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ORIGINAL RESEARCH

Thromboembolic Events in the Hemodialysis Setting: Understanding Risk Profiles and Cumulative Incidences to Inform Clinical Trial Design

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BACKGROUND: People with kidney failure have a high risk of cardiovascular morbidity/death, including thromboembolic events. Factor XIa inhibitors are a new class of anticoagulants in development that may offer antithrombotic benefits with a lower risk of incremental bleeding events than traditional therapies. We investigated major adverse vascular events (MAVEs), a relevant composite outcome for testing novel antithrombotic agents, in a large cohort of patients on hemodialysis, to better understand the key requirements to adequately design a phase 3 trial.

METHODS AND RESULTS: We included 25 211 patients on hemodialysis for >90 days in phases 4 to 7 (2009–2021) of the DOPPS (Dialysis Outcomes and Practice Patterns Study). Atherosclerotic cardiovascular disease (ASCVD) was defined as history/presence of coronary, peripheral, or cerebrovascular disease. We estimated MAVE rates and cumulative incidence, overall and by ASCVD. Over half (52%) of the cohort met the ASCVD criteria. The MAVE hospitalization/death composite rate (per 100 patient-years) was 6.0 in the overall cohort and 8.7 in the ASCVD subset. Three-year cumulative incidence of MAVE was 13% in the overall cohort and 18% in the ASCVD subset. The estimated sample size to be randomized in a hypothetical trial in the ASCVD population was ≈7000 patients.

CONCLUSIONS: Even in the enriched ASCVD group, the observed MAVE incidence combined with a high competing risk, regulatory requirements (α=0.01), and limited recruitment pool makes feasibility of a potential randomized trial targeting MAVE reduction challenging. These results highlight key considerations and challenges for developers of novel therapies targeting systemic thromboembolic events in patients on hemodialysis.

Key Words: epidemiology ■ hemodialysis ■ observational data ■ randomized trial ■ thromboembolic events

Individuals with chronic kidney disease have a high burden of cardiovascular disease (CVD),[1] a heterogeneous label that includes both a "cardiac" component (eg, cardiac arrhythmia, decompensation, sudden death) and a "vascular" or thromboembolic component (eg, myocardial infarction [MI], ischemic stroke, systemic embolism). Traditional antithrombotic agents, including oral anticoagulants and antiplatelets, can effectively reduce the risk of a vascular event[2] but with major side effects, including bleeding and vascular calcification.[3,4] As kidney function worsens, recommendations for antithrombotic agents are more

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RESEARCH PERSPECTIVE

What Is New?

- Our findings have important implications for randomized trial development, highlighting the utility of observational data to provide a framework for trial planning, and, specifically, for therapies that target reduction of thromboembolic events in the hemodialysis setting.
- The relative proportion of major adverse vascular events within the overall cardiovascular burden of patients undergoing hemodialysis was small, even in an enriched subset with history of atherosclerotic cardiovascular disease, which in combination with a high rate of competing events (eg, death, transplant, modality switch) resulted in a sample size of ≈7000 patients required to detect a clinically meaningful treatment effect in a randomized trial.

What Question Should Be Addressed Next?

- Considering the significant challenges associated with conducting a large-scale clinical trial in the hemodialysis setting, it is critically important to explore nontraditional composite outcomes, such as those including vascular access thrombosis; however, implementing these outcomes is not without its own set of challenges.

Nonstandard Abbreviations and Acronyms

DOPPS	Dialysis Outcomes and Practice Patterns Study
MAVE	major adverse vascular events
PVD	peripheral vascular disease

cautious due to increased bleeding risks,[5] with observational studies suggesting an unfavorable risk/benefit ratio for people on maintenance hemodialysis.[6,7]

Factor XIa inhibitors are a promising new class of anticoagulants[8] that may offer antithrombotic benefits with a more favorable balance of bleeding risk, with multiple agents in advanced stages of development.[9] An appropriate efficacy end point for randomized clinical trials (RCTs) of these agents in the end-stage kidney disease indication is a composite outcome of major adverse vascular events (MAVEs) of thromboembolic origin.[10,11] Cardiovascular events represent about half of all deaths in the hemodialysis setting,[12] but a primary composite end point of cardiovascular death or major adverse cardiovascular events is too broad, with many included events not being modifiable by factor XIa inhibitors. The fraction of events classified as MAVEs is likely much smaller; without a reliable quantification of MAVE rates and cumulative incidence, RCT planning for investigational antithrombotic agents is challenging.

More broadly, RCTs conducted in the hemodialysis setting have built-in advantages, including a large accessible population of potential participants, a rich history of medical records to help determine eligibility, and regimented frequent visits to sustain long-term follow-up. However, clinical development in the hemodialysis setting has remained challenging, in part due to the high overall mortality rate and the occurrence of potentially competing events including kidney transplantation, hemodialysis facility transfer, and switch to peritoneal dialysis (PD) or home hemodialysis. Before taking on enormous financial risks, developers must consider decision points beyond sample size and follow-up length—selection of inclusion/exclusion criteria, primary end point definition, and realistic retention expectations—to optimize RCT design and determine if/how to proceed with the study.

In this study, we aim to explore the incidence of the MAVE composite end point in a representative sample of patients on hemodialysis as well as in predefined high-risk subgroup(s) with implications for informing potential enrichment strategies. The exploration also aimed to clarify the proportion of CVD burden represented by thromboembolic events, the magnitude of competing risks coming from non-MAVE death, discontinuations, and other logistical hurdles. These objectives are all pertinent to the calculation of sample size for clinical trials and securing adequate statistical power to demonstrate the efficacy of investigational drugs in the hemodialysis setting.

