# Caprini Score for Venous Thromboembolism (2005)

## INPUTS

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| --- | --- |
| Age  *Years* | **Options:**   * ≤40 (0) * 41-60 (1) * 61-74 (2) * ≥75 (3) |
| Sex | **Options:**   * Male * Female |
| Type of surgery  *Minor surgery does not refer to* [*type of surgery*](https://www.youtube.com/watch?v=ZkrTteLxewQ) *but rather length of anesthesia <45 minutes.*  *Major surgery refers to procedures with* [*general*](https://pubmed.ncbi.nlm.nih.gov/6195948/) *or regional anesthesia time* [*>45 minutes*](https://www.youtube.com/watch?v=ZkrTteLxewQ) *are included. These include open, laparoscopic, or arthroscopic procedures.* [*Re-operations*](https://pubmed.ncbi.nlm.nih.gov/26821972/) *during the same hospitalization count for 2 points each if the anesthesia time exceeds 45 minutes.*  *Major lower extremity arthroplasties are high-risk procedures. However if additional risk factors are present that further increases the risk. It has been shown that in scores* [*≥10*](https://pubmed.ncbi.nlm.nih.gov/32215072/) *the VTE risk is significantly* [*greater*](https://pubmed.ncbi.nlm.nih.gov/30939898/)*. If the procedure is being done as a result of a hip* [*fracture*](https://pubmed.ncbi.nlm.nih.gov/28532441/)*, preoperative screening may be beneficial.* | **Options:**   * None (0) * Minor (1) * Major >45 min, laparoscopic >45 min, or arthroscopic (2) * Elective major lower extremity arthroplasty (5) |
| Major surgery | **Options:**   * No (0) * Yes (1) |
| CHF | **Options:**   * No (0) * Yes (1) |
| Sepsis | **Options:**   * No (0) * Yes (1) |
| Pneumonia | **Options:**   * No (0) * Yes (1) |
| Pregnancy or postpartum | **Options:**   * No (0) * Yes (1) |
| Immobilizing plaster cast | **Options:**   * No (0) * Yes (2) |
| Hip, pelvis, or leg fracture | **Options:**   * No (0) * Yes (5) |
| Stroke | **Options:**   * No (0) * Yes (5) |
| Multiple trauma | **Options:**   * No (0) * Yes (5) |
| Acute spinal cord injury causing paralysis | **Options:**   * No (0) * Yes (5) |
| Varicose veins | **Options:**   * No (0) * Yes (1) |
| Current swollen legs | **Options:**   * No (0) * Yes (1) |
| Current central venous access | **Options:**   * No (0) * Yes (2) |
| History of DVT/PE | **Options:**   * No (0) * Yes (3) |
| Family history of thrombosis | **Options:**   * No (0) * Yes (3) |
| Positive Factor V Leiden | **Options:**   * No (0) * Yes (3) |
| Positive prothrombin 20210A | **Options:**   * No (0) * Yes (3) |
| Elevated serum homocysteine | **Options:**   * No (0) * Yes (3) |
| Positive lupus anticoagulant | **Options:**   * No (0) * Yes (3) |
| Elevated anticardiolipin antibody | **Options:**   * No (0) * Yes (3) |
| Heparin-induced thrombocytopenia | **Options:**   * No (0) * Yes (3) |
| Other congenital or acquired thrombophilia | **Options:**   * No (0) * Yes (3) |
| Mobility  *Bed rest is defined as not being able to walk 30 feet (10 meters) at one time. Bathroom privileges or walking in the room are not considered ambulation. Walking this distance reduces the VTE risk by* [*50%*](https://pubmed.ncbi.nlm.nih.gov/20838741/)*. Click here for* [*VIDEO*](https://www.youtube.com/watch?v=jj0HNY4BFG4)*. PE mortality increased for those immobile for* [*>4 days*](https://pubmed.ncbi.nlm.nih.gov/22726525/)*.* | **Options:**   * Normal, out of bed (0) * Medical patient currently on bed rest (1) * Patient confined to bed >72 hours (2) |
| History of inflammatory bowel disease | **Options:**   * No (0) * Yes (1) |
| BMI >25 | **Options:**   * No (0) * Yes (1) |
| Acute MI | **Options:**   * No (0) * Yes (1) |
| COPD | **Options:**   * No (0) * Yes (1) |
| Present or previous malignancy | **Options:**   * No (0) * Yes (2) |
| Other risk factors | **Options:**   * No (0) * Yes (1) |
| On oral contraceptives or hormone replacement | **Options:**   * No (0) * Yes (1) |
| History of unexplained stillborn, ≥3 spontaneous abortions, or premature birth with toxemia or growth-restricted infant | **Options:**   * No (0) * Yes (1) |

