Atrial fibrillation therapy and stroke prevention in hemodialysis patients

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ABSTRACT

The prevalence of atrial fibrillation (AF) in patients with chronic kidney disease (CKD), especially on hemodialysis (HD) is higher compared to the general population without CKD and reaches ~20%. The risk of ischemic stroke in CKD patients is also significantly increased. However, since the risk of bleeding is also significantly increased in CKD patients and the number of bleeding events exceeds the number of thrombotic events, there are great concerns regarding the routine use of anticoagulation in this patient population. No randomized studies were performed to compare anticoagulation with placebo in patients with advanced CKD and AF. This lack of knowledge is reflected in international guidelines which refrain from clear recommendations. The use of anticoagulation for stroke prevention in HD patients with AF should be strictly individualized for each patient. Anticoagulation for stroke prevention in HD patients with AF seems justified only in selected patients with high stroke and low bleeding risk. Reduced-dose direct oral anticoagulants (especially apixaban) may prove beneficial. In patients with high thrombotic and bleeding risk, left atrial appendage closure could be considered. In this article, the results of the most relevant observational studies with anticoagulation in CKD/HD patients with AF have been presented and discussed. Furthermore, results of randomized studies comparing vitamin K antagonists with non-vitamin K antagonists in CKD patients have been discussed in detail. Finally, ongoing randomized studies with reduced doses of apixaban, factor XI inhibitors, and left atrial appendage closure in CKD patients are mentioned. A brief summary of rhythm control strategies in AF is given.

Key words: anticoagulation, atrial fibrillation, bleeding, dialysis, renal failure

INTRODUCTION — EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION AND CHRONIC KIDNEY DISEASE

Atrial fibrillation (AF) is characterized by rapid and uncoordinated electrical and mechanical activity of atrial cardiomyocytes. AF is considered the most commonly sustained arrhythmia with an estimated worldwide prevalence of 600 per 100 000 in men and 370 per 100 000 in women, with significant regional and ethnic variations [1, 2]. AF prevalence is mostly determined by age, with the prevalence spanning from 0.1% among adults under 55 years to 9.0% in those 80 years or older [3]. The overall prevalence of AF may increase significantly after thorough screenings with new rhythm monitoring devices [4]. AF is associated with increased mortality, mainly due to the increased risk of stroke and worsening of heart failure [5, 6]. Recently, AF has also been linked to increased risk of cognitive impairment and dementia [7].

Chronic kidney disease (CKD) is divided into 5 stages according to glomerular filtration rate, with CKD 5 treated by dialysis as end-stage chronic kidney disease. Novel, more patient-centered, nomenclature is now being used for patients with glomerular filtration rate (GFR) <15 ml/min/1.73 m^2 or on dialysis treatment; terms like "kidney failure" are replacing terms such as (end-stage kidney disease" (ESKD) or "end-stage renal disease" (ESRD) [8]. The prevalence of stage 5 CKD worldwide is reported to be 0.1%; the number of patients treated by hemodialysis varies significantly worldwide and is substantially higher in wealthier countries [9]. Hemodia-

lysis is the most used form of kidney replacement therapy (KRT) and accounts for nearly 70% of all patients on kidney replacement therapy and nearly 90% of dialyses (the rest being peritoneal dialysis) [10].

There is a close and bidirectional relationship between CKD and AF since patients with CKD are at higher risk of AF and AF patients are more prone to develop CKD [11–13]. AF is also associated with a significant increase in mortality of CKD patients [14]. Estimates of the prevalence of AF differ by study cohorts. For example, the nationwide United States Renal Data System states a prevalence of 21% and 16% in hemodialysis (HD) and peritoneal dialysis patients, respectively [15]. Just as in the general population, the use of novel rhythm monitoring devices has increased the number of AF patients diagnosed with kidney failure. In a study of HD patients with implanted loop recorders, 31% (18 of 59 patients) had *de novo* detection of AF episodes lasting ≥6 minutes during a 6-month follow-up [16].

The increased prevalence of AF in HD patients is not surprising given the shared risk factors for both AF and CKD, factors associated directly with advanced kidney disease, and finally with the effects of the dialysis procedure itself.

Age is one of the greatest risk factors for both AF and CKD [3] Other frequently shared risk factors are hypertension, obesity, and diabetes mellitus, all of which pose a rising global health burden [17]. The most common primary renal diagnosis (cause of kidney failure in HD patients) in the Western world is diabetes, followed by hypertension [18, 19].

The mechanisms associated with advanced kidney disease that are involved in AF development include oxidative stress, chronic inflammation, transforming growth factor-β1 (TGF-β1) signaling, hyperactivation of the renin-angiotensin-aldosterone system, and altered mineral and bone metabolism associated with CKD, most of which ultimately play a role in myocardial fibrosis [20–22].

The role of mineral and bone abnormalities in chronic kidney disease and their impact on cardiovascular disease is increasingly more recognized. Levels of fibroblast growth factor-23 (FGF-23), a circulating peptide produced by osteoblasts and osteocytes that is crucial for serum phosphate control, rise in the early stages of CKD. This cytokine activates intracellular signaling leading to cardiac hypertrophy [23]. The presumed vicious cycle is left ventricular hypertrophy leading to diastolic dysfunction, increase in left ventricular filling pressure, and then left ventricular strain with fibrosis and dilatation, which creates a substrate for AF. Thus, and not surprisingly, concentrations of FGF-23 were shown to be strongly and independently associated with increased risk of AF incidents [24]. This situation is similar to heart failure with preserved ejection fraction (HFpEF), which is, by far, the most common heart failure phenotype in HD patients [25]. It is widely known that AF and HFpEF often coexist; AF is seen in about two-thirds of HFpEF patients and is linked to a worse prognosis [26].

Finally, the dialysis procedure itself is associated with large changes in plasma constituents and volume status, which can also play a significant role in triggering atrial arrhythmias. In a study of dialysis patients with implanted cardioverter defibrillators capable of continuous rhythm monitoring, AF occurrence was analyzed in relation to the HD procedure [27]. Of all AF episodes occurring on HD days, 8% occurred before the dialysis procedure, 48% during, and 43% after dialysis. AF also occurred more often around HD with higher ultrafiltration and lower dialysate potassium concentrations (which can serve as a surrogate for a potassium shift with lower dialysate concentrations indicating higher shifts between dialysate and plasma).

Hemodialysis significantly contributes to changes in serum electrolytes: serum potassium concentration changes by a mean of 1.2 mmol/l during HD, and 40% of patients experience hypokalemia immediately after HD, and a significant post-HD decrease was also seen in magnesium and phosphate concentrations [28]. Pre-dialysis hypokalemia and lower dialysate potassium (below 2 mmol/l) are independently associated with increased risk of AF [29].

STROKE RISK ASSOCIATED WITH KIDNEY FAILURE

There are several reasons why patients with advanced kidney disease are at higher risk of stroke. The numbers of both ischemic and hemorrhagic strokes are increased in the HD population. Although ischemic stroke is more frequent than hemorrhagic (also in the HD population), the proportion of hemorrhagic to ischemic strokes is higher in HD patients compared to the general population [30].

At the pathophysiological level, the increased ischemic stroke risk and overall increased thrombogenesis involve primary and secondary hemostasis. Platelet activation and interaction, altered platelet transcriptome and secretome, platelet-derived microparticles, and endothelial dysfunction all seem to play a role, with most effects being mediated by uremic toxins [31]. A higher burden of atherosclerosis in CKD patients, including the carotid arteries, is well established [32]. Interestingly, oxidative stress, inflammation, and endothelial dysfunction associated with CKD alter brain vascular reactivity and function of the blood-brain barrier, making the brain more susceptible to ischemia and aggravating brain injury secondary to ischemia [33].

The increased risk of hemorrhagic stroke is primarily caused by platelet dysfunction discussed later. Additionally, arterial hypertension (AH) plays a role. The majority of HD patients have AH, which is often poorly controlled and resistant to pharmacotherapy [34]. AH is a leading risk factor for hemorrhagic stroke in the general and HD populations [35, 36].

