

VIII, IX, XI, and XII. Of these, factors II (prothrombin), VII, IX, and X are synthesized in the presence of vitamin K; they are classified as vitamin-K-dependent coagulation factors. Warfarin inhibits the synthesis of these factors by competitively blocking vitamin K binding, exhibiting anticoagulant actions. Simultaneously, vitamin K promotes the synthesis of an anticoagulant substance, protein C, and inhibits calcification by activating Gla protein. Therefore, Warfarin inhibits the activities of the vitamin-K-dependent coagulation factors and an anticoagulant factor, protein C, promoting calcification. Warfarin is administered to prevent or treat thrombus formation. In particular, it is recognized as a standard thrombus-formation-preventing drug for patients with atrial fibrillation (Table 1). It was reported that the incidence of atrial fibrillation increased 4-fold when the glomerular filtration rate (GFR) decreased to ≤ 30 mL/min (renal failure), and that it reached 13-fold in dialysis patients (United States

Renal Data System. 2005 Annual data report), suggesting that Warfarin is frequently considered to use in patients with renal failure or dialysis.

Is Preventive Effect of Warfarin on Cerebral Infarction Equally Expectable in Dialysis Patients?

Few studies have examined the efficacy of Warfarin in dialysis patients. Yodogawa et al. retrospectively analyzed 64 Japanese dialysis patients with atrial fibrillation by dividing them into two groups: Warfarin ($n = 30$) and non-Warfarin ($n = 34$) groups.¹⁾ The results showed that there were no differences in the incidence of stroke or mortality rate between the two groups (Fig. 2A). Wakasugi et al. also prospectively analyzed the results of Warfarin therapy in Japanese dialysis patients with atrial fibrillation.²⁾ They compared 28 Warfarin-treated patients with 32 non-Warfarin-treated patients, and indicated that there was no significant difference in the age-/sex-/underlying disease-corrected incidence of stroke between the two groups (Fig. 2B), whereas the new-onset risk of stroke, including cerebral hemorrhage, was higher in the Warfarin group (hazard ratio: 1.94). Hayashi et al. reported the results of a large-scale cohort study involving 1,057 Japanese patients receiving maintenance dialysis. In the study, the results were compared between Warfarin ($n = 365$) and non-Warfarin ($n = 692$) groups, and the annual number of stroke episodes per 100 persons in the former and latter was 2.9 and 2.7, respectively, showing no difference.³⁾ Based on these studies, it should be considered that the efficacy of Warfarin in dialysis patients remains controversial. However, in dialysis patients, anticoagulants, such as heparin, are used on dialysis; therefore, the risk of hemorrhage must be considered. For this reason, physicians tend to restrict the dose of Warfarin. In the above reported pa-

Table 1 Clinical indication of Warfarin therapy

MS, AS, and AR with Af
After artificial valve replacement
CABG
Heart failure with Af
After revascularization for PAD patients
Atrial flutter
SSS
After pacemaker implantation
MI patients with Af or a left ventricular thrombus
Prevention of cerebral infarction attacks in APS patients
Cardiogenic cerebral infarction

Quoted from the "Guidelines for anticoagulant/anti-platelet therapies in patients with cardiovascular diseases (revisions in 2009 and 2015)" reported by the study group regarding the guidelines for the diagnosis and treatment of cardiovascular diseases in 2008.