METHODS

Data Source

The DOPPS (Dialysis Outcomes and Practice Patterns Study; www.dopps.org) is a multinational prospective cohort study of adult in-center patients on hemodialysis, including longitudinal data from >120 000 patients undergoing hemodialysis treatment in >20 countries, and has evolved over 7 phases from 1996 to 2022. The DOPPS data are not publicly available but can be used by external researchers upon request and approval. Study approval and patient consent were obtained as required by national and local ethics committee regulations. The DOPPS was designed to be a "snapshot" of patients at each hemodialysis facility at baseline, through a 2-stage, stratified random sampling design.[13,14] In stage 1, facilities are randomly selected from national samples of hemodialysis facilities treating at least 20 patients stratified by region and facility type within each country. In stage 2, 20 to 40 patients on

hemodialysis are randomly selected from each facility. Representativeness of the DOPPS has been validated in comparison with census-based registries.[15–17]

Study Sample

For this analysis, we used data from the United States, Japan, and Europe in DOPPS phase 4 (2009–2011), phase 5 (2012–2015), phase 6 (2015–2018), and phase 7 (2018–2021). For patients on dialysis >90 days at DOPPS enrollment, the enrollment date was considered the index date. For patients on dialysis ≤90 days at DOPPS enrollment, the index date was shifted to day 91 after dialysis initiation to exclude the incident dialysis period when event rates are high.[18] To avoid underestimating event rates, patients dialyzing in hemodialysis facilities where cause of death or hospitalization diagnosis/procedure codes were not sufficiently completed were excluded. We defined these facilities as those where >50% of deaths had no cause reported or >50% of hospitalizations had no diagnosis/procedure codes reported. All US hemodialysis facilities in DOPPS phases 5 through 7 (2012–2021), after data capture transitioned to electronic health record transfer, were excluded due to no capture of causes of death and hospitalization.

Variables

The DOPPS data cover a broad range of patient characteristics, including demographics, comorbidity history, medication prescriptions, laboratory values, and prospective capture of cause-specific death and hospitalization. Data on demographics, comorbidity history, laboratory values, and active medication prescriptions are extracted from medical records. Data on hospitalizations (including diagnosis and procedure codes) and deaths (including cause of death) are recorded prospectively by the study coordinator at each hemodialysis facility.

We prespecified 3 nonnested subgroups of interest that could potentially be used to define patients at high risk of MAVEs: (1) at least 2 of 6 criteria: age>65 years, history of heart failure (HF), type 2 diabetes, history of peripheral vascular disease (PVD), history of MI, history of stroke; (2) at least 1 of 3 criteria: history of PVD, history of MI, history of stroke; (3) at least 1 of 6 criteria: history of PVD; history of MI; history of stroke; age>65 years; age>50 years *and* type 2 diabetes; history of atrial fibrillation *and* no oral anticoagulant prescription. Criterion 1 was intended to largely mirror a prior exercise using DOPPS data to define patients at high risk for cardiovascular events[19]; criterion 2 was intended to target those with clear clinically manifested atherosclerotic vascular disease; and criterion 3 was intended to expand inclusivity with accepting participants with 1 of 3 additional risk factors, without requiring the presence of clinical atherosclerotic disease. In all cases, the goal was to include a large proportion of the hemodialysis population to buoy clinical trial feasibility rather than embrace only a small subset with the "highest high" CVD risk.

Major adverse cardiovascular event rates with various definitions have been reported in the hemodialysis population[19,20]; in this analysis, the primary outcome of interest is a composite MAVE outcome, which includes MAVE death and MAVE hospitalization. MAVE deaths include acute MI, coronary heart disease, ischemic stroke, and pulmonary embolus. MAVE hospitalization events include inpatient hospitalizations with either a related procedure code or diagnosis code. MAVE hospitalization diagnosis codes include acute MI, ischemic stroke, angina, claudication/rest pain, and deep vein thrombosis. MAVE hospitalization procedure codes include coronary angioplasty, coronary bypass graft, and amputation. Codes are summarized in Table S1. Secondary outcomes include all-cause inpatient hospitalization, all-cause death, sudden death (death due to hyperkalemia, cardiac arrhythmia, or cardiac arrest—cause unknown), and non-MAVE death (all deaths other than MAVE death as defined above).

Statistical Analysis

In all analyses, we applied the following weights to patients from each region: 40% North America (United States and Canada), 50% Europe (Belgium, France, Germany, Italy, Spain, Sweden, and United Kingdom), 10% Japan. These weights (0.5, 0.4, 0.1) were uniformly applied to all patients from each region and defined by the estimated distribution of regional contributions in a global phase 3 clinical trial and regulatory expectations to enrollment for Japan (10%). Sample sizes varied across regions and DOPPS phases, so these prespecified weights keep these relative geographic contributions aligned with expectations for a potential planned international randomized trial. Without these weights, the international composition of the sample would reflect peculiarities of the DOPPS database, which is intended to be representative of hemodialysis patients within country but not across countries.

First, we evaluated 3 sets of criteria to define a patient as high risk for MAVEs, as described above. After estimating the proportion of patients meeting these criteria in our sample, we used a combination of the data and clinical judgment to determine that criterion 2 was the subgroup of interest that aligned with a history of atherosclerotic cardiovascular disease (ASCVD). We then presented patient characteristics of the study sample overall and by ASCVD.

For calculation of event rates and cumulative incidence for a specific outcome, patients were followed until the specific outcome occurred, death (due to a

reason other than the outcome of interest), lost to follow-up, 7 days after hemodialysis facility transfer, end of the data collection period for a specific site, or administrative end of the study phase, whichever occurred first. Event rates were calculated as the number of events per 100 person-years (with 95% CIs). Incidence rates were calculated similarly for other events, including all-cause death, all-cause hospitalizations, sudden death, and components of MAVEs. To assess how different exclusion criteria would affect MAVE rates, we also calculated MAVE rates excluding patients with different conditions at baseline: (1) hemoglobin <8 g/dL; (2) severe HF (defined as history of HF and cannot walk without assistance); (3) age ≥75 years; (4) age ≥80 years; (5) age ≥85 years. Event rates were reported overall, by region, and for patients in the ASCVD subset. In secondary analyses, we reported event rates by age and dialysis vintage (time since dialysis initiation) categories. In a sensitivity analysis, we estimated the MAVE rate using stricter criteria for facility reporting of cause of death/hospitalization, requiring >75% rather than >50% to have a cause, to better understand the extent to which missing causes may have biased event rates.

