Full Review

Should patients with advanced chronic kidney disease and atrial fibrillation receive chronic anticoagulation?

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Abstract
Atrial fibrillation is prevalent in dialysis patients. Both ischaemic and haemorrhagic stroke are common in patients on dialysis with atrial fibrillation. In the general population, warfarin is highly effective for prophylaxis of ischaemic stroke, and though warfarin use likely increases the risk of intracranial haemorrhage, the absolute increase in risk is small. In the general population, absolute and relative increases in major extracranial bleeding from warfarin use are also both modest. In patients on dialysis, the effectiveness of warfarin as a prophylaxis for ischaemic stroke and its effects on intracranial or extracranial bleeding have not been assessed in randomized trials. Cohort studies vary greatly in their estimates of the magnitude of the increased risk of bleeding from warfarin use. A single cohort study found rates of intracranial haemorrhage in patients on dialysis with atrial fibrillation to be in an order of magnitude that is greater than those in the general population with atrial fibrillation, and that intracranial haemorrhage more than doubled in association with warfarin use. Basic, translational and limited clinical observations also implicate warfarin in the pathogenesis of vascular calcification, which is likely on the causal pathway to patient-important vascular outcomes. Finally, the effect of warfarin on ischaemic stroke in three recent large observational studies has been in the direction of harm, no benefit, and modest, non-statistically significant benefit, respectively. We believe that no clear recommendation can be made between three alternative approaches. It is acceptable to withhold or discontinue warfarin in patients on dialysis, to offer anticoagulants to all dialysis patients without a contraindication whose congestive heart failure, hypertension, age, diabetes and previous stroke or transient ischaemic attack (CHADS2) score >1 or 2 and to discuss and individualize prophylaxis on a patient-by-patient basis. Randomized trials of new agents are needed in this area.

Keywords: anticoagulation; atrial fibrillation; bleeding; CKD; stroke

Overall, there is a 6-fold increased risk for stroke in dialysis patients compared with an age- and gender-matched general population [1]. Atrial fibrillation, a well-established risk factor for thrombotic stroke, has a 10- to 20-fold higher prevalence in patients on haemodialysis (HD) than in the general population: the United States Renal Data System (www.USRDS.org) reports a prevalence of 13% in HD patients and 7% in PD patients. However, the use of warfarin to prevent stroke in patients with atrial fibrillation is highly variable from country to country, with the percentage of patients treated with warfarin as low as 2% in Germany to as much as 37% in Canada (Figure 1) [2]. [The overall proportion in the Dialysis Outcomes and Practice Patterns Study (DOPPS) was 16%; overall in Europe 9% and in the USA 26% [2].] This heterogeneity reflects recognized and unrecognized uncertainty about benefit and risks. When Canadian nephrologists were surveyed about common scenarios of atrial fibrillation in HD patients, 16 to 48% expressed overt uncertainty about each given scenario, and for each scenario there was a range of opinion, with some nephrologists prescribing warfarin (4 to 80%) and others who would not (4 to 68%) [3].

Our working group has recently summarized what is known about the incidence and prevalence of atrial fibrillation in patients on dialysis [4]. The overall prevalence of atrial fibrillation in patients with end-stage renal disease (ESRD) is estimated at 11.6% [95% confidence intervals (CI) 9.6–13.7], although there is important heterogeneity in the estimates. The incidence of new atrial fibrillation in patients on dialysis is 2.7% per year (95% CI, 2.0–3.4%). This is clearly a common clinical problem that requires...
a systematic approach. One important issue for these patients is how best to mitigate the risk of stroke.

Which patients are most likely to have atrial fibrillation?

Prevalent atrial fibrillation is known to be associated with age, time with ESRD, male gender, Caucasian race, duration of dialysis, dialysate potassium, hypertension, heart failure, coronary artery disease, recurrent cellulitis, psychiatric disorder, left ventricular hypertrophy (LVH), valvular heart disease, history of cardiac arrest, pericarditis, prosthetic heart valve, cerebrovascular or peripheral arterial disease, COPD, cancer and use of warfarin, digoxin or calcium channel blockers [2, 5]. Prevalence is increasing over time. In the USA, the prevalence has tripled in the last 15 years, which, with the growth of dialysis population, results in a 7-fold increase in the absolute number of people affected: 24,000 Americans in 2006 [5].