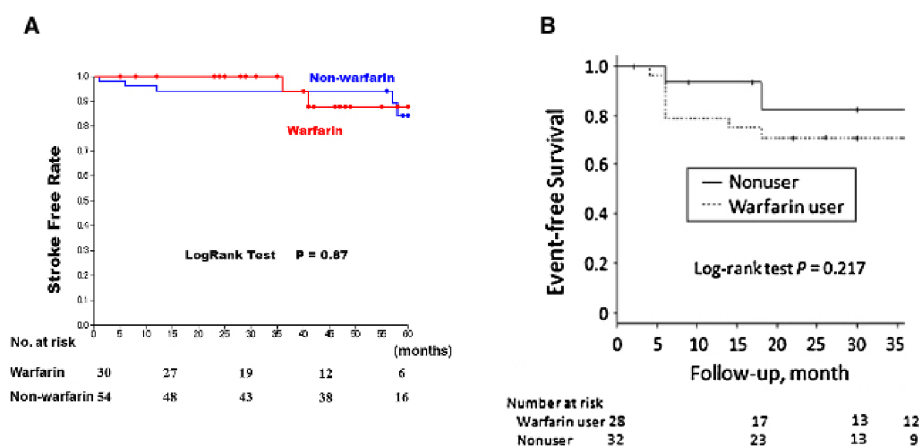


Fig. 2 Anti-stroke effect of Warfarin in Japanese patients with hemodialysis. Kaplan-Meier analysis of stroke-free survival ratio of Japanese dialysis patients with or without Warfarin reported from two independent groups. (A) Ref. 1, (B) Ref. 2.

tients, the mean PT-INR was 1.62 and 1.50, respectively. When interpreting the results of analysis, the possibility that the dose of Warfarin may have been relatively low must be considered. In fact, in other countries, where a relatively high dose of Warfarin is used, a multicenter retrospective study involving 12,284 dialysis patients with atrial fibrillation showed that Warfarin administration reduced the risk of non-hemorrhagic cerebral infarction.⁴⁾ On the other hand, Shah et al. conducted a multicenter retrospective study involving 1,626 dialysis patients with atrial fibrillation and 204,210 non-dialysis patients, and reported that the annual number of cerebral infarction episodes per 100 persons was significantly lower in the Warfarin-treated group among the non-dialysis patients (2.19 vs. 2.51, respectively), whereas there was no difference among the dialysis patients (3.37 vs. 2.91, respectively). The use of Warfarin decreased the corrected risk of cerebral infarction by 13% in the non-dialysis patients, but there was a 14% increase in the risk in the dialysis patients.⁵⁾ Thus, there is no evidence regarding the anti-stroke effects of Warfarin in dialysis patients in Japan or other countries; there might be poorly reasonable to choose Warfarin therapy in dialysis patients, excluding specific cases.

Is Hemorrhagic Risk of Warfarin in Dialysis Patients Equal to That in Non-Dialysis Patients?

We investigated whether there are differences in the incidence and hazard ratio of Warfarin-induced adverse events, such as hemorrhage, between dialysis and non-dialysis patients.

Yodogawa et al.¹⁾ analyzed the risk of hemorrhage related to Warfarin administration involving 64 dialysis

patients with atrial fibrillation, and ruled out the possibility that Warfarin administration may increase the risk of cerebral/intestinal hemorrhage. Wakasugi et al.²⁾ also reported similar results (Figs. 3A and 3B). Hayashi et al. performed a large-scale cohort study involving Japanese patients, and indicated that the annual number of hemorrhagic events per 100 persons was 7.9 in the Warfarin group and 3.5 in the non-Warfarin group, whereas there was no difference in the risk of hemorrhagic events between the two groups after correcting the results with the age, presence or absence of diabetes, or use of antiplatelet drugs.³⁾ In the above studies conducted by Yodogawa et al. and Wakasugi et al., the mean PT-INR in Warfarin-treated patients was 1.62 and 1.50, respectively, being relatively low. According to Hayashi et al., 75% of the patients showed a PT-INR of ≤ 2.09 . In these studies, the use of Warfarin may have been restricted based on the PT-INR. The results regarding the risk of hemorrhage may reflect this. In other countries, Shen et al. analyzed 12,284 dialysis patients, and reported that the risk of hemorrhage significantly increased in the Warfarin group consisting of dialysis patients.⁴⁾ The difference may be related to the dose of Warfarin. Shah et al. conducted a study involving 205,836 patients (including 1,626 dialysis patients), and indicated that the risk of hemorrhage in the Warfarin group consisting of non-dialysis patients was 19% higher than in the non-Warfarin group, whereas there was a 44% increase in the Warfarin group consisting of dialysis patients.⁵⁾ These results suggest that, when administering Warfarin to dialysis patients at the same dose as adopted for non-dialysis patients, the risk of hemorrhage is similar to or higher than that in non-dialysis patients. No study has clarified the reasons for this, but various factors, such as the deterioration of vascular calcification associated with calcium/phosphorus balance abnormalities related

