

## 9. Risk of recurrence of DVT/PE; Length of Coumadin®

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**Q1: "After I had my daughter 2 years ago I had a pulmonary embolism. Since then I have been on coumadin (= warfarin). I only had one pulmonary embolism and am only factor V Leiden heterozygous. What are my risks for another clot if I go off coumadin (= warfarin)?"**

A1: There is an approximately 22 % chance of another clot over the next 5 years after stopping coumadin (= warfarin) in patients who had a first spontaneous DVT or PE (ref 1,2). The risk is likely less, if the clot happened within 3 months of delivery or if the patient has made lifestyle changes (normalized weight, stopped smoking, stopped contraceptives or hormone replacement therapy). A recent study showed that women whose first DVT was triggered by hormones (contraceptive pill, pregnancy, or hormone replacement therapy) and who stopped coumadin after 6 months of therapy, had a lower risk of recurrent clot (8 % over 4 years) than women whose first clot was spontaneous and not associated with hormones (15 % over 4 years); however, this difference was statistically not different.

**Q2: "I am hetero FVLeiden (female, 50 years old) and had a PE one year ago. I have not been tested for any other clotting problems other than homocysteine (which was normal), and positive for IgM. Should there be any other tests? Can I go off warfarin or should I continue it?"**

A2: If this patient had a PE triggered by major surgery, trauma, or immobilization, i.e. a transient risk factor, one could discuss stopping warfarin. If she had a spontaneous PE without transient risk factors (surgery, trauma, or immobilization) long-term warfarin is probably the right thing, based on the PREVENT and ELATE trials. The fact that she had a PE (and not a DVT) as the thrombotic event would probably make me recommend a target IRN of 2.0-3.0 long-term. It is not clear what the above patient means when she says she is "positive for IgM". IgM (= immunoglobulin M) is a term referring to a huge group of antibodies, healthy ones that help us fight infections and unhealthy ones, such as IgM anticardiolipin antibodies, that can be associated with the "antiphospholipid antibody syndrome (= APLA syndrome; see "APLA", [Q/A 21](#)). If the patient clearly has the APLA-syndrome, then indefinite coumadin therapy should be considered. If she had a spontaneous clot I would do additional thrombophilia work-up (see "Thrombophilia laboratory work-up", [Q/A 49](#)) to learn why she had clotted; however, the extent of thrombophilia work-up is controversial.

**Q3: "I had a DVT two years ago and am positive factor V Leiden (hetero). The concern now is whether to come off the coumadin (=warfarin) prescription that I have been on since the episode."**

A3: For a better assessment one would also want to know whether the DVT was associated with trauma, surgery, immobility, or the intake of birth control pill, hormone replacement therapy, or with pregnancy. If the patient had a spontaneous DVT without a triggering risk factor and other thrombophilia work-up has been negative (i.e. patient does not also have antiphospholipid antibodies or the II20210 mutation) one can argue for long-term warfarin, either target INR 1.5-2.0 or 2.0-3.0.

**Q4: "My doctor wants me off of coumadin (I am 25, had a DVT while on the pill, am heterozygous for factor V Leiden, with no other disorders). He thinks the risk of bleeding is greater than that of me clotting again, if hormones are removed from my life."**

A4: If the patient has a negative D-dimer and follow-up Doppler ultrasound shows no significant residual clot, then it may be reasonable to stop warfarin. If D-dimer is positive or follow-up Doppler ultrasound shows significant residual clot, continuation of warfarin at low-dose, INR 1.5-2.0, may be the right thing to do.

### **Risk of clot recurrence and of coumadin-associated bleeding**

Several studies have been done assessing the risk of a second clot in patients who have had one episode of spontaneous deep vein thrombosis (= DVT) or pulmonary embolism (= PE), that was not triggered by surgery, trauma, or immobilization, and was not associated with cancer.

- Most recurrent clots happen in the 2 years following discontinuation of coumadin thereafter the risk decreases: approximately 15 % of patients have a recurrence in the first 2 years;
- In the 5 years after discontinuation of coumadin approximately 22 % of patients have a recurrent DVT or PE. In other words, there is a 78 % chance of not developing another clot (ref).
- Fatal blood clots in the patient who has come off coumadin are uncommon: it can be calculated that approximately 0.3 % of patients who came off coumadin after a first DVT or PE, die per year from a recurrent blood clot. Most of the recurrent clots are, thus, not life-threatening.

Coumadin is not a safe drug, since it can cause bleeding:

- 0.5 % of patients on coumadin die every year due to bleeding;
- 1 % of patients will have a life-threatening or fatal bleed per year;
- 4-5 % of patients on coumadin will have a serious bleed per year (leading to hospital admission or transfusion);
- younger patients probably have a lower bleeding risk, and if a patient has not bled during the first year of coumadin treatment, the risk is also lower;
- poorly controlled INRs lead to a higher risk of bleeding.

### 2001 Recommendations for length of coumadin therapy

Recommendations for the length of coumadin therapy that were widely accepted until the PREVENT and ELATE trials were published in 2003, have been given by the "American College of Chest Physicians" (published in Chest 2001;119:176S-193S).