Which patients have strokes, and what kind of strokes do they have? What is the risk associated with atrial fibrillation?

As expected, the excess risk of stroke in dialysis patients is disproportionately borne among the elderly. Patients on dialysis around the age of 40, compared with people of a similar age who are not on dialysis, face an increase in the risk of hospitalization for stroke of 2% per year, which rises to an excess risk of >4% per year for patients on dialysis who are ≥65 years of age [1]. Overall, the risk of total stroke is increased 6-fold, with 6-fold increases for both haemorrhagic and ischemic stroke [1].

In our meta-analysis, the risk of stroke in patients on dialysis who did not have atrial fibrillation was around 2% per year (95% CI, 1.2–2.6%), whereas for patients with atrial fibrillation it was higher at 5% per year (95% CI, 3.8–6.7%). This analysis includes patients from the large DOPPS international prevalent cohort: in these patients, the annual risk of stroke in patients with atrial fibrillation was 3.4% compared with 1.9% in those without [2]. The crude hazard ratio of 1.8 is not that different from the overall indirect difference (derived from studies that are not directly comparable) seen in our systematic review (5 versus 2%, giving an incidence ratio of 2.5). However, in the DOPPS data set, an adjusted analysis was also possible, and the adjusted hazard ratio was substantially smaller at 1.28 (95% CI, 1.01–1.62) [2]. Clearly, strokes, both related and unrelated to atrial fibrillation, are increased in patients on dialysis, but the degree to which atrial fibrillation per se accounts for this in dialysis patients is uncertain.

In patients with atrial fibrillation on dialysis, the annual risk of intracerebral haemorrhage is 1.1% in patients not on warfarin and 2.6% in those on warfarin [6]. This is dramatically higher than that observed in trials of warfarin in people with atrial fibrillation in the general population (around 0.3% per year in patients on warfarin and 0.1% per year in patients not on warfarin) [7].

How does atrial fibrillation affect the risk of death?

The increased risk of death from all causes in HD patients with atrial fibrillation has long been recognized in unadjusted analyses, with effect sizes as high as 2.7 reported [8–10]. In robust data from the US Renal Data System, unadjusted all-cause mortality is increased by 2-fold, an association that has remained remarkably static over the last decade [5]. However, in the international DOPPS cohort (as observed for the effect on stroke risk), the adjusted hazard ratio is substantially lower than the crude ratio 1.17 for death in those with compared with those without atrial fibrillation. This is comparable with the adjusted hazard ratio of 1.31 reported for death from all causes in patients with atrial fibrillation who are not on dialysis, compared with those without atrial fibrillation [2]. It seems, then, that much of the excess risk of death associated with atrial fibrillation is explained by age and co-morbidity. However, the presence of atrial fibrillation remains a useful clinical marker of a worse overall prognosis.

How strong is the evidence on the use of warfarin in the general population, and how large is the protective effect? What are the adverse effects?

At this point, it is worth quantitatively reviewing the evidence for the use of warfarin in the general population with atrial fibrillation. Meta-analysis of large concordant randomized trials conducted in patients with non-valvular atrial fibrillation who were not on dialysis shows that warfarin, adjusted to maintain international normalized ratio (INR) 2:3, reduced the risk of stroke (composite outcome
of all ischaemic stroke or intracranial haemorrhage [odds ratio (OR) 0.39 (95% CI, 0.26–0.59)] [7]. In the studies summarized in this review, the risk of stroke in patients with atrial fibrillation who were not treated with warfarin was around 6%, over variable follow-up periods between 1.2 and 2.2 years. Importantly, warfarin also decreased death from all causes [OR = 0.69 (95% CI, 0.50–0.94)]. Perhaps the most feared side effect when anticoagulants are used prophylactically to prevent ischaemic stroke is the increased risk of intracranial haemorrhage. On warfarin, the event rate was 0.4% over the 1.2 to 2.2 years follow-up, and the estimated effect size for this complication was OR 2.38 (95% CI, 0.54–10.50). Overall bleeding is also a relevant outcome in any population. In the general population, the absolute event rates for major bleeding were 1.4% on warfarin compared with 1.3% without warfarin over 1.2 to 2.2 years [OR = 1.07 (95% CI, 0.53–2.12)].