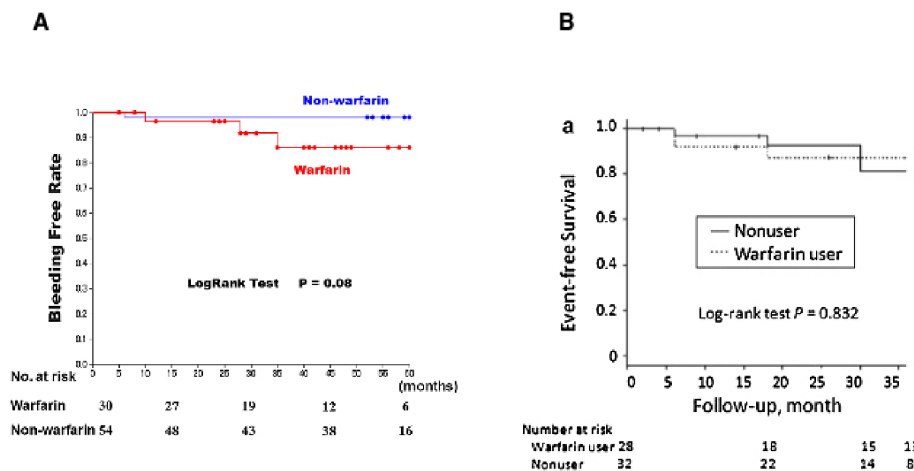


Fig. 3 Warfarin-induced hemorrhagic events in Japanese patients with hemodialysis. Kaplan–Meier analysis of event-free survival ratio of Japanese dialysis patients with or without Warfarin reported from two independent groups. (A) Ref. 1, (B) Ref. 2.

to renal impairment in addition to platelet dysfunction, which is commonly observed in patients with renal failure, or endothelial cell disorder related to chronic inflammation, may be involved. Jun et al. examined the risk of hemorrhage in 12,403 atrial fibrillation patients receiving Warfarin, among whom the kidney function (GFR) differed: normal to end-stage renal disease. The results showed that the incidence of hemorrhage, especially gastrointestinal hemorrhage, significantly increased in renal failure patients with a GFR of ≤ 30 mL/min, suggesting the association between the kidney function and risk of Warfarin-associated hemorrhage.⁶ In these studies, the incidence of hemorrhage within 30 days after the start of Warfarin administration was significantly higher; this must be considered.

Thus, restricted Warfarin use in Japan may be associated with its insufficient preventive effects on stroke. However, when administering a sufficient dose of Warfarin, the risk of Warfarin-related hemorrhage may increase in dialysis patients in comparison with non-dialysis patients.

Clinical Issues Associated with Warfarin Use—Accelerated Risk of Causing Arteriosclerosis

Clinically, it has been speculated that the long-term administration of Warfarin may promote arteriosclerosis especially in dialysis patients. Mac-Way et al. compared

the degree of aortic sclerosis between 18 Warfarin-treated and 54 non-Warfarin-treated dialysis patients (total: 72) by measuring the pulse wave velocity (PWV) at aorta.⁷ In the non-Warfarin-treated group, the PWV increased by 0.86 ± 1.87 m/sec, with a mean follow-up of 1.2 years, whereas it increased by 2.24 ± 2.68 m/sec in the Warfarin-treated group (Fig. 4A), suggesting that the long-term administration of Warfarin promotes arteriosclerosis. All vitamin-K-dependent coagulation factors have γ -carboxyglutamic acid (Gla) at the N-terminal. However, in the presence of vitamin K deficiency, glutamic acid is released into blood without being carboxylated. Such a coagulation-activity-free coagulation factor is termed protein induced by vitamin K absence or antagonist (PIVKA), and PIVKA-II refers to non-carboxylated (inactive-type) factor II. As PIVKA indirectly reflects the degree of coagulation factor activation by vitamin K, it is possible to use the blood PIVKA-II level as a surrogate marker for the concentration/activity of vitamin K. In this study, non-Warfarin-treated patients were divided into two groups (high, low) based on the PIVKA-II level to evaluate the PWV. However, as shown in Fig. 4B, the rate of increase in the PWV was smaller in patients with a low PIVKA-II level in whom vitamin-K-dependent coagulation factor activity was estimated to be high, suggesting that the progression of arteriosclerosis is slow. As shown in Fig. 1, vitamin K inhibits Gla protein activation-related calcification; therefore, a relatively low level of vitamin