Fine and Gray subdistribution hazard models were used to estimate 3-year cumulative incidence, accounting for the competing risk of non-MAVE death. Cumulative incidence was estimated using 2 methods: (1) handling patient dropout as a competing event versus (2) handling patient dropout as censored. Reasons for dropout included transplant, hemodialysis facility transfer, modality change to PD or home hemodialysis, recovery of renal function, and refusal to continue the study. Using method 1, the estimated cumulative incidence would reflect a "real-world" situation where patients who left the hemodialysis facility could not be followed further. Using method 2, the estimated cumulative incidence assumes "perfect" follow-up and would reflect the individual patients' actual risk of experiencing an event. Assuming that, in a trial situation, some patients who dropped out of DOPPS would be lost to follow-up but others could remain in the trial, method 1 reflects the "floor" of cumulative incidence (all patients who transferred facilities, received a transplant, or switched modalities would depart the trial), while method 2 reflects the "ceiling" of cumulative incidence (all facility transfers, transplants, and modality changes could remain in the trial and with the same event risk assumed).

We estimated sample sizes for a hypothetical placebo-controlled RCT in the enriched ASCVD subset, under the following assumptions:

- 1:1 randomization
- Constant hazard ratio (HR) of 0.75 (clinically relevant effect size) for new antithrombotic treatment versus placebo until the common end of follow-up (treatment policy)
- 90% power to detect superiority of the new treatment
- 2-sided 1% significance level, α (for a single pivotal RCT)
- 7 per 100 person-years incidence rate for MAVE events
- Constant recruitment rate
- At least 9 months' planned treatment
- Non-MAVE death rate of 17 per 100 person-years as competing risk
- Lost to follow-up of 1 per 100 person-years

Sample size calculations were done with the PASS 2022 software (Power Analysis and Sample Size Software; NCSS, LLC, Kaysville, UT; ncss.com/software/pass).

RESULTS

Patient Composition

This analysis included 25 211 patients on hemodialysis enrolled in the DOPPS across the United States (N=4485), Japan (N=6220), and Europe (N=14 506). Reasons for exclusion include dialysis vintage <90 days and enrollment in hemodialysis facilities where cause of death or hospitalization was not well captured; details are illustrated in Figure 1.

The proportion of included patients to meet each set of high-risk criteria was 61% for criterion 1, 52% for criterion 2, and 80% for criterion 3. Over half of the patients still met the stricter criterion 2; this group had the highest atherosclerotic burden on the basis of the prevalence of vascular comorbidities and history of related events. Thus, we chose to select the group at the highest risk for atherothromboembolic events (criterion 2, ASCVD) moving forward. The proportion of patients meeting this ASCVD criteria was 59% in North America, 53% in Europe, and 46% in Japan.

Patient characteristics of the study sample are shown in Table 1, overall and by the presence or absence of ASCVD. We observed considerable differences in comorbidities between the 3 predefined high-risk groups, with the ASCVD group being older and showing the highest prevalence of diabetes and thereby the highest risk for atherothrombotic complication. This is also reflected by the use of prescribed medications, including aspirin, clopidogrel, and oral anticoagulants. In contrast, most laboratory and biometric markers/cardiovascular risk factors were comparable between the ASCVD versus non-ASCVD groups, including body mass index, systolic blood pressure, hemoglobin, serum phosphorus, parathyroid hormone, and serum calcium. When comparing

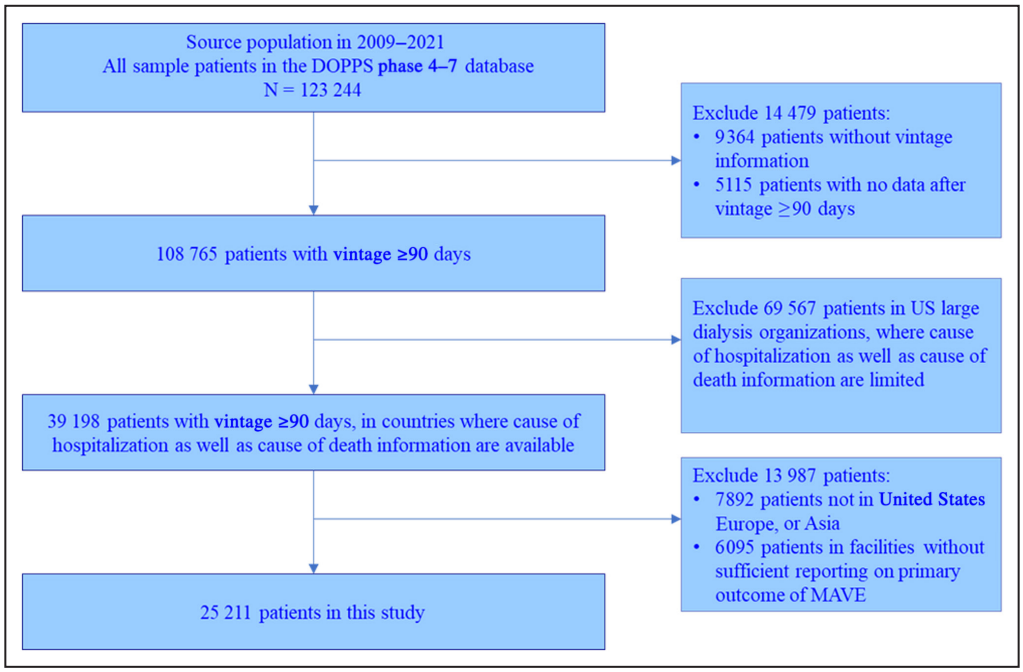

Figure 1. Flowchart of patient selection.
DOPPS indicates Dialysis Outcomes and Practice Patterns Study; and MAVE, major adverse vascular event.

patient characteristics across regions (Table S2), we observed lower body mass index and longer dialysis vintage in Japan (versus Europe and North America).