All these pathophysiological circumstances have major clinical implications and lead to an increase in the number of both ischemic and hemorrhagic strokes. A meta-analysis of cohort studies focusing on stroke risk

in relation to kidney function pooling over 2 million patients found that the stroke rate increases by 7% for every 10 ml/min/1.73 m^2 decrease in GFR [37] In HD patients, the stroke risk was found to be 3–10 times higher than in the general population [35, 36]. HD was also linked to a worse prognosis, longer in-hospital stays, worse functional status, and worse response to rehabilitation after stroke [38, 39]. Furthermore, CKD was found to be associated with higher risk of hemorrhagic transformation of ischemic stroke and with underutilization of evidence-based therapies for acute stroke patients [39, 40].

BLEEDING RISK IN HEMODIALYSIS PATIENTS

The bleeding diathesis in kidney failure is a complex phenomenon, but most abnormalities are present on the platelet count. Disturbed platelet adhesion, disturbed endothelial-thrombocyte interplay, defective platelet aggregation, an imbalance in secretory granule content, and even defects in the platelet cytoskeletal structure have been demonstrated in HD patients [31]. Most of the aberrations seem to be mediated by uremic toxins, which explains the beneficial effect of dialysis [41]. Aspirin, often prescribed to HD patients for cardiovascular primary or secondary event prevention, has an amplified impact on hemostasis compared to healthy individuals [42]. Finally, anticoagulation (most often heparin-based) used during HD to prevent blood clotting in the extracorporeal circuit also contributes to the pro-hemorrhagic milieu.

The risk of bleeding in CKD and, especially, HD patients is higher compared to the general population. For instance, a retrospective cohort study with 11 000 patients (>80% on HD) found that the annualized incidence of hospitalization for bleeding was 5.3 per 100 patient-years [43] The most frequent bleeding site was the lower gastrointestinal (GI) tract, with an incidence of 3.1 per 100 patient-years, followed by upper GI bleeding (2.1 per 100 patient-years) and intra-cerebral and subarachnoid bleeding (0.3 per 100 patient-years). In another prospective cohort study with nearly 50 000 patients, the observed rate of bleeding requiring hospitalization was 8 per 100 patients-years [44]. Bleeding rates were dramatically higher in HD patients with a history of GI bleeding in the past 12 months. A prospective cohort study of over 200 000 European dialysis patients (84% on hemodialysis) found a 12.8-fold increased risk of death caused by bleeding compared to the general population [45]. In this cohort, older age at the start of dialysis, primary kidney diseases including renal vascular disease, AH, and diabetes mellitus were all associated with an increased risk of bleeding. Older age and associated frailty affect outcomes of anticoagulated patients, irrespective of renal function [46]. A meta-analysis of studies on anticoagulation in elderly (age ≥65 years) AF patients with CKD found similar rates of ischemic stroke/transient ischemic attack in anticoagulated vs. nonanticoagulated patients (risk ratio [RR], 1.18; 95% confidence interval [CI], 0.88–1.58 for dialysis patients) and increased risk of bleeding in dialysis (RR, 1.37; 95% CI, 1.09–1.74) but not in non-dialysis patients [47]. Another large cohort study of HD patients found that current smoking, history of coronary vascular disease, and inability to walk without assistance (a sign of overall frailty) were predictive of upper GI bleeding [48].

An observational study of over 200 000 dialysis patients examined death caused by bleeding and stroke and compared the data to the general population [49]. The study found that bleeding-associated mortality was 12.8 times higher, and stroke-related mortality was 12.4 times higher than in the general population. On an absolute scale, however, mortality rates for bleeding were lower than for stroke (6.2 vs. 14.3 per 1000 person-years, respectively).

STROKE AND BLEEDING RISK-STRATIFICATION SCORES IN HEMODIALYSIS PATIENTS

In non-CKD patients, the CHA_2DS_2-VASc score has become a standard for stroke risk stratification in patients with AF and is widely used in decision-making [50, 51]. Data on the usefulness of CHA_2DS_2-VASc in CKD patients are far less substantial than for non-CKD patients; nonetheless, studies have confirmed that higher CHA_2DS_2-VASc scores are also associated with higher stroke risk in HD patients. A Taiwanese study examined the predicted risk accuracy of CHA_2DS_2-VASc scores in 11 000 non-anticoagulated HD patients with AF; the authors found that an increased score significantly predicted stroke risk [52]. In HD patients, the median score was 5; but importantly only 3.8% of this HD population had a score of 0 or 1 (compared to 20% in the population in which the scores were validated) [53]. Additionally, even low-risk patients (CHA_2DS_2-VASc score = 0) had an annualized risk of ischemic stroke of 2.1 per 100 patient-years. Thus, the score is not considered useful in clinical practice since its aim is to differentiate between low and high-stroke-risk patients (to accordingly start, or not, anticoagulation treatment), and most HD patients are automatically deemed to be at high risk.

The situation is even more complicated for scoring systems predicting bleeding risk, and evidence to support routine use of bleeding risk scores in HD patients is lacking. Two prospective cohort studies performed in 1745 and 625 patients showed that established bleeding risk scores (such as HAS-BLED, ATRIA, $HEMORR_2HAGES$, and others), performed poorly in predicting future bleeding events [54, 55].

RATE AND RHYTHM CONTROL STRATEGIES IN HEMODIALYSIS PATIENTS

In the general population without CKD, the clear prognostic benefit of rhythm control strategies was confirmed in randomized studies only in patients with left ventricular dysfunction. Therefore, in patients with preserved left ventricular function, the rhythm control strategy is recommended primarily to improve symptoms related to AF. Due to the absence of specific evidence for the CKD population, the

general recommendations are not different from the recommendations for the non-CKD population. Nonetheless, due to important distinctions in CKD patients (i.e., altered drug elimination or possible renal improvement in sinus rhythm), the following paragraph sums up the treatment possibilities of the rhythm control strategy in CKD patients.

With regard to antiarrhythmic drugs, amiodarone does not require dose-renal function adjustment, nor does propafenone, which should, however, be dosed with caution in advanced CKD, and ECG and plasma level monitoring is recommended. On the other hand, dronedarone and sotalol are contraindicated in advanced CKD, and flecainide requires careful dosing with plasma level monitoring [56].

Electrical cardioversion has a high success rate in acute rhythm control, but the maintenance of sinus rhythm (SR) in the long-term is low and the presence of CKD or even HD presents a very significant negative prognostic factor in SR maintenance [57] Compared to patients with normal eGFR, patients with eGFR less than 30 ml/min/1.73 m^2 have a 5-fold higher risk of AF recurrence within one year.

Catheter ablation presents the most effective treatment modality for the AF rhythm control strategy. No randomized study compared the effect of antiarrhythmics to catheter ablation specifically in the population of CKD patients. However, data from observational studies have shown that the efficacy of catheter ablation is approximately 2-fold lower in patients with advanced CKD compared to the general population. In the meta-analysis of observational studies by Chung et al. [58], patients with CKD had a significantly higher risk of AF recurrence (RR, 2.34; 95% CI, 1.36–4.02; P <0.01). The risk of AF recurrence continuously increases with decreasing renal function. Furthermore, patients with less impaired renal function (CKD 3) compared to the more severely impaired (CKD 4–5) not only have a better effect in terms of SR maintenance but also an improvement in renal function was observed in patients who maintained SR. For instance, in the cohort of 368 CKD-3 patients published by Takahashi et al., freedom from AF achieved by catheter ablation was associated with eGFR improvement, and similar findings were reported by others [59, 60]

In conclusion, catheter ablation in CKD patients should be considered in the same circumstances as in the general population, i.e., with the presence of symptoms or with left ventricular dysfunction. If catheter ablation is considered, it should not be postponed but performed in the early stages of renal impairment due to better efficacy and a chance of improving renal function due to SR maintenance.

STRATEGIES TO PREVENT ATRIAL-FIBRILLATION-RELATED STROKE IN KIDNEY FAILURE PATIENTS

Vitamin K antagonists

In non-CKD patients, the effect of vitamin K antagonists (VKAs; namely warfarin), was tested in several randomized studies, and all of them confirmed the superiority of VKA over placebo in terms of ischemic stroke reduction. Unfortunately, stage 4 and 5 CKD and HD patients were excluded from these seminal trials.