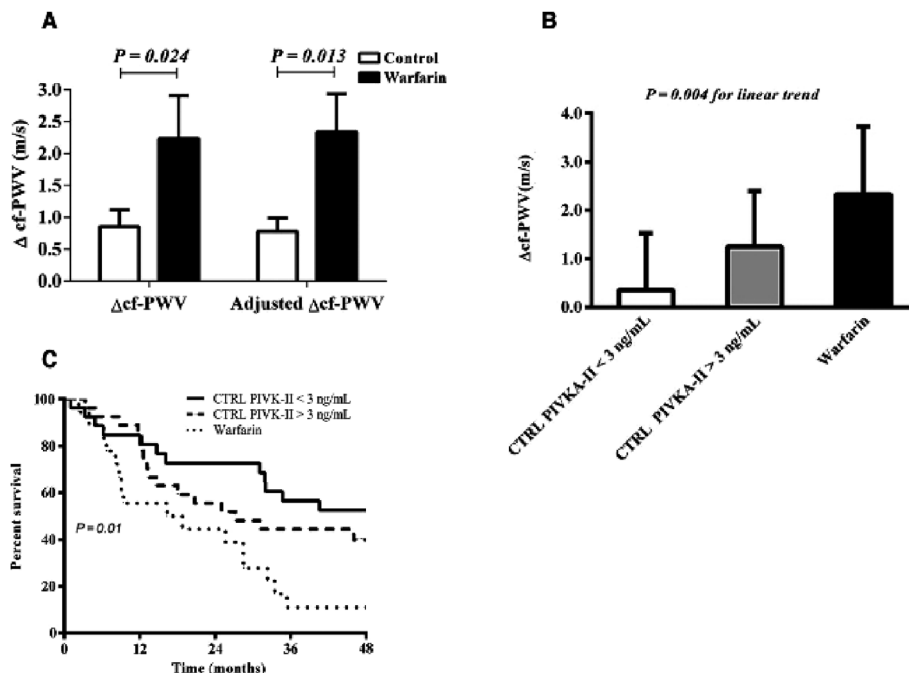


Fig. 4 Warfarin-induced progression of aortic stiffness in hemodialysis patients. (A) Changes in aortic stiffness. (B) Progression of aortic stiffness in the control group according to vitamin K status and in the Warfarin group. (C) Mortality in the control group according to vitamin K status and in Warfarin group. All figures were cited from Ref. 7.

K, reflected by a high PIVKA-II level, or inhibition of vitamin K by Warfarin may be involved in the deterioration of arteriosclerosis related to arterial calcification. The deterioration of arteriosclerosis may cause various angiopathy-related events, influencing the prognosis. This is reflected by the association between the use of Warfarin/PIVKA-II level and survival rate (Fig. 4C). In dialysis patients, the risk of vascular calcification is essentially high due to abnormalities in the calcium/phosphorus balance, and long-term vitamin K suppression related to vitamin K deficiency or Warfarin use may additively (or synergistically) act on the deterioration of arteriosclerosis. In Japan, Warfarin is not rarely administered over a long period, differing from 6-month to 1-year administration in other countries; such chronic administration-related limitations must be considered.

Diseases That May Develop during Warfarin Therapy—Calciphylaxis

Outline of calciphylaxis

Calciphylaxis is rarely observed in dialysis patients or those with a marked decrease in the GFR (≤ 15 mL/min). It refers to a condition primarily caused by calcification of minor blood vessels among refractory skin ulcers with marked pain. It is also termed calcific uremic arteriopathy. Warfarin administration is considered to be an important risk factor for the onset of this disease. In 1961, Selye et al. reported this disease as a rare skin lesion found in laboratory animals.⁸⁾ In 1986, Anderson et al. presented a patient with this disease in the presence of hyperparathyroidism.⁹⁾ Internationally, this disease is reportedly observed in 1 to 4% of dialysis patients, but, according to a national survey by the Refractory Disease-Overcoming Research Business “Survey/Research on the Diagnosis/Treatment of Calciphylaxis” Group (Director: Prof. Matsuhiko Hayashi), Ministry of Health, Labour and Welfare

in 2009, approximately 150 patients with this disease had been confirmed in Japan. It was reported that the morbidity rate estimated from the number of dialysis patients was 0.5%. Although there may be race differences in the incidence of this disease, the results suggest the low-level diagnostic capacity in Japan.