Outcomes and Event Rates

We report death and hospitalization event rates (per 100 patient-years) in Table 2, in the overall population and ASCVD subset. The rates of the MAVE composite outcome, MAVE hospitalization, and MAVE death, respectively, were 6.0, 5.3, and 1.5 in the overall sample, and 8.7, 7.8, and 2.1 in the ASCVD subset. Rates for each individual event included in the MAVE definition are shown in Table 2. In the ASCVD subset, rates of all-cause death were 2-fold higher in North America (20.6) and Europe (20.3) than in Japan (9.0); in contrast, the MAVE composite rate in Japan (7.9) was comparable with North America (8.0) and Europe (9.5). The rate of all-cause death was 14.3 overall and 19.2 in the ASCVD subset. The rate of all-cause inpatient hospitalization was 66.0 overall and 80.8 in the ASCVD subset. Region-specific rates for all event types are reported in Table S3. In the overall sample, 8% of deaths had a missing cause, 56% were not cardiovascular related, and 36% were cardiovascular related (17% sudden death, 11% MAVE death, 8% other).

Table 3 demonstrates how the MAVE rate and proportion of included patients are affected by stricter exclusion criteria. The crude MAVE rate (per 100 patient-years) was 45% higher (8.7 versus 6.0) in the ASCVD group, containing 52% of potential participants, than in the overall sample. Further reduction of the participant pool by excluding patients with severe anemia, severe HF, or older age (≥75 years, ≥80 years, ≥85 years) had minimal impact on MAVE rates (Table 3). In subgroup analyses, MAVE composite rates varied minimally by age and dialysis vintage (Table S4). MAVE composite rates also changed very little when implementing stricter criteria (75% versus 50%) for facility reporting of cause of death/hospitalization.

Cumulative Incidence of Primary End Point

Figure 2 shows the cumulative incidence of the MAVE composite outcome, treating non-MAVE death as a competing event and censoring for dropout due to transplant, modality switch, and hemodialysis facility transfer. Under these assumptions of "perfect" follow-up, 1-/2-/3-year cumulative incidence of MAVE was 6%/10%/13% in the overall sample and 8%/14%/18% in the ASCVD group. Figure 3 shows cumulative incidence of the MAVE composite outcome, treating non-MAVE death and dropout as competing events. Under these "real-world" assumptions, 1-/2-/3-year cumulative incidence of MAVE was 6%/9%/11% in the overall sample and 8%/13%/16% in the ASCVD group. Overall, 4177 (17%) patients dropped out of the study, including 6% transplanted, 1% switched modality to PD or home hemodialysis, and 9% transferred to another hemodialysis facility.

Table 1. Patient Characteristics by ASCVD

Patient characteristics	Overall (n=25211)	Non-ASCVD (n=12030)	ASCVD (n=13181)
Demographics			
Age, y	65±15	61±16	69±13
Sex, % male	60	57	63
Race, %			
Asian	12	14	9
Black	7	8	6
Other	7	6	7
White	75	71	78
Dialysis vintage, y	4.1±5.7	4.2±5.8	4.1±5.5
Primary cause of end-stage renal disease, %			
Diabetes	33	23	42
Glomerulonephritis, vasculitis	18	24	14
Hypertension	19	17	21
Other cause end-stage renal disease	30	37	24
Comorbidity history, %			
Diabetes	46	33	57
Hypertension	89	85	92
Coronary artery disease	38	0	70
Heart failure	24	12	34
Cerebrovascular disease	16	0	29
Other cardiovascular disease	30	18	40
Gastrointestinal bleeding	5	3	6
Lung disease	15	9	20
Neurologic disease	11	7	15
Peripheral vascular disease	29	1	51
Psychiatric disorder	19	16	22
Cancer	16	16	16
Cirrhosis	2	2	2
Recurrent cellulitis/gangrene	10	2	17
HIV	0.7	1.0	0.5
Laboratory/biometric markers			
Body mass index, kg/m^2	26.7±6.3	26.4±6.2	26.9±6.4
Systolic blood pressure, mm Hg	142±22	142±21	141±23
Diastolic blood pressure, mm Hg	73±13	76±13	71±13
Hemoglobin, g/dL	11.2±1.4	11.2±1.4	11.2±1.4
Severe anemia (hemoglobin <8 g/dL)	1	2	1
Serum phosphorus, mg/dL	5.1±1.6	5.2±1.6	5.0±1.6
Parathyroid hormone, pg/mL	238 (129–411)	245 (129–434)	234 (128–392)
Serum calcium, mg/dL	8.9±0.8	9.0±0.8	8.9±0.8
Serum albumin, g/dL	3.7±0.5	3.7±0.5	3.6±0.5
C-reactive protein, mg/L	5.0 (2.0–13.0)	4.4 (1.6–10.1)	5.9 (2.4–15.0)
Transferrin saturation, %	25.0 (18.6–33.0)	25.4 (19.0–34.0)	24.6 (18.1–32.1)
Ferritin, ng/mL	372 (174–651)	347 (160–624)	393 (185–675)
Treatments			
Oral anticoagulant therapy	12	7	15
Direct factor Xa inhibitors	0.1	0.0	0.1
Direct thrombin inhibitors	0.0	0.0	0.0
Fondaparinux	0.1	0.1	0.2
Vitamin K antagonists	11	7	15
Aspirin	42	28	53
Clopidogrel	10	3	16
Hemodiafiltration, %	14	15	13
ESA use	89	89	89
ESA dose among users, units/week	11 660±11 017	11 259±10 331	11 986±11 596

Prevalence (%), mean±SD, or median (interquartile range) shown; ASCVD defined as meeting at least 1 of 3 criteria: history of peripheral vascular disease, history of myocardial infarction, history of stroke. ASCVD indicates atherosclerotic cardiovascular disease; and ESA, erythropoiesis-stimulating agents. The vast majority were captured as "Other" on our questionnaire.

