Hemodialysis Vascular Access and Risk of Major Bleeding, Thrombosis, and Cardiovascular Events: A Cohort Study

Nicholas S. Roetker, Haifeng Guo, Dena Rosen Ramey, Ciaran J. McMullan, G. Brandon Atkins, and James B. Wetmore

Rationale & Objective: The risks of major bleeding, thrombosis, and cardiovascular events are elevated in patients receiving maintenance hemodialysis (HD). Our objective was to compare the risk of these outcomes in HD according to the permanent vascular access type.

Study Design: Observational cohort study.

Setting & Participants: Using data from the United States Renal Data System (2010-2015), we included patients with kidney failure who were greater than 18 years, had Medicare as the primary payer, were not using an oral antiplatelet, and were newly using an arteriovenous (AV) access for HD.

Exposure: AV graft (AVG) or AV fistula (AVF).

Outcomes: Major bleeding, venous thromboembolism, ischemic stroke, myocardial infarction, cardiovascular death, and critical limb ischemia.

Analytical Approach: Comparing 17,763 AVG and 60,929 AVF users, we estimated the 3-year incidence rates and incidence rate ratios (IRR) of each outcome using Poisson regression. IRRs were adjusted for sociodemographic and clinical covariates.

Results: The use of an AVG, compared with that of an AVF, was associated with an increased risk of venous thromboembolism (10.8 vs 5.3 events per 100 person-years; adjusted IRR, 1.74; 95% CI, 1.63-1.85) but not with the risk of major bleeding (IRR, 1.04; 95% CI, 0.93-1.17). The use of an AVG was also potentially associated with a slightly increased risk of cardiovascular death (IRR, 1.09; 95% CI, 1.01-1.16).

Limitations: This analysis focused on patients with a functioning AV access; adverse events that may occur during access maturation should also be considered when selecting a vascular access.

Conclusions: The use of an AVG, relative to an AVF, in HD is associated with an increased risk of venous thromboembolism. Given recent guidelines emphasizing selection of the “right access” for the “right patient,” the results of this study should potentially be considered as one additional factor when selecting the optimal access for HD.

Compared with the general population, patients with kidney failure receiving maintenance hemodialysis (HD) face higher risks of both bleeding and thrombosis.1-10 This apparent paradox is likely explained by a complex set of factors: the adverse effects of kidney failure lead to numerous deficiencies in hemostasis, such as platelet dysfunction and activation, vessel wall and endothelial damage, and imbalances of the coagulation cascade and fibrinolytic system.11 Furthermore, because patients receiving maintenance HD are prone to thrombosis, inflammation, a high prevalence of traditional comorbid conditions (eg, hypertension and diabetes), and disordered mineral metabolism,12 they are also at an increased risk of cardiovascular events.2,6,8,13-17

The management of these risks, particularly the balance between bleeding and thrombosis, can make the care of patients receiving maintenance HD a major clinical challenge. For example, the HD procedure is prothrombotic because it leads to activation of platelets and coagulation,18 increasing the risk of thrombosis; in contrast, anti-coagulation therapy with heparin, which is routinely used for clot prevention of the extracorporeal circuit,19 may transiently increase the risk of bleeding. Furthermore, continuous or long-term platelet activation by the hemodialyzer and associated tubing may, paradoxically, also increase the bleeding risk.20 Medications can further modify these risks: erythropoiesis-stimulating agents, which are widely used to treat anemia in patients receiving maintenance HD, prevent blood transfusion at the cost of possibly increasing the risk of thrombosis and stroke,21 whereas oral antiplatelet agents, which are sometimes used in patients receiving maintenance HD, decrease the risk of thrombosis and stroke at the cost of increasing the risk of bleeding.