Clinical features and diagnosis of calciphylaxis

Calciphylaxis is primarily detected in dialysis patients receiving Warfarin. In most cases, it appears as painful livedo-like purpura within 6 months to 1 year after the start of Warfarin administration, leading to skin ulcers (Fig. 5A). It is classified into two types: proximal type involving the trunk and distal type involving the limbs. The former is more frequent and severe. In particular, calciphylaxis of the penis is classified as the severest proximal type. In most patients, infection leads to sepsis, with a mortality rate of $\geq 50\%$. Calciphylaxis is histopathologically characterized by arteriole calcification. However, it is characterized by calcification of the media, as demonstrated for Mockerberg-type arteriosclerosis, differing from atherosclerosis with calcification of the arterial intima (Fig. 5B). With calcification, findings, such as intimal proliferation, microthrombosis, fibrosis of the vascular wall, and submucosal fat necrosis, are observed.

The diagnostic criteria proposed by the Ministry of Health, Labour and Welfare Study Group are presented in Table 2. It must be considered that skin biopsy is not always necessary. Diseases to be differentiated are shown in Table 3. If this disease is suspected, the presence or absence of previous gadolinium administration should be confirmed, and the levels of cryoglobulin, antinuclear antibody, and antiphospholipid antibody must be measured. As a disease to be differentiated, Warfarin-related skin necrosis, as described below, is particularly important.

Although the etiology of this disease remains to be clarified, it may be associated with calcification-reducing

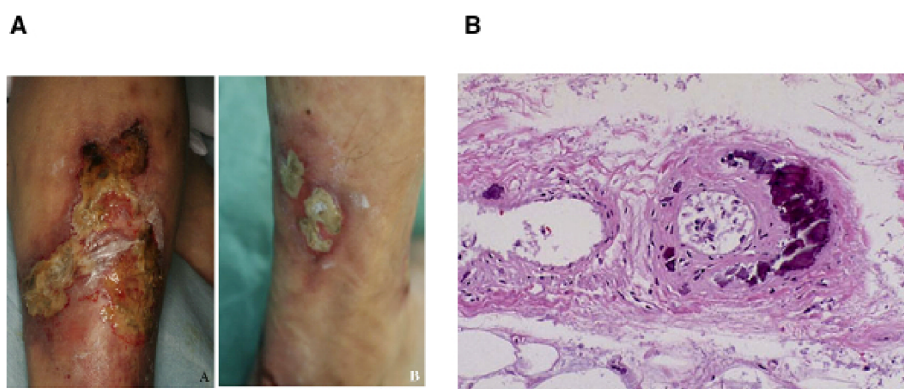


Fig. 5 Representative pictures showing skin ulcer and calcification in the middle layer of arteries. (A) Macroscopic finding showing ulcerative lesion in the lower extremities (Ref. 11). (B) Microscopic picture showing arterial calcification in the middle layer (Web from Singh, MBBS, FRCP, MBA at Thursday, December 08, 2011).

Table 2 Proposed diagnostic criteria of calciphylaxis

Patients, meeting all or two of the following 3 criteria, with characteristic histological findings on biopsy:

- (1) Presence of maintenance dialysis or end-stage renal disease (GFR: ≤ 15 mL/min)
- (2) Refractory skin ulcers at ≥ 2 points with painful purpura at the periphery
- (3) Refractory skin ulcers, involving the trunk, brachium, forearm, femoral region, lower thigh, or penis, with painful purpura at the periphery

For patients who do not meet any of the above 3 criteria, skin biopsy should be conducted.

