Anticoagulation use and the risk of stroke and major bleeding in patients on hemodialysis: From the VIVALDI, a population-based prospective cohort study

Oliver Königsbrügge | Hannah Meisel | Aljoscha Beyer | Sabine Schmaldienst | Renate Klauser-Braun | Matthias Lorenz | Martin Auinger | Josef Kletzmayr | Manfred Hecking | Wolfgang C. Winkelmayer | Irene Lang | Ingrid Pabinger | Marcus Säemann | Cihan Ay

1 Clinical Division of Hematology and Hemostaseology, Department of Medicine I, Medical University of Vienna, Vienna, Austria
2 Department of Medicine I, Clinic Favoriten, Vienna, Austria
3 Department of Medicine III, Clinic Donaustadt, Vienna, Austria
4 Vienna Dialysis Center, Vienna, Austria
5 Department of Medicine III, Clinic Hietzing, Vienna, Austria
6 Clinical Division of Nephrology, Department of Medicine III, Medical University of Vienna, Vienna, Austria
7 Section of Nephrology, Department of Medicine, Selzman Institute for Kidney Health, Baylor College of Medicine, Houston, USA
8 Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria
9 Department of Medicine VI, Clinic Ottakring, Vienna, Austria

Abstract

Background: Evidence supporting the use of anticoagulation for the prevention of stroke and thromboembolism in patients with kidney failure on hemodialysis (HD) and atrial fibrillation (AF) is limited. We prospectively assessed the incidences of stroke and major bleeding, as well as anticoagulation strategies in patients on HD with AF.

Methods: We recruited 625 prevalent HD patients into a population-based observational cohort study. The primary prospective outcomes were thromboembolic events (stroke, transient ischemic attack, systemic embolism) and major bleeding. Secondary outcomes included a composite of thromboembolic events, major bleeding, and cardiovascular death to determine net clinical harm.

Results: A total of 238 patients (38.1%) had AF, 165 (26.4%) already at baseline and 73 (15.9%) developed AF during a median follow up of 870 days. Forty (6.4%) thromboembolic events and 89 (14.2%) major bleedings occurred. Overall, 256 patients died (41.0%). In AF patients, use of vitamin K antagonists (VKAs) in 61 patients (25.6%) was not significantly associated with reduced risk of the primary thromboembolic outcome.
1 | INTRODUCTION

Patients with kidney failure on maintenance hemodialysis (HD) are at high risk of thromboembolism, including ischemic stroke and systemic embolism, as well as of bleeding, especially among those with atrial fibrillation (AF). Presence of several comorbid conditions and advanced age in the population of HD patients further increase the risks of both thromboembolism and bleeding. Clinicians face the challenge of balancing the competing risks of thromboembolism and bleeding complications when considering anticoagulation and antiplatelet strategies. Most patients on HD satisfy criteria for anticoagulation spelled out in guidelines; however, most patients are also at high bleeding risk per accepted scoring algorithms. Data on population-specific risk factors and risk assessment models for AF patients with end-stage renal disease (ESRD) on HD are scarce.

In light of the fact that until recently there were no dedicated randomized trials for stroke prevention in HD patients, and HD patients had been excluded from all prior stroke prevention in AF trials, it is not surprising that statements in clinical practice guidelines are rather reserved when it comes to anticoagulation in patients on HD with AF. In nonrandomized studies, there has been no agreement whether anticoagulation with vitamin K antagonists (VKAs) is of benefit compared with no treatment. Use of VKAs was associated with net clinical harm (adjusted SHR: 2.07; 95% CI, 1.25–3.42).

Conclusions: Although the nonrandomized nature of the study is prone to bias, anticoagulation with VKAs was not associated with decreased thromboembolic risk, but rather with increased risk of major bleeding and may be net harmful to patients with AF on HD.

KEYWORDS
anticoagulants, atrial fibrillation, chronic kidney failure, ischemic stroke, renal replacement therapy

2 | METHODS

2.1 | Study design and procedure

The Vienna Investigation of Atrial Fibrillation and Thromboembolism in Hemodialysis patients (VIVALDI) is a prospective population-based cohort study, which was initiated to investigate the incidence of AF, thromboembolism, and bleeding in patients with kidney failure on maintenance HD. The VIVALDI study was approved by the local ethics committees and was conducted in accordance with the declaration of Helsinki and its later amendments.

Patients were recruited in a cross-sectional fashion at seven HD centers in Vienna, Austria, between April 2014 and July 2015. Of approximately 860 patients receiving HD in Vienna (population of 1.8 million), we approached 814 patients; 626 patients (~73% of the potential HD population) consented to participate in writing. The inclusion criteria were age 18 years or older, kidney failure requiring maintenance HD, and ability to provide written informed consent. Patients were excluded if they were pregnant, lactating, suspected of pregnancy, incapable of consenting, or hospitalized at the time of enrollment. Trained study investigators performed structured
interviews with each patient, reviewed medical records at the participating dialysis centers, and verified findings with medical documentation and in consensus with the treating nephrologists.

Patients were prospectively followed for a maximum of 1350 days (45 months), and the occurrence of outcomes was assessed with one interim and one final personal interview, review of medical documentation at the dialysis centers, verification of events by the treating nephrologists, and verification with the Austrian death registry. One male patient (0.16%) with AF was lost to follow-up.

2.2 | Outcomes

The prespecified primary thromboembolic outcome of the study was a composite of ischemic stroke, transient ischemic attack (TIA), and systemic embolism. Thromboembolic outcome was based on objective evidence in imaging records and after ruling out a readily identifiable cause such as a tumor, seizure, or HD-related transient neurological symptoms. The primary bleeding outcome was major bleeding as defined by the International Society on Thrombosis and Haemostasis.14

Secondary outcomes were (1) the composite net clinical benefit or harm outcome of ischemic stroke, major bleeding, and cardiovascular (CV) death; (2) the composite major adverse cardiovascular outcome (3P-MACE) comprising CV death, myocardial infarction, and ischemic stroke; (3) cardiovascular death; and (4) all-cause mortality.

All outcomes were adjudicated by independent experts in neurology, cardiology, vascular disease, and hematology upon chart review and on basis of imaging evidence or autopsy findings. Autopsies were performed in only a few cases at the discretion of the treating physicians and not as a part of the study outcome verification.

