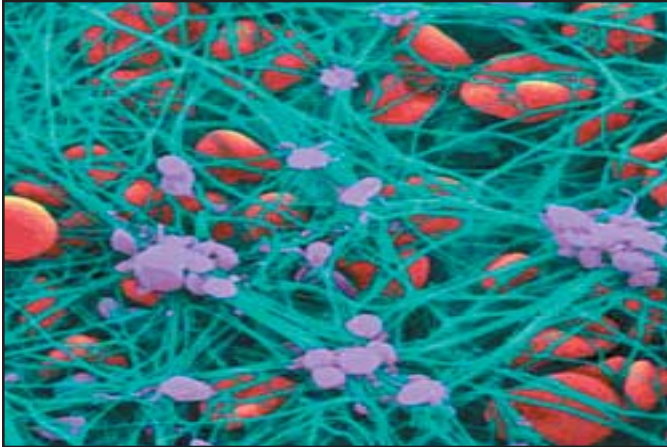


# Sometimes Less is Better: The Treatment of Venous Thromboembolism



by

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## Characters

**ED CRAMER**—*a 47-year-old mechanical engineer, married with a son and a daughter (both in high school); he enjoys fishing and working in his woodshop at home.*

**SAMANTHA SPRINGER, M.D.**—*a senior resident physician, only a few months from completing her postgraduate medical training and becoming qualified to go out into the world of medical practice. She has been Ed's doctor for the last two and a half years.*

**KATHY JOHNSON, PHARM.D.**—*a clinical pharmacist who manages the Anticoagulation Clinic under a collaborative practice agreement in the medical practice where Dr. Springer is doing her residency. She has been working with Dr. Springer and Mr. Cramer to manage his warfarin therapy.*

NARRATOR

## Dialogue

**MR. CRAMER:** “You want me to take this stuff for the rest of my life? Don't get me wrong, I'm not trying to give you a hard time, but I don't like to take medicine every day, and getting my blood drawn for tests every week hasn't exactly been my favorite thing in the whole world!”

**NARRATOR:** When he was 45 years old, Ed Cramer developed a blood clot in the lower part of his left leg, causing his leg to become red, swollen, and to hurt so badly that he could not even walk because of the pain. He spent five days in the hospital, during which time he received treatment with an intravenous medication, heparin, to help control the blood clot. After Mr. Cramer went home, he had to take an oral medication, warfarin, for the next six months to be certain that the blood clot wouldn't harm him,

During his treatment with warfarin, Ed had to get his blood tested every week or two so that Dr. Springer and Dr. Johnson could monitor the effect of the medication. Sometimes, Dr. Johnson called him after a blood test and instructed him to raise or lower his daily dose of warfarin. These changes sometimes seemed unpredictable. Dr. Johnson explained

that many medications and even some foods could change the effect of the body's processing of warfarin, resulting in a change in its effect. If the dose was too low, his blood might be more likely to clot; if the dose was too high, he might experience abnormal bleeding. There didn't seem to be a very wide margin for error.

DR. SPRINGER: "Mr. Cramer, I can appreciate the discomfort and inconvenience of sticking with this treatment, but without it you are at risk for getting another blood clot. I know that you are all too familiar with that and the possible complications."

MR. CRAMER: "You don't have to remind me."

NARRATOR: Just one year after finishing treatment for his first blood clot, Mr. Cramer had developed another—this time it nearly killed him. He was at home watching TV when suddenly he had a feeling of pressure in his chest and trouble catching his breath. A large clot had traveled through his bloodstream from a vein in his left leg, where it had formed, to a large blood vessel in his lung. The clot blocked the flow of blood through part of his lung, interfered with oxygenation of the blood, and caused the death of some of his lung tissue. Seeing him immobilized on the couch, his wife Nancy called the paramedics. He was in intensive care for more than a week. It was the most frightening experience of his life. After he was discharged from the hospital, Mr. Cramer had to take warfarin for another six months.