Sample Size Estimation

The scenarios presented below are also summarized in Table 4.

Base case: With the assumptions outlined in the Methods section (hazard ratio [HR], 0.75, 2-sided α=0.01, 7/100 person-years incidence rate for MAVE event, non-MAVE death rate of 17/100 person-years, lost to follow-up 1/100 person-year, at least 9 months' planned treatment) and with a constant recruitment rate of 180 patients per month, the trial would require randomizing at least 6860 patients during 38 months (total study duration, 47 months) to observe the 724 MAVEs needed to power the study.

If it were possible to mimic the real-world population and achieve a comparable MAVE incidence rate of 9 per 100 patient-years and still apply the same assumptions, the trial would require 5880 patients during a 32-month recruitment period (total study duration, 41 months) with a constant recruitment rate of 180 patients per month.

Table 2. Event Rates (per 100 Patient-Years) in the Overall Population and ASCVD Subset

Event	Overall	ASCVD
All-cause deaths	14.3	19.2
All cause hospitalizations	66.0	80.8
Sudden deaths	2.5	3.4
MAVE composite	6.0	8.7
MAVE hospitalizations	5.3	7.8
MI hospitalizations	2.5	3.6
Stroke hospitalizations	0.3	0.4
Angina hospitalizations	1.7	2.5
Limb ischemia hospitalizations	0.9	1.4
Amputation hospitalizations	0.4	0.7
Deep venous thrombosis hospitalizations	0.3	0.1
MAVE deaths	1.5	2.1
MI deaths	1.2	1.8
Stroke deaths	0.2	0.3
Pulmonary embolism deaths	0.04	0.03

ASCVD defined as meeting at least 1 of 3 criteria: history of peripheral vascular disease, history of MI, history of stroke. ASCVD indicates atherosclerotic cardiovascular disease; MAVE, major adverse vascular events, and MI, myocardial infarction.

If health authorities could accept a 2-sided 5% significance level for a single pivotal RCT to enable market authorization, the trial would require fewer MAVE events (N=510) and thus fewer total patients (N=5400) to enroll during a 32-month recruitment period (total study duration, 41 months), if we still followed the same assumptions outlined in the Methods section and had a constant recruitment rate of 180 patients per month.

Table 3. MAVE Rates (per 100 Patient-Years) and Proportion of Patients Included: Impact of Additional Exclusion Criteria

Patient population	% of patients	MAVE rate
Overall	100	6.0
ASCVD	55	8.7
ASCVD, excluding hemoglobin <8 g/dL	54	8.8
ASCVD, excluding severe heart failure	46	8.4
ASCVD, excluding age 75+	35	9.0
ASCVD, excluding age ≥80 y	43	8.9
ASCVD, excluding age ≥85 y	50	8.8

ASCVD defined as meeting at least 1 of 3 criteria: history of peripheral vascular disease, history of myocardial infarction, history of stroke. Severe heart failure is defined as congestive heart failure and cannot walk without assistance (based on medical questionnaire completed by study coordinator). ASCVD indicates atherosclerotic cardiovascular disease; and MAVE, major adverse vascular event.

Finally, if we took all assumptions of the base case but chose speed of completion as the primary goal/driver of study conduct, an overall 36-month clinical trial would require the enrollment of 8030 patients, if the recruitment period could be completed in 27 months, and 8550 if the recruitment would take 30 months.

DISCUSSION

Using data from the large international DOPPS cohort, we explored the requirements for the design of a potential phase 3 randomized trial focusing on potentially modifiable thromboembolic events in the hemodialysis setting. We investigated MAVE rates, cumulative incidence, and realistic retention expectations across risk profiles and potential inclusion/exclusion criteria. Prior large phase 3 trials[21] and observational studies[19] with more broadly defined cardiovascular end points showed rates of major adverse cardiovascular events, defined as a composite of all-cause death and nonfatal cardiovascular events, ranging from 15 to 20 per 100 patient-years in the hemodialysis setting. We observed a much lower rate of the MAVE composite outcome, not including all-cause death, in the overall hemodialysis population (6.0) and even when restricting to an enriched ASCVD subgroup (8.7). When considering this small contribution of thromboembolic events to overall cardiovascular death, the high rate of competing events (eg, sudden death, noncardiac death) and patient dropout (eg, transplant, modality switch, hemodialysis facility transfer), the large sample size and hence challenging feasibility of a potential randomized trial targeting MAVE reduction by a novel antithrombotic therapy in the hemodialysis setting becomes quickly intuitive.

The MAVE composite outcome rates were much lower than all-cause death (14.3), and, in contrast with all-cause death, varied minimally by age and dialysis vintage. Three-year cumulative incidence of MAVEs was 11% to 13% overall and 16% to 18% in the ASCVD subset, depending on the competing event assumptions. When considering this modest expected accumulation of events, power calculations point to a large RCT required (≈6860 patients needed), which has not been feasible traditionally for drug developers when also considering the limited patient recruitment pool, long timelines, and pending residual risks.