2.3 | Definition of anticoagulation treatment

Anticoagulation treatment for stroke prevention in AF was based on chart and prescription review at the dialysis centers, and personal verification with the patient. Anticoagulation treatment was reevaluated at the interim data capture after 1 year and at the final data capture at the end of the study. Because anticoagulation treatment changed during the course of the observation time in some patients, anticoagulation treatment was analyzed in an intention-to-treat approach. Intention-to-treat was considered if patients with AF at baseline had active anticoagulation treatment and maintained anticoagulation for at least 1 month, or if one of the primary or secondary outcomes occurred during the first month of observation while the patient was on anticoagulation. In patients with de novo AF, intention-to-treat was considered if anticoagulation was begun upon AF diagnosis and treatment was continued for at least 1 month.

Phenprocoumon was the VKA agent exclusively used in this cohort, and the target international normalized ratio for stroke prevention in AF was set at 2.0 to 3.0. Time in therapeutic international normalized ratio range (TTR) was calculated with the linear interpolation/Rosendaal method.15 The low molecular weight heparin (LMWH) treatment used at all centers was enoxaparin 4000 anti-Xa units once daily on non-HD days. Only a few patients (N = 5) received enoxaparin 6000 or 8000 anti-Xa units on non-HD days. For systemic anticoagulation during HD sessions, 569 patients received LMWH, 23 unfractionated heparin, 11 citrate dialysis, and 22 other agents (fondaparinux, argatroban).

2.4 | Statistical analysis

Patient characteristics at baseline are reported as counts and proportions or median values with the interquartile range (IQR), where appropriate. Differences between anticoagulation treatment groups were assessed with the chi-squared test for categorical variables and Mann-Whitney U test for continuous variables.

We recorded the incidence of primary and secondary outcomes in the total cohort and the AF group and calculated the incidence and 30-day case fatality rates.

To analyze risk factors for the primary outcomes in the full cohort and the AF group, we computed the univariable subdistribution hazard ratios (SHRs) and 95% CI, using competing risk regression according to Fine and Gray and treating all-cause death as the competing endpoint. Because de novo AF occurred during the observation period, AF was treated as a time-dependent covariate based on the time of AF diagnosis.

Effectiveness and safety of VKA and LMWH was compared to no anticoagulation in the AF group, in a multivariable competing risk regression model adjusted for antiplatelet medication and the age, sex, congestive heart failure, hypertension, stroke/transient ischemic accident/thromboembolism, vascular disease, and diabetes history (CHA2DS2-VASc) score and treating all-cause death as the competing endpoint. In patients with de novo AF, the observation time was set to zero at the time of AF diagnosis. A total of 113 patients (18.1%) received kidney transplants and were censored at time of transplantation from analysis.

All calculations were performed with STATA (Version 15.1, STATA Corp.).

3 | RESULTS

Baseline patient characteristics of the enrolled cohort (N = 625) are provided in Table 1. The median age was 66 years (IQR, 54.5-75.0) and 394 (63.0%) were male. Cardiovascular diseases and risk factors were frequent concomitant disorders.

3.1 | Composite outcome of stroke, TIA, systemic embolism in the total cohort

During a median observation time of 870 days (IQR, 391-1234 days), 40 (6.4%) patients had a qualifying event of the composite thromboembolic outcome (stroke, N = 28; TIA, N = 7; systemic embolism, N = 5), which corresponds to an event rate of 29.0 per 1000
### TABLE 1  Patient characteristics

|                                | All Patients | AF Cohort | No Anticoagulation | Phenprocoumon Group | p Value | Enoxaparin Group | p Value |
|--------------------------------|--------------|-----------|--------------------|----------------------|---------|------------------|---------|
| Patients, n (%)                | 625 (100)    | 238 (100) | 139 (100)          | 61 (100)             | -       | 38 (100)         | -       |
| Male (%)                       | 394 (63.0)   | 159 (66.8)| 89 (64.0)          | 42 (68.9)            | 0.524   | 28 (73.7)        | 0.335   |
| Age, median (IQR)              | 66 (54.5–75.0)| 71.5 (64.0–79.0)| 73.0 (62.0–80.0)| 70.0 (63.5–76.0) | 0.401   | 73.0 (67.8–77.3) | 0.895   |
| BMI, median (IQR)              | 25.7 (22.4–29.5)| 26.0 (22.9–29.6)| 25.5 (22.4–29.7)| 26.7 (24.3–30.2) | 0.119   | 25.7 (22.9–28.0) | 0.686   |
| Time in therapeutic INR range, median % (IQR) | n.a. | n.a. | n.a. | 57.2 (39.5–72.3) | n.a. | n.a. | n.a. |
| Etiology of ESRD, n (%)        | -            | -         | -                  | -                    | -       | -                | -       |
| Diabetic NP                    | 160 (25.6)   | 63 (26.5) | 35 (25.2)          | 20 (32.8)            | 0.303   | 8 (21.1)         | 0.674   |
| Vascular NP                    | 121 (19.4)   | 50 (21.0) | 31 (22.3)          | 12 (19.7)            | 0.713   | 7 (18.4)         | 0.663   |
| Glomerulonephritis             | 81 (13.0)    | 22 (9.2)  | 11 (7.9)           | 6 (9.8)              | 0.783   | 5 (13.2)         | 0.341   |
| Atrophic NP                    | 57 (9.1)     | 21 (8.8)  | 13 (9.4)           | 4 (6.6)              | 0.594   | 4 (10.5)         | 0.999   |
| Cystic nonhereditary NP        | 36 (5.8)     | 17 (7.1)  | 11 (7.9)           | 3 (4.9)              | 0.558   | 3 (7.9)          | 0.999   |
| Hereditary NP                  | 31 (5.0)     | 10 (4.2)  | 7 (5.0)            | 1 (1.6)              | 0.439   | 2 (5.3)          | 0.999   |
| Nephrectomy                    | 20 (3.2)     | 11 (4.6)  | 4 (2.9)            | 6 (9.8)              | 0.070   | 1 (2.6)          | 0.999   |
| Toxic NP                       | 28 (4.5)     | 16 (6.7)  | 9 (6.5)            | 3 (4.9)              | 0.759   | 4 (10.5)         | 0.481   |
| Other causes                   | 91 (14.6)    | 28 (11.8) | 18 (12.9)          | 6 (9.8)              | 0.641   | 4 (10.5)         | 0.789   |
| Dialysis history, n (%)        | -            | -         | -                  | -                    | -       | -                | -       |
| History of kidney transplantation | 90 (14.4) | 33 (13.9) | 16 (11.5)          | 8 (13.1)             | 0.814   | 9 (23.7)         | 0.068   |
| History of peritoneal dialysis | 46 (7.4)     | 17 (7.1)  | 9 (6.5)            | 5 (8.2)              | 0.765   | 3 (7.9)          | 0.999   |
| Dialysis parameters, median (IQR) | -       | -         | -                  | -                    | -       | -                | -       |
| Remaining diuresis, ml/day      | 500 (0–1000) | 500 (0–1000) | 500 (0–1000) | 400 (0–1000) | 0.336 | 200 (0–1000) | 0.344   |
| Time on hemodialysis, years    | 2.7 (1.0–5.0) | 3.0 (1.0–6.0) | 3.0 (1.0–6.0) | 3.0 (1.7-7.0) | 0.420 | 2.3 (1.0–5.0) | 0.588   |
| Comorbidities, n (%)           | -            | -         | -                  | -                    | -       | -                | -       |
| History of stroke or TIA       | 127 (20.3)   | 63 (26.5) | 25 (18.0)          | 24 (39.3)            | **0.002** | 14 (36.8) | **0.016** |
| History of myocardial infarction | 104 (16.6) | 51 (21.4) | 31 (22.3)          | 12 (19.7)            | 0.713   | 8 (21.1)         | 0.999   |
| Coronary artery disease        | 232 (37.1)   | 111 (46.6)| 62 (44.6)          | 29 (47.5)            | 0.759   | 20 (52.6)        | 0.463   |
| Artificial heart valve         | 43 (6.9)     | 22 (9.2)  | 10 (7.2)           | 8 (13.1)             | 0.188   | 4 (10.5)         | 0.737   |
| History of VTE                 | 61 (9.8)     | 33 (13.9) | 16 (11.5)          | 13 (21.3)            | 0.082   | 4 (10.5)         | 0.999   |
| Deep vein thrombosis           | 43 (6.9)     | 24 (10.1) | 10 (7.2)           | 10 (16.4)            | 0.070   | 4 (10.5)         | 0.737   |
| Pulmonary embolism             | 32 (5.1)     | 16 (6.7)  | 7 (5.0)            | 8 (13.1)             | 0.076   | 1 (2.6)          | 0.690   |