MR. CRAMER: "This medication is nothing to fool around with either. Do you remember when this medication put me back in the hospital?"

NARRATOR: Once while on warfarin therapy, Mr. Cramer's back went out and he began to take ibuprofen regularly for relief of back pain. He did not let Dr. Springer or Dr. Johnson know he was taking the ibuprofen. After approximately two weeks of taking the maximum dose of ibuprofen recommended on the package (six 200mg tablets per day), he noticed that he was regularly passing black, tarry looking stool. He had to go back to the hospital and get a transfusion of two pints of blood to replace the blood that he had lost. He had developed gastritis from taking too much ibuprofen. With his body's blood clotting system partially disabled by warfarin, this was enough to cause a significant bleed.

Ed felt that smoking had caused his clotting problem. After trying three times, he finally succeeded in kicking the habit. Nearing the end of his second six-month course of treatment with warfarin, he looked forward to getting it over with.

DR. JOHNSON: "Mr. Cramer, I think that your treatment could be a lot easier than what you've been through so far while taking warfarin. A new study has come out showing that treatment with warfarin at a low dose could reduce your risk of having another serious blood clot, with a low risk of causing severe bleeding. So, low dose warfarin treatment would probably be safer than your current treatment. For this reason, you would not need to get your blood tested as often—possibly as infrequently as every two months."

MR. CRAMER: "That doesn't sound too bad, but does it work? I mean, for the last six months I've had to get my blood drawn almost once a week and the warfarin is adjusted up and down to get it just right. I've had serious blood clots twice. Can this low dose treatment really protect me from getting another one? And what exactly is a 'low risk' of severe bleeding? Is this treatment really worth it?"

NARRATOR: These were good questions and Dr. Springer did not have the answers off the top of her head.

DR. SPRINGER: “As I said, this study has just recently come out and I haven’t had a chance to go over it in detail. Low dose warfarin may be a good option for you. How about if I get some additional information on the benefits and risks of this treatment and we can go over it at a follow-up visit in one month?”

MR. CRAMER: “That sounds fine. I’ll be due to come in for a physical, anyway. See you then.”

## Background Information

Approximately 2 million people annually develop venous thromboembolism (VTE) in the United States; of those, 600,000 are hospitalized and 60,000 die. Many more are “clinically silent.”

Venous thromboembolism (VTE) is a potentially life-threatening medical condition that has a propensity for recurrence after an initial diagnosis of either deep vein thrombosis (DVT) or pulmonary embolism (PE).

Pharmacotherapeutic management often consists of a brief period (approximately one week) of intravenous heparin or subcutaneous low molecular weight heparin (LMWH) anticoagulant in conjunction with the initiation of oral warfarin therapy. While warfarin therapy, if maintained within a narrow therapeutic range, is successful in preventing the recurrence of DVT and PE, it has many associated problems, including frequent monitoring, many drug interactions, and potentially significant adverse effects, particularly when nearing the upper limit of the therapeutic range. There is, therefore, a desire within the medical community to find options that improve the margin of safety (lower therapeutic ranges), improve patient convenience and adherence (less frequent monitoring), and help to clarify the question of how long a patient should be maintained on warfarin therapy and at what intensity of anticoagulation.

The three primary risk factors for development of venous thrombosis (also known as Virchow’s triad) include: (1) stasis, (2) vascular damage, and (3) hypercoaguability. Predisposing factors for each are outlined below:

Chart 1. Virchow’s triad.		
Stasis	Vascular Damage	Hypercoaguability
<i>Immobilization</i> Acute myocardial infarction Congestive heart failure Stroke Post-operative recovery	<i>Surgery</i> Orthopedic Thoracic Abdominal Genitourinary  <i>Trauma</i> Fractures of spine Fractures of pelvis Fractures of femur or tibia Spinal cord injuries  <i>Venulitis</i> Thromboangiitis obliterans Behcet’s disease Homocysteinuria	<i>Hypercoaguable States</i> Factor V Leiden Antithrombin III deficiency Protein C deficiency Protein S deficiency Antiphospholipid antibodies Systemic lupus erythematosus Myeloproliferative diseases Dysfibrinogenemia Disseminated intravascular coagulation  <i>Other</i> Pregnancy Estrogen use Neoplasms (lung, ovary, testes, breast, pancreas, stomach, urinary tract)