## FORMULA

Addition of the selected points:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | 0 points | 1 point | 2 points | 3 points | 5 points |
| Age (years) | ≤40 | 41-60 | 61-74 | ≥75 | -- |
| Type of surgery | -- | Minor | Major >45 min, laparoscopic >45 min, arthroscopic | -- | Elective major lower extremity arthroplasty |
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| Recent (<1 month) event | None | Major surgery, CHF, sepsis, pneumonia, pregnancy or postpartum (if female) | Immobilizing plaster cast | -- | Hip, pelvis, or leg fracture; stroke; multiple trauma; acute spinal cord injury causing paralysis |
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| Venous disease or clotting disorder | None | Varicose veins, current swollen legs | Current central venous access | History of DVT/PE, family history of thrombosis, positive Factor V Leiden, positive prothrombin 20210A, elevated serum homocysteine, positive lupus anticoagulant, elevated anticardiolipin antibody, heparin-induced thrombocytopenia, other congenital or acquired thrombophilia | -- |
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| Mobility | Normal, out of bed | Medical patient currently on bed rest | Patient confined to bed >72 hours | -- | -- |
| Other present and past history | None | History of inflammatory bowel disease, BMI >25, Acute MI, COPD, other risk factors, on oral contraceptives or hormone replacement  (if female), history of unexplained stillborn, ≥3 spontaneous abortions, or premature birth with toxemia or growth-restricted infant (if female) | Present or previous malignancy | -- | -- |
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Input definitions:

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| --- | --- |
| **Input** | **Definition** |
| Age | Venous thromboembolism is [rare](https://pubmed.ncbi.nlm.nih.gov/17367492/) in children and young adults unless they have strong predisposing risk factors. These may include cancer, trauma, indwelling lines , systemic infection, or family history of thrombosis. Patients who are greater than [40 years](https://pubmed.ncbi.nlm.nih.gov/6195948/) of age remain at significantly increased risk compared to younger patients and the risk approximately doubles with each subsequent [decade](https://pubmed.ncbi.nlm.nih.gov/12814980/). |
| Type of surgery | Minor surgery does not refer to [type of surgery](https://www.youtube.com/watch?v=ZkrTteLxewQ) but rather length of anesthesia <45 minutes. Major surgery is defined as procedures with [general](https://pubmed.ncbi.nlm.nih.gov/6195948/) or regional anesthesia [>45](https://www.youtube.com/watch?v=ZkrTteLxewQ) minutes are included. These include open, laproscopic, or arthroscopic procedures. [Reoperations](https://pubmed.ncbi.nlm.nih.gov/26821972/) during the same hospitalization count for 2 points each if the anesthesia time exceeds 45 minutes. Major lower extremity arthroplasties are high-risk procedures if additional risk factors are present that further increases the risk. It has been shown that once the score reaches [≥10](https://pubmed.ncbi.nlm.nih.gov/32215072/) the VTE risk is significantly [greater](https://pubmed.ncbi.nlm.nih.gov/30939898/). If the procedure is being done as a result of a hip [fracture](https://pubmed.ncbi.nlm.nih.gov/28532441/), preoperative screening may be beneficial. |
| Major surgery (within one month) | Major surgery done during the preceding month includes past staged procedures. |
| CHF | The Venous Thromboembolism risk is similar for those with preserved or reduced ejection fraction. A variety of criteria fit the definition of this risk factor. |
| Sepsis | We define this factor as those requiring IV antibiotics.  A wide variety of infections have been identified as a risk factor for [thrombosis](https://pubmed.ncbi.nlm.nih.gov/22026462/). “Infection promotes thrombosis through endothelial injury, tissue factor-induced activation of the procoagulant pathway, down-regulation of the endogenous anticoagulant pathway, and inhibition of fibrinolysis.” |
| Pneumonia | Preoperative pneumonia is a significant risk factor for [VTE](https://pubmed.ncbi.nlm.nih.gov/26817651/). Postoperative pneumonia is also a significant  VTE risk [factor](https://pubmed.ncbi.nlm.nih.gov/17264013/). Do not count an additional point for infection unless another source of infection is identified. |
| Immobilizing plaster cast | This includes any [device](https://pubmed.ncbi.nlm.nih.gov/24796824/) that interferes with calf muscle pumping action by limiting ankle [motion](https://pubmed.ncbi.nlm.nih.gov/31654551/). Patients who are not weight bearing are also at-risk since no improvement in baseline blood flow [occurs](https://pubmed.ncbi.nlm.nih.gov/25249319/). |
| Hip, pelvis, or leg fracture | These fractures are associated with an increased risk of VTE and the degree of risk varies with location of the [fracture](https://pubmed.ncbi.nlm.nih.gov/31519436/). Although no clear guidelines are available, the presence of additional risk factors increases the degree of thrombotic risk.  The incidence of pulmonary emboli may occur with equal frequency for above vs. below knee thrombosis and temporary IVC filters can prevent these emboli depending upon the clinical [circumstances](https://pubmed.ncbi.nlm.nih.gov/31075462/). |
| Stroke | Stroke is the 3rd leading cause of death and frequently leads to [venous thromboembolism](https://pubmed.ncbi.nlm.nih.gov/30700139/). A paradoxical embolus can occur in a patient from a DVT that travels to the heart and through a patent foramen [ovale](https://pubmed.ncbi.nlm.nih.gov/20403094/) (PFO) entering the systemic circulation leading to a thrombotic stroke. Another common cause of an embolic stroke occurs in patients with [atrial fibrillation](https://pubmed.ncbi.nlm.nih.gov/30144419/). Thrombotic strokes in the past should be counted as a previous thrombosis and scored as 3 [points](https://pubmed.ncbi.nlm.nih.gov/31213164/). |
| Multiple trauma | This includes patients with multiple injuries involving fractures, severe chest and abdominal contusions, and internal injuries. The presence of venous thromboembolism increases mortality and prophylaxis is paramount in these [patients](https://pubmed.ncbi.nlm.nih.gov/19608183/). Bleeding issues in these patients preventing proper anticoagulation can be addressed with a program of surveillance and/or judicious use of temporary venacava [filters](https://pubmed.ncbi.nlm.nih.gov/19554085/). |
| Acute spinal sord injury causing paralysis | Patients often do not report symptoms due to the nature of their nerve damage. Initial VTE presentation may include extensive [thrombosis](https://pubmed.ncbi.nlm.nih.gov/19236977/) and/or death. Management requires a multidisciplinary [approach](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4981016/). |
| Varicose veins | These include visible bulging veins and not spider veins or telangiectasia. Varicose veins represent a risk factor for [thrombosis](https://pubmed.ncbi.nlm.nih.gov/29486040/). This risk is especially true in cancer [patients](https://pubmed.ncbi.nlm.nih.gov/24112869/). The notion that varicose veins are a harmless benign disorder is not well [founded](https://pubmed.ncbi.nlm.nih.gov/22915533/). |
