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# “ANTICOAGULAZIONE”

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BOLOGNA 25-26 GENNAIO 2018

## Il peso della storia familiare nella decisione di effettuare le indagini e nelle misure di profilassi primaria


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Genetica Medica
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## Il peso della storia familiare

- nella decisione di effettuare le indagini

- nelle misure di profilassi primaria

# Il peso della storia familiare

- nella decisione di effettuare le indagini

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# The Value of Family History as a Risk Indicator for VTE

**Table 3. Family History of Venous Thrombosis and Prevalence of Genetic Risk Factors**

| Family History[a] | Known Genetic Risk Factor[b] Yes | Known Genetic Risk Factor[b] No | Predictive Value, % (95% CI) | Sensitivity, % (95% CI) |
|---|---|---|---|---|
| **Patients With Venous Thrombosis (n=1605)** | | | | |
| Negative | 243 | 857 | 78 (75 to 80) | NA |
| Positive | | | | |
| Any relative | 150 | 355 | 30 (26 to 34) | 38 (33 to 43) |
| Relative <50 y | 80 | 160 | 33 (27 to 39) | 20 (15 to 26) |
| >1 Relative | 35 | 62 | 36 (27 to 46) | 9 (4 to 14) |
| **Control Subjects (n=2159)** | | | | |
| Negative | 190 | 1596 | 89 (88 to 91) | NA |
| Positive | | | | |
| Any relative | 53 | 320 | 14 (11 to 18) | 22 (17 to 27) |
| Relative <50 | 19 | 125 | 13 (8 to 19) | 8 (2 to 14) |
| >1 Relative | 9 | 31 | 23 (10 to 35) | 4 (–3 to 11) |

Abbreviations: CI, confidence interval; NA, not applicable.
[a] History of venous thrombosis among parents, brothers, and sisters.
[b] Low levels of antithrombin, protein C, or protein S; factor V Leiden mutation; or prothrombin 20210A mutation. Data are given as number of participants.

Bezemer et al. Arch Intern Med. 2009

# Family history as a risk factor for VTE

data on hospitalizations before 1977. If a strong association exists between genetic factors and the severity of pulmonary embolism, this selection bias would probably lead to an underestimation of the risk caused by genetic susceptibilities. Some prevalent cases of venous thromboembolism surviving the first hospital admission before the study period might also be misclassified as incident cases if admitted for a recurrent episode during the study period. Venous thromboembolism may have been mis-

ated with deficiencies in coagulation factors
respectively. Hemophilias are disorders with
tein function, whereas gain of function (hi
trations of factors VIII or IX) has been linke
bophilia.[31,32] High factor VIII levels ag
families,[33] pointing towards a genetic origin
th genetic disorder is apparently not sex
thus cannot explain the absence of detecta
effects among females in our study. It is no



**Bjerregaard Larsen, et al. Epidemiology 2003**

# Family history as a risk factor for VTE

and a central venous catheter, are necessary to provoke often a specialist. The low spouse correlation

**Table 4. Familial Standardized Incidence Ratio for Venous Thromboembolism in Siblings by Number of Affected Siblings (**

| | Males | | | Females | | | All | | |
|---|---|---|---|---|---|---|---|---|---|
| No. of Affected Siblings (Probands) | Observed No. of Cases | SIR | 95% CI | Observed No. of Cases | SIR | 95% CI | Observed No. of Cases | SIR | |
| 1 proband sibling | 1139 | 2.33* | 1.55* 3.49* | 1050 | 2.22* | 1.47* 3.33* | 2186 | 2.27* | 1.5 |
| 2 proband siblings | 99 | 63.42* | 36.45* 109.22* | 78 | 42.13* | 23.54* 74.38* | 177 | 51.87* | 31.4 |
| ≥3 proband siblings | 17 | 59.59* | 24.49* 135.21* | 13 | 47.53* | 17.82* 115.28* | 30 | 53.69* | 25.5 |
| All | 1252 | 2.52* | 1.69* 3.77* | 1141 | 2.37* | 1.58* 3.56* | 2393 | 2.45* | 1.6 |

SIR indicates stan zed incidence ratio; CI, confidence interval. The risks in males and females were calculated without taking the sex of the account.
*95% CI does not ude 1.00.



**Zoller et al. Circulation 2011**

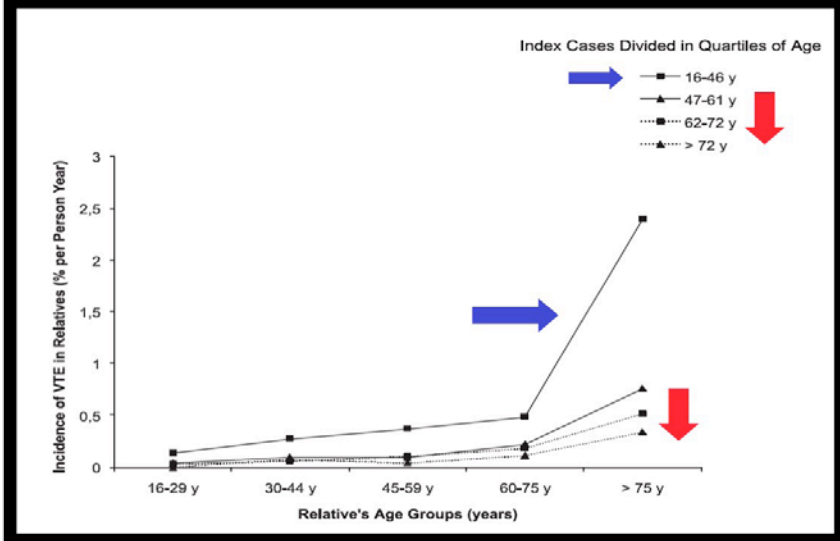
| | | | | |
|---|---|---|---|---|
| 45–49 | 68 | 32.7 | 29 360 | 2.08 (1.6 |
| ≥ 50 | 47 | 25.4 | 16 340 | 1.85 (1.3 |