The majority of thrombus forms in the lower extremities, although they can form anywhere. Once a thrombus is formed, the following may result:

- Asymptomatic (“clinically silent”)
- Lysis
- Obstruction in venous circulation
- Growth into more proximal veins
- Embolus

Chart 2. Symptoms.	
<b>Symptoms of Deep Vein Thrombosis (DVT)</b>	<b>Symptoms of Pulmonary Embolism (PE)</b>
<ul style="list-style-type: none"> <li>unilateral leg swelling</li> <li>local leg pain</li> <li>local leg tenderness</li> <li>local leg redness</li> <li>local leg warmth</li> </ul>	<ul style="list-style-type: none"> <li>difficulty breathing</li> <li>increased respiratory rate</li> <li>increased heart rate</li> <li>chest pain</li> <li>coughing up blood</li> </ul>

## Oral Anticoagulation Therapy: Warfarin (Coumadin®)

### I. Pharmacology

#### A. Mechanism of Action

Warfarin inhibits the reductase enzymes responsible for vitamin K recycling, thereby resulting in a slowing of the rate of synthesis of vitamin K-dependent coagulation factors (II, VII, IX, X) and anticoagulant proteins C and S. There is a dose-dependent effect of warfarin on the vitamin K-dependent coagulation factors—the higher the dose, the greater the effect.

During initiation of therapy with warfarin, the anticoagulant effects achieved are dependent on the half-lives of the coagulation factors (VII—4 to 6 hrs, IX—24 hrs, X—48 to 72 hrs, and II—60 hrs), anticoagulant proteins (C—8 hrs and S—30 hrs), and the dose.

Warfarin therapy only prevents: thrombus formation, extension of a previously formed thrombus, and secondary thromboembolic complications. It does not result in thrombolysis of a formed clot nor does it reverse ischemic damage that has already occurred.

#### B. Monitoring

The anticoagulant effect of warfarin is assessed utilizing the International Normalized Ratio (INR), a standardized method for monitoring warfarin therapy. The formula for calculating the INR is as follows:

$$\text{INR} = \left( \frac{\text{Patient PT}}{\text{Control PT}} \right)^C$$

PT refers to the prothrombin time, a measure that reflects the effects of warfarin on three of the four vitamin K-dependent coagulation factors (II, VII, and X) as a function of the half-lives of these factors. C is a power value representing the International Sensitivity Index (ISI). This is a measure of the responsiveness of a reagent (thromboplastin), utilized in the determination of the PT, to reduction of the vitamin K-dependent coagulation factors as compared to an international reference.

Depending on the patient specific indication for warfarin, the target INR range will either be 2.0 to 3.0 or 2.5 to 3.5.

## II. Pharmacokinetics

When administered orally, bioavailability is >90%. Warfarin undergoes stereoselective hepatic metabolism in the CYP450 isoenzyme system (primary) and by reductases (secondary). The S isomer, which is 3–5 times more potent than the R isomer, is principally metabolized by CYP450 2C9. R-warfarin is metabolized by CYP450 1A2 and 3A4. The half-life of S-warfarin is approximately 20 to 45 hours while that of R-warfarin is approximately 35 to 90 hours. Inactive warfarin metabolites are excreted in urine (major) and bile (minor).

## III. Adverse Effects

The predominant adverse effect of warfarin is bleeding ranging from mild (ecchymosis, epistaxis, petechiae) to major or life-threatening (intracranial, retroperitoneal, ocular, gastrointestinal). The incidence of minor bleeding may likely be >15% annually while that of major bleeding is likely 5–9% annually, with a 2X higher incidence when the INR is >3.

