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# The relationship between vitamin K content in the body and insufficient coagulation control

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# Introduction

**Prosthetic heart valve thrombosis is a rare but serious complication of a heart valve replacement procedure, most often encountered with mechanical prostheses. Therefore, after prosthetic valve replacement, warfarin is administered to prevent thromboembolic outcomes such as peripheral artery thromboembolism, pulmonary embolism and deep vein thrombosis.**

**A dosage of warfarin has been decided mainly on the basis of prothrombin time-international normalized ratio (PT-INR) values. However, despite administration of warfarin, thromboembolic complications develop on occasion. Thrombin generation may play also an important role in the development thromboembolic complications. Therefore, Thrombin-antithrombin III complexes (TAT) and prothrombin fragment 1+2 (F1+2) are being evaluated as parameters of thrombin generation.**

**Therefore, Thrombin-antithrombin III complexes (TAT) and prothrombin fragment 1+2 (F1+2) are being evaluated as parameters of thrombin generation.**

**We have previously measured various parameters in patients undergoing artificial valve replacement. (Artery; 1992, Nakamura K, *Thrombosis Research*; 1997, Nakamura K)**

# Object

**We conducted a retrospective analysis of the relationship between poor coagulation control and inhibitory effects of the vitamin K cycle by administration of warfarin in patients undergoing artificial valve replacement.**

# Blood coagulation-related parameters

- 1) Warfarin
- 2) Vitamin (V) K<sub>1</sub>
- 3) Menaquinone (MK)-4, MK-7
- 4) VK<sub>1</sub>-epoxide
- 5) Protein C antigen
- 6) Protein induced by vitamin K absence or antagonists (PIVKA)-II
- 7) Thrombin-antithrombin III complexes (TAT)

# Method

## 1. Patients

- 1) All patients (n = 15) were treated with warfarin alone after artificial valve replacement.**
- 2) Postoperative administration was started at 3 mg and adjusted to control PT-INR in the range of 1.85 – 2.15.**
- 3) On postoperative day (POD)-7, the patients were classified into two groups.**



**4) Group A (n = 5); warfarin of 5 mg/day or more.**

**5) Group B (n=10); warfarin of 3 mg/day.**

**The protocol was approved by the local ethics committee and informed written consent was obtained from all participants.**

# Table 1 Characteristics

	Group A (n=5)	Group B (n=10)	P value
Age (years)	54.3 ± 10.6	51.4 ± 9.8	n.s.
Men	3	4	n.s.
<b>Technique of operation</b>			
Aortic valve replacement (AVR)	2	4	n.s.
Mitral valve replacement (MVR)	1	3	n.s.
AVR + MVR	2	3	n.s.

Group A: patients received warfarin of 5 mg/day or more.

Group B: patients received warfarin of 3 mg/day. n.s.: not significant.

## **2. Blood sampling**

**Blood samples were collected from each patient's the median cubital vein in tubes containing 3.8% sodium citrate from the heart valve diseases patients. Collected blood samples were immediately centrifuged at  $1610 \times g$  (3,000 rpm) for 10 minutes to obtain plasma.**