| Current swollen legs | [Swollen legs](https://journals.sagepub.com/doi/10.1177/1358863X16672576) include pitting edema of any level, loss of definition of the Bony prominences, obscured surface foot veins, or indentation of the leg when a stocking is removed. This factor refers to either one or two legs affected. The physical exam should include pretibial pressure to see if an indentation is present indicating leg [swelling](https://pubmed.ncbi.nlm.nih.gov/7877400/). |
| Current central venous access | [Catheter](https://pubmed.ncbi.nlm.nih.gov/26340226/) in a blood vessel in the arm, neck, or chest that delivers blood or medicine directly to the heart within the last month ([central venous access](https://pubmed.ncbi.nlm.nih.gov/32479699/), port, PICC line). |
| History of DVT, PE, or thrombotic stroke | Each episode of venous thrombosis in any location as well as pulmonary emboli are included.  The combination of a DVT and PE remains three points. Subsequent surgical procedures in a patient with a thrombotic history are associated with a very high incidence of [thrombosis](https://pubmed.ncbi.nlm.nih.gov/6161550/). Extended prophylaxis for up to one month may be [indicated](https://pubmed.ncbi.nlm.nih.gov/18521515/). |
| Family history of thrombosis | One of the most [powerful](https://pubmed.ncbi.nlm.nih.gov/19307525/) risk factors for thrombosis and also frequently not asked or included in some risk models, and frequently not included in [clinical trials](https://pubmed.ncbi.nlm.nih.gov/23348971/). Increased risk has been documented in first, second, and [third-degree](https://www.youtube.com/watch?v=GJC5xRN6tpU) relatives. This includes any DVT, PE, or thrombotic [stroke](https://pubmed.ncbi.nlm.nih.gov/26252207/). |
| Other congenital or acquired thrombophilia | Thrombophilia is a congenital or acquired condition characterized by an imbalance in hemostasis producing a hypercoagulable state. A family member with a history of a VTE would score 3. If that family member had a positive thrombophilia marker, the patient score would be 6 points. Multiple thrombophilia markers together increase the VTE potential and are scored as 3 for each [factor](https://pubmed.ncbi.nlm.nih.gov/11309638/). |
| Mobility | Bed rest is defined as not being able to walk 30 feet (10 meters) at one time. Bathroom privileges or walking in the room are not considered ambulation. Walking this distance reduces the VTE risk by [50%](https://pubmed.ncbi.nlm.nih.gov/20838741/). Click here for [VIDEO](https://www.youtube.com/watch?v=jj0HNY4BFG4). PE mortality increased for those immobile for [>4 days](https://pubmed.ncbi.nlm.nih.gov/22726525/). |
| History of inflammatory bowel disease | This risk factor includes regional ileitis, ulcerative colitis, and not irritable bowel syndrome. Patients with inactive as well as active disease should be [included](https://pubmed.ncbi.nlm.nih.gov/30294897/). The thrombotic risk is increased during active disease. Extended prophylaxis post operatively may be of benefit in the presence of acute [disease](https://pubmed.ncbi.nlm.nih.gov/29420429/). |
| BMI >25 | This factor was derived from several sources including criteria associated with readmission following total [joint replacement](https://pubmed.ncbi.nlm.nih.gov/11114314/), and in patients taking birth control [pills](https://pubmed.ncbi.nlm.nih.gov/12624633/). |
| Acute MI | This risk factor is associated with a transient increased VTE risk for the first six months independent of traditional atherosclerotic [risk factors](https://pubmed.ncbi.nlm.nih.gov/27061154/). The strength of this risk factor decreases after three [months](https://pubmed.ncbi.nlm.nih.gov/21900083/). |
| COPD | COPD Is a leading cause of morbidity and mortality worldwide characterized by systemic inflammation and venous thromboembolism in up to 30% of these [patients](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4382082/). The presence of idiopathic pulmonary fibrosis in Association with COPD poses a higher risk for VTE. |
| Present or previous malignancy | This factor excludes basal cell skin cancer except for melanoma. Cancer is a major factor for developing [VTE](https://pubmed.ncbi.nlm.nih.gov/22828139/). VTE in the cancer patient is one of the leading causes of death and is associated with a decrease in quality of [life](https://pubmed.ncbi.nlm.nih.gov/16505267/). |
| Other congenital or acquired thrombophilia | Thrombophilia is a congenital or acquired condition characterized by an imbalance in hemostasis producing a hypercoagulable state. A family member with a history of a VTE would score 3. If that family member had a positive thrombophilia marker, the patient score would be 6 points. Multiple thrombophilia markers together increase the VTE potential and are scored as 3 for each [factor](https://pubmed.ncbi.nlm.nih.gov/11309638/). |
| Positive Factor V Leiden | The most common inherited gene mutation that is rarely seen in Asian or African populations. It is associated with an increased VTE risk especially in the rare homozygous form. It involves resistance of Factor V that is associated with an increased chance of arterial or venous thrombosis. A synergistic effect for VTE risk exists when combined with other [risk factors](https://pubmed.ncbi.nlm.nih.gov/21116184/). |