## IV. Interactions

Warfarin has numerous drug-drug, drug-herbal product, and drug-food/nutrient interactions. Interactions may occur as a result of the following:

- Displacement from plasma protein (primarily albumin) binding sites
- Hepatic dysfunction
- Concurrent use of CYP450 enzyme inhibitors or inducers
  - CYP450 2C9 is primarily responsible for metabolizing S-warfarin
  - CYP450 1A2 and 3A4 are primarily responsible for metabolizing R-warfarin
- Genetic polymorphisms
- Up to 25% of Caucasians may have CYP450 2C9 mutations that decrease the clearance of S-warfarin

There are many common agents and medications that have been proven or are implicated in interactions with warfarin. As many patients who are receiving warfarin therapy are also on concomitant therapies, these interactions make managing warfarin challenging (the list below is not intended to be all-inclusive):

Chart 3. Warfarin Interactions.		
Drug – Drug	Drug – Herbal	Product Drug – Food/Nutrient
Acetaminophen	Co-enzyme Q10	Cranberry
Anticonvulsants	Danshen	Enteral feedings
Anti-retroviral protease inhibitors	Dong quai	Ethanol
Antineoplastic agents	Feverfew	Garlic
Azole antifungals	Ginko biloba	Ginger
Barbiturates	Ginseng	Vitamin K
Cephalosporins	Horse chestnut	Tobacco
Estrogens/oral contraceptives	Kava kava	Vitamin A
HMG Co-A reductase inhibitors	St. John's Wort	Vitamin C
Macrolides	Went Yeast	Vitamin E
NSAIDs		
Quinolones		
Salicylates		
SSRIs		
Sulfonamides		
Sulfonylureas		
Tetracyclines		
Thrombolytic agents		

## Questions

Please answer the questions below after reading the article “Long-Term, Low-Intensity Warfarin Therapy for the Prevention of Recurrent Venous Thromboembolism” by P. M Ridker et al. in *The New England Journal of Medicine*, 348(15): 1425–1434. The tables and figures that appear below are used with permission, copyright © 2003 Massachusetts Medical Society, all rights reserved.

1. What is the most likely design for a study to evaluate the efficacy of this new treatment approach?
2. What information does Table 1 below represent in relation to the similarities and/or differences of the Placebo and Warfarin treatment groups?