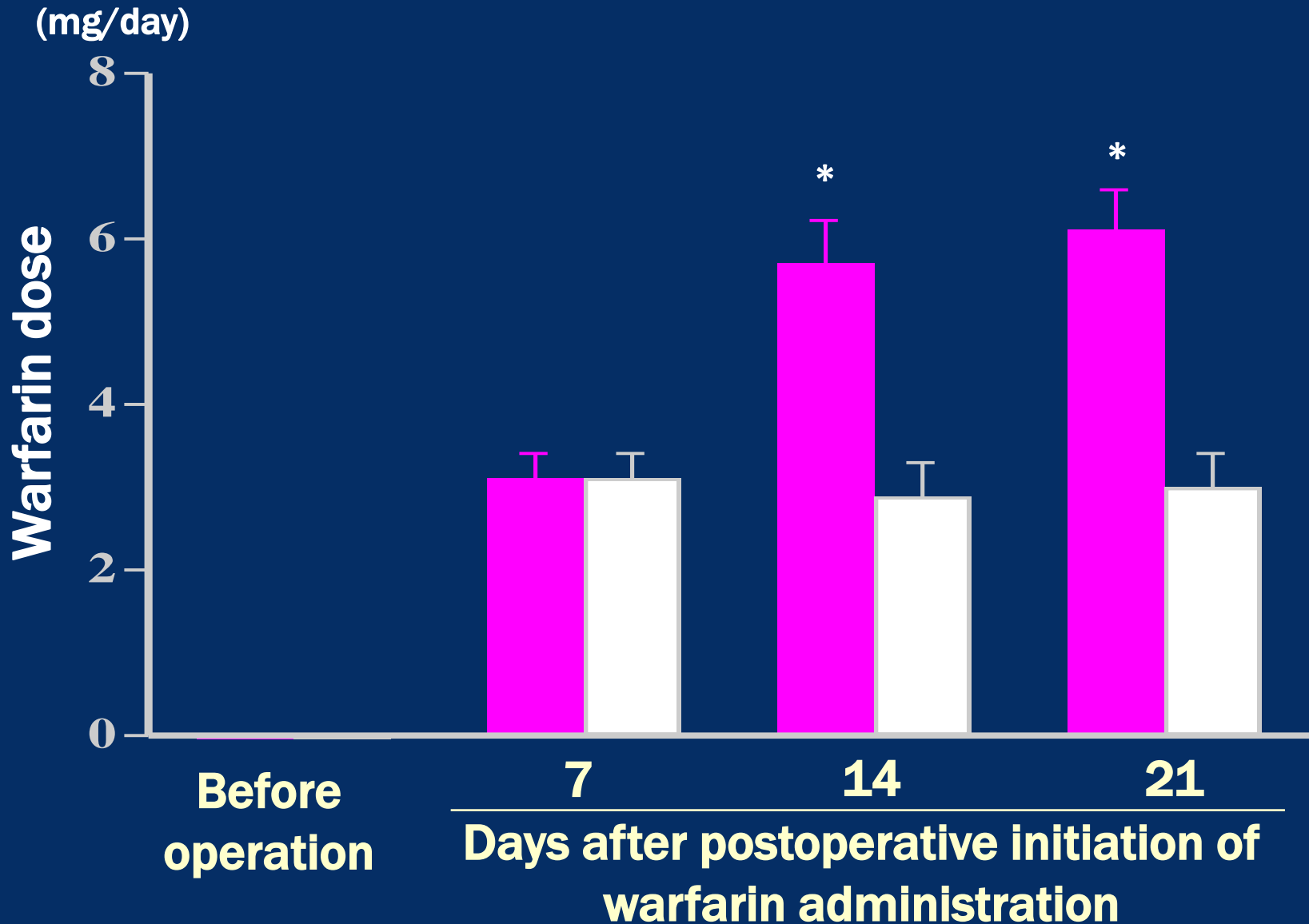
### **3. Sampling points**

- 1) 7 days before the operations.**
- 2) Post operations; 7th day, 14th day, and 21th day after postoperative initiation of warfarin administration.**
- 3) On postoperative day (POD)-7, the patients were classified into two groups.**

## **4. Measurement parameters**

- 1. PT-INR and protein C antigen levels :  
our previous reports (Nakamura, 1992,  
1993).**
- 2. Plasma levels of warfarin, VK<sub>1</sub>, MK-4,  
Mk-7, and VK<sub>1</sub>-epoxide: HPLC**
- 3. Plasma levels of PIVKA-II and TAT: ELISA**