**Patients on dialysis are different. First, what is the risk of bleeding and how much is it increased by the use of anticoagulants?**

In patients on dialysis, particularly in those on HD, our concern is that overall bleeding rates may be much higher than those observed in studies of the general population, owing to gastrointestinal co-morbidity, contervention with antiplatelet agents, frailty and risk of falling, anaemia, uraemia-related abnormalities of thrombosis, thrombosis, and platelet function and, among HD patients, the use of regular anticoagulants for the dialysis procedure. Although there are data to support this common clinical concern, they are remarkably limited. In the general population, the validated HEMORR2HAGES score includes renal insufficiency as a risk factor associated with increased bleeding in patients prescribed warfarin. Only three controlled trials of warfarin in patients on dialysis have been reported; each studied a couple of hundred patients, and all three studied low-intensity warfarin [11–13]. Annual bleeding risks in these studies in patients on warfarin varied from 0 to 20%, and on placebo from 0 to 15%, with relative risk of bleeding from 1.3 to infinity. In cohort studies, similar heterogeneity is seen. The annual risk of bleeding on warfarin is reported between 3 and 50% and the risk of bleeding in patients not taking warfarin is reported between 0.8 and 25% [6, 14–19]. Relative risks varied from 1 to 25. In a detailed single-centre cohort study of 255 patients on HD over 1028 patient-months, multivariable analysis of the effect of drugs on major bleeding showed a rate ratio (RR) of 4.1 (95% CI, 1.1–15.2, P = 0.076) for warfarin alone, a RR of 5.7 (95% CI, 1.82–17.8, P = 0.002) for aspirin and a RR of 8.2 (95% CI, 2.2–30.6, P = 0.006) for the combination of aspirin and warfarin [18]. Warfarin use is also associated with hospitalization and death. In a large US administrative data set from Fresenius Medical Care, the adjusted hazard ratio for death associated with warfarin was 1.77 (0.82 to 3.82) and that for hospitalization was 1.46 (95% CI, 1.1–1.81) [20]. In contrast to these findings, a cohort study of incident dialysis patients, who were US Medicare beneficiaries, observed no difference in the rate of gastrointestinal bleeding when patients on warfarin were compared with those without: 13.4 versus 13.6% per year, respectively [hazard ratio 0.96 (95% CI, 0.70–1.31)], although the absolute risk in each group was very high compared with the incidence of major bleeding in patients with atrial fibrillation who were not on dialysis [6, 7]. Between-study variation in the degree of confounding by indication (the tendency not to prescribe warfarin to those at greatest risk of bleeding) likely accounts for the heterogeneity observed. No robust estimates for the increase in risk associated with the prescription of warfarin to high- or low-risk patients will be available until randomized trials of this question are conducted in dialysis patients.

**Are there other adverse effects of warfarin which are peculiar to patients on dialysis?**

Warfarin may contribute to heterotrophic calcification. Heterotopic calcification is a prominent feature of vascular disease in dialysis patients [21–23], and is an active cell-mediated process in which vascular smooth muscle cells undergo osteoblastic differentiation and express proteins that regulate mineralization [23, 24]. Matrix Gla protein (MGP) is an inhibitory regulator of tissue mineralization. This calcification inhibitor is activated by gamma-carboxylation of glutamate residues, a process that requires vitamin K as a cofactor. Intracellular vitamin K levels depend on intracellular recycling of vitamin K which is mediated by vitamin K oxidoreductase. This enzyme is the therapeutic target of warfarin. Therapeutic depletion of intracellular vitamin K in dialysis patients who take warfarin quite likely occurs on the background of nutritional vitamin K inadequacy. A typical renal diet is estimated to contain 80 mcg or less of vitamin K per day, but recommended daily intakes are 120 mcg per day for men and 90 mcg per day for women [25]. Patients with a low glomerular filtration rate (GFR) and patients on peritoneal dialysis have been shown to have a suboptimal vitamin K status [26, 27].

Animal models attest to the importance of this regulatory pathway: the MGP knock-out mouse develops rapidly fatal vascular calcifications [28]. However, clinical correlates in warfarin-treated patients have received little attention. Three small cross-sectional studies have been conducted in the general population, showing association between warfarin use and calcification in univariate [29, 30] but not multivariate analysis [31]. In 2009, a study of 1155 patients with atrial fibrillation identified a higher prevalence of valvular calcification in warfarin users (OR = 2.6, 95% CI, 1.9–3.5) than in non-users after adjusting for age, sex, race, diabetes mellitus, hypertension and coronary artery disease [32]. In patients with a low GFR, the vitamin K status was associated with coronary artery calcification [33], and in HD patients, a history of ≥18 months of warfarin
use, compared with shorter or no use, gave an adjusted OR of 3.77 (95% CI, 0.97–14.7, P = 0.055) for the presence of aortic valve calcification by echocardiography [34]. The most severe form of heterotrophic calcification is calcific uraemic arteriolopathy (CUA, also known as calciphylaxis) and numerous case reports [35, 36] and in the last few months, a case–control study [37], have linked the initiation or use of warfarin with the development of CUA.