As such, the effect of VKAs in kidney failure patients has only been assessed using observational studies, and often with conflicting results. A meta-analysis of 15 observational studies with nearly 50 000 patients (22% on warfarin) showed that warfarin use, compared to no anticoagulation, was not associated with a significant reduction in ischemic strokes (hazard ratio [HR], 0.96; 95% CI, 0.82–1.13) and had no effect on mortality (HR, 0.95; 95% CI, 0.83–1.09) [61]. The risk of hemorrhagic stroke was significantly increased (HR, 1.49; 95% CI, 1.03–1.94), but surprisingly, the increase of all-cause major bleeding did not reach statistical significance (HR, 1.2; 95% CI, 0.99–1.47). In another observational study of older dialysis patients (over 65 years), a significant increase in major bleeding was reported [62]. VKA treatment must be interpreted relative to long-term international normalized ratio values; a higher time in the therapeutic range (TTR) is associated with a reduction in the number of strokes [63]. Real-world data show that international normalized ratio values in dialysis patients are often subtherapeutic, with a low TTR even in closely monitored clinical trial patients [64]. In addition, a rare but serious complication in kidney failure is calcific uremic arteriolopathy (sometimes wrongly called calciphylaxis). It presents as extensive, painful ischemic skin lesions caused by skin arteriole wall calcification and obstruction, with 1-year mortality nearing 50% [65]. Warfarin treatment is linked to this condition and is possibly causal, with VKAs antagonizing the action of matrix Gla protein (MGP), a protein that inhibits arterial wall calcification.

Direct oral anticoagulants in renal kidney patients

In the non-CKD population, direct oral anticoagulants (DOACs) have replaced VKAs due to similar efficacy in terms of ischemic stroke reduction, and a significantly lower intracranial bleeding risk. All DOACs are excreted by the kidneys to some extent, with approximate renal clearance being 80% for dabigatran, 50% for edoxaban, 35% for rivaroxaban, and 25% for apixaban [66]. Furthermore, 60% of dabigatran, 9% of edoxaban, 7% of apixaban, and 1% of rivaroxaban are removed by hemodialysis. Essentially, from the pharmacokinetic perspective, apixaban presents the potentially most favorable DOAC for CKD patients.

Regrettably, patients with advanced CKD (i.e., CrCl <30 ml/min; <25 ml/min for apixaban) have been excluded from the landmark trials. Table 1 summarizes currently completed randomized trials on anticoagulation strategies in HD patients.

Apixaban — the most promising DOAC in hemodialysis patients

Due to its aforementioned pharmacokinetics, apixaban has garnered the greatest attention in the search for the "best"

Table 1. Published randomized studies on anticoagulation strategies in dialysis patients

First author, study name	Cohort	Comparison (number of patient)	Endpoints	Outcomes and conclusions	Comment
De Vriese et al. *The Valkyrie study* (76)	HD patients *Mean CHA_2DS_2-VASc score = 5*	VKA n = 44 vs. rivaroxaban n = 45 vs. rivaroxaban + vitamin K2 = 42	*Primary*: vascular calcification measures *Secondary*: mortality, stroke, bleeding, modified MACE, valve calcification	No significant changes in vascular calcification. All cause death, stroke, and cardiovascular event rates similar between the groups. Bleeding outcomes not significantly different (except for a lower number of life-threatening and major bleeding episodes in rivaroxaban arms vs. VKA arm)	Not designed or powered to compare VKA vs. DOAC in stroke prevention or bleeding
Pokorney et al. *Renal-AF trial* (70)	HD patients *Mean CHA_2DS_2-VASc score = 4.5*	Apixaban n = 82 vs. VKA n = 72	*Primary:* major or clinically relevant nonmajor bleeding (ISTH definitions) *Secondary:* SSE, death, medication adherence, pharmacokinetics	Trial stopped prematurely for enrollment challenges Inadequate power to draw conclusions regarding primary bleeding outcomes Clinically relevant bleeding events were ≈10-fold more frequent than stroke or systemic embolism Death was the most common major event in the apixaban and warfarin arms The AUC for the 2.5 mg dose in RENAL-AF did not differ from the AUC for patients with eCrCl ≥15 and <90 ml/min from the ARISTOTLE trial	Initial targeted sample size 762 patients Reduce dose apixaban in 29% of apixaban patient. Median TTR in VKA patient = 44%
Reinecke et al. *The AXADIA-AF-NET 8 Study* (64)	HD patients *Mean CHA_2DS_2-VASc score = 4.0*	Apixaban n =48 vs. VKA n = 49	*Primary:* composite of all-cause death, major bleeding, clinically relevant nonmajor bleeding (ISTH definitions) *Secondary:* composite of MI, ischemic stroke, all cause death, DVT, PE	No significant differences in primary or secondary outcomes Non-inferiority of apixaban could not be shown because of insufficient enrollment	Original sample size 222 patients Median TTR in VKA patients = 50.7%

Abbreviations: DVT, deep vein thrombosis; HD, hemodialysis; ISTH, International Society on Thrombosis and Haemostasis; MACE, major adverse cardiovascular events; MI, myocardial infarction; PD, peritoneal dialysis; PE, pulmonary embolism; SSE, stroke and systemic embolism; TTR, time in therapeutic range; VKA, vitamin K antagonist

anticoagulant in HD patients. A pharmacokinetic study in eight HD patients found that apixaban 2.5 mg b.i.d. resulted in a comparable drug exposure as the standard dose (5 mg b.i.d.) in patients without renal impairment; however, 5 mg b.i.d. in HD patients produced supratherapeutic levels [67]. A retrospective cohort study of over 25 thousand Medicare beneficiaries with kidney disease and anticoagulation for AF compared apixaban and warfarin patients matched at a ratio of 1:3 based on prognostic scores (dabigatran and rivaroxaban prescriptions were negligible and thus not tracked) [68]. There was no difference in stroke and systemic embolism (SSE) between apixaban and warfarin (HR, 0.88; 95% CI, 0.69–1.12), but apixaban was associated with significantly lower risk of major bleeding (HR, 0.72; 95% CI, 0.59–0.87). In sensitivity analyses, the standard dose of apixaban was associated with significantly lower risk of SSE and death compared to the reduced dose or warfarin treatment. This study served as the background for the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines recommending the use of standard-dose apixaban in HD patients [51]. Due to the observational nature of the study, these results must be interpreted cautiously. The positive effect of the higher (i.e., standard) dose may be explained by selection bias caused by prescribing standard doses of apixaban to healthier patients who are less prone to bleeding (and *vice versa*), along with an overall worse prognosis for patients meeting criteria for dose reduction.

A later smaller retrospective study analyzed outcomes in 500 HD patients receiving apixaban and 1500 matched non-anticoagulated HD patients [69]. Compared to no anticoagulation, apixaban did not lower the risk of new stroke (ischemic or hemorrhagic), transient ischemic attack, or systemic embolism. However, treatment with apixaban was associated with a 2.7 higher risk of fatal/intracranial bleeding, with rates translating to fatal/intracranial bleeding occurring in 1 in 30 patients on apixaban per year. In subgroup analyses, a significantly higher rate of SSE and a significantly higher incidence of fatal or intracranial bleeding was seen in the subgroup of patients treated with the standard dose, compared to no anticoagulation at all. This did not apply to the reduced dose. As in the previous study, apixaban was connected to lower all-cause mortality. However, the authors also analyzed the incidence of hip fractures and pneumonia, which were lower in apixaban-treated patients. Since these clinical events are definitively associated with frailty and cannot be directly affected by apixaban, it emphasizes the systematic selection bias associated with the observational nature of the study.