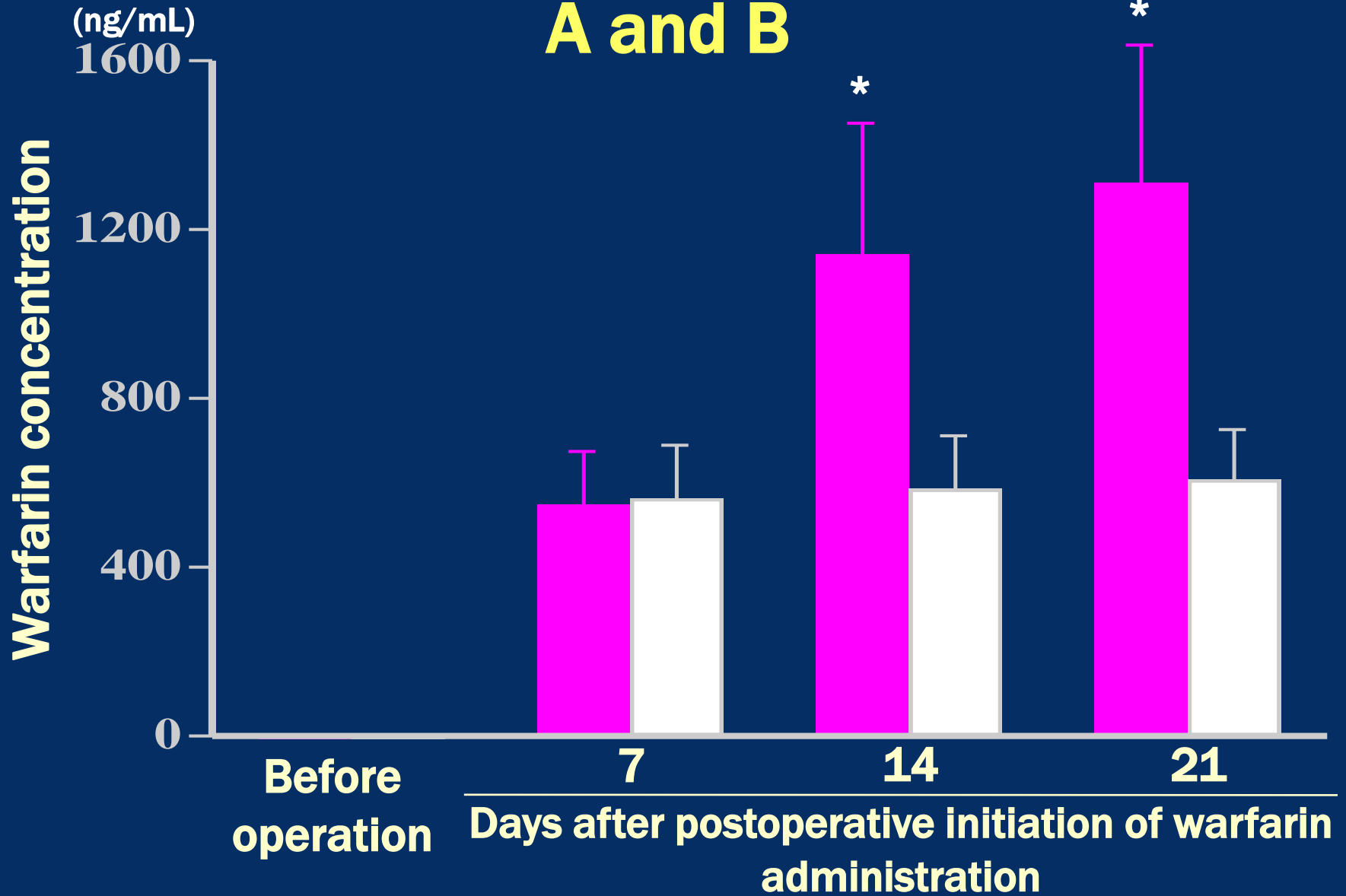
# Changes in warfarin dose in groups A and B



\* $p < 0.01$ , compared with group B.

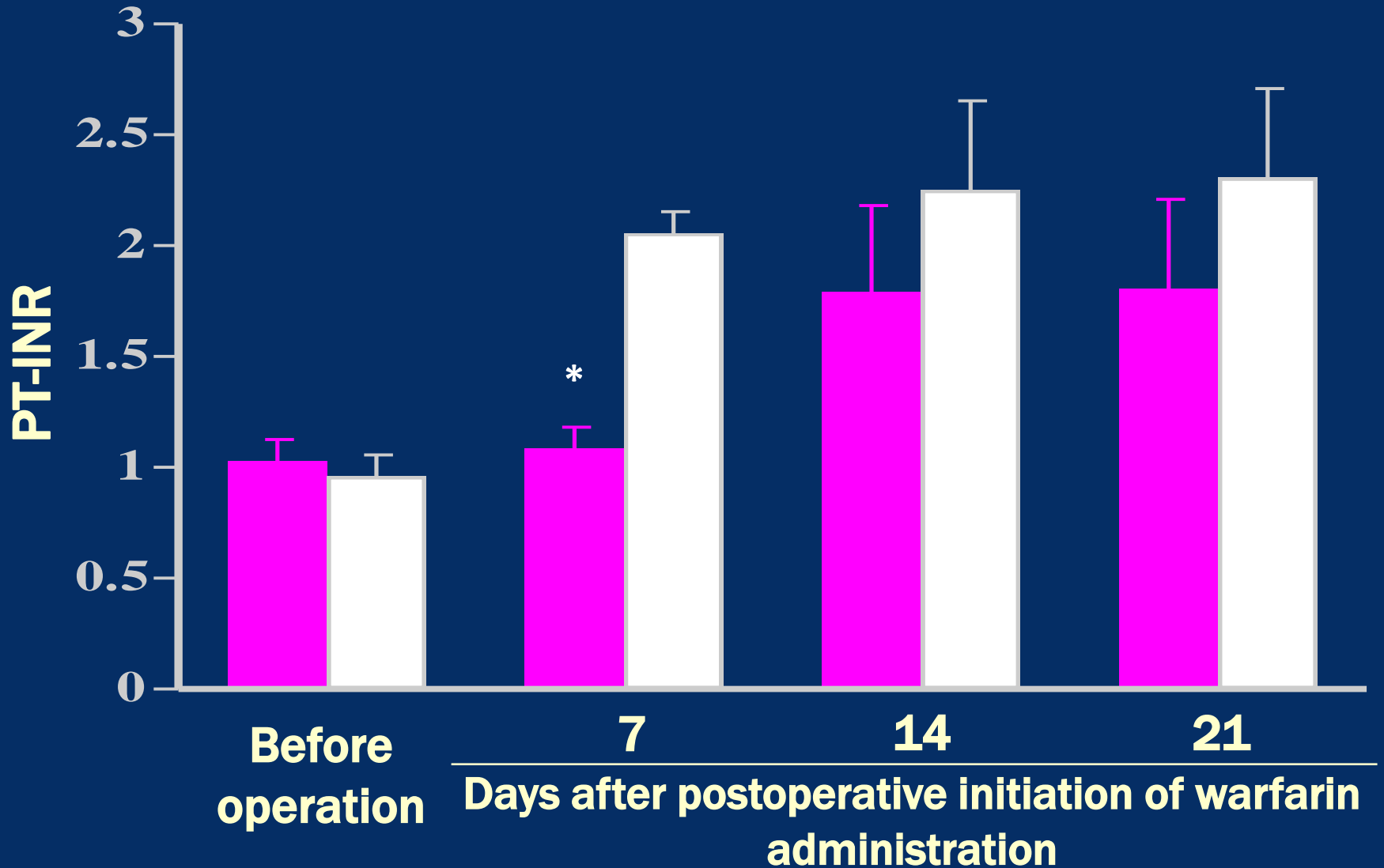
# Changes in warfarin concentration in groups