cases, the SIRs were 2.97 (95% CI 2.47–3.57) for thromboembolism in a female sibling and 2.63 (95% C 3.17) for that in a male sibling ($P$ = 0.37). For ma cases, the SIRs for venous thromboembolism among and male siblings were 2.59 (95% CI 2.13–3.15) a (95% CI 3.39–4.17), respectively ($P$ = 0.001).

The SIRs decreased with the age of the index cas 11.42 (95% CI 6.76–19.28) for index cases below the 19 years to 1.85 (95% CI 1.39–2. ) for index cases ag than 50 years ($P$ for trend < 0. ). However, there

**Sorensen et al. JTH 2011**

# Family history as a risk factor for VTE




Couturaud F, et al. Blood 2014

75 years for both male and female offspring, altho
overall familial SIR was slightly higher for males t
females with one affected parent: SIR 2.08, 95% CI 2.
vs. SIR 1.91, 95% CI 1.84–1.99 (not shown in any
Although the familial SIRs decreased with age (Table

**Table 1** Age-specific number of venous thromboembolism (VT

| Age at diagnosis (years) | Males: Without parental history of VTE N | IR | 95% CI | | Males: With parental history of VT N | IR |
|---|---|---|---|---|---|---|
| < 10 | 65 | 0.6 | 0.5 | 0.7 | 2 | 1.5 |
| 10–19 | 283 | 2.6 | 2.3 | 2.9 | 21 | 10.0 |
| 20–29 | 1102 | 10.2 | 9.6 | 10.8 | 122 | 31.7 |
| 30–39 | 2065 | 19.5 | 18.7 | 20.4 | 341 | 54.4 |
| 40–49 | 4128 | 40.9 | 39.6 | 42.1 | 735 | 95.2 |
| 50–59 | 6447 | 80.9 | 78.9 | 82.9 | 820 | 145.6 |
| 60–69 | 4670 | 145.1 | 140.9 | 149.2 | 437 | 247.1 |
| 70–75 | 727 | 231.4 | 214.6 | 248.2 | 39 | 339.0 |
| All | 19 487 | 30.1 | 29.7 | 30.5 | 2517 | 87.6 |

CI, confidence interval.

Zoller et al. JTH 2011

# Family history as a risk factor for VTE

| No. of Affected Siblings (Probands) | Observed No. of Cases | SIR | 95% CI | | Observed No. of Cases | SIR | 95% CI | | Observed No. of Cases | SIR | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 proband sibling | 1136 | 2.33* | 1.55* | 3.49* | 1050 | 2.22* | 1.47* | 3.33* | 2186 | 2.27* | 1.54 |
| 2 proband siblings | 99 | 63.42* | 36.45* | 109.22* | 78 | 42.13* | 23.54* | 74.38* | 177 | 51.87* | 31.47 |
| ≥3 proband siblings | 17 | 59.59* | 24.49* | 135.21* | 13 | 47.53* | 17.82* | 115.28* | 30 | 53.69* | 25.59 |
| All | 1252 | 2.52* | 1.69* | 3.77* | 1141 | 2.37* | 1.58* | 3.56* | 2393 | 2.45* | 1.66 |

SIR indicates standardized incidence ratio; CI, confidence interval. The risks in males and females were calculated without taking the sex of the p account.

*95% CI does not include 1.00.



Zoller et al. Circulation 2011

**Table 4. Risk of VTE according to the number with thromboses in the family**

| Number with VTE in the family* | Number of families, n | Number of included FDR, n | Size of families, mean (SD) | Annual incidence of VTE in FDR, percentage 100 person-years (95% CI) | Adjusted OR, estimate (95% CI)† | P |
|---|---|---|---|---|---|---|
| 1 | 405 | 1998 | 7.8 (3.0) | 0.41 (0.37-0.45) | Reference | <.001 |
| 2 | 82 | 462 | 8.1 (3.3) | 0.79 (0.68-0.92) | 2.47 (1.98-3.09) | <.001 |
| 3 | 19 | 145 | 9.7 (3.1) | 0.88 (0.67-1.13) | 3.54 (2.49-5.04) | <.001 |
| 4 | 1 | 12 | 15 | 0.75 (0.18-1.60) | 5.17 (1.55-17.28) | <.001 |
| ≥2 | 102 | 619 | 8.5 (3.3) | 0.81 (0.70-0.91) | 2.71 (2.22-3.31) | <.001 |

Couturaud F, et al. Blood 2014

# Family history as a risk factor for VTE

**Table 2** Risk of recurrent venous thromboembolism (VTE) (hazard ratio [HR] and 95% confidence interval [CI] in VTE patients by type and family history of VTE

| | Univariate HR (95% CI) | *P*-value | Multivariate HR* (95% CI) | *P*-value‡ |
|---|---|---|---|---|
| All VTE ($n$ = 1044) | | | | |
| Family history of VTE | | | | |
| No | Reference | | Reference | |
| Yes | 1.5 (1.02–2.11) | 0.038 | 1.4 (0.99–2.1) | 0.054 |
| DVT location | | | | |
| Distal | Reference | | Reference | |
| Proximal | 1.8 (1.13–2.7) | 0.012 | 1.7 (1.05–2.6) | 0.03 |
| Subanalysis on unprovoked VTE ($n$ = 610) | | | | |
| Family history of VTE | | | | |
| No | Reference | | Reference | |
| Yes | 1.9 (1.2–3.0) | 0.005 | 1.9 (1.2–2.9)† | 0.008 |
| DVT location | | | | |
| Distal | Reference | | Reference | |
| Proximal | 1.5 (0.9–2.4) | 0.16 | 1.4 (0.80–2.4)† | 0.25 |

