Does warfarin safely prevent clotting of hemodialysis catheters: a review of efficacy and safety

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CRD summary
The authors concluded that there is insufficient evidence to recommend the routine administration of warfarin for preventing thrombosis in tunneled cuffed catheters in haemodialysis patients. The authors’ conclusions appear to reflect the limited evidence presented. However, poor reporting of the review methods make it difficult to comment on the strength of the evidence underlying these conclusions.

Authors' objectives
To evaluate the efficacy and safety of warfarin used to prevent thrombosis in tunneled cuffed catheters (TCC) in patients undergoing haemodialysis.

Searching
PubMed, EMBASE, the Cochrane Library and Google Scholar were searched to April 2007; the search terms were reported. In addition, the reference lists of relevant reports were screened.

Study selection
Prospective and retrospective studies that evaluated the efficacy and safety of warfarin for preventing thrombosis in haemodialysis patients who were receiving dialysis through a TCC were eligible for inclusion. In efficacy studies, prophylactic warfarin or a similar coumarin derivative had to be used to prevent thrombosis in the TCC used for haemodialysis. In safety studies, warfarin could be used to prevent catheter thrombosis or for other indications. The included studies were randomised controlled trials (RCTs), prospective non-randomised controlled studies and observational studies. Efficacy studies evaluated a variety of warfarin regimens including fixed minidose warfarin (1 mg/day) and warfarin titrated to various international normalised ratios (INRs of 1.5 to 2, 1.8 to 2.5 and 2.0 to 3.0). The studies varied with respect to interventions and controls.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
For each efficacy study, outcome data were presented with the level of statistical significance.

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
The individual studies were described separately.

Results of the review
Six studies evaluated efficacy: 2 RCTs (n=249), 2 prospective non-randomised controlled studies (n=128) and 2 observational studies (182 patients in a retrospective chart review and 41 episodes of catheter malfunction in a case series).

The table of safety studies reported on 6 studies: 3 three RCTs (n=336) and 3 prospective non-randomised controlled studies (n=367). The review also reported safety data from 3 additional studies.
Efficacy.

One double-blind RCT (105 patients receiving first cuffed TCC randomised, 85 completed and analysed) reported no significant difference between minidose warfarin (1 mg/day) and placebo in the number of days of thrombosis-free TCC survival until TCC failure and removal because of late malfunction.

One non-randomised controlled study (35 high-risk patients receiving warfarin titrated to INR of 1.5 to 2.0 versus 30 low-risk patients not receiving warfarin, all prevalent haemodialysis patients) reported no significant difference between groups in TCC thrombotic events.

One RCT (144 patients with warfarin titrated to INR of 1.8 to 2.5) reported that patients who received warfarin early (12 hours) after a TCC insertion had a significantly lower rate of malfunction events per year than patients who did not receive warfarin until a catheter thrombosis or malfunction (0.16 events per year versus 1.65, p<0.001).

One prospective observational study (63 patients) reported that primary patency was significantly longer in patients already taking warfarin for other indications (INR titrated to 2.0 to 3.0) and patients allocated to aspirin (325 mg/day) than patients taking neither drug. There was no significant difference between warfarin and aspirin groups.

One case series (41 episodes of catheter malfunction in patients who had undergone fibrinolysis with urokinase before starting warfarin) reported 13 episodes of catheter dysfunction during treatment with warfarin, with most (11 episodes) occurring with a mean INR of 1.46.

One retrospective chart review (182 patients of which 21 had taken warfarin in the previous 4 years; indications for warfarin were not reported) reported a statistically significant increase in TCC thrombosis in patients receiving warfarin compared with those who had not (0.13 versus 0.03 events per 100 catheter days).

Safety.

One RCT (n=85) reported minimal risk of bleeding with minidose warfarin (1 patient with cerebral emboli and peripheral haemorrhage).

One non-randomised study (n=65) reported no major bleeds in high-risk patients taking warfarin (target INR 1.5 to 2.0).

One RCT (n=107) reported no bleeds in patients taking warfarin (target INR 1.8 to 2.5) plus ticlopidine.

One RCT (144 patients with arterio-venous grafts) reported a statistically significant increase in major bleeds in patients taking warfarin (target INR 1.4 to 1.9) compared with no warfarin (8.9% versus 0%); all 5 major bleeds were in patients taking concurrent antiplatelet therapy.

One non-randomised study (n=42) reported an increase in major bleeds in patients taking warfarin compared with no warfarin (3 out of 11 patients versus 0 out of 31).

One observational study (n=240) reported an increase in major bleeds in patients taking warfarin for cardiovascular reasons compared with no warfarin (relative risk 2.36, 95% confidence interval, CI: 1.19, 4.27).

One observational study (number of participants not reported) reported gastrointestinal bleeding in 8.0% of haemodialysis patients on warfarin and 8.7% on aspirin per year.

It was not reported whether patients in the following 2 studies were receiving haemodialysis. One study (number of participants not reported) reported a significant increase in calcification of surgically removed heart valves in patients taking a coumarin derivative compared with control (37% versus 16%, p=0.02). The other study reported significantly increased coronary and valvular calcification in patients taking long-term warfarin.

Authors' conclusions
There is insufficient evidence to recommend the routine administration of warfarin for the prevention of TCC thrombosis in all patients undergoing haemodialysis, owing mainly to concerns about safety. Haemodialysis patients taking warfarin are at increased risk of bleeding.

**CRD commentary**

The quality of the evidence for each intervention was estimated using U.S. Preventive Services Task Force criteria and the Agency for Healthcare Research and Quality scale (high, medium or low). The review question was stated and inclusion criteria were defined for the intervention and participants; inclusion criteria for the study design and outcomes were broad. Several relevant sources were searched, but no specific attempts were made to locate unpublished studies and it is unclear whether any language restrictions were applied. Study validity was not assessed, so the reliability of data derived from the included studies cannot be fully assessed. The methods used to select studies and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer errors and bias. In view of the many differences between the studies, it was appropriate not to attempt to combine the studies statistically. However, the authors made no attempts to synthesise the studies and evidence from higher-quality studies was not highlighted. The authors’ conclusions about the absence of sufficient evidence appear to be supported by the limited evidence presented. However, lack of reporting of the review methods make it difficult to comment on the strength of the evidence underlying these conclusions.

**Implications of the review for practice and research**

Practice: The authors stated that if it is decided to give warfarin to haemodialysis patients, a target INR of 1.5 to 2.5 should be adequate. Patients receiving warfarin should be carefully monitored for bleeding, particularly if they are concurrently taking antiplatelet drugs.

Research: The authors stated that there is need for further research to examine the relationship between warfarin and tissue calcification in patients with chronic renal disease.

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