The first randomized trial addressing anticoagulation strategies in HD patients was the RENAL-AF trial [70]. Study details can be found in Table 1. This trial enrolled

HD patients with AF and randomized them to apixaban or warfarin treatment. The primary endpoints were stroke or clinically relevant non-major bleeding; secondary outcomes were stroke, mortality, and apixaban pharmacokinetics. Unfortunately, the trial was stopped prematurely due to slow enrollment (the target sample was 760 patients, but only 154 patients were enrolled), which resulted in a lack of statistical power. Nevertheless, several findings from the study are noteworthy. Pharmacokinetic data revealed that the standard dose of 2 × 5 mg in HD patients in the RENAL-AF study resulted in significantly higher area under the curve (AUC) 0–12 values (12-hour area under the curve; a pharmacokinetic measure describing maximum exposure to the drug on a non-dialysis day) than in patients on the same dose of apixaban but with normal renal function in the ARISTOTLE trial. Interestingly, the AUC of patients on 2 × 5 mg apixaban on HD in the RENAL study was similar to the AUC of CKD 3b-4 patients on 2 × 5 mg apixaban in the ARISTOTLE trial, but CKD 5 patients without HD on apixaban 2 × 5 mg in the ARISTOTLE had an even higher AUC than HD patients on apixaban 2 × 5 mg in the RENAL study. On the other hand and very importantly, the AUC of apixaban at 2.5 mg dose in HD patients in the RENAL-AF study did not differ from the AUC of 2.5 mg dose in patients with only mild CKD in the ARISTOTLE trial. Interestingly, there was a relation between pharmacokinetic values of patients with and without bleeding, whereas higher levels of apixaban correlated with more bleeding and *vice versa*. In the RENAL AF study, the primary outcome of major or clinically relevant non-major bleeding (as defined by the International Society on Thrombosis and Hemostasis) occurred at similar frequencies in both groups, i.e., 26% of patients on apixaban and 22% of patients on warfarin, which documented the high risk of bleeding in this population. There was only one hemorrhagic stroke in each group. SSE occurred in 3% of apixaban patients and 3.3% of warfarin patients. Bleeding was 10-fold more frequent than SSE, and HD access site bleeding events comprised the majority of clinically relevant non-major bleeding. The use of a standardized bleeding definition in this study must be appreciated since many observational studies use different definitions of bleeding and bleeding severity, thus hindering data comparison. The low and slow enrollment seen in RENAL-AF is, unfortunately, common in trials with HD patients. In the RENAL-AF trial, a partial explanation for its insufficient enrollment was that some patients were not deemed suitable for the trial by their treating physicians (a factor that can potentially introduce an unintended selection bias). The situation in which physicians prevent patients from participating in trials because they are deemed "clinically unstable" has also been seen in other HD trials [71]. HD patients also experience a high burden of treatment side effects, which partially explains the high drop-out rates, leading to reduced statistical power [71, 72]. Moreover, high mortality in this group is one of the leading causes of low retention rates in trials involving HD patients.

AXADIA-AFNET 8 is the most recent randomized trial on stroke prevention in HD patients with AF [64]. As with the RENAL-AF trial, the study also suffered from insufficient enrollment (for details, see Table 1). In this trial, HD patients were randomized either to reduced-dose apixaban or warfarin treatment. The annualized incidence of the primary outcome, i.e., International Society on Thrombosis and Haemostasis major/non-major bleeding or all-cause death, was similar in both groups and occurred in 36.1% of apixaban patients and 36.6% of warfarin patients. All-cause mortality was also similar between groups (14.8%/year in the apixaban group vs. 17.6%/year in the warfarin group). However, due to insufficient enrollment, apixaban did not meet the non-inferiority criteria.

Rivaroxaban in hemodialysis patients

After apixaban, rivaroxaban is the second most studied DOAC in stroke prevention in HD patients, also due to its relatively low renal clearance (30%) and very low hemodialysis removal (<1%). In the largest observational study comparing 1896 stage 4 or 5 CKD patients (88% on HD), rivaroxaban (39% on reduced doses) did not significantly reduce the risk of SSE but was associated with a significant reduction in major bleeding compared to warfarin [73]. On the contrary, a smaller observational study comparing (n = 173) these two drugs found similar rates of major bleeding but lower rates of SSE (90% of patients on reduced-dose rivaroxaban) [74]. A multinational observational registry of 1461 patients with advanced CKD (eGFR between 15 and 49 ml/min/1.73 m^2) compared outcomes of AF patients treated with rivaroxaban vs. warfarin. After one year of follow-up, rivaroxaban was associated with net clinical benefit, lower event rates for stroke, major bleeding, and all-cause mortality [75]. However, the study was observation and non-randomized, and again, the results have to be interpreted with caution.

The Valkyrie study was so far the only randomized study to compare the effect of VKAs and rivaroxaban on vascular calcifications and observe SSE and bleeding as secondary outcomes [76]. Patients (n = 143) were randomized to VKA, rivaroxaban 10 mg, or rivaroxaban 10 mg + vitamin K2 supplement treatment. The 10 mg dose was chosen based on a pharmacokinetics study by the same group, which showed similar drug exposure of rivaroxaban 10 mg in HD patients compared to healthy individuals, with no accumulation after multi-day dosing [77]. The primary outcome (extent of vascular calcifications) did not differ between the two groups. Interestingly, the rate of stroke was also similar in the groups. A significantly smaller number of life-threatening and major bleeding episodes was observed in rivaroxaban compared to VKA-treated patients. Analogous to other studies, the bleeding rate

was substantially higher than the stroke rate (22/100 person-years vs. 1.22/100 person-years, respectively). It should be noted that the study was not designed or powered to compare DOACs vs. VKAs in HD patients.

Low-molecular-weight heparins

Low-molecular-weight heparin (LMWH), typically given as a single intravenous bolus into the arterial limb when starting dialysis, is used to prevent blood clot formation in the extracorporeal dialysis circuit. LMWH application on non-HD days is also used as a primary stroke prevention strategy for specific patients (in the US and Austria) and is the most preferred option, for instance, in the Czech Republic [78, 79]. However, there is no evidence to support this praxis.

Novel therapeutic stroke prevention approaches

Two promising novel therapeutic approaches are currently being tested. The first is a pharmacological intervention that enompasses of coagulation factor (F)XI inhibition. The development of synthetic FXI inhibitors was based on observations that patients with inherited FXI deficiency, also known as hemophilia C, have a decreased risk of venous thromboembolism and strokes and a relatively low risk of spontaneous bleeding [80]. In the PACIFIC study on AF patients, asundexian (a direct inhibitor of activated FXI) showed reduced bleeding compared to apixaban [81]. However, very recently, a large study (OCEANIC-AF; NCT05643573) comparing asundexian with apixaban was stopped due to the inferiority of asundexian in SSE prevention. In CKD or HD patients, the risk-benefit profile seems appropriate, and, currently, there are two ongoing drug-testing clinical trials in HD patients (NCT04523220 and NCT04534114).

The other approach is based on the fact that the left atrial appendage is the source of cardiac emboli in the majority of cases. Left atrial appendage closure (LAAC) is a procedure offering the potential for long-term stroke prophylaxis without the need for long-term anticoagulation therapy. A meta-analysis of three trials comparing LAAC with anticoagulation showed similar rates of stroke compared to OAC; however, there was a significant reduction in hemorrhagic stroke, non-procedure-related bleeds, cardiovascular death, and all-cause death [82]. LAAC would appear to be an ideal alternative for patients at high risk of bleeding including HD patients, although patients must endure an invasive procedure with appreciable complications and a period of antithrombotic treatment (usually 3 months of dual antiplatelet treatment and life-long aspirin), which is required for epithelialization of the LAAC device. In an observational cohort study, 92 dialysis patients with AF on HD who underwent LAAC were compared to two similarly sized cohorts of HD patients with AF either on warfarin or without antithrombotic treatment [83]. No difference in bleeding was present between LAAC and warfarin patients during the first three months after the procedure; however, there was a significantly higher risk of bleeding in warfarin patients over the next 21 months (HR, 6.4; 95% CI, 1.21–31.72). Overall mortality was higher in both the warfarin (HR, 2.76; 95% CI, 1.31–5.86) and no-antithrombotic therapy (HR, 3.09; 95% CI, 1.59–5.98) arms compared to LAAC patients.

On the other hand, observational data show that older age, impaired eGFR, diabetes, and heart failure are independently associated with increased risk of death within 1 year of the procedure [84]. Therefore, whether this procedure conveys a long-term benefit in the highly comorbid and frail HD population, with its many competing causes of death, remains a question. Fortunately, a randomized controlled trial comparing LAAC with the best medical treatment (LAA-KIDNEY) in HD patients with AF is currently ongoing (NCT05204212).