**What direct evidence do we have on the risks and benefits of warfarin in dialysis patients with atrial fibrillation?**

Given the heightened concerns for patients on dialysis about bleeding (particularly intracranial bleeding) and about calcification, large randomized controlled trials in these patients, examining all clinically relevant outcomes, would be very helpful; however these are lacking. A number of large cohort studies have, however, been reported. In the first study, patients on dialysis with atrial fibrillation discharged from hospital on warfarin compared with those not on warfarin experienced substantially lower mortality, P ≤ 0.001 [10]. The second study, of 2193 incident patients with prevalent atrial fibrillation on HD at Fresenius facilities in the USA, found that the risk of stroke was increased in patients taking, compared with not taking, warfarin, with hazard ratio of 1.74 (95% CI, 1.11–2.72) in a model adjusted for covariates by propensity scoring [38]. The third study, of 2188 prevalent patients on HD with prevalent atrial fibrillation sampled in the DOPPS, point estimates for the risk of stroke associated with warfarin were 1.29 and 1.35 in patients ≤65 years, and 66 to 75 years respectively, neither value was statistically significant. However, in patients >75 years of age, the hazard ratio for stroke associated with warfarin use was 2.17 (95% CI, 1.04–4.53) [2]. In the fourth and most recent study, Medicare data were used to examine incident patients on HD with incident atrial fibrillation. In an intention-to-treat analysis, the risk of ischaemic stroke was 7.4% per year in patients taking warfarin and 7.6% per year in those not taking warfarin, with the hazard ratio not statistically significant but in the protective direction of 0.92 (95% CI, 0.61–1.37). However, the risk of haemorrhagic stroke was substantially and statistically significantly increased in association with warfarin use, with a hazard ratio of 2.38 (1.15 to 4.96). In contrast to the absolute risk of intracranial haemorrhage in warfarin-treated patients not on dialysis of 0.4% over 1.2- to 2.2-year follow up [7], the absolute risk in patients on dialysis was 2.6% per year in those on warfarin and 1.1% per year in those not on warfarin [6]. The results from the intention-to-treat analysis and an as-treated analysis, in which patients’ data were censored at discontinuation of warfarin, were similar.

Of these three most recent papers describing the association between warfarin and stroke [2, 6, 38], the most recent [6] is the most robust in terms of design, studying patients incident to dialysis who develop incident atrial fibrillation. Of the three papers, this produces the estimates most favourable to the use of warfarin prophylaxis, which though not large or statistically significant, tend towards benefit from warfarin. The other two analyses showed associations with either no benefit [2] or harm [38]. It is very likely that in all cohort studies patients for whom warfarin is prescribed are those at greatest risk of stroke, and that this plays out as a greater observed stroke rate in these patients. Although this effect, termed confounding by indication, may account for bias in the direction of no benefit or even harm, the data are nonetheless disturbing.

**How should we integrate all this information and make clinical decisions under uncertainty?**

Given the lack of certainty about warfarin use in dialysis patients, one approach is to attempt to risk stratify and prescribe only to patients deemed to be at high risk of thrombotic stroke. In the general population, the CHADS2 score is a validated predictor of stroke risk [39], and all major guidelines endorse treating patients with CHADS2 scores >2, or even >1, with warfarin [40]. The CHADS2 score has been validated in dialysis patients in a retrospective cohort of DOPPS patients. With the exception of a CHADS2 score of 1, which is associated with a 0.6% annual risk of stroke in the general population and 2.1% annual risk of stroke in dialysis patients, the score shows a graded increase is stroke risk with CHADS2 score and is surprisingly similarly calibrated in dialysis patients (i.e., the absolute risk in dialysis patients is numerically similar to that in the general population) [2].

