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DOACs least harmful for patients with calciphylaxis on hemodialysis needing anticoagulation

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ABSTRACT A critical appraisal and clinical application of King BJ, El-Azhary RA, Mcevoy MT, et al. Direct oral anticoagulant medications in calciphylaxis. *International Journal of Dermatology*. 30 August 2017;56(1):1065-1070. doi: [10.1111/ijd.13685](https://doi.org/10.1111/ijd.13685)

Keywords: *calciphylaxis, anticoagulation, end stage renal disease*

Clinical Context

A 43-year-old Caucasian woman presented with a 7cm × 5cm necrotic wound in the right upper medial thigh. The patient's past medical history was significant for end stage renal disease on hemodialysis, left below the knee amputation and right foot diabetic ulcers secondary to uncontrolled diabetes, as well as a lower extremity deep venous thrombosis (DVT) in the right lower extremity. The patient was transferred from an outside hospital for escalation of care, after she received multiple surgical debridements. Upon examination, the necrotic wound had a rim of black eschar with surrounding erythema. Dermatology was consulted, and an excisional skin biopsy was performed, which confirmed calciphylaxis, a disorder associated with kidney failure, which causes calcification of the arterioles and skin necrosis. The patient was started on sodium thiosulfate.¹ During her hospital stay, the patient was receiving heparin due to her recent history of lower extremity DVT. While planning for the patient's discharge, outpatient anticoagulation choices were discussed. Warfarin is contraindicated in calciphylaxis² and there is evidence that heparin can contribute to the disease. The team wondered if a direct oral anticoagulant (DOAC) would be safer in this patient with calciphylaxis on hemodialysis.

Clinical Question

What is the safety of direct oral anticoagulant (DOAC) medications in patients with calciphylaxis on hemodialysis?

Research Article

King BJ, El-Azhary RA, Mcevoy MT, et al. Direct oral anticoagulant medications in calciphylaxis. *International Journal of Dermatology*. 30 August 2017;56(1):1065-1070. doi: [10.1111/ijd.13685](https://doi.org/10.1111/ijd.13685).

Related Literature

On PubMed Advanced Search Builder, title and abstract terms used as input included "calciphylaxis" OR "calcific uremic arteriopathy" AND "anticoagulation" NOT "thiosulfate". This returned 34 citations, all of which were reviewed for relevance to the clinical question.

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There is limited literature on the topic of calciphylaxis. Other strategies in PubMed were used, such as the “clinical queries” function and “similar articles” function. This and other search term combinations verified that all relevant articles were found.

El-Azhary et al. conducted a retrospective study indicating that 60% patients with a clinical diagnosis of calciphylaxis had thrombophilia.³ The patients were placed into three treatment categories for comparison of survival: they found no statistically significant survival difference between those on warfarin, other anticoagulants and no anticoagulants. This study is less relevant because it did not subcategorize patients on dialysis; the primary objective was to investigate the prevalence of thrombotic disorders in patients with calciphylaxis

Carter et al. discussed a case report of a patient with recalcitrant calciphylaxis affecting nearly 50% of both legs, which responded to daily subcutaneous unfractionated heparin therapy.⁴ However, a clinical decision for our patient cannot be based on a case report.

Speeckaert et al. published “Fondaparinux as an alternative to vitamin K antagonists in hemodialysis patients.”⁵ It is a case series of six patients that had heparin replaced with fondaparinux during dialysis. However, the anticoagulation was only during the procedure and the patients did not have calciphylaxis.

The article by King et al. is a retrospective study of 16 patients with calciphylaxis who received novel anticoagulants.⁶ A subset of the patients were on dialysis as well. Given the limited data on the topic of calciphylaxis and the anticoagulation treatment options, this study was one of the only retrospective studies addressing the potential effects of different anticoagulation methods in patients suffering with calciphylaxis. In addition, this study was found to be most relevant to our clinical questions and patient concerns. The Level of Evidence is C according to the SORT criteria based on a case series.

Critical Appraisal

The article by King et al. is a retrospective study of 16 patients with calciphylaxis who received novel anticoagulants (apixaban, rivaroxaban, dabigatran). The purpose of the study was to report outcomes with the use of DOACs in patients with calciphylaxis.