- (1) Skin ulcers/necrosis/submucosal fat necrosis with calcification of the media and internal elastic membrane of arterioles to medium-sized arteries
- (2) Concentric contraction related to edematous intimal thickening of arterioles to medium-sized arteries

Quoted from a report published by the Refractory Disease-Overcoming Research Business "Survey/Research on the Diagnosis/Treatment of Calciphylaxis" Group, Ministry of Health, Labour and Welfare.

actions through Gla protein activation by vitamin K. As risk factors for the onset of this disease other than the use of Warfarin, the presence of peritoneal dialysis, hypoalbuminemia, use of non-oral iron preparations, hypercalcemia, and hyperphosphemia have been epidemiologically reported. Therefore, malnutrition or abnormalities in the calcium/phosphorus balance may be closely involved. With respect to the details, see the literature.^{10–13)}

Treatment of calciphylaxis

Primary treatment is to discontinue Warfarin therapy. In addition, wound care, antimicrobial therapy for infection, and debridement at the ulcer site are performed. Peritoneal dialysis is reported to promote the onset/deterioration of this disease in comparison with hemodialysis; it should be switched to hemodialysis. Abnormalities in calcium/phosphorus metabolism are considered to be risk/exacerbation factors for this disease, and whether parathyroidectomy should be indicated must be reviewed for patients with secondary hyperparathyroidism. In many dialysis patients, phosphorus adsorbents are used, but, for patients receiving calcium carbonate, it should be switched to non-calcium adsorbents, such as sevelamer hydrochloride (RenaGel[®], Phosblock[®]), bicalomer (Kiklin[®]), lanthanum carbonate (Fosrenol[®]), and ferric citrate (Riona[®]), from the viewpoint of inhibition of an increase in the concentration of calcium. In particular, the efficacy of a calcium mimetic, cinacalcet (Regpara[®]), for this disease was indicated. With respect to the details, see the literature.^{11,14)} No study has reported the efficacy of systemic steroid therapy for this disease, and this therapy may become a factor that exacerbates infection, which may always occur; therefore, it is

Table 3 Clinical attention and differential diagnosis of calciphylaxis

Confirmation of previous gadolinium use (nephrogenic systemic fibrosis: NSF)

Measurement of cryoglobulin, antinuclear antibody, and antiphospholipid antibody

Diseases to be differentiated

Diabetic gangrene

Skin necrosis related to heparin-induced thrombopenia

Skin necrosis related to Warfarin use

Scleroderma

Cholesterin embolism

Cellulitis

Treatment with hydroxyurea (Hydrea[®]) for CML

Antiphospholipid syndrome (APS)

Burns

Necrotic fasciitis

Venous congestion

Ectopic calcification of the skin

Quoted from a report published by the Refractory Disease-Overcoming Research Business "Survey/Research on the Diagnosis/Treatment of Calciphylaxis" Group, Ministry of Health, Labour and Welfare.

not recommended. In contrast, a study reported it as a risk factor.¹⁵⁾ However, this does not apply to topical steroids, and they are effective for ulcerative lesions. Recently, many studies reported the efficacy of intravenously administered sodium thiosulfate for this disease.^{14,16–19)} This drug has been used to reduce cyanide poisoning. As its actions on this disease, it removes calcium by forming the calcium thiosulfate complex. In addition, this drug may also be useful as an antioxidant. Recovery from pain is reportedly achieved in a few weeks, and that from skin lesions in 6 months to 1 year; this treatment method should be considered for patients with this disease. Although detailed administration protocol slightly differed among reports, majority of reports adopted drip infusion at approximately 25 g (100 mL of 25% solution) over 30 to 60 minutes after every session of dialysis (3 times a week). As sodium thiosulfate is a low-molecular-weight substance (248 Da), its dialysability is favorable, and it may not be accumulated. However, thiosulfate loading increases the acid level between dialysis sessions, and a high incidence of metabolic acidosis must be considered.

Disease That May Develop during Warfarin Therapy—Warfarin-Related Skin Necrosis

Disease outline

Painful purpura, hemorrhagic skin pustules, and skin ulcers are observed early (1 to 2 weeks) after the start of Warfarin administration. Common sites include the limbs, gluteal region, and thoracic region. Warfarin-related skin