## A and B



\* $p < 0.01$ , compared with group B.

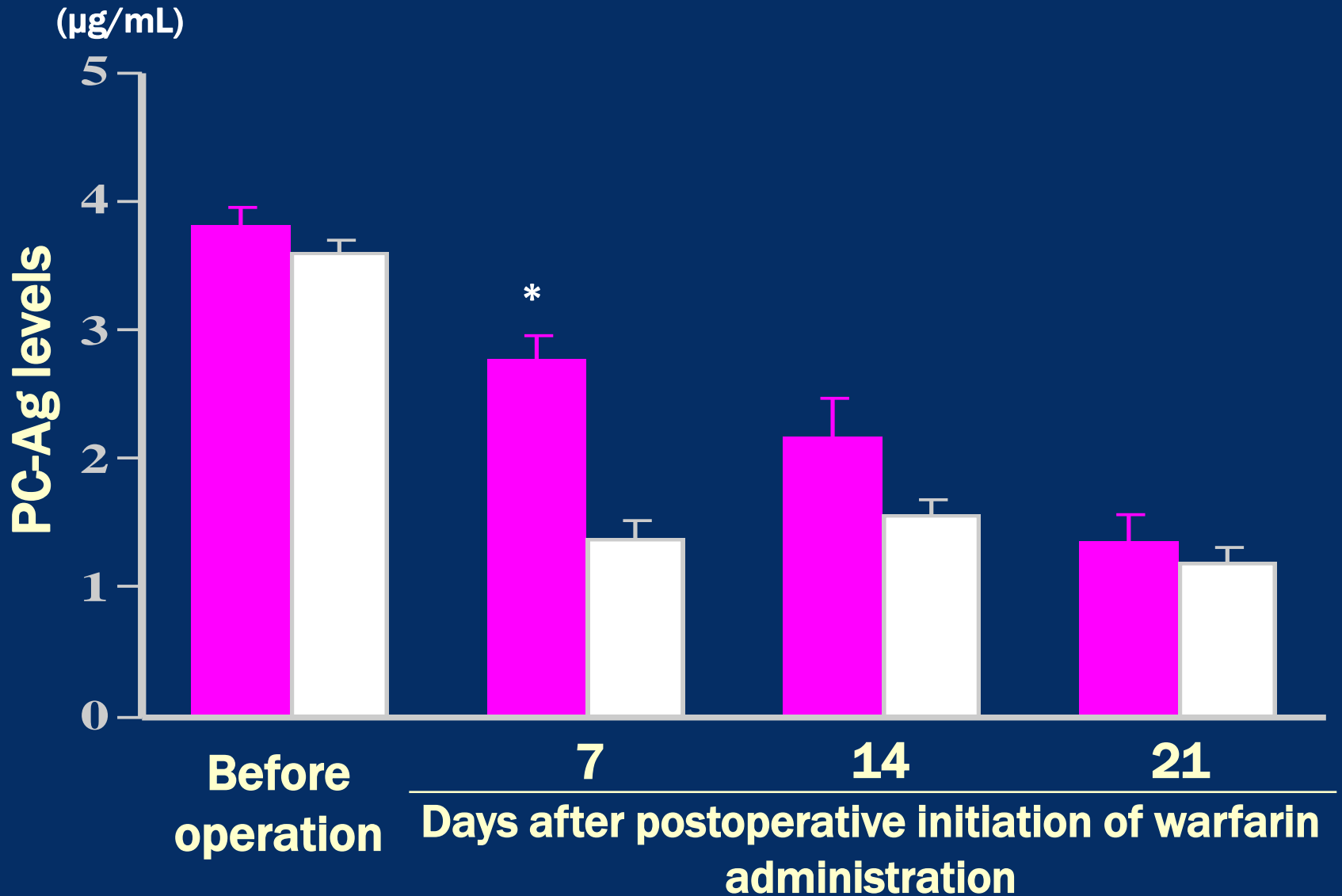
# Changes in PT-INR in groups A and B



\* $p < 0.01$ , compared with group B.