ANTICOAGULATION IN KIDNEY FAILURE PATIENTS WITH ATRIAL FIBRILLATION — SUMMARY OF THE CURRENT GUIDELINES

The distinctiveness of the HD population is apparent throughout the international guidelines on anticoagulation treatment in those with AF; many societies refrain from making specific statements on the topic. The ESC 2020 guidelines for diagnosis and management of AF state that up-to-date knowledge is "limited and to some extent controversial" and restate the lack of approval of NAOCs in patients with CrCl <15 ml/min or on dialysis [50]. The 2021 European Heart Rhythm Association (EHRA) Practical Guide on DOAC treatment in AF patients summarizes the existing data and states that "given the lack of strong evidence the decision to anticoagulate and (if so) whether to use a NOAC or VKA in patients with end-stage renal failure or on dialysis requires a high degree of individualization" [85]. EHRA goes on to state that DOAC plasma level measurement also lacks robust evidence and should be reserved to highly specialized centers; EHRA also emphasizes the need for shared decision-making between physicians and patients regarding off-label use of anticoagulants. Based on a small pharmacokinetic study on eight patients, the Food and Drug Administration approved apixaban in HD patients in 2012 [86]. Reflecting this, the 2019 AHA/ACC/HRS guidelines updated recommendations for AF management by stating that either warfarin or apixaban "*might be reasonable*" in patients with ESKD (CrCl <15 ml/min) or on dialysis with a IIb class of recommendation and moderate quality evidence based on non-randomized data. These guidelines go as far as to not recommend the use of rivaroxaban and edoxaban in ESKD/dialysis patients for "lack of evidence from clinical trials that benefit exceeds risk" [51]. The 2018 guidelines from Australia and New Zealand advise that the decision to anticoagulated in ESKD should be individualized "with knowledge that an estimate of benefits and harms cannot be provided" and suggest the use of warfarin in severe

Table 2. Upcoming randomized studies on anticoagulation strategy in dialysis patients

Study name, NCT number	Cohort	Endpoints	Comparison	Original estimated enrollment	Actual enrollment	Recruitment status	Estimated study completion date
Oral Anticoagulation in Haemodialysis Patients (AVKDIAL) *NCT02886962*	HD patients	Cumulative incidence of severe bleedings and thrombosis	No anticoagulation vs. VKA	n = 855	n = 50	Active, not recruiting	December 2023
Strategies for the Management of Atrial Fibrillation in patiEnts Receiving Dialysis (SAFE-D) *NCT03987711*	HD / PD patients	*Primary*: adequate recruitment and retainment (evaluation of feasibility of conducting a RCT comparing anticoagulation strategies in dialysis patients) *Secondary:* major bleeding, SSE, all-cause mortality, dialysis access site events, non-fatal MI	Warfarin vs. Apixaban vs. No anticoagulation	n = 150	n = 151	Completed	December 2022
The Danish Warfarin-Dialysis Study — Safety and Efficacy of Warfarin in Patients With Atrial Fibrillation on Dialysis (DANWARD) *NCT03862859*	HD patients	*Primary:* TIA, ischemic stroke, unspecified stroke; fatal or non-fatal major bleeding (ISTH definitions) *Secondary:* number of participants with stroke, number of deaths	Warfarin vs. No anticoagulation	n = 718	-	Recruiting	December 2025
Stroke Prophylaxis With Apixaban in Chronic Kidney Disease Stage 5 Patients With Atrial Fibrillation (SACK) *NCT05679024*	HD patients, CKD5 nonHD	*Primary:* ischemic stroke; intracranial bleeding and fatal bleeding *Secondary*: all-cause mortality, cardiovascular events, major bleeding (modified ISTH definitions)	Apixaban (reduced dose) vs. No anticoagulation	n = 1400	-	Recruiting	December 2028

Abbreviations: CKD, chronic kidney disease; TIA, transient ischemic attack; other — see Table 1

CKD (low quality of evidence, strong recommendation), emphasizing that DOACs are contraindicated [87]. The Canadian guidelines recommend against the routine use of antithrombotic therapy for stroke prevention in AF patients in stage 5 CKD (weak recommendation, low quality of evidence) but also state that therapy should be individualized and anticoagulation "might be appropriate for some patients in whom the benefit of preventing stroke outweighs the increased risk of bleeding" [88]. Nephrology guidelines directly on anticoagulation treatment in advanced CKD are scarce. A 2011 Kidney Disease Improving Global Outcomes (KDIGO) clinical update on cardiovascular disease states that in contradiction to previous recommendations, routine use of anticoagulation in stroke prevention in stage 5 CKD patients is not indicated [89]. The 2012 KDIGO guidelines suggest using lower doses of warfarin with close monitoring of eGFR <30 ml/min/1.73 m^2. A KDIGO international interdisciplinary conference on CKD and arrhythmias took place in 2016, and the conference report stated that there is insufficient high-quality evidence to recommend VKAs for stroke prevention in stage 5 CKD patients [90]. The attendees suggested considering reduced doses of apixaban b.i.d.

The lack of clear recommendations and discrepancies in various guidelines only emphasize the unknowns surrounding AF treatment in HD patients.

CURRENT PRACTICE OF ANTITHROMBOTIC TREATMENT IN KIDNEY FAILURE PATIENTS WITH ATRIAL FIBRILLATION

As indicated above, most of our knowledge of anticoagulation strategies for stroke prevention in HD patients comes from observational studies. No randomized study comparing anticoagulation (either VKA or DOAC) vs. placebo has been conducted in stage 4–5 CKD or HD patients. Several randomized studies comparing anticoagulants have been conducted but all were finished prematurely due to low enrollment, and none had a placebo arm. Furthermore, the stroke risk and bleeding risk stratification scores that are used in non-CKD patients are not applicable to renal failure patients. As a consequence of the aforementioned reasons, an evidence-based approach to the anticoagulation treatment in stage 4–5 CKD patients is not possible. Currently, in surveys on real-world treatment, some HD patients are treated with VKAs, some by DOACs (mostly apixaban) or LMWH; some HD patients receive antiplatelet drugs instead of anticoagulants and some patients go without anticoagulation treatment.

A crucial question is whether to initiate anticoagulation at all, and randomized trials exploring anticoagulation therapy versus no anticoagulation are desperately needed. Fortunately, several ongoing trials to explore this issue are currently ongoing (Table 2).

Clinical perspective on stroke prevention in HD patients with AF

Fundamentally, HD patients' preferences must be taken into account. In a survey of HF patients' preferences, "mortality" was ranked 14th, after outcomes such as dialysis-free time, fatigue, and ability to travel [91]. From this perspective, preventing the probabilistically less likely event of stroke at the cost of more frequent bleeding episodes that are inherently associated with increased medical care is of questionable justification, especially since HD patients have high co-morbidity, and many competing causes of morbidity and mortality result in longer hospitalization with more frequent complications [92, 93].

Translating the current data into clinical practice, routine prescription of anticoagulation for stroke prevention in HD patients with AF does not seem warranted due to the potential for net clinical harm. Anticoagulation should be reserved for those with a high risk of stroke, which is not offset by high bleeding risk, with careful consideration of patients' preferences and treatment goals. Reduced-dose apixaban seems superior to other anticoagulants in this population. Non-pharmacological approaches (i.e., LAAC) should be considered in selected patients. Furthermore, physicians involved in HD patient care should contribute to broadening knowledge by enrolling their patients in ongoing trials.

CONCLUSION

Kidney failure patients with atrial fibrillation are a distinct cohort of patients. Current knowledge on stroke prevention in atrial fibrillation patients in the general population does not apply to kidney failure patients. Data on the most suitable anticoagulant in HD patients are mostly observational and show that VKA treatment is not desirable and that the reduced-dose apixaban is the most promising agent. However, left atrial appendage closure or the new class of FXI inhibitors may prove beneficial. The frequency of clinically significant bleeding in HD patients greatly surpasses the frequency of ischemic strokes. Keeping in mind the dictum of medical ethics, "*primum non nocere*" or "first, do no harm," care for these patients must be individualized to prevent unnecessary harm from overtreatment. To resolve this lack of guidance, randomized studies assessing either pharmacological or non-pharmacological treatments vs. placebo are badly needed.