Sundquist K, et al. JTH 2015

# Key Points About Positive Family History

- Positive family history (1st degree relative) is a risk factor for VTE (2.5-4.2 fold increased risk)
- Risk is inversely related to age when VTE occurred
- Higher the number of relatives affected, higher the risk for VTE

# The Value of Family History as a Risk Indicator for VTE

**Table 3. Predictors of VTE in all first-degree relatives**

| Characteristic | Univariable (each variable separately) Odds ratio | P | Multivariable (only variables with P < .1 in the univariable model) Odds ratio | P |
|---|---|---|---|---|
| **Index case** | | | | |
| Unprovoked vs provoked * | 2.50 (1.54-4.00) | <.001 | 2.38 (1.43-3.85) | .001 |
| FVL and/or PGM vs neither | 1.70 (1.16-2.50) | .007 | 1.34 (0.89-2.01) | .16 |
| Age at diagnosis (per year)† | 0.98 (0.97-0.99) | <.001 | 0.97 (0.96-0.99) | <.001 |
| Female vs male | 0.96 (0.67-1.38) | .81 | | |
| Pulmonary embolism vs deep vein thrombosis | 0.91 (0.63-1.31) | .61 | | |
| **First-degree relatives** | | | | |
| Female vs male | 1.62 (1.12-2.35) | .011 | 1.37 (0.94-2.02) | .11 |
| Age (per year) | 1.04 (1.03-1.05) | <.001 | 1.06 (1.04-1.07) | <.001 |
| Relationship to index case | | <.001 | | .33 |
| Parent | 4.76 (2.58-8.76) | <.001 | 0.59 (0.18-1.90) | .37 |
| Sibling | 3.37 (1.81-6.16) | <.001 | 0.94 (0.43-2.10) | .89 |
| Child | Reference | | Reference | |
| Dead vs alive | 0.69 (0.45-1.06) | .09 | 0.44 (0.28-0.72) | .001 |

Couturaud F, et al. Blood 2014

# The Value of Family History as a Risk Indicator for VTE

| | Univariate HR (95% CI) | P-value | Multivariate HR* (95% CI) | P-value |
|---|---|---|---|---|
| No family history and no thrombophilia | Reference | | Reference | |
| Only family history | 1.7 (0.84–3.3) | 0.14 | 1.6 (0.81–3.2) | 0.173 |
| Only thrombophilia | 1.9 (1.1–3.3) | 0.03 | 1.8 (1.02–3.2) | 0.043 |
| Both family history and thrombophilia | 3.3 (1.8–5.9) | <0.0001 | 3.2 (1.8–5.9) | <0.0001 |

Sundquist K, et al. JTH 2015

**Table 4** Prothrombotic variants, family history of venous thrombosis (VT) and the risk of VT

| Factor V Leiden/ prothrombin mutation | Family history | Controls | Patients (*n* provoked/ *n* unprovoked) | OR overall* (95% CI) | OR provoked* (95% CI) | OR unprovoked* (95% CI) |
|---|---|---|---|---|---|---|
| – | – | 350 | 99/168 | 1† | 1† | 1† |
| – | + | 51 | 26/60 | 2.1 (1.4–3.1) | 1.7 (1.0–2.9) | 2.3 (1.5–3.6) |
| + | – | 23 | 10/20 | 1.7 (0.9–2.9) | 1.4 (0.7–3.2) | 1.7 (0.9–3.3) |
| + | + | 2 | 3/8 | 7.6 (1.6–35.7) | 4.1 (0.7–25.3) | 9.9 (2.0–48.9) |

Karasu A, et al. JTH 2016

**Table 1** Baseline characteristics of patients and controls

| | Controls | Patients |
|---|---|---|
| *n* | 431 | 401 |
| Men, *n* (%) | 209 (48.5) | 166 (41.4) |
| Age, mean (range) | 77.5 (70–96) | 78.7 (70–101) |

# Key Points About Positive Family History

- Positive family history (1st degree relative) is a risk factor for VTE (2.5-4.2 fold increased risk)
- Risk is inversely related to age when VTE occurred
- Higher the number of relatives affected, higher the risk for VTE
- Risk is independent of presence of known genetic thrombophilias
- Risk is due to unknown/additional thrombophilias

# Estimates of VTE from different genetic backgrounds

| Population | Incidence Risk Ratio for Idiopathic VTE | Rate of diagnosis of VTE per 100,000 per year | Adjusted standardized VTE incidence rates per 100,000 | Rate/10,000 Person-Years | Incidence rate per 100,000 people | |
|---|---|---|---|---|---|---|
| | | | | | DVT | PE |
| African American | 1.27 | 134-155 | 141 | 2.2 | | |
| Hispanic | 0.60 | | 55 | 0.9 | 11 | |
| American Indians | | 34-71 | 33.1* | | | |
| Asian or Pacific Islander | 0.26 | | 21 | 0.2 | 12.5-17.1 | 3.9-6.2 |
| Caucasian | 1.0 | 122-131 | 104 | 2.1 | 124<br>108-182† | 60 |