| Positive prothrombin 20210A | The second most common inherited gene mutation found in Caucasians involving elevated levels of plasma coagulation factor II that represent a risk factor for venous thrombosis especially the rare homozygous [form](https://pubmed.ncbi.nlm.nih.gov/10190951/). Heterozygous factor V Leiden combined with heterozygous prothrombin gene mutation are associated with an increased level of thrombotic risk similar to a single homozygous [defect](https://pubmed.ncbi.nlm.nih.gov/23900608/). |
| Heparin-induced thrombocytopenia | A powerful and sometimes life-threatening immune reaction to heparin that results in thrombocytopenia and in some cases thrombosis (HITT). This reaction is much less with the use of LMWH compared to unfractionated [heparin](https://pubmed.ncbi.nlm.nih.gov/24319250/). |
| Methylenetetrahydrofolate reductase (MTHFR) | This enzyme plays a central role in folate metabolism and measurements of the genetic variants especially C677T have been linked to thrombotic [events](https://pubmed.ncbi.nlm.nih.gov/30466296/). Recent studies have shown an effect only when combined with another [defect](https://pubmed.ncbi.nlm.nih.gov/23900608/). A deficiency of MTHFR could result in hyperhomocyteinemia. Elevated serum homocysteine levels have not been proven to be associated with [venous thrombosis](https://pubmed.ncbi.nlm.nih.gov/31257573/). A large proportion of patients carry these genetic defects. This is a controversial area regarding the link to VTE. |
| Antiphospholipid syndrome (APS) | This syndrome is associated with both venous and arterial thrombotic events especially [obstetrical](https://pubmed.ncbi.nlm.nih.gov/30463994/) complications. The laboratory defects include Lupus anticoagulant (LA), anticardiolipin antibody (ACA), and B2 glycoprotein antibodies. Patients may remain positive long after the clinical event. |
| **Other risk factors (Not validated in the original model)** | |
| BMI >40 | Individuals who are physically fit or athletes but very large are not exempt from this risk factor. The stress on the cardiovascular system due to their size and bulk can result in cardiac hypertrophy, hypertension, valvular disease related to heart strain, sleep apnea, and diabetes requiring insulin. A linear increase in VTE events is seen with increased weight and those with a BMI >35 experience a [sixfold](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3769947/) increase in these events. The VTE risk increases further with a [BMI> 40](https://pubmed.ncbi.nlm.nih.gov/12020191/). |
| Blood transfusion | The infusion of 1-2 unit of blood >28 days old increases the DVT rate and mortality in trauma [patients](https://pubmed.ncbi.nlm.nih.gov/19772604/). The incidence of DVT is increased in [ventral hernia](https://pubmed.ncbi.nlm.nih.gov/30923979/), and [bariatric](https://pubmed.ncbi.nlm.nih.gov/29101558/) surgery patients and receiving blood transfusions and many of these events up to 50% occur following discharge. VTE rates in [cancer](https://pubmed.ncbi.nlm.nih.gov/31430787/) patients are higher when they receive RBC transfusions. |
| Smoking | Smoking is defined as the inhalation of anything that burns, including [marijuana](https://pubmed.ncbi.nlm.nih.gov/32209959/), or vaping. Smokers were more likely to develop postoperative [VTE](https://pubmed.ncbi.nlm.nih.gov/23481621/) than never smokers. |
| Diabetes mellitus requiring insulin | The overall incidence of DVT and PE was higher in the type 2 [diabetes mellitus](https://pubmed.ncbi.nlm.nih.gov/26271946/) patients than in the controls. Type 1 and 2 patients are at increased risk for recurrent [VTE](https://pubmed.ncbi.nlm.nih.gov/22560173/). |
| Human immunodeficiency virus | This disease is characterized by activation of multiple inflammatory, immunologic, and coagulation pathways and as a result these patients are at increased risk of [VTE](https://pubmed.ncbi.nlm.nih.gov/30566969/). |
| Chemotherapy | VTE incidence is increased in patients treated with [chemotherapy](https://pubmed.ncbi.nlm.nih.gov/16388837/). Incidental VTE is a relative common finding in patients with solid tumors, especially in the first months of [chemotherapy](https://pubmed.ncbi.nlm.nih.gov/20806119/). Patients with [multiple myeloma](https://pubmed.ncbi.nlm.nih.gov/21232658/) are at an increased risk of venous thromboembolism (VTE), especially when treated with thalidomide and lenalidomide, in combination with dexamethasone and/or chemotherapy. [Neoadjuvant therapy](https://pubmed.ncbi.nlm.nih.gov/29754426/) for cancer is associated with an increased risk of VTE. Current ASCO guidelines address the use of chemotherapy in a wide variety of clinical [scenarios](https://pubmed.ncbi.nlm.nih.gov/31381464/) in patients with cancer. |
| Superficial venous thrombosis (SVT) | SVT is a risk factor for VTE particularly in conjunction with other risk factors. Roach, R. et al. report that “superficial vein thrombosis combined with an acquired thrombotic risk factor increases the risk of venous thrombosis [10 to 100-fold](https://pubmed.ncbi.nlm.nih.gov/24184685/).” Frequently isolated SVT progresses to [DVT](https://pubmed.ncbi.nlm.nih.gov/29928127/) and PE. Cancer patients with SVT have a poor prognosis similar to cancer patients with DVT, and a high rate of recurrence is also [observed](https://pubmed.ncbi.nlm.nih.gov/29789147/). |