(Continues)
| Condition                        | All Patients | AF Cohort | No Anticoagulation Group | Phenprocoumon Group | p Value | Enoxaparin Group | p Value |
|---------------------------------|--------------|-----------|--------------------------|---------------------|---------|------------------|---------|
| Peripheral artery disease       | 197 (31.5)   | 86 (36.1) | 48 (34.5)                | 20 (32.8)           | 0.872   | 18 (47.4)        | 0.185   |
| Diabetes                        | 237 (37.9)   | 102 (42.9)| 63 (45.3)                | 28 (45.9)           | 0.999   | 11 (28.9)        | 0.094   |
| Hypertension                    | 574 (91.8)   | 219 (92.0)| 128 (92.1)               | 57 (93.4)           | 0.783   | 34 (89.5)        | 0.742   |
| Congestive heart failure        | 183 (29.3)   | 92 (38.7) | 49 (35.3)                | 27 (44.3)           | 0.269   | 16 (42.1)        | 0.453   |
| Cancer history or active        | 152 (24.3)   | 76 (31.9) | 44 (31.7)                | 19 (31.1)           | 0.999   | 13 (34.2)        | 0.845   |
| Current and past smokers        | 305 (48.8)   | 114 (47.9)| 64 (46.0)                | 37 (60.7)           | 0.814   | 13 (34.2)        | 0.068   |
| History of major bleeding       | 67 (10.7)    | 29 (12.2) | 20 (14.4)                | 5 (8.2)             | 0.223   | 4 (10.5)         | 0.538   |
| History of intracranial bleeding| 18 (2.9)     | 10 (4.2)  | 7 (5.0)                  | 2 (3.3)             | 0.581   | 1 (2.6)          | 0.527   |
| CHA\textsubscript{2}-VASc score, median (IQR) | 4 (2-5)  | 4 (3-5)  | 4 (3-5)                  | 3 (2-5)             | 0.423   | 4 (3-5)          | 0.959   |
| HAS-BLED score, median (IQR)    | 3 (2-4)      | 4 (3-4)  | 4 (3-4)                  | 3 (2-4)             | 0.065   | 4 (3-5)          | 0.766   |
| Antiplatelet medication         | 345 (55.2)   | 137 (57.6)| 98 (70.5)                | 18 (29.5)           | <0.001  | 21 (55.3)        | 0.083   |

Abbreviations: AF, atrial fibrillation; BMI, body mass index; ESRD, end-stage renal disease; INR, international normalized ratio; IQR, interquartile range; NP, nephropathy; TIA, transient ischemic attack; VTE, venous thromboembolism.

p-values calculated with chi-squared test for categorical variables and Mann-Whitney U test for continuous variables. Bold values signify statistical significance.
patient-years (Table 2). Occurrence of the composite outcome significantly increased with older age (SHR per year increase 1.05, 95% CI, 1.02-1.07), and presence of AF (SHR 3.12, 95% CI, 1.64-5.91), history of stroke (SHR 2.00, 95 CI, 1.05-3.81), history of myocardial infarction (SHR 2.02, 95% CI, 1.03-3.97), diabetes (SHR 2.38, 95% CI, 1.26-4.47), CHA2DS2-VASc score (SHR per point increase 1.59, 95% CI, 1.31-1.93), the HAS-BLED score (SHR per point increase 1.41, 95% CI, 1.13-1.76), and antiplatelet comedication (SHR 3.10, 95% CI, 1.43-6.70; Table 3).

3.2 | Major bleeding in the total cohort

Major bleeding events occurred in 89 patients (14.2%) including 14 intracranial hemorrhage events, 41 gastrointestinal bleeds, 13 other critical organ hemorrhage, and 20 other major bleeding events. Vascular nephropathy (SHR: 1.86, 95% CI, 1.18-2.92, p = .007), the HAS-BLED score (SHR per point increase 1.22, 95% CI, 1.05-1.42, p = .008), and antiplatelet comedication (SHR: 1.55, 95% CI, 1.00-2.40, p = .051) were associated with increased risk of major bleeding in the full cohort (Table 3).

3.3 | Secondary outcomes in the total cohort

During the observation period, 256 patients died (41.0%), corresponding to a mortality rate of 181.9 per 1000 patient-years. Cardiovascular death occurred in 105 patients (16.8%) for a rate of 74.6 per 100 patient-years. The 3P-MACE outcome occurred in 154 patients (24.6%), with an event-rate of 115.2 per 1000 patient-years. Myocardial infarction events occurred in 38 patients (6.1%) with an event rate or 27.8 per 1000 patient-years. The 30-day case fatality rates for all primary and secondary outcomes are provided in Table 2.