Margaglione and Grandone. Thromb Haemost. 2011

## Estimated prevalences of carriers of genetic abnormalities of components of the coagulation pathway

| Region | AT (%) | PC (%) | PS (%) | FV Leiden (%) | FII A20210 (%) |
|---|---|---|---|---|---|
| African | 1-6 | 4-6 | 2-3 | <0.1 | <0.1 |
| American | 0 | 5 | 2 | 0-1 | <0.1 |
| Asian | 2-5 | 8-19 | 8-30 | <0.1 | <0.1 |
| European | 1 | 3 | 1-2 | 3-7 | 2-4 |
| Oceania | --- | --- | --- | <0.1 | <0.1 |

Margaglione and Grandone. Thromb Haemost. 2011

## Key Points About Positive Family History

- Positive family history (1st degree relative) is a risk factor for VTE (2.5-4.2 fold increased risk)
- Risk is inversely related to age when VTE occurred
- Higher the number of relatives affected, higher the risk for VTE
- Risk is independent of presence of known genetic thrombophilias
- Risk is due to unknown/additional thrombophilias
- Knowledge of ancestry can be clinically important providing information on additional genetic risk factors.

American Heart Association.

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## Risk Factors for Venous Thromboembolism (VTE)

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VTE can affect men and women of all ages, races and ethnicities. People at the highest risk, like those with cancer, having surgery, or with major trauma like fractures or immobilization, should ask about getting prevention treatments. Hospitalization for any reason increases the risk, so people in the hospital should ask about prevention.

**VTE risk factors include:**

- Major general surgery
- Major orthopedic surgery
- Lower-extremity paralysis due to spinal cord injury
- Fracture of the pelvis, hip or long bones
- Multiple trauma
- Cancer — all cancers increase the risk, especially if the cancer has spread widely, and if it is cancer of the lung, brain, lymphoma, gynecologic system (like ovary or uterus), or gastrointestinal tract (like pancreas or stomach). In patients with cancer, chemotherapy and surgery for cancer further increase the risk.

**Additional factors:**
Individually, the factors below are not enough to justify preventive measures for VTE. But a combination of two or more may be cause for action – and could influence the type and duration of the prevention treatment.

- **Prior VTE** — Patients with a previous episode of VTE have a high chance of recurrence.
- **Age** — Patients older than 40 years are at higher risk, and that risk doubles with each subsequent decade.
- **Obesity** — people with obesity have 2 times the risk of VTE as people with normal weight, and the higher the weight, the higher the risk.
- **Immobility** — Prolonged immobility combined with other major risk factors increases the likelihood of VTE.
- **Oral Contraceptives or Estrogen Treatment for Menopause symptoms**
- **Family History of VTE** — especially if this is in a first-degree relative (parent, sibling, child)
- **Physical Inactivity**
- **Genetic blood conditions that affect clotting**

**VTE and Pregnancy:**
Women who are pregnant, or have just had a baby are at greater risk of developing a blood clot. The risk is greater in the presence of the following other factors:

- Previous VTE
- A genetic predisposition to VTE or a family history of VTE (especially in a first degree relative – parent, sibling)
- Obesity
- Immobilization, such as bed rest and long distance travel
- Twin gestation
- Older maternal age
- Other medical illness during pregnancy, like cancer, serious infection or toxemia/pre-eclampsia

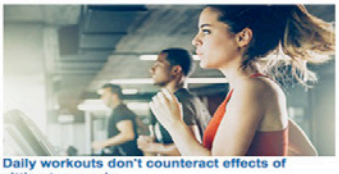
### Venous Thromboembolism (VTE)

- Home
- What is VTE?
- Symptoms and Diagnosis
- Prevention and Treatment
- Risk Factors

### Red Hot News

**Can Athletes Get Abnormal Blood Clots? Yes!**

*Mary Cushman, MD, MSc, is a hematologist at the University of Vermont Medical Center and currently serves on the national board of directors for the American Heart Association.*



**Daily workouts don't counteract effects of sitting too much**

### VTE Resources

***Heart Insight* article:**
**Risks in the Veins**
When clots form in leg veins, they can travel and cause serious problems.

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### RISK FACTORS

VTE does not discriminate. It affects people of all ages, races and ethnicities, and occurs in both men and women. Certain factors and situations can increase the risk of developing potentially deadly blood clots.