**Table 1. Base-Line Characteristics of the Study Participants.**

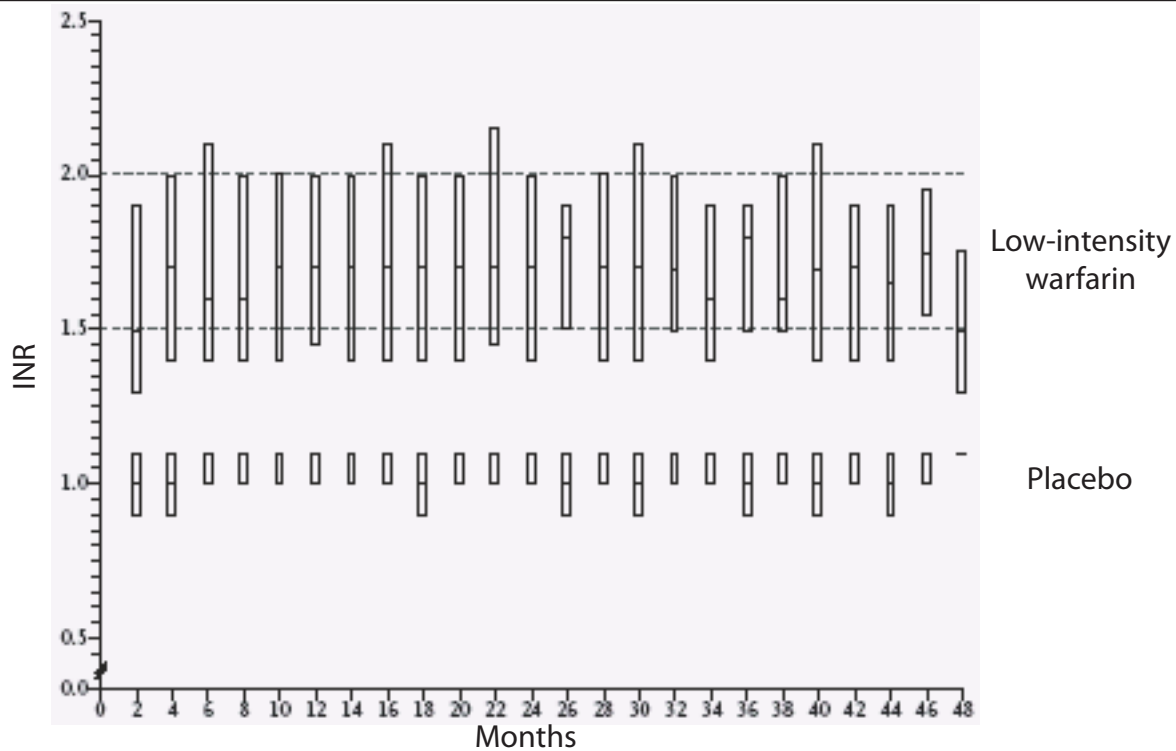
Characteristic	Placebo Group (N=253)	Warfarin Group (N=255)	P Value
Age (yr)			0.82
Median	53	53	
Interquartile range	47–64	46–65	
Female sex (%)	47.4	47.1	0.93
Race or ethnic group (%)			0.32
Non-Hispanic white	86.6	88.2	
Non-Hispanic black	10.3	9.0	
Hispanic	0.8	2.0	
Other	2.4	0.8	
Body-mass index*			0.89
Median	29.9	29.9	
Interquartile range	26.6–34.3	26.6–34.2	
History of Diabetes (%)	8.7	6.7	0.39
≥2 Previous venous thromboembolisms (%)	36.8	40.0	0.45
Family history of venous thromboembolism (%)	31.6	26.3	0.18
Factor V Leiden (%)	26.6	22.0	0.23
Prothrombin mutation (%)	4.8	4.7	0.98
Duration of full-dose warfarin therapy before enrollment (mo)			0.15
Median	6.4	6.7	
Interquartile range	5.7–9.0	5.9–10.8	
Time between cessation of full-dose warfarin therapy and enrollment (mo)			0.57
Median	1.4	2.0	
Interquartile range	0.9–5.1	0.9–4.3	

\*The body-mass index is the weight in kilograms divided by the square of the height in meters.

3. Why is the information in Table 1 important in assessing the results of the study?

4. Based on the information in Figure 1 below, were the investigators successful in demonstrating a statistically significant difference between the Placebo and Warfarin Groups in relation to the anticoagulant effect as measured by the INR?

**Figure 1.** Distribution of International Normalized Ratio (INR) Levels at the Bimonthly Follow-up Visits, According to Randomized Treatment Assignment.



Each bar represents the interquartile range, and the horizontal line within the bar represents the median.