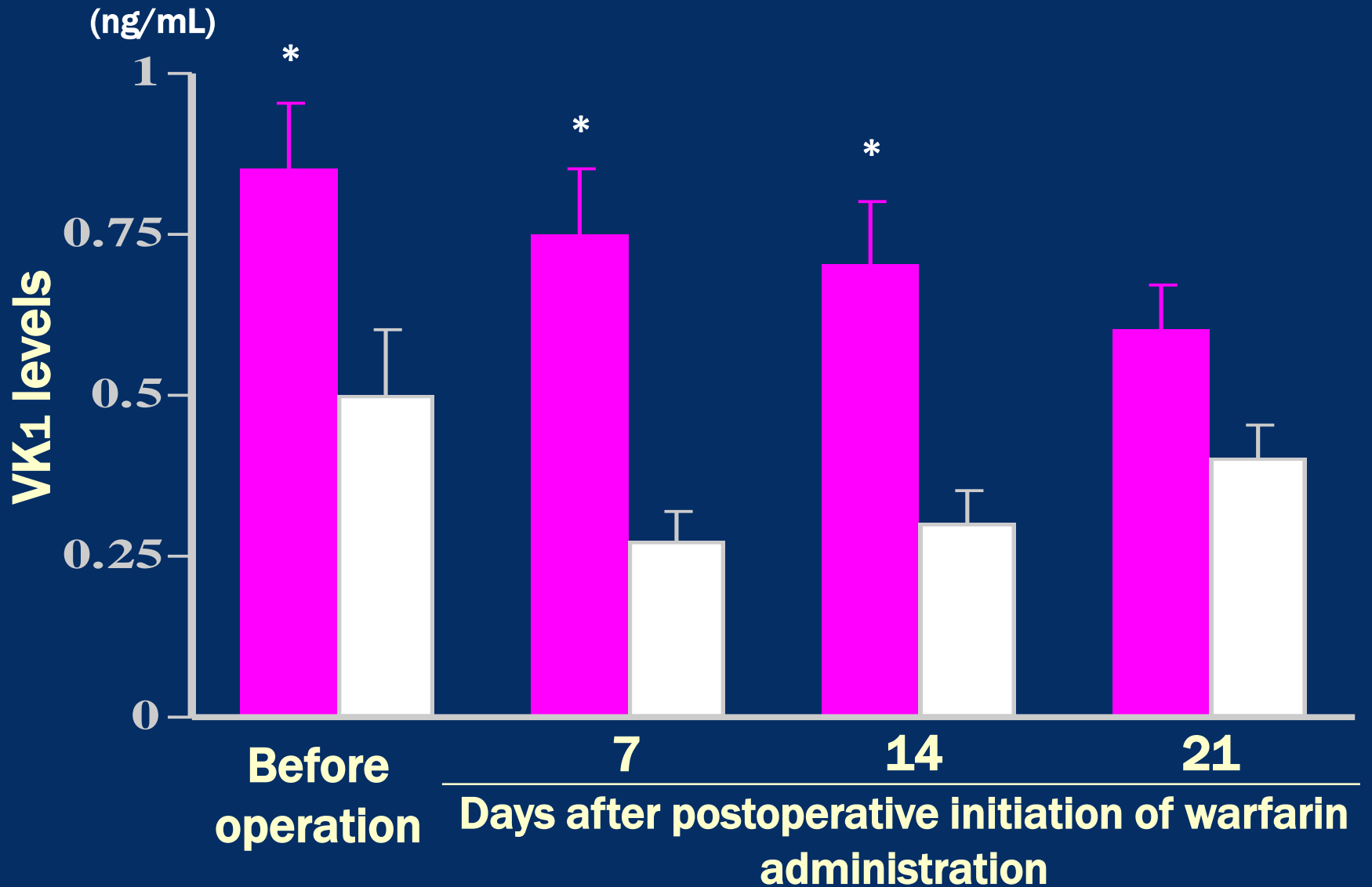


# Changes in PC-Ag in groups A and B