### TABLE 2 Incidence of adverse events and 30-day case fatality rates

| Event | Total Cohort | Non-AF Cohort | AF Cohort |
|-------|--------------|---------------|----------|
| Patient count (%) | 625 (100) | 387 (61.9) | 238 (38.1) |
| Incidence rate, de novo AF | 75.0 | n.a. | n.a. |
| Incidence rate, composite thromboembolic outcome | 29.0 | 17.4 | 48.4 |
| Incidence rate, major bleeding | 67.8 | 57.8 | 84.0 |
| Incidence rate, intracranial hemorrhage | 10.7 | 8.1 | 14.0 |
| Incidence rate, 3P-MACE | 115.2 | 90.0 | 157.0 |
| Incidence rate, myocardial infarction | 27.8 | 27.2 | 28.7 |
| Incidence rate, CV death | 74.6 | 54.9 | 106.5 |
| Incidence rate, all-cause death | 181.9 | 142.0 | 246.7 |
| 30-day case fatality after de novo AF | 8.2% | n.a. | n.a. |
| 30-day case fatality after stroke | 22.5% | 13.3% | 28% |
| 30-day case fatality after major bleeding | 19.1% | 17.0% | 21.4% |
| 30-day case fatality after intracranial hemorrhage | 28.5% | 28.4% | 28.6% |
| 30-day case fatality after myocardial infarction | 18.4% | 13.0% | 26.7% |

Abbreviations: 3P-MACE, composite major adverse cardiovascular outcome; AF, atrial fibrillation; CV, cardiovascular. All incidence rates are expressed per 1000 person-years.

3.4 | Primary and secondary outcomes in the group of patients with atrial fibrillation

The group of patients with AF consisted of 165 patients (26.4%), who had AF at baseline, and 73 patients (15.9% of previously non-AF patients) who developed de novo AF during the observation time. Thus, the AF cohort included 238 patients (38.1%). The incidence of de novo AF was 75.0 per 1000 patient-years. The incidence rates for the primary thromboembolic outcome were 48.4 per 1000 patient-years and 84.0 per 1000 patient-years for major bleeding and therefore higher in AF patients than in the total HD cohort (Table 2).

Increasing age (SHR per year increase 1.05, 95% CI, 1.02-1.07) and the CHA2DS2-VASc score (SHR per point increase 1.36, 95% CI, 1.02-1.81) were the only risk factors associated with the occurrence of the composite thromboembolic outcome in univariable competing risk regression models (Table 4). A prior period of peritoneal dialysis was the only factor associated with increased risk of major bleeding (SHR: 3.07, 95% CI, 1.27-7.43) in AF patients. AF patients with diabetes (SHR: 0.48, 95% CI, 0.23-1.00) or heart failure (SHR: 0.47, 95% CI, 0.23-0.98) were at decreased risk of major bleeding event occurrence (Table 4).
Anticoagulation treatment and risk of primary and secondary outcomes in patients with atrial fibrillation

Vitamin K antagonists were used for stroke prevention in 61 AF patients (25.6% of all AF patients), LMWH on non-HD days in 38 patients (16.0%), and 139 AF patients (58.4%) received no long-term anticoagulation (Table 1). The median TTR in the group of VKA patients was 57.2%. Patients with a history of stroke were more frequently treated with VKA ($p=0.002$) or LMWH on non-HD days ($p=0.016$) compared with patients with AF without a history of stroke. Patients receiving antiplatelet therapy were less frequently treated with VKA ($p<0.001$).

| Characteristic | Univariable SHR for Thromboembolic Outcome | Univariable SHR for Major Bleeding |
|---------------|-------------------------------------------|------------------------------------|
| Age, mean centered | 1.05 (1.02–1.07) | 1.00 (0.99–1.02) |
| BMI, mean centered | 1.00 (0.96–1.04) | 0.99 (0.96–1.03) |
| Female | 1.45 (0.78–2.70) | 1.16 (0.76–1.77) |
| Etiology of ESRD, n (%) | | |
| Diabetic NP | 1.54 (0.80–2.97) | 0.87 (0.53–1.42) |
| Vascular NP | 1.16 (0.55–2.43) | 1.86 (1.18–2.92) |
| Glomerular nephritis | 0.63 (0.19–2.05) | 0.43 (0.18–1.07) |
| Atrophic NP | 1.55 (0.60–3.99) | 0.75 (0.33–1.71) |
| Cystic nonhereditary NP | 0.83 (0.21–3.30) | 1.21 (0.53–2.80) |
| Hereditary NP | 0.53 (0.07–3.81) | 1.46 (0.67–3.19) |
| Nephrectomy | 1.55 (0.40–6.08) | 1.77 (0.75–4.18) |
| Toxic NP | 1.03 (0.25–4.28) | 1.78 (0.82–3.86) |
| Other causes | 0.29 (0.07–1.18) | 0.39 (0.17–0.89) |
| Dialysis history, n (%) | | |
| History of renal transplantation | 0.92 (0.36–2.39) | 0.98 (0.54–1.78) |
| Previous peritoneal dialysis | 0.01 (0.01–0.01) | 1.29 (0.59–2.80) |
| Dialysis parameters | | |
| Remaining diuresis, ml/day | 1.00 (1.00–1.00) | 1.00 (1.00–1.00) |
| Time on hemodialysis, years | 0.93 (0.86–1.01) | 0.99 (0.95–1.03) |
| Comorbidities, n (%) | | |
| History of stroke or TIA | 2.00 (1.05–3.81) | 1.21 (0.75–1.95) |
| History of myocardial infarction | 2.02 (1.03–3.97) | 1.00 (0.58–1.69) |
| Coronary artery disease | 1.83 (0.97–3.40) | 1.38 (0.91–2.09) |
| Atrial fibrillation | 3.12 (1.64–5.91) | 1.73 (1.13–2.65) |
| Artificial heart valve | 2.01 (0.78–5.22) | 0.96 (0.42–2.17) |
| History of VTE | 0.99 (0.36–2.76) | 0.88 (0.43–1.80) |
| Deep vein thrombosis | 0.67 (0.16–2.77) | 0.75 (0.31–1.82) |
| Pulmonary embolism | 0.99 (0.24–4.03) | 1.41 (0.62–3.17) |
| Peripheral artery disease | 1.35 (0.72–2.55) | 1.43 (0.94–2.19) |
| Diabetes | 2.38 (1.26–4.47) | 0.73 (0.47–1.14) |
| Hypertension | 1.13 (0.35–3.67) | 1.58 (0.64–3.88) |
| Congestive heart failure | 1.56 (0.83–2.94) | 0.79 (0.49–1.26) |
| Cancer, history or active | 1.76 (0.93–3.33) | 1.00 (0.62–1.60) |
| Current and past smokers | 0.77 (0.41–1.44) | 0.96 (0.63–1.46) |
| History of bleeding | 1.06 (0.56–1.99) | 1.55 (1.02–2.34) |
| CHA2DS2-VASc score | 1.59 (1.31–1.93) | 1.06 (0.95–1.17) |
| HAS-BLED score | 1.41 (1.13–1.76) | 1.22 (1.05–1.42) |
| Antiplatelet medication | 3.10 (1.43–6.70) | 1.55 (1.00–2.40) |