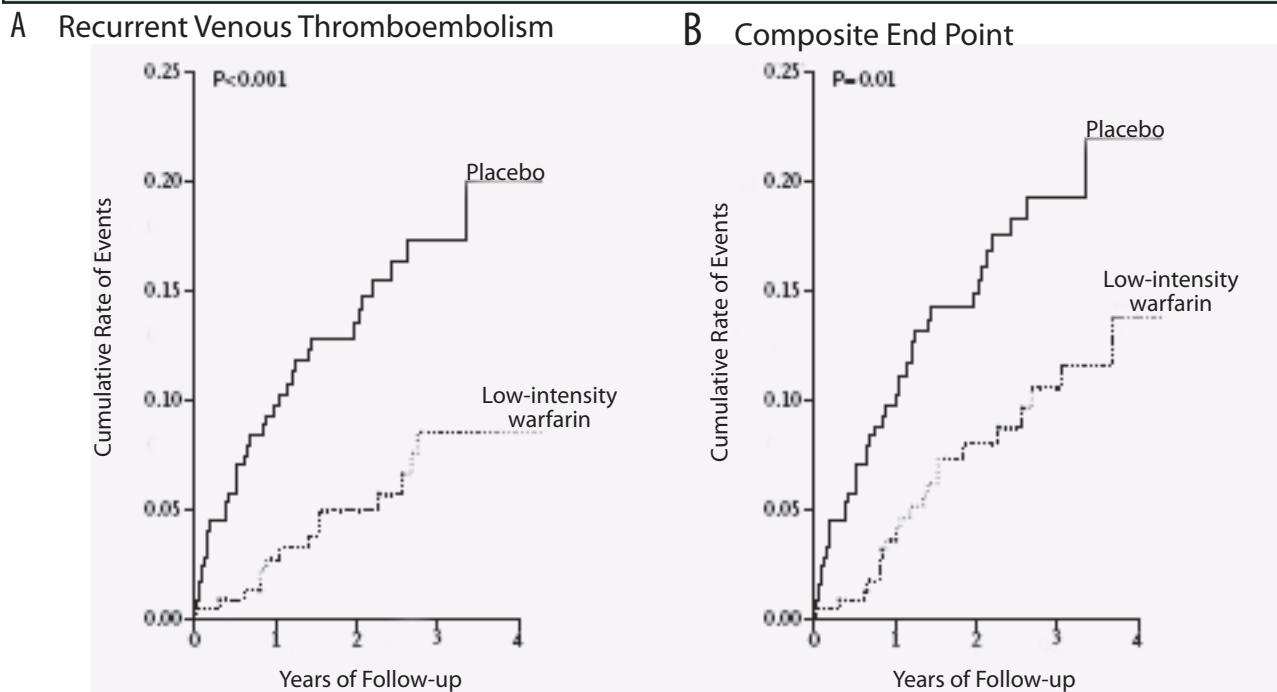
5. Based on the information in Table 2 and Figure 2 below, what do the data suggest with respect to the efficacy of this therapy, specifically in regard to recurrent VTE events and the composite endpoint? Do these results demonstrate a statistically significant difference between the Placebo and Warfarin Groups?

**Table 2.** Major Study End Points According to Treatment Group.\*

Outcome	Placebo Group		Warfarin Group		Hazard Ratio (95% CI)	P Value
	No. of Events	No./100 Person-Yr	No. of Events	No./100 Person-Yr		
Recurrent venous thromboembolism	37	7.2	14	2.6	0.36 (0.19–0.67)	<0.001
Bleeding episode						
Major	2	0.4	5	0.9	2.53 (0.49–13.03)	0.25
Minor	34	6.7	60	12.8	1.92 (1.26–2.93)	0.002
Death	8	1.4	4	0.7	0.50 (0.15–1.68)	0.26
Cancer	9	1.6	4	0.7	0.45 (0.14–1.47)	0.18
Myocardial infarction	2	0.4	3	0.5	1.54 (0.26–9.24)	0.63
Composite end point (recurrent venous thromboembolism, major bleeding episode, or death)	41	8.0	22	4.1	0.52 (0.31–0.87)	0.01

\*Major bleeding episodes were defined as episodes resulting in hospitalization, transfusion of packed red cells, or hemorrhagic stroke. CI denotes confidence interval.

**Figure 2.** Cumulative Risk of the Primary Study End Point of Recurrent Venous Thromboembolism (Panel A) and of the Composite Study End Point of Recurrent Venous Thromboembolism, Major Hemorrhage, or Death from Any Cause (Panel B).median.



6. What do the data in Table 2 and Figure 2 suggest with respect to the safety of this therapy, specifically in relation to both major and minor bleeding episodes?

7. What information contained within Table 3 below is relevant in your consideration of this new treatment approach for Mr. Cramer?