**STRONG RISK**

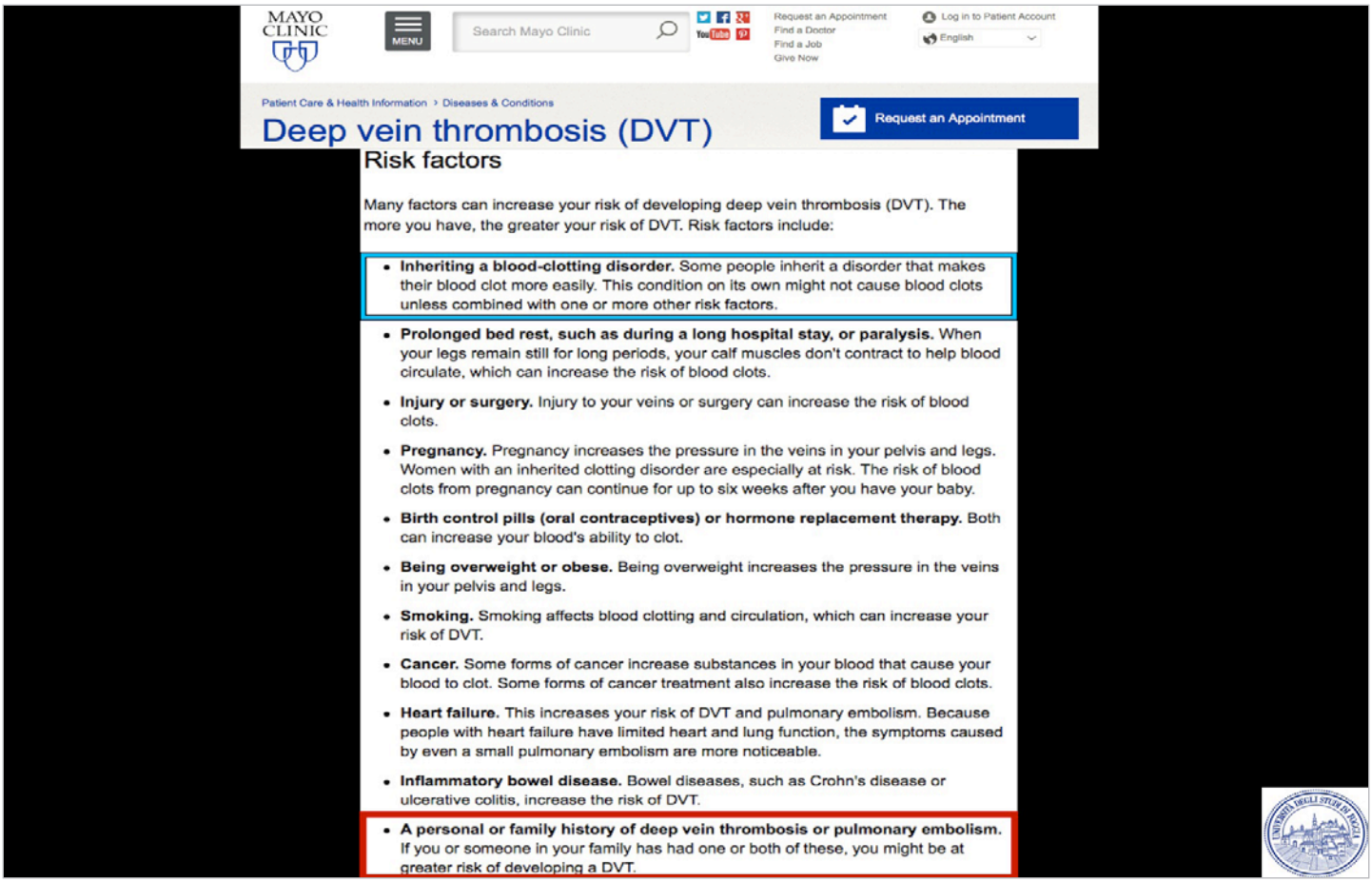
- Being in the hospital for an extended period of time
- Having surgery (*especially hip, knee and cancer-related surgery*)
- Not moving for long periods of time (*e.g., due to bedrest or long-duration travel*)

**MODERATE RISK**

- Age (60+)
- Personal or family history of blood clots
- Cancer/chemotherapy
- Using estrogen-based medication (*e.g., oral contraceptives or hormone replacement therapy*)

