Caldora P, eds. *Perioperative Medical Management for Total Joint Arthroplasty: How to Control Hemostasis, Pain and Infection.* Switzerland: Springer International Publishing; 2015:61–72.
56. Nunley R, Nam D, Keeney JA, et al. Increased patient satisfaction with mobile compression devices for venous thromboembolism prophylaxis. AAOS National Meeting 2015; Poster No. 020. Available at: <http://aaos2015.conferencespot.org/58906-aaos-1.1965581/t002-1.1973805/f002-1.1973806/a012-1.1974730/p020-1.1974902>. Accessed March 2, 2017.
57. Colwell CW Jr, Froimson MI, Anseth SD, et al. A mobile compression device for thrombosis prevention in hip and knee arthroplasty. *J Bone Joint Surg Am.* 2014;96:177–183.
58. Froimson MI, Murray TG, Fazekas AF. Venous thromboembolic disease reduction with a portable pneumatic compression device. *J Arthroplasty.* 2009;24:310–316.
59. Ho KM, Tan JA. Stratified meta-analysis of intermittent pneumatic compression of the lower limbs to prevent venous thromboembolism in hospitalized patients. *Circulation.* 2013;128:1003–1020.
60. Lachiewicz PF, Soileau ES. Multimodal prophylaxis for THA with mechanical compression. *Clin Orthop Relat Res.* 2006;453:225–230.
61. American Academy of Orthopaedic Surgeons. Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. Evidence-based guideline and evidence report. Available at: [http://www.aaos.org/research/guidelines/VTE/VTE\\_full\\_guideline.pdf](http://www.aaos.org/research/guidelines/VTE/VTE_full_guideline.pdf). Accessed March 2, 2017.
62. Jacobs JJ, Mont MA, Bozic KJ, et al. American Academy of Orthopaedic Surgeons clinical practice guideline on: preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. *J Bone Joint Surg Am.* 2012;94:746–747.
63. Chen AH, Frangos SG, Kilaru S, Sumpio BE. Intermittent pneumatic compression devices—physiological mechanisms of action. *Eur J Vasc Endovasc Surg.* 2001;21:383–392.
64. Knight MT, Dawson R. Effect of intermittent compression of the arms on deep venous thrombosis in the legs. *Lancet.* 1976;2:1265–1268.
65. Cahan MA, Hanna DJ, Wiley LA, Cox DK, Killewich LA. External pneumatic compression and fibrinolysis in abdominal surgery. *J Vasc Surg.* 2000;32:537–543.
66. Killewich LA, Cahan MA, Hanna DJ, et al. The effect of external pneumatic compression on regional fibrinolysis in a prospective randomized trial. *J Vasc Surg.* 2002;36:953–958.
67. Salvati EA, Sharrock NE, Westrich G, Potter HG, Valle AG, Sculco TP. The 2007 ABJS Nicolas Andry Award: three decades of clinical, basic, and applied research on thromboembolic disease after THA: rationale and clinical results of a multimodal prophylaxis protocol. *Clin Orthop Relat Res.* 2007;459:246–254.
68. Zhao JM, He ML, Xiao ZM, Li TS, Wu H, Jiang H. Different types of intermittent pneumatic compression devices for preventing venous thromboembolism in patients after total hip replacement. *Cochrane Database Syst Rev.* 2014;CD009543.
69. Rahman S. Deep vein thrombosis prophylaxis: friend or foe. *Am J Ther.* 2009;16:300–303.
70. Sharrock NE, Gonzalez Della Valle A, Go G, Lyman S, Salvati EA. Potent anticoagulants are associated with a higher all-cause

- mortality rate after hip and knee arthroplasty. *Clin Orthop Relat Res.* 2008;466:714–721.
71. Vulcano E, Gesell M, Esposito A, Ma Y, Memtsoudis SG, Gonzalez Della Valle A. Aspirin for elective hip and knee arthroplasty: a multimodal thromboprophylaxis protocol. *Int Orthop.* 2012;36:1995–2002.
  72. Anderson DR, Dunbar MJ, Bohm ER, et al. Aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: a randomized trial. *Ann Intern Med.* 2013;158:800–806.
  73. Jameson SS, Charman SC, Gregg PJ, Reed MR, van der Meulen JH. The effect of aspirin and low-molecular-weight heparin on venous thromboembolism after hip replacement: a non-randomised comparison from information in the National Joint Registry. *J Bone Joint Surg Br.* 2011;93:1465–1470.
  74. Westrich GH, Bottner F, Windsor RE, Laskin RS, Haas SB, Sculco TP. VenaFlow plus Lovenox vs VenaFlow plus aspirin for thromboembolic disease prophylaxis in total knee arthroplasty. *J Arthroplasty.* 2006;21:139–143.
  75. Eikelboom JW, Kearon C, Guyatt G, et al. Perioperative aspirin for prevention of venous thromboembolism: The PeriOperative ISchema Evaluation-2 Trial and a Pooled Analysis of the Randomized Trials. *Anesthesiology.* 2016;125:1121–1129.
  76. Brimmo O, Glenn M, Klika AK, Murray TG, Molloy RM, Higuera CA. Rivaroxaban use for thrombosis prophylaxis is associated with early periprosthetic joint infection. *J Arthroplasty.* 2016;31:1295–1298.
  77. Gaertner S, Cordeanu EM, Nouri S, Mirea C, Stephan D. Statins and prevention of venous thromboembolism: myth or reality? *Arch Cardiovasc Dis.* 2016;109:216–222.
  78. Rosendaal FR. Statins and venous thrombosis: a story too good to be true? *PLoS Med.* 2012;9:e1001311.
  79. Smith NL, Harrington LB, Blondon M, et al. The association of statin therapy with the risk of recurrent venous thrombosis. *J Thromb Haemost.* 2016;14:1384–1392.
  80. Herroeder S, Pecher S, Schönherr ME, et al. Systemic lidocaine shortens length of hospital stay after colorectal surgery: a double-blinded, randomized, placebo-controlled trial. *Ann Surg.* 2007;246:192–200.
  81. Delis KT, Knaggs AL, Mason P, Macleod KG. Effects of epidural-and-general anesthesia combined versus general anesthesia alone on the venous hemodynamics of the lower limb. A randomized study. *Thromb Haemost.* 2004;92:1003–1011.
  82. González Della Valle A, Serota A, Go G, et al. Venous thromboembolism is rare with a multimodal prophylaxis protocol after total hip arthroplasty. *Clin Orthop Relat Res.* 2006;444:146–153.
  83. Pellegrini VD Jr, Sharrock NE, Paiement GD, Morris R, Warwick DJ. Venous thromboembolic disease after total hip and knee arthroplasty: current perspectives in a regulated environment. *Instr Course Lect.* 2008;57:637–661.
  84. Mannucci PM, Franchini M. Classic thrombophilic gene variants. *Thromb Haemost.* 2015;114:885–889.
  85. Vandenbroucke JP, Rosing J, Bloemenkamp KW, et al. Oral contraceptives and the risk of venous thrombosis. *N Engl J Med.* 2001;344:1527–1535.