**Table 3.** Rates and Hazard Ratios for Recurrent Venous Thromboembolism in Clinically Important Subgroups, According to Treatment-Group Assignment.

Characteristic	Placebo Group		Warfarin Group		Hazard Ratio (95% CI)*	P Value for Interaction**
	No. of Events	No./100 Person-Yr	No. of Events	No./100 Person-Yr		
Factor V Leiden or prothrombin mutation						0.51
Present	14	8.6	3	2.2	0.25 (0.07–0.87)	
Absent	23	6.6	11	2.7	0.42 (0.20–0.86)	
Sex						0.23
Male	22	8.6	11	3.9	0.47 (0.23–0.96)	
Female	15	5.9	3	1.1	0.20 (0.06–0.67)	
Age						0.87
30–44 yr	8	7.6	4	3.3	0.45 (0.14–1.51)	
45–64 yr	20	7.3	5	1.7	0.24 (0.09–0.65)	
65–89 yr	9	6.7	5	4.0	0.57 (0.19–1.70)	
No. of previous venous thromboembolic events						0.42
≥ 2	21	11.4	10	4.8	0.43 (0.20–0.90)	
1	16	4.9	4	1.2	0.25 (0.08–0.74)	
Time since randomization						0.16
≤ 1 yr	22	10.1	6	2.7	0.27 (0.11–0.66)	
> 1 yr	15	5.1	8	2.5	0.49 (0.21–1.16)	
Time since cessation of full-dose warfarin therapy						0.69
> 2 mo	14	5.9	7	2.5	0.42 (0.17–1.04)	
≤ 2 mo	23	8.4	7	2.7	0.33 (0.14–0.76)	

\* CI denotes confidence interval.

\*\* The null hypothesis is that there are no differences among subgroups; for age and time since randomization, the interaction tested is between the continuous variable and treatment.

8. How would you present the information in Table 3 about this new treatment approach to Mr. Cramer to assist him in making a decision based on the results of this study?

9. Do you feel that you require additional information to make an informed decision regarding therapy for Mr. Cramer? If yes, what information would be helpful?

## Further Research

Read the following abstract for the article “Comparison of Low-Intensity Warfarin Therapy with Conventional-Intensity Warfarin Therapy for Long-Term Prevention of Recurrent Venous Thromboembolism” by Clive Kearon et al. in *The New England Journal of Medicine*, 349(7): 631–639.

### Abstract

**Background:** Warfarin is very effective in preventing recurrent venous thromboembolism but is also associated with a substantial risk of bleeding. After three months of conventional warfarin therapy, a lower dose of anticoagulant medication may result in less bleeding and still prevent recurrent venous thromboembolism.

**Methods:** We conducted a randomized, double-blind study, in which 738 patients who had completed three or more months of warfarin therapy for unprovoked venous thromboembolism were randomly assigned to continue warfarin therapy with a target international normalized ratio (INR) of 2.0 to 3.0 (conventional intensity) or a target INR of 1.5 to 1.9 (low intensity). Patients were followed for an average of 2.4 years.

**Results:** Of 369 patients assigned to low-intensity therapy, 16 had recurrent venous thromboembolism (1.9 per 100 person-years), as compared with 6 of 369 assigned to conventional-intensity therapy (0.7 per 100 person-years; hazard ratio, 2.8; 95 percent confidence interval, 1.1 to 7.0). A major bleeding episode occurred in nine patients assigned to low-intensity therapy (1.1 events per 100 person-years) and eight patients assigned to conventional-intensity therapy (0.9 event per 100 person-years; hazard ratio, 1.2; 95 percent confidence interval, 0.4 to 3.0). There was no significant difference in the frequency of overall bleeding between the two groups (hazard ratio, 1.3; 95 percent confidence interval, 0.8 to 2.1).

**Conclusions:** Conventional-intensity warfarin therapy is more effective than low-intensity warfarin therapy for the long-term prevention of recurrent venous thromboembolism. The low-intensity warfarin regimen does not reduce the risk of clinically important bleeding.

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