**OTHER FACTORS**

- Obesity
- Pregnancy or recent birth
- Smoking
- Alcohol consumption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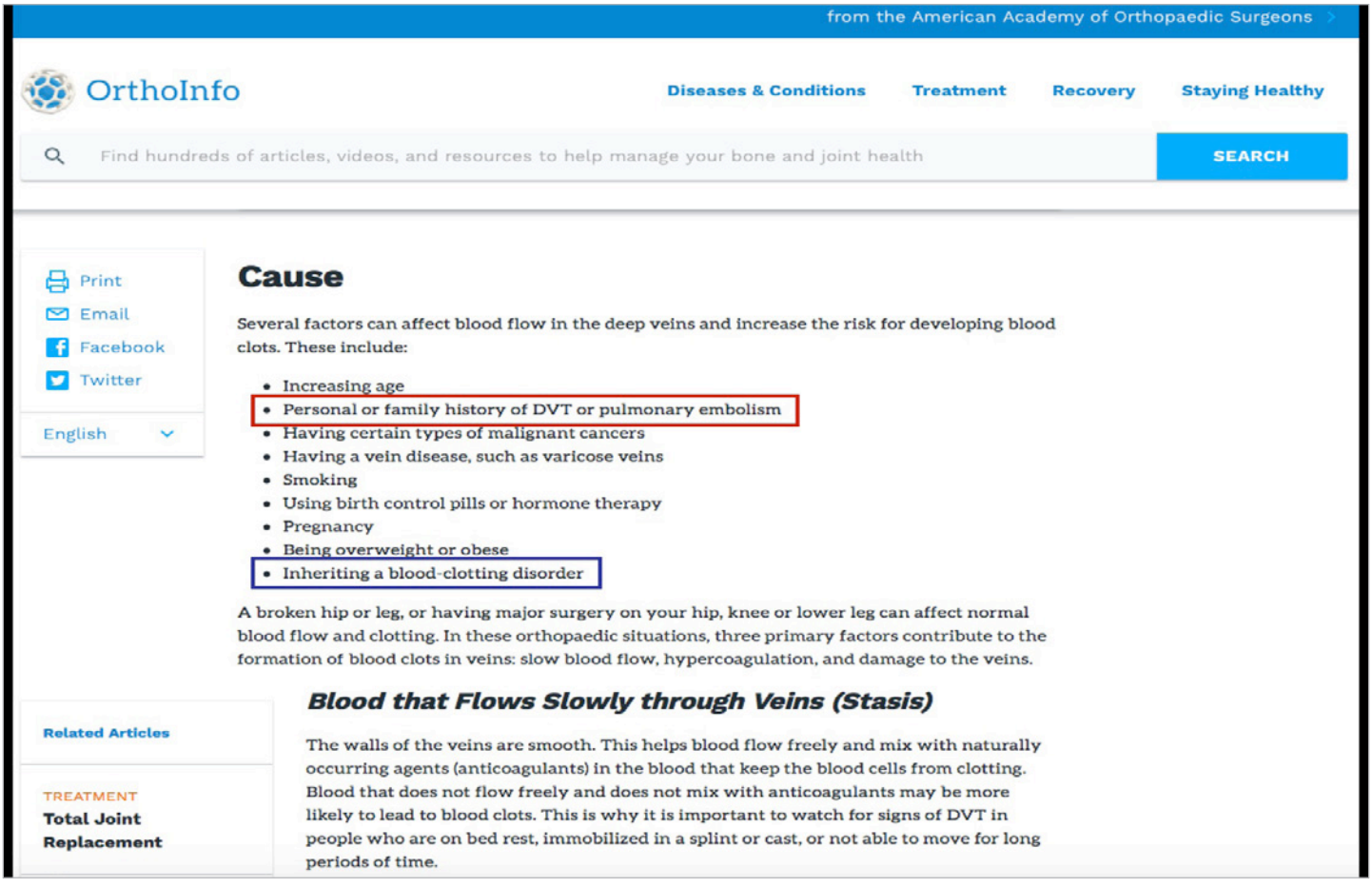
Deep vein thrombosis (DVT)
Request an Appointment
Risk factors
Many factors can increase your risk of developing deep vein thrombosis (DVT). The more you have, the greater your risk of DVT. Risk factors include:
Inheriting a blood-clotting disorder. Some people inherit a disorder that makes their blood clot more easily. This condition on its own might not cause blood clots unless combined with one or more other risk factors.
Prolonged bed rest, such as during a long hospital stay, or paralysis. When your legs remain still for long periods, your calf muscles don't contract to help blood circulate, which can increase the risk of blood clots.
Injury or surgery. Injury to your veins or surgery can increase the risk of blood clots.
Pregnancy. Pregnancy increases the pressure in the veins in your pelvis and legs. Women with an inherited clotting disorder are especially at risk. The risk of blood clots from pregnancy can continue for up to six weeks after you have your baby.
Birth control pills (oral contraceptives) or hormone replacement therapy. Both can increase your blood's ability to clot.
Being overweight or obese. Being overweight increases the pressure in the veins in your pelvis and legs.
Smoking. Smoking affects blood clotting and circulation, which can increase your risk of DVT.
Cancer. Some forms of cancer increase substances in your blood that cause your blood to clot. Some forms of cancer treatment also increase the risk of blood clots.
Heart failure. This increases your risk of DVT and pulmonary embolism. Because people with heart failure have limited heart and lung function, the symptoms caused by even a small pulmonary embolism are more noticeable.
Inflammatory bowel disease. Bowel diseases, such as Crohn's disease or ulcerative colitis, increase the risk of DVT.
A personal or family history of deep vein thrombosis or pulmonary embolism. If you or someone in your family has had one or both of these, you might be at greater risk of developing a DVT.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Diseases & Conditions
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Recovery
Staying Healthy
Find hundreds of articles, videos, and resources to help manage your bone and joint health
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Cause
Several factors can affect blood flow in the deep veins and increase the risk for developing blood clots. These include:
Increasing age
Personal or family history of DVT or pulmonary embolism
Having certain types of malignant cancers
Having a vein disease, such as varicose veins
Smoking
Using birth control pills or hormone therapy
Pregnancy
Being overweight or obese
Inheriting a blood-clotting disorder
A broken hip or leg, or having major surgery on your hip, knee or lower leg can affect normal blood flow and clotting. In these orthopaedic situations, three primary factors contribute to the formation of blood clots in veins: slow blood flow, hypercoagulation, and damage to the veins.
Blood that Flows Slowly through Veins (Stasis)
The walls of the veins are smooth. This helps blood flow freely and mix with naturally occurring agents (anticoagulants) in the blood that keep the blood cells from clotting. Blood that does not flow freely and does not mix with anticoagulants may be more likely to lead to blood clots. This is why it is important to watch for signs of DVT in people who are on bed rest, immobilized in a splint or cast, or not able to move for long periods of time.
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# Il peso della storia familiare

- nella decisione di effettuare le indagini

- nelle misure di profilassi primaria

## Prevention of VTE in Nonorthopedic Surgical Patients

**Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines**

**Table 7—*Caprini Risk Assessment Model***

| 1 Point | 2 Points | 3 Points | 5 Points |
|---|---|---|---|
| Age 41-60 y | Age 61-74 y | Age ≥ 75 y | Stroke (< 1 mo) |
| Minor surgery | Arthroscopic surgery | History of VTE | Elective arthroplasty |
| BMI > 25 kg/m² | Major open surgery (> 45 min) | Family history of VTE | Hip, pelvis, or leg fracture |
| Swollen legs | Laparoscopic surgery (> 45 min) | Factor V Leiden | Acute spinal cord injury (< 1 mo) |
| Varicose veins | Malignancy | Prothrombin 20210A | |
| Pregnancy or postpartum | Confined to bed (> 72 h) | Lupus anticoagulant | |
| History of unexplained or recurrent spontaneous abortion | Immobilizing plaster cast | Anticardiolipin antibodies | |
| Oral contraceptives or hormone replacement | Central venous access | Elevated serum homocysteine | |
| Sepsis (< 1 mo) | | Heparin-induced thrombocytopenia | |
| Serious lung disease, including pneumonia (< 1 mo) | | Other congenital or acquired thrombophilia | |
| Abnormal pulmonary function | | | |
| Acute myocardial infarction | | | |
| Congestive heart failure (< 1 mo) | | | |
| History of inflammatory bowel disease | | | |
| Medical patient at bed rest | | | |

