A Pint of Sweat Will Save a Gallon of Blood:
A Call for Randomized Trials of Anticoagulation in End Stage Renal Disease

Running title: *Granger et al.; A Call for Randomized Trials of Anticoagulation*

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Approximately 430,000 patients were receiving maintenance dialysis in the United States in 2011\(^1\). Compared to the general population, atrial fibrillation is far more common\(^2\) and associated with a much higher risk of stroke in the dialysis population\(^3\). Thus, there is an important need to define and apply strategies to reduce stroke in patients receiving dialysis with atrial fibrillation.

Warfarin for atrial fibrillation is one of the most successful treatments in all of medicine, preventing nearly two-thirds of strokes in the general atrial fibrillation population\(^4\). Approximately one-fifth of all strokes are related to atrial fibrillation, and these strokes are more frequently disabling or fatal than strokes associated with other conditions. It is now well established that impaired kidney function is associated with increased risks of stroke and of bleeding associated with the use of anticoagulation\(^5\). Patients with mild-to-moderate chronic kidney disease and atrial fibrillation experience greater relative and absolute benefits from warfarin therapy\(^6\). Despite the lack of evidence derived from randomized clinical trials in the dialysis population, Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines published in 2006\(^7\) recommended that warfarin be used as per American Heart Association guidelines for atrial fibrillation with the caveat that “dialysis patients are at increased risk for bleeding and careful monitoring should accompany intervention.”

Since then, several observational studies have questioned the benefit of warfarin for stroke prevention, particularly when balancing the risks of bleeding in this population\(^8\). Using data from the international Dialysis Outcomes and Practice Patterns Study (DOPPS), Wizeman and colleagues found that warfarin use was independently associated with a higher risk of stroke, particularly in patients over age 75 where the risk was twice as high with warfarin\(^2\). A second large observational study used data from Fresenius Medical Care North America and found that
warfarin was associated with nearly twice the risk of stroke after adjustment for comorbidities\textsuperscript{9}. A third study showed a higher risk of hemorrhagic stroke and no lower risk of ischemic stroke with warfarin in hemodialysis using claims data from Medicare patients augmented with the United States Renal Data System (USRDS)\textsuperscript{10}. While another study from Denmark found a lower risk of stroke with warfarin use for patients with atrial fibrillation receiving dialysis\textsuperscript{3} and data included in the 2013 USRDS Annual Data Report found a lower risk of stroke in warfarin-treated patients, there was enough uncertainty that the KDIGO summary in 2011 changed the recommendation to not advise warfarin for stroke prevention in end stage renal disease\textsuperscript{11}. This group highlighted the need for clinical trials of anticoagulants in advanced chronic kidney disease (CKD) (stage 4 and 5, including persons on dialysis) as an area for future research. The Canadian Cardiovascular Society Atrial Fibrillation Guidelines, likewise, no longer recommend warfarin for atrial fibrillation for patients on dialysis\textsuperscript{12} and called for randomized trials.

In this issue of Circulation, Shah and coauthors have provided additional data to inform this debate\textsuperscript{13}. The authors identified patients admitted to hospitals in Ontario and Quebec with atrial fibrillation and analyzed outcomes according to subsequent use of warfarin and according to dialysis status. Among the 1626 patients on dialysis, nearly half were prescribed warfarin. The authors found no reduction in stroke risk associated with warfarin use after adjusting for other predictors (hazard ratio 1.14, 95\% confidence interval (95\% CI) 0.78 to 1.67), but a significantly higher risk of bleeding (hazard ratio 1.44, 95\% CI 1.13 to 1.85), similar to findings reported by Winkelmayer et al\textsuperscript{10}. The study by Shah et al included a broad population base, adjusted for key determinants of stroke and bleeding (components of the CHADS\textsubscript{2} and HAS-BLED scores), and employed propensity score adjustment to address confounding by indication. But even with careful adjustment, observational studies are limited by the effects of unmeasured
confounders and selection bias and are thus unreliable when attempting to estimate treatment effects. There is evidence that this is the case in the analysis by Shat et al, where the 13% relative reduction in stroke with warfarin in the population not treated with dialysis is an underestimate compared with the more reliable 64% relative risk reduction seen in randomized trials of this population.