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REFERENCES

1. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014; 129(8): 837–847, doi: 10.1161/CIRCULATIONAHA.113.005119, indexed in Pubmed: 24345399.
2. Kornej J, Börschel CS, Benjamin EJ, et al. Epidemiology of atrial fibrillation in the 21st century: novel methods and new insights. Circ Res. 2020; 127(1): 4–20, doi: 10.1161/CIRCRESAHA.120.316340, indexed in Pubmed: 32716709.
3. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001; 285(18): 2370–2375, doi: 10.1001/jama.285.18.2370, indexed in Pubmed: 11343485.
4. Svendsen JH, Diederichsen SZ, Højberg S, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial. Lancet. 2021; 398(10310): 1507–1516, doi: 10.1016/S0140-6736(21)01698-6, indexed in Pubmed: 34469766.
5. Chen LY, Sotoodehnia N, Bůžková P, et al. Atrial fibrillation and the risk of sudden cardiac death: the atherosclerosis risk in communities study and cardiovascular health study. JAMA Intern Med. 2013; 173(1): 29–35, doi: 10.1001/2013.jamainternmed.744, indexed in Pubmed: 23404043.
6. Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation. 1998; 98(10): 946–952, doi: 10.1161/01.cir.98.10.946, indexed in Pubmed: 9737513.
7. Papanastasiou CA, Theochari CA, Zareifopoulos N, et al. Atrial fibrillation is associated with cognitive impairment, all-cause dementia, vascular dementia, and alzheimer's disease: a systematic review and meta-analysis. J Gen Intern Med. 2021; 36(10): 3122–3135, doi: 10.1007/s11606-021-06954-8, indexed in Pubmed: 34244959.
8. Levey AS, Eckardt KU, Dorman NM, et al. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int. 2020; 97(6): 1117–1129, doi: 10.1016/j.kint.2020.02.010, indexed in Pubmed: 32409237.
9. Thurlow JS, Joshi M, Yan G, et al. Global epidemiology of end-stage kidney disease and disparities in kidney replacement therapy. Am J Nephrol. 2021; 52(2): 98–107, doi: 10.1159/000514550, indexed in Pubmed: 33752206.
10. Bello AK, Okpechi IG, Osman MA, et al. Epidemiology of haemodialysis outcomes. Nat Rev Nephrol. 2022; 18(6): 378–395, doi: 10.1038/s41581-022-00542-7, indexed in Pubmed: 35194215.
11. Alonso A, Lopez FL, Matsushita K, et al. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. Circulation. 2011; 123(25): 2946–2953, doi: 10.1161/CIRCULATIONAHA.111.020982, indexed in Pubmed: 21646496.
12. Watanabe H, Watanabe T, Sasaki S, et al. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. Am Heart J. 2009; 158(4): 629–636, doi: 10.1016/j.ahj.2009.06.031, indexed in Pubmed: 19781424.
13. Bansal N, Fan D, Hsu Cy, et al. Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease. Circulation. 2013; 127(5): 569–574, doi: 10.1161/CIRCULATIONAHA.112.123992, indexed in Pubmed: 23275377.
14. Massicotte-Azarniouch D, Kuwornu JP, Carrero JJ, et al. Incident atrial fibrillation and the risk of congestive heart failure, myocardial infarction, end-stage kidney disease, and mortality among patients with a decreased estimated GFR. Am J Kidney Dis. 2018; 71(2): 191–199, doi: 10.1053/j.ajkd.2017.08.016, indexed in Pubmed: 29153994.
15. Annual Data Report | USRDS n.d. https://usrds-adr.niddk.nih.gov/2022/end-stage-renal-disease/1-incidence-prevalence-patient-characteristics-and-treatment-modalities (accessed: May 2, 2023).
16. Koplan BA, Winkelmayer WC, Costea AI, et al. Implantable loop recorder monitoring and the incidence of previously unrecognized atrial fibrillation in patients on hemodialysis. Kidney Int Rep. 2022; 7(2): 189–199, doi: 10.1016/j.ekir.2021.10.001, indexed in Pubmed: 35155858.