Electronic health records were reviewed retrospectively to determine the outcomes of the patients on novel anticoagulation with calciphylaxis. The term calciphylaxis was cross-referenced against the following treatment terms: apixaban, or rivaroxaban, or dabigatran. The patients included in the study had received these treatments for at least one week. Clinical notes were reviewed from diagnosis through follow-up, and patients were stratified into response groups such as progressed, stabilized, improved, and resolved. However, these classifications are subjective. Twenty-eight patients with calciphylaxis from the same period did not receive DOAC therapy and were therefore excluded from the study. The patient population was predominantly white female Caucasians, with a high prevalence of obesity, with involvement of high adipose body sites. All patients had multiple medical comorbidities such as clinical obesity, chronic kidney disease, on dialysis, hyperparathyroidism, diabetes, peripheral vascular disease, congestive heart failure, atrial fibrillation, and a history of deep venous thrombosis or pulmonary embolism. All patients received a multidisciplinary approach to treatment, which included wound care, sodium thiosulfate, hyperbaric oxygen therapy, surgical debridement, and normalization of metabolic abnormalities.

In the study, seven (7) patients had history of DVT or pulmonary embolism, but the authors do not specify which ones. Additionally, eight (8) patients had ESRD on dialysis, but it is unknown if it was hemodialysis or peritoneal dialysis. Furthermore, nine (9) patients are said to have a hypercoagulable state, but authors do not specify which patients. This makes it impossible to determine which patients had similar comorbidities to our patient on hemodialysis with DVTs. The authors provided a summary table listing attributes of each of the sixteen patients. Seven patients died; the surviving patients had a substantially longer time of follow up, but no inference can be made regarding causation. This does provide some prognostic information however.

The advantage to using apixaban was the multiple routes of elimination, including liver, renal and fecal metabolism. The drug does not need to be renally dosed according to the U.S. Food and Drug Administration. The only information that is reported by the authors is that there were “no reported complications” among the patients who had ESRD. The parameters for determining the safety of DOAC use in calciphylaxis patients were disease progression, non-major bleeding events, and major bleeding events. These are sufficiently relevant clinical outcomes for our patient, although the efficacy of DVT prophylaxis is not mentioned.



There are a few good qualities to this study. First, the study population closely resembled our patient with regards to demographics and comorbidities. Given the limited amount of literature and evidence for anticoagulation in calciphylaxis patients with ESRD, this study proves to be useful in clinical practice. Warfarin has been linked to increasing occurrence of calciphylaxis, and many of these patients require anticoagulation due to the prothrombotic nature of calciphylaxis. This study suggests that DOACs, particularly apixiban, are probably reasonable for use in patients with ESRD on dialysis.

Despite these strengths, the study has many flaws. First and perhaps the most important is the small population size, indicating a lower power for the study. Another flaw is that multiple concomitant treatment strategies were used in the management of the patients, which does not clearly outline the true effects of the DOAC versus other managements. In addition, the patients had different comorbidities, which could affect the results of the study. There is no subcategorization of the patients' comorbidities, type of dialysis, or DVT status. The patients were also given different doses of DOACs, which should recommend that the patients be subcategorized to help further differentiate the true effects. The authors did not address the quality of anticoagulation. The study's results were based on the patients' initial experience with DOAC therapy, and there was a lack of long-term follow-up.

Clinical Application

In the study by King et al., it was suggested that DOAC therapy should be considered as a therapeutic option in a multidisciplinary approach for patients with calciphylaxis, and apixiban should be considered for those with ESRD due to its pharmacologic profile. The patient is in the appropriate age range of the study, and the data from this study supports the use of novel anticoagulants, particularly apixiban, in calciphylaxis patients in the setting of ESRD. The benefit of applying this research is preventing further thromboses in our patient; however, there is a small possibility of bleeding as a complication. With regards to the medical management of our patient, we used this study as a guide to recommend apixaban as outpatient anticoagulation with close follow-up.

It is important for doctors to communicate the diagnosis of calciphylaxis to patients, as the treatment is multidisciplinary as well as limited. Regular follow-up with physicians is necessary for patients with this condition since it is associated with a poor prognosis. In addition, these patients do have a higher risk of thrombosis, as was seen in our patient, so patients should be informed of the clinical signs and symptoms of deep vein thrombosis and pulmonary embolism. Therefore, anticoagulation is important to consider in the management of these patients, and novel anticoagulants such as apixiban are particularly useful in end stage renal disease patients.

The lessons learned are that:

1. anticoagulation is appropriate for patients who have calciphylaxis;
2. there is limited evidence showing that novel anticoagulants have had a positive impact on patients with this disease; and
3. more research is needed in the form of a randomized clinical trial to determine the specific efficacy and use of the different novel anticoagulants.

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