**Chest 2012**

**3.6.1. For general and abdominal-pelvic surgery patients at very low risk for VTE (< 0.5%; Rogers score, < 7; Caprini score, 0), we recommend that no specific pharmacologic (Grade 1B) or mechanical (Grade 2C) prophylaxis be used other than early ambulation.**

**3.6.2. For general and abdominal-pelvic surgery patients at low risk for VTE (~1.5%; Rogers score, 7-10; Caprini score, 1-2), we suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C).**

**3.6.3. For general and abdominal-pelvic surgery patients at moderate risk for VTE (~3.0%; Rogers score, > 10; Caprini score, 3-4) who are not at high risk for major bleeding complications, we suggest LMWH (Grade 2B), LDUH (Grade 2B), or mechanical prophylaxis, preferably with IPC (Grade 2C), over no prophylaxis.**

Chest 2012

**VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy**

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

**9.2.1. For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and have a positive family history for VTE, we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B).**

**9.2.2. For pregnant women with all other thrombophilias and no prior VTE who have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis with prophylactic- or intermediate-dose LMWH or, in women who are not protein C or S deficient, vitamin K antagonists targeted at INR 2.0 to 3.0 rather than routine care (Grade 2C).**

**9.2.3. For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and who do not have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or vitamin K antagonists targeted at INR 2.0 to 3.0 rather than routine care**

**9.2.4. For pregnant women with all other thrombophilias and no prior VTE who do not have a positive family history for VTE, we suggest antepartum and postpartum clinical vigilance rather than pharmacologic prophylaxis (Grade 2C).**

Chest 2012

**VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy**

**Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines**

**Table 7—*[Section 9.2.1-9.2.4] Risk of Pregnancy-Related VTE in Women With Thrombophilia Stratified by Family History for VTE***

| Thrombophilic Defect, n/No. Women With Thrombophilia | Estimated Relative Risk, OR (95% CI)[a] | Observed or Estimated Absolute Risk of VTE Antepartum and Postpartum Combined, % Pregnancies (95% CI)[b,c] |
|---|---|---|
| Antithrombin/protein C/protein S deficiency combined | | |
| Family studies, 7/169[219] | … | 4.1 (1.6-8.3) |
| Antithrombin deficiency | | |
| Family studies, 1/33[219] | … | 3.0 (0.08-15.8) |
| Nonfamily studies, 8/11[151] | 4.7 (1.3-17.0) | 0.7 (0.2-2.4) |
| Protein C deficiency | | |
| Family studies, 1/60[219] | … | 1.7 (0.4-8.9) |
| Nonfamily studies, 23/32[151] | 4.8 (2.2-10.6) | 0.7 (0.3-1.5) |
| Protein S deficiency | | |
| Family studies, 5/76[219] | … | 6.6 (2.2-14.7) |
| Nonfamily studies, 16/28[151] | 3.2 (1.5-6.9) | 0.5 (0.2-1.0) |
| Factor V Leiden, heterozygous | | |
| Family studies, 26/828[220-222, 223] | … | 3.1 (2.1-4.6) |
| Nonfamily studies, 96/226[151] | 8.3 (5.4-12.7) | 1.2 (0.8-1.8) |
| Factor V Leiden, homozygous | | |
| Family studies, 8/57[224-226] | … | 14.0 (6.3-25.8) |
| Nonfamily studies, 29/91[153] | 34.4 (9.9-120.1) | 4.8 (1.4-16.8) |
| Prothrombin G20201A mutation, heterozygous | | |
| Family studies, 6/228[227,228] | … | 2.6 (0.9-5.6) |
| Nonfamily studies, 42/61[151] | 6.8 (2.5-18.8) | 1.0 (0.3-2.6) |
| Prothrombin G20201A mutation, homozygous | | |
| Family studies, n/a | … | … |
| Nonfamily studies, 2/2[151] | 26.4 (1.2-559.3) | 3.7 (0.2-78.3) |

**Chest 2012**

Recommendations

**6.2.1. For women undergoing cesarean section without additional thrombosis risk factors, we recommend against the use of thrombosis prophylaxis other than early mobilization** (Grade 1B).

**6.2.2. For women at increased risk of VTE after cesarean section because of the presence of one major or at least two minor risk factors (Table 3), we suggest pharmacologic thromboprophylaxis (prophylactic LMWH), or mechanical prophylaxis (elastic stockings or intermittent pneumatic compression) in those with contraindications to anticoagulants while in the hospital following delivery rather than no prophylaxis** (Grade 2B).

**6.2.3. For women undergoing cesarean section who are considered to be at very high risk for VTE and who have multiple additional risk factors for thromboembolism that persist in the puerperium, we suggest that prophylactic LMWH be combined with elastic stockings and/or intermittent pneumatic compression over LMWH alone** (Grade 2C).

**6.2.4. For selected high-risk patients in whom significant risk factors persist following delivery, we suggest extended prophylaxis (up to 6 weeks after delivery) following discharge from the hospital** (Grade 2C).