17. Kazancioğlu R. Risk factors for chronic kidney disease: an update. Kidney Int Suppl (2011). 2013; 3(4): 368–371, doi: 10.1038/kisup.2013.79, indexed in Pubmed: 25019021.
18. Annual Data Report | USRDS n.d. https://usrds-adr.niddk.nih.gov/2022/end-stage-renal-disease/1-incidence-prevalence-patient-characteristics-and-treatment-modalities (accessed: August 25, 2023).
19. Astley ME, Boenink R, Abd ElHafeez S, et al. The ERA Registry Annual Report 2020: a summary. Clin Kidney J. 2023; 16(8): 1330–1354, doi: 10.1093/ckj/sfad087, indexed in Pubmed: 37529647.
20. Akhtar Z, Leung LW, Kontogiannis C, et al. Arrhythmias in chronic kidney disease. Eur Cardiol. 2022; 17: e05, doi: 10.15420/ecr.2021.52, indexed in Pubmed: 35321526.
21. Ding WY, Gupta D, Wong CF, et al. Pathophysiology of atrial fibrillation and chronic kidney disease. Cardiovasc Res. 2021; 117(4): 1046–1059, doi: 10.1093/cvr/cvaa258, indexed in Pubmed: 32871005.
22. Everett TH, Olgin JE. Atrial fibrosis and the mechanisms of atrial fibrillation. Heart Rhythm. 2007; 4(Suppl 3): S24–S27, doi: 10.1016/j.hrthm.2006.12.040, indexed in Pubmed: 17336879.
23. Grabner A, Faul C. The role of fibroblast growth factor 23 and Klotho in uremic cardiomyopathy. Curr Opin Nephrol Hypertens. 2016; 25(4): 314–324, doi: 10.1097/MNH.0000000000000231, indexed in Pubmed: 27219043.
24. Mehta R, Cai X, Lee J, et al. Association of fibroblast growth factor 23 with atrial fibrillation in chronic kidney disease, from the chronic renal insufficiency cohort study. JAMA Cardiol. 2016; 1(5): 548–556, doi: 10.1001/jamacardio.2016.1445, indexed in Pubmed: 27434583.
25. Malik J, Valerianova A, Pesickova SS, et al. Heart failure with preserved ejection fraction is the most frequent but commonly overlooked phenotype in patients on chronic hemodialysis. Front Cardiovasc Med. 2023; 10: 1130618, doi: 10.3389/fcvm.2023.1130618, indexed in Pubmed: 37324637.
26. Zakeri R, Chamberlain AM, Roger VL, et al. Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction: a community-based study. Circulation. 2013; 128(10): 1085–1093, doi: 10.1161/CIRCULATIONAHA.113.001475, indexed in Pubmed: 23908348.
27. Buiten MS, de Bie MK, Rotmans JI, et al. The dialysis procedure as a trigger for atrial fibrillation: new insights in the development of atrial fibrillation in dialysis patients. Heart. 2014; 100(9): 685–690, doi: 10.1136/heartjnl-2013-305417, indexed in Pubmed: 24670418.
28. Correa S, Scovner KM, Tumlin JA, et al. Electrolyte changes in contemporary hemodialysis: a secondary analysis of the monitoring in dialysis study. Kidney360. 2021; 2(4): 695–707, doi: 10.34067/KID.0007452020, indexed in Pubmed: 34676372.
29. Hu A, Liu S, Montez-Rath ME, et al. Associations of serum and dialysate potassium concentrations with incident atrial fibrillation in a cohort study of older US persons initiating hemodialysis for kidney failure. Kidney Int Rep. 2023; 8(2): 305–316, doi: 10.1016/j.ekir.2022.11.003, indexed in Pubmed: 36815107.
30. Wang HH, Hung SY, Sung JM, et al. Risk of stroke in long-term dialysis patients compared with the general population. Am J Kidney Dis. 2014; 63(4): 604–611, doi: 10.1053/j.ajkd.2013.10.013, indexed in Pubmed: 24290244.
31. Lutz PD, Jurk PdD. Platelets in advanced chronic kidney disease: two sides of the coin. Semin Thromb Hemost. 2020; 46(3): 342–356, doi: 10.1055/s-0040-1708841, indexed in Pubmed: 32259877.
32. Yu FP, Zhao YC, Gu B, et al. Chronic kidney disease and carotid atherosclerosis in patients with acute stroke. Neurologist. 2015; 20(2): 23–26, doi: 10.1097/NRL.0000000000000044, indexed in Pubmed: 26280286.
33. Chelluboina B, Vemuganti R. Chronic kidney disease in the pathogenesis of acute ischemic stroke. J Cereb Blood Flow Metab. 2019; 39(10): 1893–1905, doi: 10.1177/0271678X19866733, indexed in Pubmed: 31366298.
34. Hörl MP, Hörl WH. Hemodialysis-associated hypertension: pathophysiology and therapy. Am J Kidney Dis. 2002; 39(2): 227–244, doi: 10.1053/ajkd.2002.30542, indexed in Pubmed: 11840363.
35. Wang HH, Hung SY, Sung JM, et al. Risk of stroke in long-term dialysis patients compared with the general population. Am J Kidney Dis. 2014; 63(4): 604–611, doi: 10.1053/j.ajkd.2013.10.013, indexed in Pubmed: 24290244.
36. Power A, Chan K, Singh SK, et al. Appraising stroke risk in maintenance hemodialysis patients: a large single-center cohort study. Am J Kidney Dis. 2012; 59(2): 249–257, doi: 10.1053/j.ajkd.2011.07.016, indexed in Pubmed: 21944665.
37. Masson P, Webster AC, Hong M, et al. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. Nephrol Dial Transplant. 2015; 30(7): 1162–1169, doi: 10.1093/ndt/gfv009, indexed in Pubmed: 25681099.
38. Cohen-Hagai K, Nacasch N, Rozenberg I, et al. Clinical outcomes of stroke in hemodialysis patients: a retrospective single-center study. Int Urol Nephrol. 2019; 51(8): 1435–1441, doi: 10.1007/s11255-019-02218-x, indexed in Pubmed: 31264088.
39. Ovbiagele B, Schwamm LH, Smith EE, et al. Patterns of care quality and prognosis among hospitalized ischemic stroke patients with chronic kidney disease. J Am Heart Assoc. 2014; 3(3): e000905, doi: 10.1161/JAHA.114.000905, indexed in Pubmed: 24904017.
40. Lee JG, Lee KB, Jang IM, et al. Low glomerular filtration rate increases hemorrhagic transformation in acute ischemic stroke. Cerebrovasc Dis. 2013; 35(1): 53–59, doi: 10.1159/000345087, indexed in Pubmed: 23428997.
41. Remuzzi G, Livio M, Marchiaro G, et al. Bleeding in renal failure: altered platelet function in chronic uraemia only partially corrected by haemodialysis. Nephron. 1978; 22(4-6): 347–353, doi: 10.1159/000181474, indexed in Pubmed: 740096.
42. Gaspari F, Viganò G, Orisio S, et al. Aspirin prolongs bleeding time in uremia by a mechanism distinct from platelet cyclooxygenase inhibition. J Clin Invest. 1987; 79(6): 1788–1797, doi: 10.1172/JCI113020, indexed in Pubmed: 3108321.
43. Sood MM, Bota SE, McArthur E, et al. The three-year incidence of major hemorrhage among older adults initiating chronic dialysis. Can J Kidney Health Dis. 2014; 1: 21, doi: 10.1186/s40697-014-0021-x, indexed in Pubmed: 25780611.
44. Sood MM, Larkina M, Thumma JR, et al. Major bleeding events and risk stratification of antithrombotic agents in hemodialysis: results from the DOPPS. Kidney Int. 2013; 84(3): 600–608, doi: 10.1038/ki.2013.170, indexed in Pubmed: 23677245.
45. Ocak G, Noordzij M, Rookmaaker MB, et al. Mortality due to bleeding, myocardial infarction and stroke in dialysis patients. J Thromb Haemost. 2018; 16(10): 1953–1963, doi: 10.1111/jth.14254, indexed in Pubmed: 30063819.
46. Liao JN, Chan YH, Kuo L, et al. Optimal anticoagulation in elderly patients with atrial fibrillation: Which drug at which dose? Kardiol Pol. 2022; 80(2): 128–136, doi: 10.33963/KP.a2022.0046, indexed in Pubmed: 35167115.
47. He W, Zhang H, Zhu W, et al. Effect of anticoagulation therapy in older patients with chronic kidney disease and atrial fibrillation: A meta-analysis. Medicine (Baltimore). 2019; 98(42): e17628, doi: 10.1097/MD.0000000000017628, indexed in Pubmed: 31626146.
48. Wasse H, Gillen DL, Ball AM, et al. Risk factors for upper gastrointestinal bleeding among end-stage renal disease patients. Kidney Int. 2003; 64(4): 1455–1461, doi: 10.1046/j.1523-1755.2003.00225.x, indexed in Pubmed: 12969166.
49. Ocak G, Noordzij M, Rookmaaker MB, et al. Mortality due to bleeding, myocardial infarction and stroke in dialysis patients. J Thromb Haemost. 2018; 16(10): 1953–1963, doi: 10.1111/jth.14254, indexed in Pubmed: 30063819.
50. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021; 42(5): 373–498, doi: 10.1093/eurheartj/ehaa612, indexed in Pubmed: 32860505.
51. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. Circulation. 2019; 140(2): e125–e151, doi: 10.1161/CIR.0000000000000665, indexed in Pubmed: 30686041.
52. Chao TF, Liu CJ, Wang KL, et al. Incidence and prediction of ischemic stroke among atrial fibrillation patients with end-stage renal disease requiring dialysis. Heart Rhythm. 2014; 11(10): 1752–1759, doi: 10.1016/j.hrthm.2014.06.021, indexed in Pubmed: 24952148.