While the rate of cardiovascular events is much higher in the hemodialysis setting than in the general population, the composition of these cardiovascular events is quite different in the hemodialysis setting (versus general population), with a disproportionately higher rate of coronary artery disease, HF, arrhythmia, and sudden cardiac death.[1] When considering the mechanism of action of the investigational drug

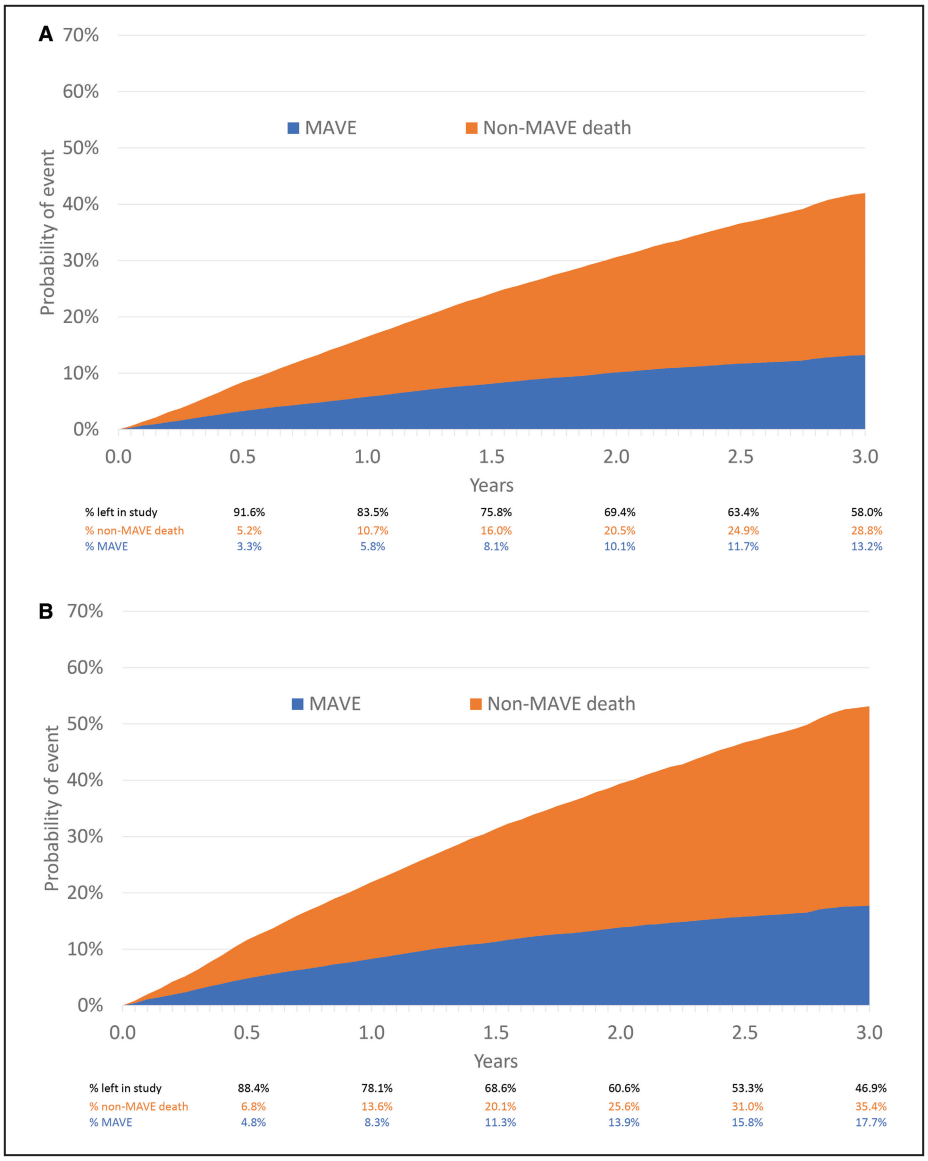

Figure 2. Cumulative incidence of MAVE, treating non-MAVE death as competing event and lost to follow-up as a censoring event, in the (A) overall population and (B) ASCVD subset.
ASCVD defined as meeting at least 1 of 3 criteria: history of peripheral vascular disease, history of myocardial infarction, history of stroke. ASCVD indicates atherosclerotic cardiovascular disease; and MAVE, major adverse vascular events.

potentially limiting modifiability to a subset of cardiovascular events only, this heterogeneity of cardiovascular events is an important consideration for RCT planning. If the majority of deaths (in this case, 89%) are not modifiable and cannot be included in the primary efficacy end point, the consequences are not only a lower event rate but also a higher risk of discontinuation due to competing events (eg, sudden death, noncardiac death, death caused by non–cardiovascular disease). The MAVE composite outcome, selected to align with the antithrombotic mechanism of factor XIa antagonists, was relatively uncommon in this cohort, and driven mostly by MAVE hospitalizations. MAVE deaths were of relatively small proportion, with only 11% (≈30% of cardiovascular deaths) of deaths attributable to MAVE. The overall proportion attributed to sudden death was 18% (approximately half of cardiovascular deaths). Inclusion of sudden death in the MAVE composite definition could have substantially increased the event rate, but ultimately, we were not confident about the modifiability of these events by a factor XIa inhibitor.

Strategic selection of inclusion/exclusion criteria is important to enrich the population with patients at high risk for the primary efficacy outcome, while minimizing competing events and maintaining external validity.