Abbreviations: BMI, body mass index; ESRD, end-stage renal disease; NP, nephropathy; SHR, subdistribution hazard ratio; TIA, transient ischemic attack; VTE, venous thromboembolism. Bold values signify statistical significance.

TABLE 3 Risk factors for occurrence of prospective outcomes in the full cohort
Use of VKA and LMWH on non-HD days was not associated with a decreased risk of the composite thromboembolic outcome: the adjusted SHR for VKA and LMWH were 1.41 (95% CI, 0.49-4.07) and 0.49 (95% CI, 0.11-2.18), respectively compared with AF patients with no anticoagulation. However, VKA use was associated with more than double the risk of major bleeding (adjusted SHR: 2.28, 95% CI, 1.09-4.79) and with an increased risk of 3P-MACE outcome compared with AF patients with no anticoagulation, albeit at borderline significance (SHR: 1.69, 95% CI, 0.99-2.89), after adjustment for CHA\textsuperscript{2}DS\textsubscript{2}-VASc score and antiplatelet comedication (Table 5). LMWH use was not associated with the risk of major bleeding (SHR: 1.86, 95% CI, 0.81-4.28) compared with AF patients with no anticoagulation. The risk of occurrence of the composite outcome indicating net clinical benefit or harm (stroke, TIA, systemic embolism, major

| Characteristic                          | Univariable SHR for Thromboembolic Outcome | Univariable SHR for Major Bleeding |
|-----------------------------------------|---------------------------------------------|-----------------------------------|
| Age, mean centered                      | 1.04 (1.00-1.07)                            | 0.99 (0.96-1.02)                  |
| BMI, mean centered                      | 1.01 (0.96-1.07)                            | 0.96 (0.91-1.02)                  |
| Female sex                              | 1.33 (0.58-3.05)                            | 0.86 (0.42-1.73)                  |
| Etiology of ESRD, n (%)                 |                                             |                                   |
| Diabetic NP                             | 1.46 (0.62-3.44)                            | 0.92 (0.43-1.99)                  |
| Vascular NP                             | 0.71 (0.24-2.10)                            | 1.02 (0.47-2.23)                  |
| Glomerular nephritis                    | 0.55 (0.07-4.13)                            | 0.63 (0.16-2.54)                  |
| Atrophic NP                             | 1.57 (0.46-5.37)                            | 0.95 (0.28-3.14)                  |
| Cystic nonhereditary NP                 | 0.58 (0.08-4.23)                            | 1.83 (0.62-5.42)                  |
| Hereditary NP                           | 1.26 (0.17-9.12)                            | 2.42 (0.82-7.20)                  |
| Nephrectomy                             | 1.89 (0.50-7.20)                            | 1.73 (0.61-4.88)                  |
| Toxic NP                                | 1.39 (0.31-6.29)                            | 1.25 (0.40-3.89)                  |
| Other causes                            | 0.33 (0.05-2.37)                            | 0.20 (0.03-1.47)                  |
| Dialysis history, n (%)                 |                                             |                                   |
| History of renal transplantation        | 0.56 (0.13-2.41)                            | 1.21 (0.52-2.83)                  |
| Previous peritoneal dialysis            | 0.01 (0.01-0.01)                            | 3.07 (1.27-7.43)                  |
| Dialysis parameters, median (25th-75th percentile) | | |
| Remaining diuresis, ml/day               | 1.00 (1.00-1.00)                            | 1.00 (1.00-1.00)                  |
| Time on hemodialysis, years             | 0.91 (0.81-1.03)                            | 1.00 (0.95-1.04)                  |
| Comorbidity, n (%)                      |                                             |                                   |
| History of stroke or TIA                | 2.18 (0.96-4.98)                            | 1.19 (0.59-2.40)                  |
| History of myocardial infarction        | 1.67 (0.69-4.05)                            | 0.85 (0.37-1.92)                  |
| Coronary artery disease                 | 1.41 (0.62-3.22)                            | 1.21 (0.63-2.32)                  |
| Artificial heart valve                  | 2.04 (0.68-6.11)                            | 0.80 (0.25-2.60)                  |
| History of VTE                          | 0.58 (0.14-2.41)                            | 0.57 (0.17-1.88)                  |
| Deep vein thrombosis                    | 0.40 (0.05-2.89)                            | 0.82 (0.25-2.75)                  |
| Pulmonary embolism                      | 0.65 (0.09-4.58)                            | 0.41 (0.06-3.02)                  |
| Peripheral artery disease               | 0.94 (0.40-2.21)                            | 1.31 (0.67-2.55)                  |
| Diabetes                                | 2.06 (0.89-4.75)                            | 0.48 (0.23-1.00)                  |
| Hypertension                            | 0.99 (0.24-4.11)                            | 3.48 (0.50-23.9)                  |
| Congestive heart failure                | 0.52 (0.20-1.32)                            | 0.47 (0.23-0.98)                  |
| Cancer history or active                | 1.87 (0.84-4.21)                            | 0.98 (0.49-1.94)                  |
| Current and past smokers                | 0.63 (0.27-1.49)                            | 0.91 (0.47-1.76)                  |
| History of bleeding                     | 0.72 (0.31-1.67)                            | 1.49 (0.77-2.88)                  |
| CHA\textsuperscript{2}DS\textsubscript{2}-VASc score | 1.36 (1.02-1.81)            | 0.91 (0.76-1.09)                  |
| HAS-BLED score                          | 1.28 (0.95-1.73)                            | 1.17 (0.91-1.50)                  |
| Antiplatelet comedication               | 2.05 (0.81-5.15)                            | 1.14 (0.59-2.21)                  |

Abbreviations: AF, atrial fibrillation; BMI, body mass index; ESRD, end-stage renal disease; NP, nephropathy; SHR, subdistribution hazard ratio; TIA, transient ischemic attack; VTE, venous thromboembolism. Bold values signify statistical significance.
bleeding, and CV death) was double in AF patients on anticoagulation with VKA compared with no anticoagulation (adjusted SHR 2.07, 95% CI, 1.25-3.42).