## FACTS & FIGURES

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| **Caprini Score** | **Risk category** | **Risk percent\*** | **Recommended prophylaxis\*\*** | **Duration of chemoprophylaxis** |
| 0 | Lowest | Minimal | Early frequent ambulation only, OR at discretion of surgical team:  Pneumatic compression devices OR graduated compression stockings | During hospitalization |
| 1–2 | Low | Minimal | Pneumatic compression devices ± graduated compression stockings | During hospitalization |
| 3–4 | Moderate | 0.7% | Pneumatic compression devices ± graduated compression stockings | During hospitalization |
| 5–6 | High | 1.8% | Pneumatic compression devices AND low dose heparin OR low molecular weight heparin | 7–10 days total |
| 7-8 | High | 4.0% | Pneumatic compression devices AND low dose heparin OR low molecular weight heparin | 7–10 days total |
| ≥9 | Highest | 10.7% | Pneumatic compression devices AND low dose heparin OR low molecular weight heparin | 30 days total |

\*From [Pannucci 2017](https://www.ncbi.nlm.nih.gov/pubmed/28106607).

\*\*From [Bahl 2010](https://www.ncbi.nlm.nih.gov/pubmed/19779324).

## EVIDENCE APPRAISAL

The original Caprini Score for VTE was developed in 1991 by [Joseph Caprini and colleagues](https://www.ncbi.nlm.nih.gov/pubmed/1754886), who studied 538 patients admitted for surgery including general, urologic, orthopedic, gynecologic, and head and neck procedures. Twenty weighted risk factors were obtained from a face-to-face history and a total risk score obtained, and patients were stratified into low, moderate, and high risk depending on the score.

Although no protocol for prophylaxis was studied in the original derivation, the Caprini Score has since been validated in multiple separate cohorts, including plastic and reconstructive surgery ([Pannucci 2011](https://www.ncbi.nlm.nih.gov/pubmed/21093314)), surgical critical care ([Obi 2015](https://jamanetwork.com/journals/jamasurgery/fullarticle/2426414)), thyroid and parathyroid surgery ([Macht 2017](https://www.ncbi.nlm.nih.gov/pubmed/28161482)), ear/nose/throat surgery ([Shuman 2012](https://www.ncbi.nlm.nih.gov/pubmed/22261490)), foot and ankle surgery ([Saragas 2014](https://www.ncbi.nlm.nih.gov/pubmed/24796824)), and others.

[Pannucci et al in 2017](https://www.ncbi.nlm.nih.gov/pubmed/28106607) published a meta-analysis including 14,776 patients in 11 studies and found that VTE risk varied from 0.7% to 10.7% among surgical patients who did and did not receive chemoprophylaxis, respectively. Patients with higher Caprini Scores were significantly more likely to have VTE, and those with Caprini Scores of >7 had significant reduction in VTE risk (OR 0.60, 95% CI 0.37-0.97 for Caprini Score 7 and OR 0.41, 95% CI 0.26-0.65 for Caprini Scores ≥8) after surgery with chemoprophylaxis.

The Caprini Score is the risk assessment model recommended by the [2012 Chest guidelines for VTE prevention](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278061/).