The HEMORR2HAGES score, in the general population, is a validated predictor of annual bleeding risk, which has not, to our knowledge, been validated in patients on dialysis [41]. However, examination of the HEMORR2HAGES and CHADS2 scores shows that there is a great deal of shared variance: older age, hypertension and previous stroke appear in both risk scores. The HEMORR2HAGES score includes renal disease as a risk factor, so that all patients with ESRD would start with a baseline score of 1, or perhaps 2 if one were to consider their controlled moderate anaemia to fulfil the anaemia criteria in the HEMORR2HAGES score. The shared variance between the scores and the high floor values in the HEMORR2HAGES score limit the usefulness of these scores in dialysis patients.

Trading off the risk between major bleeding and stroke is also not straightforward. When people (who were not on dialysis) were presented with a scenario in which patients with mild atrial fibrillation experience an additional two major bleeds over a 2-year period caused by warfarin prophylaxis, most (71%) patients would find prophylaxis acceptable if it prevented just one stroke. However, only 39% of physicians felt this would be a reasonable trade off, and 26% of physicians felt that to offset these two bleeds, ≥4 strokes would have to be prevented [42]. It seems that both patient and physician preferences vary widely and, importantly, that patients are more stroke averse than their physicians.
In the past, we and others [43–45] have suggested specifically trading off the risks and benefits of bleeding and stroke, assuming warfarin as effective in dialysis patients as in the general population, and using the ratio of two major bleeds acceptable for each stroke prevented suggested by common patient preferences in the general population. We now recognize that this approach is fundamentally limited by the multiple assumptions that must be made at every step. The most serious of these assumptions is of course the assumption that warfarin is all effective, which is shaken by the absence of any strong association with benefit in three large observational studies [2, 6, 38]. Furthermore, the scenarios on which the preference data are based did not include fatal stroke, fatal bleeding or intracranial bleeding, and these are extremely important outcomes. The quantitative importance of intracranial bleeding in patients with atrial fibrillation on dialysis (annual risk of 1.1% in patients not on warfarin and 2.6% in those on warfarin [6]) is new and important information. Finally, scenarios were generated in the general population and do not necessarily reflect the perspective of dialysis patients [42].

What then should we do?

In summary, we know that atrial fibrillation is prevalent in patients on dialysis and that stroke is frequent in these patients. We know that atrial fibrillation is associated with the risk of stroke in these patients and that warfarin is associated with an increased risk of bleeding. However, we do not know whether warfarin reduces the risk of stroke in patients with atrial fibrillation on dialysis. Current evidence makes inferences and recommendations about therapy very difficult. There are three possible clinical responses to this knowledge gap. We could anticoagulate no one for this indication, as it appears to be common practice in Germany, for example [2]. Or we could anticoagulate all patients with CHADS₂ scores >1 or 2 unless there is a strong contraindication, generalizing from data in the general population, or anticoagulate selectively those who have had previous embolic stroke. Or, finally, we could individualize according to risk of bleeding, stroke and patient preferences, and attempt to optimize time within therapeutic INR range through rapid turnaround and response to results. We believe that each of these approaches is acceptable based on current evidence, and that the literature does not permit us to recommend one approach over another.

In the future, we hope that alternative anticoagulants can be developed that can be dosed safely in patients on dialysis. Perhaps better understanding of the pharmacokinetic properties of the new oral direct Xa and IIa inhibitors will allow them to be studied for this indication, at modified doses, in patients on dialysis [46]. Perhaps the longer-acting low molecular weight heparins can be used for both circuit anticoagulation and stroke prophylaxis in patients on HD. New agents with different mechanisms of action would avoid the theoretical risk of calcification that is specific to our dialysis population.

This review has focused on patients on dialysis, and most of the studies discussed are of patients on HD. Very little is known about this problem in patients on peritoneal dialysis. Furthermore, in patients not on dialysis, low GFR is associated with atrial fibrillation [47], and both low GFR and proteinuria are independent predictors of stroke risks [48]. Our enquiry into optimal anticoagulation strategies in patients with ESRD will lead us also to question optimal strategies in the much larger population of patients with very low GFR (Stage 4 or 5 chronic kidney disease, CKD) who are not on dialysis. The scarcity of information in this area was recognized by a recent Kidney Disease: Improving Global Outcomes conference [49]. Uncertainty will remain for all these patients until adequately powered randomized trials are conducted.

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References

4. Zimmerman et al. For peer review in parallel with this invited review