- 3-6 months: 1st event with reversible or time-limited risk factor, such as surgery, trauma, immobilization, estrogen use), independent of whether the patient has factor V Leiden or the prothrombin 20210 mutation.
- >6 months: 1st event of spontaneous DVT or PE
- 12 months to lifetime:
  - 1st event with
    - a. cancer, until resolved
    - b. antiphospholipid antibodies
    - c. antithrombin deficiency
  - recurrent event

Until 2003 many thrombosis specialists considered 6 months of full-dose coumadin (target INR 2.0-3.0) to be standard therapy for patients with one episode of spontaneous DVT or PE. In those patients who would develop a 2nd DVT or PE after having stopped coumadin, indefinite coumadin treatment was often recommended. The treatment approach has changed, however, since 2003, after the low-dose warfarin (INR 1.5-2.0) trials PREVENT and ELATE were published and showed that low-dose warfarin is, to some degree, effective in preventing recurrent DVT and PE (see further discussion below). It would be nice to know, which patients will develop another clot (a recurrence) and which patients will not. One could then treat the ones in whom another clot is expected with long-term coumadin, and the others not. Unfortunately, this is only partially known.

- a. High risk of recurrence: We know that 5 groups of patients have a particularly high risk of recurrence. These are patients with
  1. antiphospholipid antibody syndrome (= repeatedly clearly positive anticardiolipin antibodies or lupus anticoagulant),
  2. antithrombin III deficiency,
  3. combination of heterozygous factor V Leiden plus heterozygous prothrombin 20210 mutation,
  4. homozygous factor V Leiden,
  5. cancer.

One can make a good argument for keeping these patients on long-term full-dose coumadin after their first clot.
- b. Average risk of recurrence: Patients who are heterozygous for factor V Leiden or heterozygous for the prothrombin 20210 mutation have a similar risk of recurrence after discontinuation of coumadin as patients who do not have these mutations, i.e. approximately 22 % over 5 years. The risk of recurrence in patients with protein C or protein S deficiency varies from family to family - some family have a high risk of thrombosis, others an average risk. The risk of recurrence in patients who are homozygous for the prothrombin 20210 mutation has not been studied, but may not be much higher than the 22 % over 5 years.

### Thrombosis risk factors

Any treatment decision and recommendation always needs to be individualized, depending on the patient's thrombosis risk factors. Issues that factor into the decision on the best treatment are:

- Did your deep vein thrombosis (= DVT) or pulmonary embolism (= PE) develop spontaneously, or was it triggered by surgery, trauma, or immobilization?
- Did it start as a superficial clot and extend into the deep vein system?
- Was it a DVT below the knee, or one that involved the vein behind the knee or veins above the knee?
- Were you taking contraceptives or hormone replacement at the time of DVT? Did you have the clot while you

were pregnant or in the 6 weeks after delivery?

- Were you overweight when you had the clot and have you lost weight?
- How sedentary is your job and lifestyle?
- Do you have a strong family history of DVT or PE?
- What lab tests for a clotting disorder were done and were any of them abnormal in you?
- Do you still have a lot of leg symptoms, such as swelling?
- Did you smoke at the time of DVT? Have you stopped?

### **PREVENT study**

In this study patients with a deep vein thrombosis who had been treated for at least 3 months with full-dose warfarin (INR 2.0-3.0), received either low-dose warfarin (INR 1.5-2.0) or nothing over the subsequent several years. The study showed that low-dose warfarin prevented recurrent clots without causing a significant increase in risk of major bleeding, i.e. it was effective and safe. While 22 % of patients had a recurrent clot over 4 years if they did not receive any further warfarin, only 8 % of patients in the low-dose warfarin group had recurrent clot.

### **ELATE study**

In this study patients with a deep vein thrombosis who had been treated for at least 3 months with full-dose warfarin (INR 2.0-3.0), received either low-dose warfarin (INR 1.5-2.0) or full-dose warfarin (INR 2.0-3.0) over the subsequent several years. The study showed that full-dose warfarin was more effective in preventing recurrent clots without causing more major bleeding, i.e. it was more effective than low-dose warfarin, but equally safe. While 6 % of patients had a recurrent clot over 4 years if they received low-dose warfarin, only 2 % of patients in the full-dose warfarin group had recurrent clot.

### **D-dimer studies**

A few studies have shown that an elevated D-dimer, which can be detected with a simple blood test (see [Q/A 19](#)), predisposes to recurrent clot (ref 5,6)

### **Residual DVT on Doppler ultrasound**

A few studies have shown that residual DVT as determined by Doppler ultrasound predisposes to recurrent clot (ref 7,8).

**Personal comment:** What I often discuss with the patient who has had a spontaneous deep vein thrombosis or pulmonary embolism (who, on thrombophilia testing, does not have APLA, ATIII deficiency, homozygous factor V Leiden, or double heterozygous FVLeiden plus II20210 mutation):

- a. If the DVT or PE was associated with birth control pill, or hormone replacement therapy:
  - if D-dimer is negative and the follow-up Doppler ultrasound shows no residual clot, stop warfarin
  - if D-dimer is positive or follow-up Doppler ultrasound shows significant residual clot, consider continuation of warfarin at low-dose, INR 1.5-2.0
- b. If DVT was spontaneous and not associated with hormonal therapy
  - if D-dimer is negative and the follow-up Doppler ultrasound shows no residual clot, take low-dose warfarin, INR 1.5-2.0, indefinitely
  - if D-dimer is positive or follow-up Doppler ultrasound shows significant residual clot, continue warfarin. Consider low-dose warfarin, INR 2.0-3.0
- c. If patient had a spontaneous PE not associated with hormonal therapy: long-term full-dose warfarin, INR 2.0-3.0.

However: individual decisions are always necessary.

### **References:**

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  8. Siragusa S et al.: "Residual vein thrombosis assessment establishes the optimal duration of oral anticoagulants in patients with idiopathic or provoked deep vein thrombosis". *Blood* 2003; Dec supplement; volume 102:abstract 183.