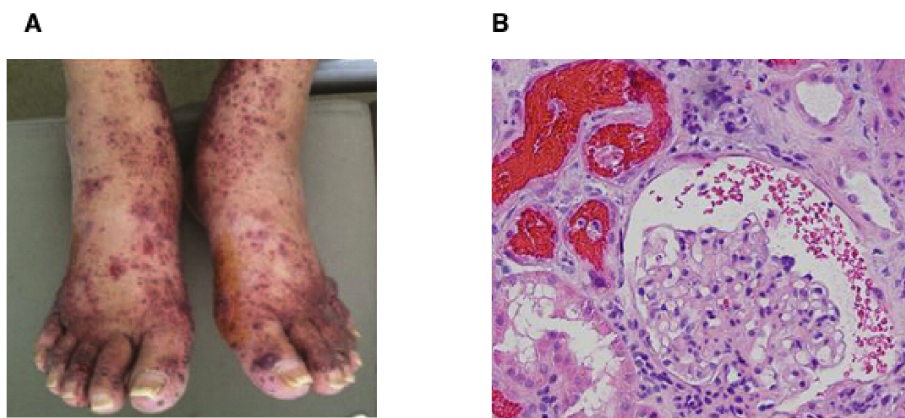


Fig. 6 Skin lesion of Warfarin skin necrosis, and renal biopsy finding of Warfarin-related nephropathy. **(A)** Skin lesion of Warfarin skin necrosis showing erythematous pustules with tenderness (Ref. 20). **(B)** Renal biopsy of Warfarin-related nephropathy showing RBC occlusive casts in multiple tubules and glomerular hemorrhage (Ref. 21).

necrosis must be differentiated from calciphylaxis with similar skin lesions (Fig. 6A). Pathologically, marked necrosis at the ulcer site is detected.²⁰⁾

Etiology and Warfarin-related transient hypercoagulability

This disease may be primarily associated with transient hypercoagulability immediately after Warfarin administration. As shown in Fig. 1, vitamin K activates coagulation factors, but it simultaneously activates protein C; activated protein C inactivates factors Va and VIIIa by acting on protein S. Briefly, vitamin K exhibits two conflicting actions: the promotion of coagulation and anti-coagulation. Protein C activity disappears the day after Warfarin administration. However, 3 to 7 days are required until Warfarin exhibits stable effects with the loss of vitamin-K-dependent coagulation factor activity. Therefore, protein C inactivation-related hypercoagulability appears early after the start of Warfarin administration, that is, before the appearance of an antagonism against this, anticoagulant action. Microthrombus formation related to this phenomenon, termed transient hypercoagulability after Warfarin administration, may be involved in the etiology of this disease.

Treatment

As systemic steroid therapy is effective, it is important to differentiate this disease from calciphylaxis. The two diseases can be differentiated based on differences in the duration until disease onset (appearance of dermal signs) from the beginning of Warfarin therapy. However, if differentiation is difficult, skin biopsy should be considered. Based on the histopathological findings, the two diseases must be differentiated by the presence or absence of medial calcification (calciphylaxis), necrosis, or thrombus

formation.

Disease That May Develop during Warfarin Therapy—Warfarin-Associated Nephropathy

This disease is rarely observed in the presence of an excessive anticoagulant state (PT-INR >3.0) related to excessive Warfarin administration or drug interactions. It leads to acute kidney injury (AKI). This disease is characterized by a rapid decrease in the GFR, moderate proteinuria, and marked hematuria early after administration of Warfarin. On kidney biopsy, a large number of erythrocytic casts and tubulointerstitial damage are observed. Glomerular hemorrhage may be involved in the pathogenesis of this disease²¹⁾ (Fig. 6B). Its incidence is high in patients with chronic kidney disease (CKD), especially in those with a reduction in the GFR; caution is required.^{22,23)} The systemic administration of prednisolone would be effective.

CYP2C9 is associated with Warfarin sensitivity, and the risk of hemorrhage is high in patients with specific genetic polymorphisms. Genetic polymorphisms at G1639A and C1173T, which correspond to the non-translation areas of CYP2C9, may be involved in the pathogenesis of this disease.²³⁾

Conclusion

As described above, clinical efficacy and risk of Warfarin in patients with reduced glomerular function or dialysis therapy are not the same as those in non-renal damaged, non-dialysis patients. We also have to pay attention to the rare but serious Warfarin-related complications. When the administration of Warfarin is considered in patients with dialysis or renal failure, we have to notice the differences for the clinical efficacy and safety.

Disclosure Statement

In this article, there is no conflict of interest.

Additional Note

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