While the balance of risks and benefits of warfarin appear favorable in patients with mild-to-moderate CKD, too few patients with advanced CKD have been included in randomized trials, including no patients with creatinine clearance of less than 25 ml/min in the trials of direct acting oral anticoagulants in atrial fibrillation\textsuperscript{14-17}. A potential role of the direct acting oral anticoagulants in patients with advanced CKD is supported by data showing consistent benefits compared to warfarin in patients with moderate CKD\textsuperscript{14-18}. Whether another strategy to prevent stroke, left atrial occluder devices\textsuperscript{19}, is appropriate for the dialysis population also requires further study. Trials of statins have shown us that the dialysis population is sufficiently different that treatment effects may fundamentally differ from those observed in the general population\textsuperscript{20}.

Where are we in understanding the effect of warfarin for atrial fibrillation in dialysis patients? We have compelling evidence of benefit of warfarin for stroke prevention in atrial fibrillation and evidence that the benefit is as great or greater in patients with moderate renal impairment (\textbf{Table 1}). At the same time we have reasonably consistent findings from observational studies that there are similar or higher stroke rates and higher bleeding rates with warfarin in the dialysis population. Given the unreliability of using observational studies to estimate treatment effects, the truth may be that oral anticoagulation provides important benefit. But the study by Shah et al adds to the evidence that it is also possible that warfarin is harmful in this setting. It is ironic that we are routinely treating many patients with renal disease and atrial fibrillation with warfarin.
fibrillation every day with great uncertainty as to benefit or harm without their consent, and at the same time major regulatory and ethical barriers exist that prevent efficient enrollment of patients into clinical trials that are needed to answer this (and other) important questions.

General George S. Patton, Jr. famously stated that “a pint of sweat will save a gallon of blood.” Large-scale, randomized clinical trials require considerable effort and expense. Yet given that atrial fibrillation in advanced CKD (and in end stage renal disease) is common and consequential, placebo-controlled clinical trials comparing one or more anticoagulation strategies in patients with atrial fibrillation are long overdue.

**Conflict of Interest Disclosures:** Dr. Chertow serves on the Board of Directors of Satellite Healthcare, Inc., a non-profit dialysis provider. Dr Granger discloses that, in the past 3 years, he has received compensation for research grants as well as from consulting/honaria from BMS/Pfizer, Boehringer Ingelheim, Janssen, Bayer, Daiitchi Sankyo, and Sanofi-Aventis. Full disclosure is available on https://www.dcri.org/about-us/conflict-of-interest.

**References:**


R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. Circulation. 2013;127:224-232.


Table 1. Evidence of benefit vs. risk of warfarin for stroke prevention in atrial fibrillation.

<table>
<thead>
<tr>
<th>Evidence favoring warfarin treatment</th>
<th>Evidence challenging warfarin treatment</th>
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<tbody>
<tr>
<td>RCTs of warfarin in AF show overwhelming benefit in reducing stroke</td>
<td>But patients on dialysis are fundamentally different</td>
</tr>
<tr>
<td>RCTs show that patients with stage 3 CKD and AF have more benefit from warfarin than patients with normal renal function, making it likely that the benefit extends to ESRD</td>
<td>But no patients with more advanced kidney disease have been included in RCTs of warfarin and other oral anticoagulants in AF</td>
</tr>
<tr>
<td>But observational studies are hopelessly confounded and cannot reliably estimate modest treatment effects, nor can they define lack of treatment effects</td>
<td>Observational studies, in aggregate, show warfarin use is associated with higher risk of bleeding and no reduction in stroke</td>
</tr>
<tr>
<td>But risk of thrombosis and risk of stroke is higher and therefore anticoagulation could be even more important in dialysis patients</td>
<td>Platelet function is perturbed in ESRD; frequent antibiotic use, dietary restrictions, impaired nutritional status and drug-drug interactions render anticoagulation unpredictable, placing patients at higher risk of bleeding</td>
</tr>
</tbody>
</table>

RCT=randomized clinical trial; CKD = chronic kidney disease; AF = atrial fibrillation; ESRD = end stage renal disease
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