Should Dialysis Patients Ever Receive Warfarin and for What Reasons?

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Warfarin is rapidly absorbed from the gastrointestinal tract. It is 99% bound to protein, specifically albumin. It has a half-life of approximately 40 h, although certain factors such as factor VII are inhibited more rapidly (half-life of 5 h), whereas factors IX, II, and X have half-lives of 24 to 48 h. When the shorter acting coagulation factors are inhibited, the international normalized ratio (INR) is abnormal but the patient needs an additional 4 to 5 d to become fully anticoagulated because of the slower effect of warfarin on other coagulation factors. Common variables that affect warfarin anticoagulation are the amount of vitamin K in the diet, the acuity of illness, and, of course, liver function. In addition, the effects of vitamin K that are generated by intestinal bacteria can be markedly reduced by concomitant antibiotics. Warfarin has many drug–drug interactions usually via albumin binding/displacement or liver clearance effects. An INR of 2 to 3 is considered low-intensity anticoagulation, and 3 to 4.5 is considered high-intensity anticoagulation.

Warfarin inhibits a vitamin K epoxide reductase enzyme. This prevents γ carboxylation of glutamic acid residues (2) (Figure 1). Warfarin’s activity on the epoxide enzyme reduces the number of residues added to 7 to 8 as opposed to the normal 10 to 13 per clotting factor molecule (2,3). Anticoagulation with warfarin represents a complex interaction of known procoagulant and anticoagulant proteins. It is beyond the scope of this article to review coagulation in detail except to say that protein C, antithrombin III, and protein S are major procoagulant stimuli that when deficient as a result of loss in the urine, failure of synthesis, or a lack of activity in various disease states can promote clotting.

The published efficacy of warfarin anticoagulation in dialysis patients for access maintenance is unimpressive. Mokrzycki et al. (4) followed for 1 yr 105 patients who were randomly assigned to placebo versus minidose warfarin therapy. Eight catheters failed in each group, and there was no effect of warfarin on thrombosis-free survival or time to urokinase manipulation. Crowther et al. (5) in 2002 reported 107 patients who had polytetrafluoroethylene grafts and were randomly assigned to warfarin with INR between 1.4 to 1.9 versus placebo. The likelihood of vascular graft survival was increased in the placebo group, although this value was not statistically significant. There were five major bleeds in the warfarin patients and none in the placebo group. The examples from older literature suggested that anticoagulants in hemodialysis patients were a risk factor for subdural hematoma and other major hemorrhages.
Another, more recent study examined tunneled catheters and compared aspirin versus warfarin versus neither. This was a nonrandomized trial of 63 patients. The number of open catheters at 120 d was 91% with aspirin, 73% with warfarin, and only 29% with neither (8). The prospective Dialysis Outcomes and Practice Patterns Study (DOPPS) study of US dialysis patients comprised a cohort of 900 fistula patients and 1944 vascular graft patients. Technical failure within 30 d was excluded from analysis. Taking aspirin after a previous access failure was associated with better secondary graft patency with a relative risk of 0.7 (Figure 2). However, warfarin was worse in maintaining primary vascular grafts, with a relative risk of 1.33 for failure. These studies, of course, may be severely confounded by the selection of patients who were at high risk for the warfarin interventions (9). A recent study by Ziai et al. (10) examined the effect of warfarin on clotting of the dialyzer. This was a randomized, crossover study of 10 warfarin-treated patients that compared low molecular weight heparin versus no additional anticoagulation for the purpose of dialysis. The authors showed that an INR between 2 to 3 was insufficient to prevent dialyzer clotting on the basis of observation and D-dimer measurement.

Figure 1. Interaction of warfarin and vitamin K. Illustration by Josh Gramling—Gramling Medical Illustration.

Figure 2. Secondary (assisted survival) patency for grafts by drug therapy (aspirin [dashed line] versus no aspirin [solid line]). Survival estimates are adjusted for age, gender, race, body mass index, incidence to ESRD, diabetes, hypertension, valvular disease, chronic obstructive pulmonary disease, aortic aneurysm, deep venous thrombosis, and number of previous permanent accesses.
ized trial. Although the “common sense” practice of using warfarin to prevent access thrombosis seems logical, such anticoagulation has no documented benefit to offset the risks of such therapy.

**Conclusion**

Warfarin is of little proven benefit in dialysis patients, at least in those without defined hypercoagulable states. Bleeding complications are enhanced, and unplanned emergency surgeries such as deceased-donor renal transplantation are complicated. To answer the question posed in the title, my view is that until efficacy is proved, the answer to the question should be, “Practically never.”

**References**


A risk equation for early determination of the likelihood of AV fistular failure to mature may mitigate the tendency to use anticoagulants for hemodialysis patients. See Lok et al. (pp. 3204–3212) in this month’s issue of JASN.