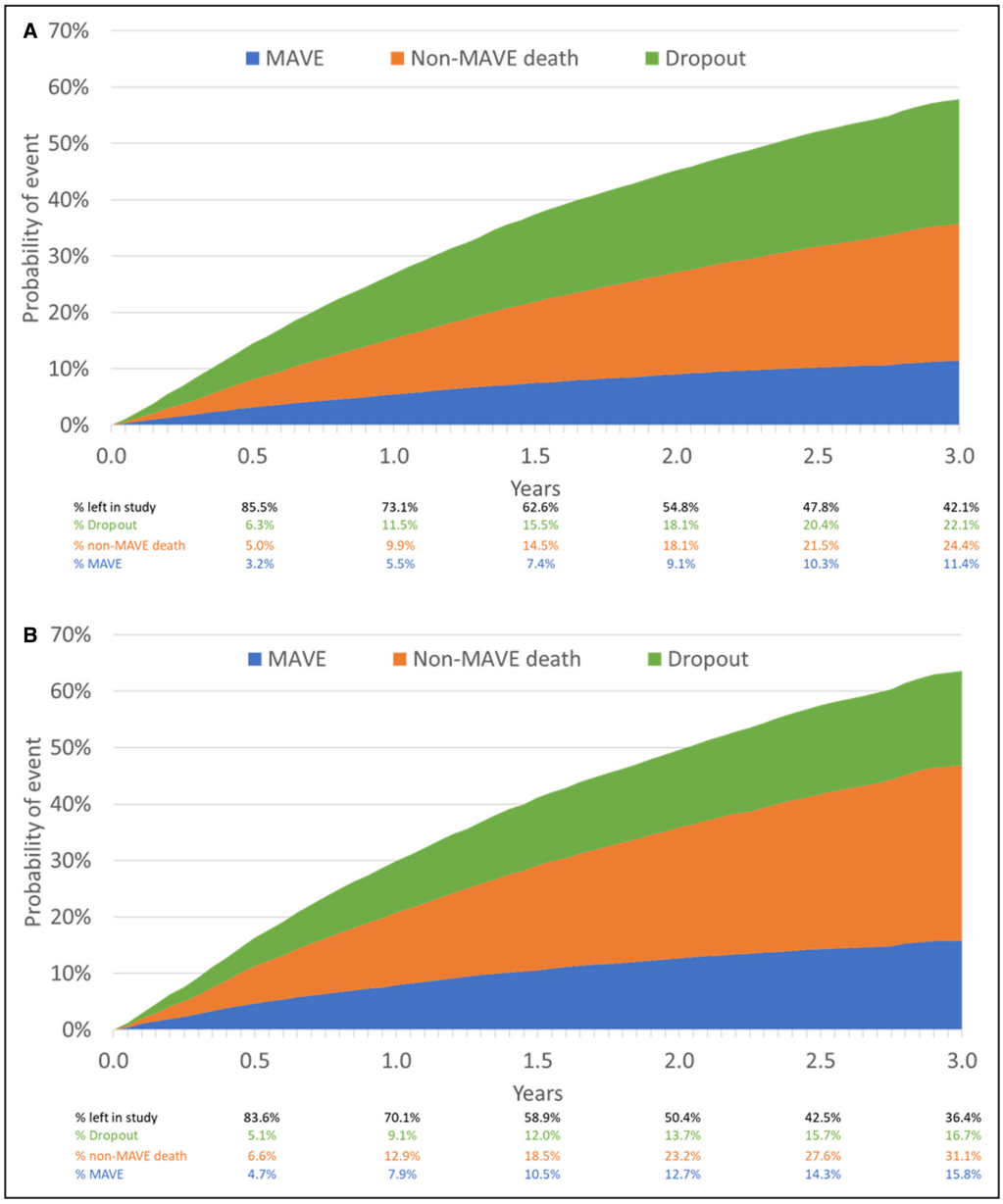

Figure 3. Cumulative incidence of MAVE, treating non-MAVE death and dropout as competing events, in the (A) overall population and (B) ASCVD subset.
ASCVD defined as meeting at least 1 of 3 criteria: history of peripheral vascular disease, history of myocardial infarction, history of stroke. Among patients who dropped out of the study, 34% were transplanted, 6% switched modality to peritoneal dialysis or home hemodialysis, and 55% transferred to another hemodialysis facility. ASCVD indicates atherosclerotic cardiovascular disease; and MAVE, major adverse vascular events.

The proportion of the target population represented by the trial participants can vary widely on the basis of these decisions. While risk prediction models can help identify patients with >10% likelihood of experiencing the primary composite outcome within a defined time window, these methods are less useful to determine exclusion criteria because individual risk factors are the basis for exclusions in RCTs. As such, we chose to use clinical judgment to define potential high-risk groups more flexibly for trial enrichment rather than taking a purely data-driven approach.

Comparing MAVE rates across subgroups and baseline risk factors provided insights into the differences in MAVE rates between the overall and enriched ASCVD group. While mortality rate increases continuously with age, MAVE rates peaked in the age 65 to 69 year group (Table S4). Analogously, while mortality rate is highest in the first year of dialysis,[18] we observed

Table 4. Estimated Sample Sizes for an RCT in the ASCVD Subset Using Estimated Incidence Rates

MAVE in the placebo group per 100 person-years	α (2-sided), %	N	E*	Recruitment/total study duration, mo	Recruitment rate (constant), per mo
7	1	6860	724	38/47†	≈180
7	1	8030	724	27/36†	≈300
7	1	8550	724	30/36‡	≈285
7	5	5400	510	30/39†	≈180
9	1	5880	723	32/41†	≈180

Conditions: 1:1 randomization, HR=0.75, non-MAVE death rate: 17 per 100 person-years (0.0142/person-months), lost to follow-up: 1 per 100 person-years (0.0008/person-months). ASCVD indicates atherosclerotic cardiovascular disease; MAVE, major adverse vascular events; and RCT, randomized clinical trial. ASCVD defined as meeting at least 1 of 3 criteria: history of peripheral vascular disease, history of myocardial infarction, history of stroke.

*Required number of patients with events (depends on the hazard ratio, which is estimated according to treatment policy).

†At least 9 months of planned study treatment.

‡At least 6 months of study treatment.

minimal variation in MAVE rates by time since dialysis initiation (Table S4). Further, despite all-cause mortality rates being 2- to 3-fold higher in Europe and North America compared with Japan, MAVE rates were more comparable across regions (Table S3). A plausible explanation for these findings is that MAVE rates (per 100 patient-years) were driven more so by MAVE hospitalizations (5.3) rather than MAVE deaths (1.5) (Table 2). Thus, traditional enrichment strategies to restrict to older patients or patients on incident dialysis do not effectively increase the rate of thromboembolic events, and in fact, may be counterproductive by increasing the likelihood of non-MAVE death.