AF patients treated with LMWH on non-HD days had significantly increased all-cause mortality compared with those without anticoagulation (adjusted SHR 1.88, 95% CI, 1.20-2.92). Figure 1 shows the cumulative probabilities of the composite outcome of thromboembolism, major bleeding, 3P-MACE, and net clinical benefit in AF patients with separate lines according to anticoagulation treatment.

Compared with non-AF patients without anticoagulation, AF patients treated with VKA also had increased risks for occurrence of primary and secondary outcomes (Table 5). Surprisingly, AF patients without anticoagulation did not have statistically increased risks for thromboembolic outcomes, major bleeding, CV death, and 3P-MACE compared with non-AF non-anticoagulated patients (Table 5).

### DISCUSSION

In this prospective population-based cohort study of HD patients encompassing the majority of patients undergoing HD in a large metropolitan area, we found an event rate of 29 per 1000 patient-years for the composite outcome of stroke, TIA, and systemic embolism, and 68 per 1000 patient-years for major bleeding. In contrast to most previous studies that used insurance claims to ascertain these events, all events were independently adjudicated by expert clinicians using imaging evidence. Patients with AF had higher event rates of all primary and secondary outcomes compared with the full cohort. AF patients receiving anticoagulation with VKA or LMWH did not benefit in terms of reduced thromboembolic risk or better survival compared with AF patients without anticoagulation, but their risk of bleeding was significantly and sizably increased, resulting in a two-fold increased risk for the net clinical harm outcome.

Despite being diligently adjudicated, the incidences identified were on the higher range of previous reports, where the incidence of ischemic stroke ranged from 10 to 38 per 1000 patient-years, and 20 to 69 per 1000 patient-years for major bleeding. In contrast to previous studies that used insurance claims to ascertain these events, all events were independently adjudicated by expert clinicians using imaging evidence. Patients with AF had higher event rates of all primary and secondary outcomes compared with the full cohort. AF patients receiving anticoagulation with VKA or LMWH did not benefit in terms of reduced thromboembolic risk or better survival compared with AF patients without anticoagulation, but their risk of bleeding was significantly and sizably increased, resulting in a two-fold increased risk for the net clinical harm outcome.

Despite being diligently adjudicated, the incidences identified were on the higher range of previous reports, where the incidence of ischemic stroke ranged from 10 to 38 per 1000 patient-years. However, the incidence of ischemic stroke ranged from 20 to 69 per 1000 patient-years for major bleeding. In contrast to previous studies that used insurance claims to ascertain these events, all events were independently adjudicated by expert clinicians using imaging evidence. Patients with AF had higher event rates of all primary and secondary outcomes compared with the full cohort. AF patients receiving anticoagulation with VKA or LMWH did not benefit in terms of reduced thromboembolic risk or better survival compared with AF patients without anticoagulation, but their risk of bleeding was significantly and sizably increased, resulting in a two-fold increased risk for the net clinical harm outcome.

### TABLE 5

| Outcome                                      | No AF, No Anticoagulation | AF, No Anticoagulation | AF, VKA Anticoagulation | AF, LMWH on non-HD days |
|----------------------------------------------|---------------------------|------------------------|-------------------------|-------------------------|
| N (%)                                        | 347 (55.5)                | 139 (58.4)             | 61 (25.6)               | 61 (25.6)               |
| Composite thromboembolic outcome             | 15 (4.3)                  | 16 (11.5)              | 16 (25.6)               | 16 (25.6)               |
| 3P-MACE                                      | 65 (18.7)                 | 42 (30.2)              | 42 (65.6)               | 42 (65.6)               |
| CV death                                     | 40 (11.5)                 | 30 (21.6)              | 21 (34.4)               | 21 (34.4)               |
| Major bleeding outcome                       | 42 (12.1)                 | 51 (36.7)              | 35 (57.4)               | 35 (57.4)               |
| Net clinical benefit or harm in terms of ischemic stroke or major bleeding and CV death | 107 (30.8) | 68 (48.9) | 107 (30.8) | 68 (48.9) |

**Abbreviations:** 3P-MACE, composite major adverse cardiovascular outcome; AF, atrial fibrillation; CV, cardiovascular; LMWH, low molecular weight heparin; SHR, subdistribution hazard ratio; VKA, vitamin K agonist
The high incidence (48.4 per 1000 patient-years) and case fatality of strokes (28% after 30 days) in this cohort indicates that HD patients with AF could theoretically benefit considerably from anticoagulation treatment for stroke prevention. Because the use of direct oral anticoagulants in HD patients is off-label in Austria, and hence not reimbursable, VKAs were the only available oral agents. Use of VKAs in HD patients is, however, seen critical because of its role in mediating progression of vascular calcification, manifest inherent vitamin K deficiency in HD patients, fear of associated calciphylaxis, difficulty maintaining treatment in the therapeutic range because of the downregulation of cytochrome P450 isoenzymes in chronic uremic conditions, and feared risk of bleeding complications. Using prospective data, we confirmed that anticoagulation with phenprocoumon, a VKA used in Austria, resulted in a 2.3-fold increased risk of major bleeding compared with no anticoagulation in AF patients, whereas there was no reduction in the risk of occurrence of the composite thromboembolic outcome. There are some prior observational studies investigating efficacy and safety of the warfarin, another VKA, in AF patients on HD with mixed results. Shen et al. reported marginally reduced risk of ischemic stroke in incident AF patients on HD, but Shah et al. reported no significant difference in the risk of ischemic stroke but increased risk of hemorrhage in warfarin-treated AF patients on HD, which is consistent with our data. Entirely contradictory, Olesen et al. reported significantly decreased risk of ischemic stroke and systemic embolism and no increase in the risk of bleeding in patients on VKA with ESRD requiring renal replacement therapy but not differentiating between HD and peritoneal dialysis. The observational character of these studies precludes establishing a causal effect and limitations regarding selection bias, verification of drug exposure, and outcome validation apply. In systematic meta-analyses, albeit limited by the heterogeneous character of the included observational studies, use of warfarin in HD patients with AF did not have a favorable risk-benefit profile. The only randomized, control trial of anticoagulation in the HD setting, VALKYRIE study, evaluated ischemic and hemorrhagic strokes as a secondary outcome in 132 patients treated with VKA versus rivaroxaban 10 mg once daily. Although no significant difference was found, hemorrhagic strokes occurred less frequently in the rivaroxaban arm. In prior observational studies on the use of direct oral anticoagulant in HD patient with AF, Chan et al. reported higher risk for bleeding in patients on dabigatran or rivaroxaban compared with warfarin, whereas Siontis et al. and
Coleman\textsuperscript{41} reported lower risk of bleeding in direct oral anticoagulant compared with warfarin users. The ongoing trials AXADIA\textsuperscript{42} and SAFE-D (apixaban vs. VKA),\textsuperscript{43} as well as AVKDIAL\textsuperscript{44} and DANWARD\textsuperscript{45} (VKA vs. no anticoagulation) are awaited with great anticipation.