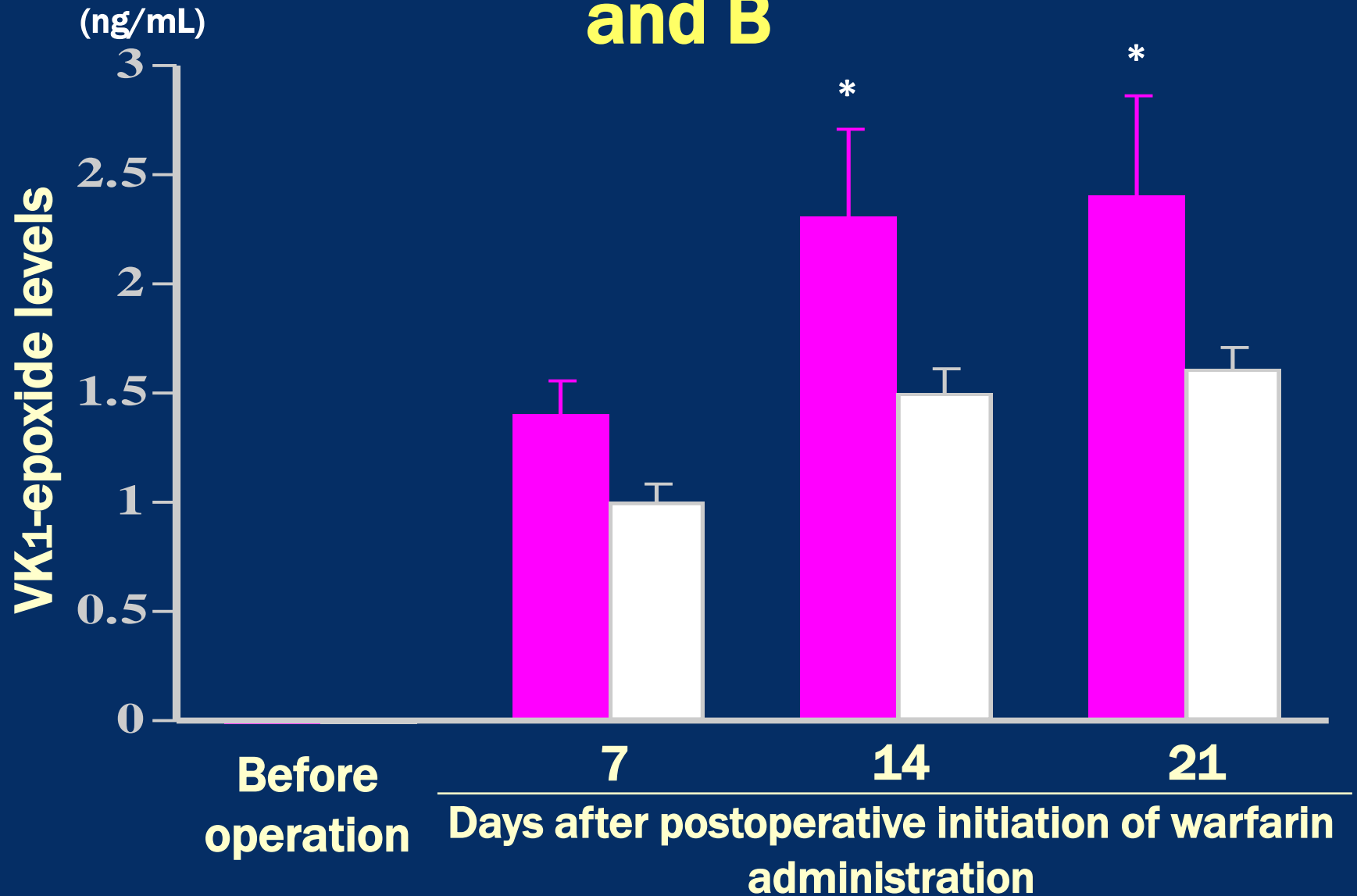
\* $p < 0.01$ , compared with group B.