53. Olesen JB, Lip GYH, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ. 2011; 342: d124, doi: 10.1136/bmj.d124, indexed in Pubmed: 21282258.
54. Ocak G, Ramspek C, Rookmaaker MB, et al. Performance of bleeding risk scores in dialysis patients. Nephrol Dial Transplant. 2019; 34(7): 1223–1231, doi: 10.1093/ndt/gfy387, indexed in Pubmed: 30608543.
55. Nopp S, Spielvogel CP, Schmaldienst S, et al. Bleeding risk assessment in end-stage kidney disease: validation of existing risk scores and evaluation of a machine learning-based approach. Thromb Haemost. 2022; 122(9), doi: 10.1055/a-1754-7551, indexed in Pubmed: 35098518.
56. Khouri Y, Stephens T, Ayuba G, et al. Understanding and managing atrial fibrillation in patients with kidney disease. J Atr Fibrillation. 2015; 7(6): 1069, doi: 10.4022/jafib.1069, indexed in Pubmed: 27957157.
57. Schmidt M, Rieber J, Daccarett M, et al. Relation of recurrence of atrial fibrillation after successful cardioversion to renal function. Am J Cardiol. 2010; 105(3): 368–372, doi: 10.1016/j.amjcard.2009.09.037, indexed in Pubmed: 20102950.
58. Chung I, Khan Y, Warrens H, et al. Catheter ablation for atrial fibrillation in patients with chronic kidney disease and on dialysis: a meta-analysis and review. Cardiorenal Med. 2022; 12(4): 155–172, doi: 10.1159/000525388, indexed in Pubmed: 35820393.
59. Navaravong L, Barakat M, Burgon N, et al. Improvement in estimated glomerular filtration rate in patients with chronic kidney disease undergoing catheter ablation for atrial fibrillation. J Cardiovasc Electrophysiol. 2015; 26(1): 21–27, doi: 10.1111/jce.12530, indexed in Pubmed: 25142836.
60. Takahashi Y, Takahashi A, Kuwahara T, et al. Renal function after catheter ablation of atrial fibrillation. Circulation. 2011; 124(22): 2380–2387, doi: 10.1161/CIRCULATIONAHA.111.047266, indexed in Pubmed: 22042886.
61. Randhawa MS, Vishwanath R, Rai MP, et al. Association between use of warfarin for atrial fibrillation and outcomes among patients with end-stage renal disease: a systematic review and meta-analysis. JAMA Netw Open. 2020; 3(4): e202175, doi: 10.1001/jamanetworkopen.2020.2175, indexed in Pubmed: 32250434.
62. Tan J, Bae S, Segal JB, et al. Warfarin use and the risk of stroke, bleeding, and mortality in older adults on dialysis with incident atrial fibrillation. Nephrology (Carlton). 2019; 24(2): 234–244, doi: 10.1111/nep.13207, indexed in Pubmed: 29219209.
63. Friberg L, Benson L, Lip GYH. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. Eur Heart J. 2015; 36(5): 297–306, doi: 10.1093/eurheartj/ehu139, indexed in Pubmed: 24722803.
64. Reinecke H, Engelbertz C, Bauersachs R, et al. A randomized controlled trial comparing apixaban with the vitamin K antagonist phenprocoumon in patients on chronic hemodialysis: the AXADIA-AFNET 8 study. Circulation. 2023; 147(4): 296–309, doi: 10.1161/circulationaha.122.062779.
65. Nigwekar SU, Kroshinsky D, Nazarian RM, et al. Calciphylaxis: risk factors, diagnosis, and treatment. Am J Kidney Dis. 2015; 66(1): 133–146, doi: 10.1053/j.ajkd.2015.01.034, indexed in Pubmed: 25960299.
66. Chan KE, Giugliano RP, Patel MR, et al. Nonvitamin K anticoagulant agents in patients with advanced chronic kidney disease or on dialysis with AF. J Am Coll Cardiol. 2016; 67(24): 2888–2899, doi: 10.1016/j.jacc.2016.02.082, indexed in Pubmed: 27311528.
67. Mavrakanas TA, Samer CF, Nessim SJ, et al. Apixaban pharmacokinetics at steady state in hemodialysis patients. J Am Soc Nephrol. 2017; 28(7): 2241–2248, doi: 10.1681/ASN.2016090980, indexed in Pubmed: 28302754.
68. Siontis KC, Zhang X, Eckard A, et al. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. Circulation. 2018; 138(15): 1519–1529, doi: 10.1161/CIRCULATIONAHA.118.035418, indexed in Pubmed: 29954737.
69. Mavrakanas TA, Garlo K, Charytan DM. Apixaban versus no anticoagulation in patients undergoing long-term dialysis with incident atrial fibrillation. Clin J Am Soc Nephrol. 2020; 15(8): 1146–1154, doi: 10.2215/CJN.11650919, indexed in Pubmed: 32444398.
70. Pokorney SD, Chertow GM, Al-Khalidi HR, et al. Apixaban for patients with atrial fibrillation on hemodialysis: a multicenter randomized controlled trial. Circulation. 2022; 146(23): 1735–1745, doi: 10.1161/CIRCULATIONAHA.121.054990, indexed in Pubmed: 36335914.
71. Roberts MA, Pilmore HL, Ierino FL, et al. The β-blocker to lower cardiovascular dialysis events (BLOCADE) feasibility study: a randomized controlled trial. Am J Kidney Dis. 2016; 67(6): 902–911, doi: 10.1053/j.ajkd.2015.10.029, indexed in Pubmed: 26717861.
72. Fellström BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009; 360(14): 1395–1407, doi: 10.1056/NEJMoa0810177, indexed in Pubmed: 19332456.
73. Coleman CI, Kreutz R, Sood N, et al. Rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation and severe kidney disease or undergoing hemodialysis. Am J Med. 2019; 132(9): 1078–1083, doi: 10.1016/j.amjmed.2019.04.013, indexed in Pubmed: 31054829.
74. Lin YC, Chen BL, Shih CM, et al. Effectiveness and safety of rivaroxaban versus warfarin in Taiwanese patients with end-stage renal disease and nonvalvular atrial fibrillation: A real-world nationwide cohort study. PLoS One. 2021; 16(4): e0249940, doi: 10.1371/journal.pone.0249940, indexed in Pubmed: 33831130.
75. Kreutz R, Deray G, Floege J, et al. Rationale and design of XARENO: XA inhibition in RENal patients with non-valvular atrial fibrillation. Observational registry. Kardiol Pol. 2021; 79(11): 1265–1267, doi: 10.33963/KP.a2021.0134, indexed in Pubmed: 34643264.
76. De Vriese AS, Caluwé R, Pyfferoen L, et al. Multicenter randomized controlled trial of vitamin K antagonist replacement by rivaroxaban with or without vitamin K2 in hemodialysis patients with atrial fibrillation: The Valkyrie study. J Am Soc Nephrol. 2020; 31(1): 186–196, doi: 10.1681/ASN.2019060579, indexed in Pubmed: 31704740.
77. De Vriese AS, Caluwé R, Bailleul E, et al. Dose-finding study of rivaroxaban in hemodialysis patients. Am J Kidney Dis. 2015; 66(1): 91–98, doi: 10.1053/j.ajkd.2015.01.022, indexed in Pubmed: 25804678.
78. Pon TK, Dager WE, Roberts AJ, et al. Subcutaneous enoxaparin for therapeutic anticoagulation in hemodialysis patients. Thromb Res. 2014; 133(6): 1023–1028, doi: 10.1016/j.thromres.2014.03.036, indexed in Pubmed: 24718051.
79. Königsbrügge O, Posch F, Antlanger M, et al. Prevalence of atrial fibrillation and antithrombotic therapy in hemodialysis patients: cross-sectional results of the vienna investigation of atrial fibrillation and thromboembolism in patients on hemodialysis (VIVALDI). PLoS One. 2017; 12(1): e0169400, doi: 10.1371/journal.pone.0169400, indexed in Pubmed: 28052124.
80. Seligsohn U. Factor XI deficiency in humans. J Thromb Haemost. 2009; 7 (Suppl 1): 84–87, doi: 10.1111/j.1538-7836.2009.03395.x, indexed in Pubmed: 19630775.
81. Piccini JP, Caso V, Connolly SJ, et al. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. Lancet. 2022; 399(10333): 1383–1390, doi: 10.1016/S0140-6736(22)00456-1, indexed in Pubmed: 35385695.
82. Turagam MK, Osmancik P, Neuzil P, et al. Left atrial appendage closure versus oral anticoagulants in atrial fibrillation: a meta-analysis of randomized trials. J Am Coll Cardiol. 2020; 76(23): 2795–2797, doi: 10.1016/j.jacc.2020.08.089, indexed in Pubmed: 33272374.
83. Genovesi S, Porcu L, Slaviero G, et al. Outcomes on safety and efficacy of left atrial appendage occlusion in end stage renal disease patients undergoing dialysis. J Nephrol. 2021; 34(1): 63–73, doi: 10.1007/s40620-020-00774-5, indexed in Pubmed: 32535831.
84. Mesnier J, Cruz-González I, Arzamendi D, et al. Incidence and predictors of early death in patients undergoing percutaneous left atrial appendage closure. JACC Clin Electrophysiol. 2022; 8(9): 1093–1102, doi: 10.1016/j.jacep.2022.06.012, indexed in Pubmed: 36137713.
85. Steffel J, Collins R, Antz M, et al. External reviewers. 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Europace. 2021; 23(10): 1612–1676, doi: 10.1093/europace/euab065, indexed in Pubmed: 33895845.
86. Apixaban FDA approval 2012 n.d. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202155s002lbl.pdf (accessed: May 9, 2023).
87. Brieger D, Amerena J, Attia J, et al. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018. Heart Lung Circ. 2018; 27(10): 1209–1266, doi: 10.1016/j.hlc.2018.06.1043, indexed in Pubmed: 30077228.

88. Andrade JG, Aguilar M, Atzema C, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the management of atrial fibrillation. Can J Cardiol. 2020; 36(12): 1847–1948, doi: 10.1016/j.cjca.2020.09.001, indexed in Pubmed: 33191198.
89. Herzog CA, Asinger RW, Berger AK, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2011; 80(6): 572–586, doi: 10.1038/ki.2011.223, indexed in Pubmed: 21750584.
90. Turakhia MP, Blankestijn PJ, Carrero JJ, et al. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. Eur Heart J. 2018; 39(24): 2314–2325, doi: 10.1093/eurheartj/ehy060, indexed in Pubmed: 29522134.
91. Urquhart-Secord R, Craig JC, Hemmelgarn B, et al. Patient and caregiver priorities for outcomes in hemodialysis: an international nominal group technique study. Am J Kidney Dis. 2016; 68(3): 444–454, doi: 10.1053/j.ajkd.2016.02.037, indexed in Pubmed: 26968042.
92. D'Agata EM, Mount DB, Thayer V, et al. Hospital-acquired infections among chronic hemodialysis patients. Am J Kidney Dis. 2000; 35(6): 1083–1088, doi: 10.1016/s0272-6386(00)70044-8, indexed in Pubmed: 10845821.
93. Tam-Tham H, Ravani P, Zhang J, et al. Association of initiation of dialysis with hospital length of stay and intensity of care in older adults with kidney failure. JAMA Netw Open. 2020; 3(2): e200222, doi: 10.1001/jamanetworkopen.2020.0222, indexed in Pubmed: 32108896.