In clinical practice, the risks associated with VKA use in HD patients with AF have increasingly been recognized, and we observed in our cohort that treating nephrologists, who in Austria would usually be making this treatment determination and managing it, opted not to use anticoagulation in 58\% of their patients with AF. The only baseline factor associated with the use of anticoagulants was a history of ischemic stroke. An alternative anticoagulation strategy observed in this cohort was LMWH on non-HD days in a low once-daily dose. It is a pragmatic approach for patients who tolerate long-term subcutaneous injections and those with contraindications for VKA or refusal of VKA treatment. LMWH on non-HD days likely provides a continuous state of anticoagulation because elimination is limited by renal function, and patients receive systemic anticoagulation during HD sessions. In our study, we found that AF patients on LMWH on non-HD days had no increased risk for the occurrence of the composite outcome of stroke and thromboembolism, 3P-MACE, CV death, or major bleeding. However, it also did not provide a net clinical benefit in terms of ischemic stroke and thromboembolism, major bleeding, and CV death and was significantly associated with a near doubling of all-cause mortality. We observed that among patients receiving antiplatelet therapies use of LMWH was more common than that of VKA. As we described in a previous publication, the majority of HD patients in this cohort qualify for secondary cardiovascular disease prevention.\textsuperscript{16} It appears plausible that patients on anticoagulation would benefit from discontinuation of antiplatelet medication regarding bleeding risk, but this decision would have to be made with consideration to the individual indication for antiplatelet therapy.

We also investigated net clinical benefit or harm using a composite endpoint of stroke, TIA, systemic embolism, major bleeding, and cardiovascular death and found a statistically increased risk with VKA indicating net clinical harm. No association of LMWH with net clinical benefit or harm was found, but the small LMWH sample size limited statistical power. Compared with HD patients without AF and without anticoagulation, AF patients without anticoagulation did not have increased risk of thromboembolic outcome, leading to the rationale that randomized trials on stroke prevention in HD patients with AF may have to compare an investigational drug to placebo instead of VKA.

There are certain limitations and strengths of our study that merit consideration. Although previous observational studies and registries have highlighted the risks of anticoagulation treatment in HD patients, they based their definition of AF, and their ascertained thromboembolic and bleeding events on billing claims. This provided substantially larger sample sizes than our prospective cohort study, along with the ability to conduct adjustment for observed baseline characteristics. By contrast, our study is smaller in sample size, with lesser ability to conduct regression adjustment, but fully generalizable to the overall population of HD patients with the presence of AF as well as the occurrence of key outcomes were adjudicated by academic clinical experts. The VIVALDI study had negligible loss to follow-up and a physician saw patients at every HD session and documented concurrent medical issues. Admittedly, some HD patients were in end-of-life situations at the time of suspected thromboembolic events, and their treating physicians did not perform exhaustive diagnostics in these situations. Thus, the adjudication committee only adjudicated events that were supported by objective evidence (i.e., imaging tests). Finally, the allocation of anticoagulation treatment to patients with AF was not randomized and done at the discretion of the treating physicians. Patients with a history of stroke more frequently received VKA or LMWH and patients with antiplatelet comedication more frequently received LMWH than VKA. Beyond that, we found no correlates of anticoagulation treatment practice. The patients’ preferences expected life expectancy, and anticipated adherence may have significantly factored into these treatment decisions on an individual basis.

5 | CONCLUSION

From this carefully conducted prospective study of HD patients in a large metropolitan area, we found that AF was a heavy burden on this population, associated with high risks of stroke, bleeding complications, and mortality. Our findings support the notion that HD patients with AF may not benefit from oral anticoagulation with VKA in terms of stroke prevention and may be exposed to undue harm from increased risk of major bleeding events compared with patients with AF not receiving anticoagulation. Thus, it is quite possible that anticoagulation treatment may result in net clinical harm. There is an unmet clinical need for effective and safe treatment options in this special patient population, and results of randomized controlled studies using VKAs, or other novel anticoagulants, are awaited with great interest.

ACKNOWLEDGMENTS

We acknowledge the members of the adjudication committee: Julia Riedl, Johannes Thaler, Christoph Kopp, Thomas Gremmel, and Fritz Leutmezer.

CONFLICT OF INTERESTS

Dr. Winkelmayer has served as scientific advisor to Akebia, AstraZeneca, Bayer, Daichii-Sankyo, Janssen, Merck, Reata, Relypsa, and Vifor FMC Renal Pharma. The other authors declare no competing interests.

AUTHOR CONTRIBUTIONS

Concept and design: Oliver Königsbrügge, Ingrid Pabinger, Marcus Säemann, Cihan Ay; acquisition, analysis, or interpretation of data: Oliver Königsbrügge, Hannah Meisel, Aljoscha Beyer, Ingrid Pabinger, Cihan Ay; drafting of the manuscript: Oliver Königsbrügge, Cihan Ay; critical revision of the manuscript for
important intellectual content: all authors; statistical analysis: Oliver Königsbrügge, Hannah Meisel; administrative, technical, or material support: Sabine Schmaldienst, Renate Klauser-Braun, Matthias Lorenz, Martin Auinger, Josef Kletzmayr, Manfred Hecking, Ingrid Pabinger, Marcus Säemann, Cihan Ay; supervision: Ingrid Pabinger, Cihan Ay.