# Changes in VK1 levels in groups A and B



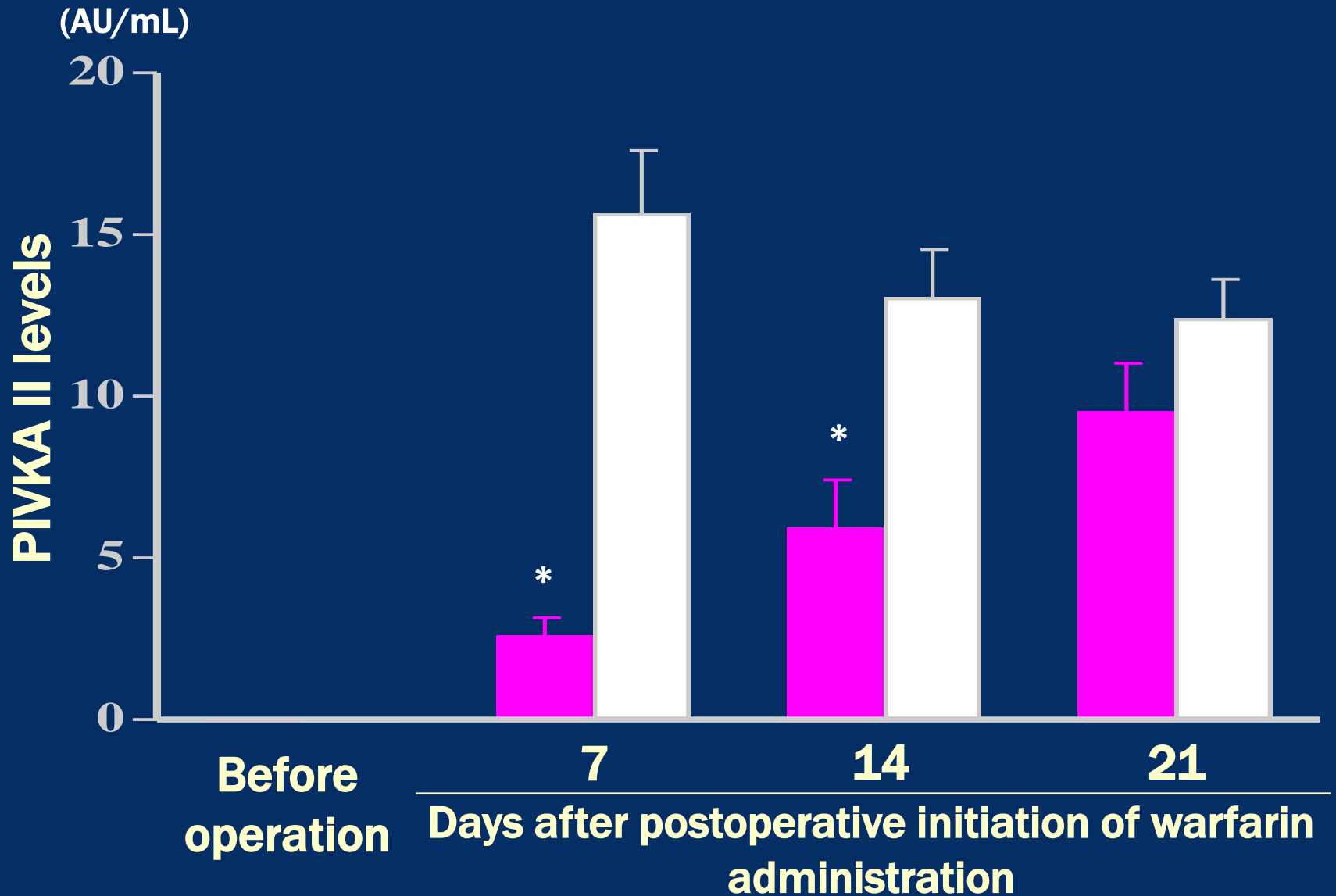
\* $p < 0.01$ , compared with group B.