**Table 3—*[Section 6.2.1-6.2.4] Risk Factors for VTE Resulting in a Baseline Risk of Postpartum VTE of > 3%***

| |
|---|
| Major risk factors (OR > 6): presence of at least one risk factor suggests a risk of postpartum VTE > 3% |
| Immobility (strict bed rest for ≥ 1 week in the antepartum period) |
| Postpartum hemorrhage ≥ 1,000 ml with surgery |
| Previous VTE |
| Preeclampsia with fetal growth restriction |
| Thrombophilia |
| Antithrombin deficiency[a] |
| Factor V Leiden (homozygous or heterozygous) |
| Prothrombin G20210A (homozygous or heterozygous) |
| Medical conditions |
| Systemic lupus erythematosus |
| Heart disease |
| Sickle cell disease |
| Blood transfusion |
| Postpartum infection |
| Minor risk factors (OR > 6 when combined): presence of at least two risk factors or one risk factor in the setting of emergency cesarean section suggests a risk of postpartum VTE of > 3% |
| BMI > 30 kg/m² |
| Multiple pregnancy |
| Postpartum hemorrhage > 1 L |
| Smoking > 10 cigarettes/d |
| Fetal growth restriction (gestational age + sex-adjusted birth weight < 25th percentile) |
| Thrombophilia |
| Protein C deficiency |
| Protein S deficiency |
| Preeclampsia |

**Risk factors for VTE**

| Pre-existing risk factors | Tick | Score |
|---|---|---|
| Previous VTE (except a single event related to major surgery) | | 4 |
| Previous VTE provoked by major surgery | | 3 |
| Known high-risk thrombophilia | | 3 |
| Medical comorbidities e.g. cancer, heart failure; active systemic lupus erythematosus, inflammatory polyarthropathy or inflammatory bowel disease; nephrotic syndrome; type I diabetes mellitus with nephropathy; sickle cell disease; current intravenous drug user | | 3 |
| Family history of unprovoked or estrogen-related VTE in first-degree relative | | 1 |
| Known low-risk thrombophilia (no VTE) | | 1[a] |
| Parity ≥ 3 | | 1 |
| Mid-cavity or rotational operative delivery | | 1 |
| Immobility, dehydration | | 1 |
| TOTAL | | |

[a] If the known low-risk thrombophilia is in a woman with a family history of VTE in a first-degree relative postpartum thromboprophylaxis should be continued for 6 weeks.

Royal College of Obstetricians & Gynaecologists

Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium

Green-top Guideline No. 37a
April 2015

- If total score ≥ 4 antenatally, consider thromboprophylaxis from the first trimester.
- If total score 3 antenatally, consider thromboprophylaxis from 28 weeks.
- If total score ≥ 2 postnatally, consider thromboprophylaxis for at least 10 days.
- If admitted to hospital antenatally consider thromboprophylaxis.
- If prolonged admission (≥ 3 days) or readmission to hospital within the puerperium consider thromboprophylaxis.

**All women should undergo a documented assessment of risk factors for VTE in early pregnancy or prepregnancy.** C

**Risk assessment should be repeated if the woman is admitted to hospital for any reason or develops other intercurrent problems.** C

**Risk assessment should be repeated again intrapartum or immediately postpartum.** C

**Table 3.** Other international guidelines for post-caesarean pharmacologic prophylaxis

| Queensland, Australia | Swedish guidelines |
|---|---|
| Heparin administered for ≥1 major or ≥2 minor risk factors | Heparin administered if risk score is 2 points or higher |
| **Major risk factors (≥1)** | **≥2 points** |
| Previous VTE | Prior VTE |
| Antenatal anticoagulation | Antenatal anticoagulation |
| Caesarean in labour | High risk thrombophilia |
| Asymptomatic thrombophilia | Immobilization |
| Family history of VTE | Mechanical heart prosthesis |
| BMI >30 kg/m$^2$ BMI | **1 point** |
| Immobilisation | Low risk thrombophilia |
| Pre-eclampsia | BMI >28 kg/m$^2$ |
| Medical co-morbidity | Family history of VTE |
| Systemic infection | Age >40 |
| **Minor risk factors (≥2)** | Pre-eclampsia |
| Age >35 | Hyperhomocysteinaemia |
| Gross varicose veins | Placental abruption |
| Labour >24 hours | Inflammatory bowel disease |
| PPH >1 litre | Other major risk factors |
| Smoker | |
| Extensive perineal trauma and prolonged repair | |

Under RCOG guidelines, 85.0% of patients would receive post-caesarean pharmacologic prophylaxis (95% CI 80.5–88.6%). In comparison, 1.0% of patients would receive pharmacologic prophylaxis under ACOG guidelines (95% CI 0.3–3.0%) and 34.8% of patients would receive prophylaxis under Chest guidelines (95% CI 29.6–40.4%).

**Risk factors according to different GLs** **Heparin use according to different GLs**

## Conclusion

Our findings highlight a major concern regarding strategies to reduce obstetric thromboembolism: what is the optimal management for postpartum patients at increased risk for an event? Current recommendations diverge significantly, with the ACOG recommending pharmacologic prophylaxis for a small minority of patients, and the RCOG recommending treatment for a large majority of patients. Research on obstetric VTE is challenging because of relatively low incidence, but VTE is one of the leading causes of maternal morbidity and severe morbidity, and there is an urgent clinical need to clarify optimal prophylaxis regimens.

**Palmerola KL et al, BJOG 2015**