Two different outcomes with the same event rate could yield a different number of cumulative events during RCT follow-up; that is, including all-cause death in the primary end point will inherently increase statistical power by reducing the number of competing deaths. Further, the impact of study retention rates on cumulative incidence must be considered in the context of RCT sample size considerations. In our observational study, the 3 primary reasons why surviving patients did not complete follow-up were transplant, hemodialysis facility transfer, and modality switch from in-center hemodialysis to PD or home hemodialysis. If we treat these departures as censoring events, the true (RCT) 3-year cumulative incidence of MAVE (13.2%; Figure 2) is likely overestimated because we assume that all RCT patients who experienced a kidney transplantation, hemodialysis facility transfer, or modality switch would remain in the trial and accrue events at the same rate. If we treat these departures as competing events, the true 3-year cumulative incidence of MAVEs (11.4%; Figure 3) is likely underestimated because we assume that all RCT patients who experienced 1 of the aforementioned events would be lost to follow-up and thus could not experience the primary end point. These estimates thus provide a range of outcomes of what could be expected in an RCT. Understanding the primary reasons for the high turnover rate at hemodialysis facilities can help RCT planning by proactively excluding potential participants who are more likely to experience a competing event during follow-up, not only those at a high risk of non-MAVE death, but also patients expected to receive a transplant, switch modalities, or transfer to another hemodialysis facility in the next 6 months.

Our study has several notable strengths. We used data from the DOPPS, a large international cohort of patients undergoing hemodialysis shown to be representative of national hemodialysis populations.[15–17] DOPPS is designed to be a snapshot of patients at each hemodialysis facility at baseline, with data covering a broad range of clinical and patient-reported data, including patient characteristics, comorbidities, medication use, laboratory values, and dialysis prescriptions and procedures. The uniform and standardized data collection processes allow for comparisons across subgroups and regions. Further, hospitalization diagnosis/procedure codes and cause of death are prospectively captured in DOPPS, allowing us to precisely define and measure the MAVE outcome of interest.

Our study also has some limitations. First, cause of death/hospitalization was not adjudicated in our study, which may lead to some misclassification bias; research staff use a range of sources to complete these forms including patient notes and discharge summaries/codes, but some MAVE deaths still may have been misclassified as a sudden death or noncardiac death (and vice versa). Second, US DOPPS data after 2015 were excluded, following the DOPPS transition to electronic health record transfer data that do not capture cause of death/hospitalization. The overall sample size is thus lowered, although with no notable new therapies or changes in practice; we do not anticipate that US MAVE rates were substantially different after (versus before) 2015. Third, all sample size calculations are subject to the validity of the underlying assumptions. We reported on the impact of varying these assumptions, and the required number of subjects remained high (N>5000) in all tested

scenarios. Fourth, 4% of hospitalizations and 21% of deaths had a missing cause, which could lead to an underestimation of MAVE rates. To address this, we excluded hemodialysis facilities where >50% of deaths/hospitalizations had a missing cause in the primary analysis; a sensitivity analysis used even stricter criteria and excluded hemodialysis facilities where >25% of deaths/hospitalizations had a missing cause. MAVE rates in the sensitivity analysis were essentially unchanged; thus, even if a cause was known for every death/hospitalization, only a marginal increase in MAVE rates would be observed. Despite these limitations in event capturing due to the scale of this large multinational observational study, event rates in DOPPS have been aligned historically with rates observed in other studies; for example, the all-cause mortality rate per 100 patient-years we observed in North America (15.6) is similar to the rate reported (16.3) in the 2022 United States Renal Data System Annual Data Report.[22]

In the hemodialysis setting, observational data are particularly useful to better understand the feasibility of a potential RCT, and for planning to improve the trial's chances of success. Beyond the basic parameters of sample size, event rate, and follow-up length, it is crucial to understand the implications of decisions related to primary end point definition, selection of inclusion/exclusion criteria, and avoidance of competing events, for example, by not recruiting patients with a much higher likelihood of death or transplant than reaching the primary end point. Further, potential exclusion criteria that reduce generalizability without increasing cumulative incidence of the primary end point should be avoided.

Our findings have important implications for RCT development in general, highlighting the utility of observational data to provide a framework for trial planning, and specifically for therapies that target reduction of thromboembolic events in the hemodialysis setting. The relative proportion of MAVE events within the overall cardiovascular burden of patients on hemodialysis was small, with MAVE rates lower compared with RCTs that have included all-cause death or even all cardiovascular deaths in their primary efficacy end points.[23,24] The observed MAVE rates, even in the enriched ASCVD subset, together with the high rate of competing events (non-MAVE death, transplant, modality switch to PD or home hemodialysis, hemodialysis facility transfer), resulted in a high sample size (N=6860) required to detect a clinically meaningful treatment effect of 25% on MAVE in an RCT. The efficacy of anticoagulants/antithrombotic interventions is usually not known at entry to phase 3 because phase 2 trials do not have sufficient power to detect robust signals. Considering the recruitment time, overall duration, and residual risks that initial assumptions may turn out incorrect in the enrolled population, such a trial poses major challenges in execution. Further considerations are needed regarding whether additional *modifiable* events might contribute to the composite MAVE outcome, thereby reducing sample size demands for a phase 3 trial. These results highlight key considerations for developers of novel antithrombotic therapies targeting reduction of MAVE (atherothrombotic burden) in patients undergoing hemodialysis and at the same time illustrate how real-world observational data can be used to help to assess the feasibility of clinical trials in the hemodialysis setting and beyond.

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Supplemental Material

Tables S1–S4

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