**ORCID**
Olive Königsbrügge [https://orcid.org/0000-0002-6183-3685](https://orcid.org/0000-0002-6183-3685)
Cihan Ay [https://orcid.org/0000-0003-2607-9717](https://orcid.org/0000-0003-2607-9717)

**REFERENCES**

1. 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;36:297-306.
2. Seliger SL, Gillen DL, Longstreth WT, Kestenbaum B, Stehman-Breen CO. Elevated risk of stroke among patients with end-stage renal disease. *Kidney Int*. 2003;64:603-609.
3. Go AS, Fang MC, Udaltsova N, et al. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Circulation*. 2009;119:1363-1369.
4. 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:e0169400.
5. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296-1305.
6. Molnar AO, Bota SE, Garg AX, et al. The risk of major hemorrhage with CKD. *J Am Soc Nephrol*. 2016;27:2825-2832.
7. 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 R. *J Am Coll Cardiol*. 2019;74:104-132.
8. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace*. 2016;18:1609-1678.
9. Pisters R, Lane DA, Nieuwlaat R, De Vos CB, Crijs HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093-1100.
10. Turakhia MP, Blankstein 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;39:2314-2325.
11. Königsbrügge O, Ay C. Atrial fibrillation in patients with end-stage renal disease on hemodialysis: magnitude of the problem and new approach to oral anticoagulation. *Res Pract Thromb Haemost*. 2019;3:578-588.
12. Kumar S, Lim E, Covic A, et al. Anticoagulation in concomitant chronic kidney disease and atrial fibrillation: JACC review topic of the week. *J Am Coll Cardiol*. 2019;74:2204-2215.
13. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest*. 2018;154:1121-1201.
14. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *J Thromb Haemost*. 2015;13:2119-2126.
15. Rosendaal F, Cannegieter S, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost*. 1993;69:236-239.
16. Wiesholzer M, Harm F, Tomasec G, Barbieri G, Putz D, Balcke P. Incidence of stroke among chronic hemodialysis patients with non-rheumatic atrial fibrillation. *Am J Nephrol*. 2001;21:35-39.
17. Wang HH, Hung SY, Sung JM, Hung KY, Wang JD. Risk of stroke in long-term dialysis patients compared with the general population. *Am J Kidney Dis*. 2014;63:604-611.
18. Shih C-J, Ou S-M, Chao P-W, et al. Risks of death and stroke in patients undergoing hemodialysis with new-onset atrial fibrillation: a competing-risk analysis of a nationwide cohort. *Circulation*. 2016;133:265-272.
19. Airy M, Chang TI, Ding YV, et al. Risk profiles for acute health events after incident atrial fibrillation in patients with end-stage renal disease on hemodialysis. *Nephrol Dial Transplant*. 2017;33:1590-1597.
20. Chao T-F, Liu C-J, Wang K-L, et al. Incidence and prediction of ischemic stroke among atrial fibrillation patients with end-stage renal disease requiring dialysis. *Heart Rhythm*. 2014;11:1752-1759.
21. Wizemann V, Tong L, Satayathum S, et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. *Kidney Int*. 2010;77:1098-1106.
22. Shah M, Avgil Tasdok M, Jawkecivius CA, et al. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. *Circulation*. 2014;129:1196-1203.
23. Shen JI, Turakhia MP, Winkelmayer WC. Anticoagulation for atrial fibrillation in patients on dialysis: are the benefits worth the risks? *Curr Opin Nephrol Hypertens*. 2012;21:600-606.
24. Chan KE, Lazarus JM, Thadhari R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. *J Am Soc Nephrol*. 2009;20:2223-2233.
25. Olesen JB, Lip GYH, Kamper A-L, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med*. 2012;367:625-635.
26. 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;123:2946-2953.
27. Vazquez E, Sanchez-Perales C, Garcia-Garcia F, et al. Atrial fibrillation in incident dialysis patients. *Kidney Int*. 2009;76:324-330.
28. Shroff RC, McNair R, Figg N, et al. Dialysis accelerates medial vascular calcification in part by triggering smooth muscle cell apoptosis. *Circulation*. 2008;118:1748-1757.
29. London GM, Guerin AP, Marchais SJ, Métévier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: Impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant*. 2018;03:1731-1740.
30. Westenfeld R, Krüger T, Schlieper G, et al. Effect of vitamin K supplementation on functional vitamin K deficiency in hemodialysis patients: a systematic review of bleeding rates. *Nephrol Dial Transplant*. 2018;03:1731-1740.
hemodialysis patients with newly diagnosed atrial fibrillation. Am J Kidney Dis. 2015;66:677-688.

36. Dahal K, Kunwar S, Rijal J, Schulman P, Lee J. Stroke, major bleeding, and mortality outcomes in warfarin users with atrial fibrillation and chronic kidney disease: a meta-analysis of observational studies. Chest. 2016;149:951-959.

37. 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 Open. 2020;3:1-13.

38. 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;31:186-196.

39. Chan KE, Edelman ER, Wenger JB, Thadhani RI, Maddux FW, Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. Circulation. 2015;131:972-979.

40. Siontis K, 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;128:1519-1529.

41. Coleman CI, Kreutz R, Sood NA, et al. Rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation and severe kidney disease or undergoing hemodialysis. Am J Med Elsevier Inc. 2019;132:1078-1083.

42. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT02933697. Compare Apixaban and Vitamin-K Antagonists in Patients With Atrial Fibrillation (AF) and End-Stage Kidney Disease (ESKD) (AXADIA), 2016. Available from https://clinicaltrials.gov/ct2/show/NCT02933697?term=AXADIA&draw=2&rank=1

43. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03987711. Strategies for the Management of Atrial Fibrillation in patients Receiving Dialysis (SAFE-D), 2019. Available from https://clinicaltrials.gov/ct2/show/NCT03987711?term=SAFE-D&draw=2&rank=2

44. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT02886962. Oral Anticoagulation in Haemodialysis Patients (AVKDIAL), 2016. Available from https://clinicaltrials.gov/ct2/show/NCT02886962

45. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03862859. The Danish Warfarin-Dialysis Study - Safety and Efficacy of Warfarin in Patients With Atrial Fibrillation on Dialysis (DANWARD), 2019. Available from https://clinicaltrials.gov/ct2/show/NCT03862859?term=DANWAR&D&draw=2&rank=1

46. Königsbrügge O, Schmaldienst S, Auinger M, et al. Antithrombotic agents for primary and secondary prevention of cardiovascular events in patients with end-stage renal disease on chronic hemodialysis. Atherosclerosis. 2020;298:1-6.

How to cite this article: Königsbrügge O, Meisel H, Beyer A, et al. Anticoagulation use and the risk of stroke and major bleeding in patients on hemodialysis: From the VIVALDI, a population-based prospective cohort study. J Thromb Haemost. 2021;19:2984-2996. https://doi.org/10.1111/jth.15508