# Changes in VK1-epoxide levels in groups A and B



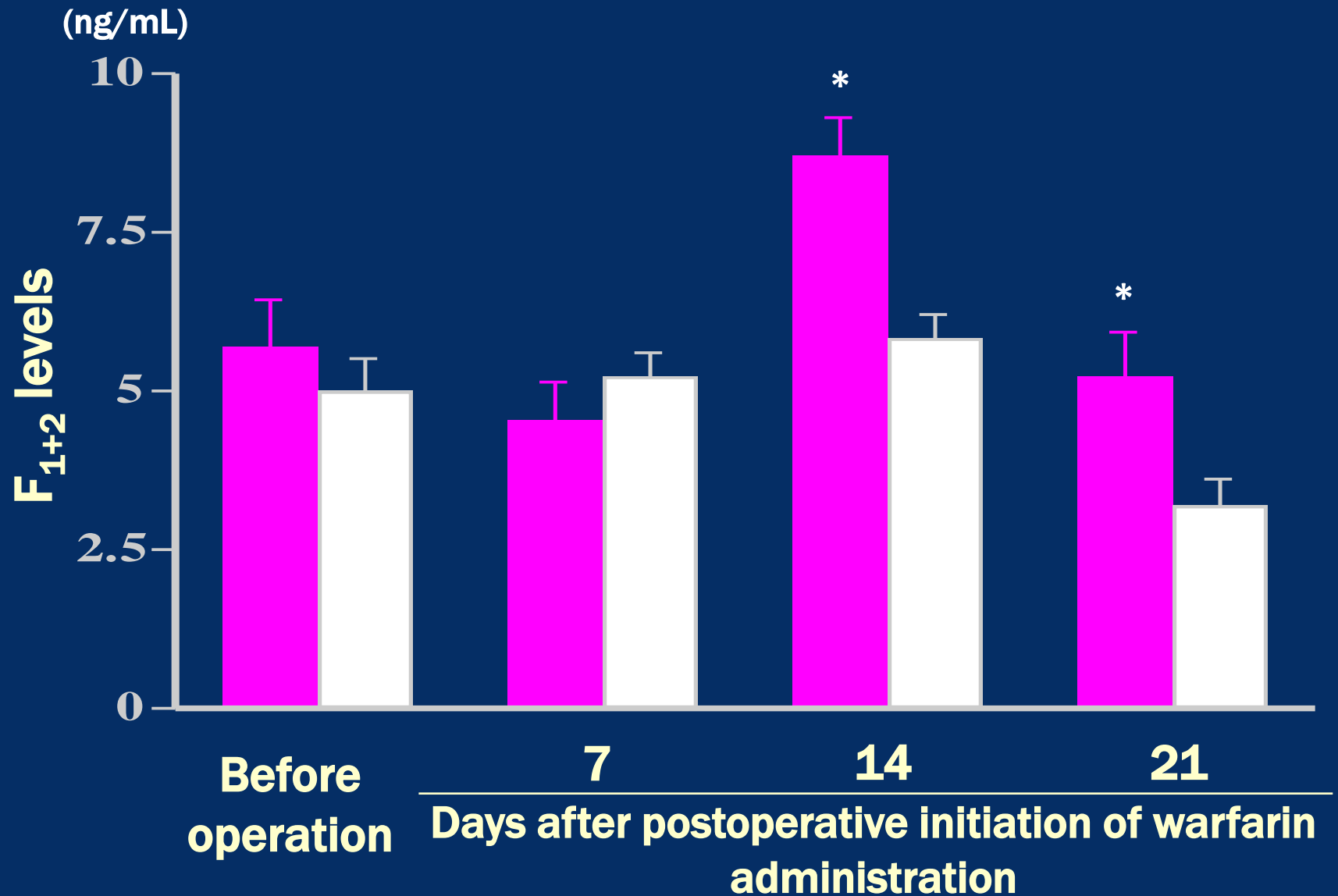
\* $p < 0.01$ , compared with group B.

# Changes in PIVKA-II levels in groups A and B



\* $p < 0.01$ , compared with group B.

# Changes in F<sub>1+2</sub> levels in groups A and B



\* $p < 0.01$ , compared with group B.

# Discussion

In this study, no thrombosis developed in any patient during postoperative anticoagulant therapy. We predicted that the VK cycle would be inhibited by warfarin so that much lower levels of VK<sub>1</sub> could be obtained (Nakamura, 1994). When PT-INR values on the 7th day in group A were below the therapeutic range, plasma levels of VK<sub>1</sub> were significantly higher than those in group B. Our data suggest that the VK content in group A may have been more abundant than in group B.

**Consequently, the inhibitory effects of warfarin on the vitamin K cycle in group A may have been insufficient, leading to a greater production of protein C antigen in comparison with group B. Plasma levels of VK<sub>1</sub>-epoxide on 21st day in group A were double those in group B. These results may be also related with an abundant VK<sub>1</sub> content in the bodies of patients in group A. In contrast, in group A the plasma levels of PIVKA-II on the 7th day were extremely low.**

**These results may reflect an inadequate effect of warfarin on the vitamin K cycle by the 7th day. On the 14th day, plasma levels of TAT were significantly higher in group A than in group B, suggesting that the risk of thrombosis may be increased on the 14th day after the initiation of warfarin administration.**



# Conclusion

**The inhibition of the vitamin K cycle may be inadequate in patients who receive warfarin in a dosage of 5 mg/day or more owing to the abundance of vitamin K in the body. Therefore, these patients may be at a greater risk of postoperative thrombosis after valve replacement surgery.**

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