Vascular access bleeding and thrombotic complications, although rarely fatal on their own,22,23 are also an important consideration for patients receiving maintenance HD. Because of having much lower rates of complications, particularly infection and thrombosis, permanent accesses (arteriovenous [AV] fistula [AVF] or graft [AVG]) are much preferred over a central venous catheter for vascular access. AVGs are particularly at risk of thrombosis, although they are often easier to declot than AVFs.24 Both AV accesses are at risk of bleeding, although an AVG may have a greater risk of prolonged bleeding.25 It is possible that, given their thrombogenic nature, AVGs also confer an increased risk of thrombotic events as a whole. Likewise, we hypothesized that continuous platelet
activation may result from contact between the blood and the artificial graft material in a manner similar to the effect of a dialyzer, which could also lead to a higher risk of systemic bleeding among AVG users.

Thus, although an AVF is generally preferred to an AVG to minimize vascular access complications, given recent guidelines suggesting tailoring the access type to the clinical circumstances of each patient, a better understanding of the risks of bleeding, thrombosis, and other cardiovascular endpoints could help guide the choice of the type of permanent AV access. In this observational study, we used a nationwide end-stage kidney disease registry to create a cohort of patients receiving maintenance HD with an AV access who were not using oral anticoagulants. We compared the rates of major bleeding, venous thromboembolism, ischemic stroke, myocardial infarction, cardiovascular death, and critical limb ischemia between AVF and AVG users. The findings of this work might contribute to the understanding of the risks and benefits of choosing a vascular access for maintenance HD.

METHODS

Data Sources

This study used standard analysis files from the 2010-2015 US Renal Data System End-Stage Renal Disease registry database. Specifically, we used the End-Stage Renal Disease Medical Evidence Report (CMS-2728) and Death Notification (CMS-2746) forms, core patient files, treatment history files, and Medicare Parts A (institutional), B (physician and/or supplier), and D (prescription drug) claims files. The institutional review board (IRB-FY2021-175) at Hennepin Healthcare approved the research protocol and waived the requirement for informed consent for this study. Data use agreements between the Hennepin Healthcare Research Institute and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) were in place. Subject to the terms of a data use agreement, qualified individuals can freely obtain data used in this analysis from the US Renal Data System.

Study Design

This study used a retrospective cohort design. Patients considered for inclusion were those treated for kidney failure using HD with an AV vascular access. The date of first use of an AV access for HD, which could occur on or after the date of kidney failure incidence, was defined as the index date. To ensure that we could observe the full history of modality, vascular access, and medication use, individuals without continuous Medicare as the primary payer and Part D coverage from kidney failure incidence to the index date were excluded. Patients younger than 18 years on the index date or who had a Part D claim for an oral anticoagulant within 90 days before the index date were excluded. The latter patients were excluded to allow the study of the background risks of bleeding and thrombotic events independent of the effects of anticoagulation therapy.

Modality and Vascular Access

HD modality was determined using the treatment history files. The CMS-2728 form or outpatient dialysis claims were used to identify those whose date of first use of an AV access for HD (ie, index date) occurred on or after the date of kidney failure incidence, respectively. For those in the latter category, the index date was defined as the date of the first outpatient HD claim with a Healthcare Common Procedure Coding System modifier code of V6 (AVG) or V7 (AVF) but no V5 (catheter) modifier. Following the index date, subsequent outpatient dialysis claims were used to define the time that the patient received HD with an AV access. Claims with modifier V5 alone or modifier V5 in combination with modifiers V6 or V7 were considered HD sessions using a catheter. Patients were followed as long as they continued to use an AV access, allowing for periods of temporary catheter use of no more than 30 days.

Patient Characteristics

Sociodemographic characteristics included age, sex, race, and enrollment in Medicaid. Clinical characteristics included body mass index, primary cause of kidney failure, use of a catheter at HD initiation, time since the onset of kidney failure, comorbid conditions, prior acute disease events, and prescription medications. Comorbid conditions were defined using information from the CMS-2728 form in combination with Medicare claims in the year before the index date; the definitions are listed in Table S1. Prior acute disease events in the year before the index date were defined in accordance with the outcome definitions described below. The use of antiplatelet, statin,
antihypertensive, antiarrhythmic, or antidiabetic medications on the index date was determined using Part D claims.

Outcomes

Outcomes of interest were identified primarily using Medicare Part A/B claims. In addition, the CMS-2746 form

| Characteristic | AVF (N = 60,329) | AVG (N = 17,763) |
|----------------|------------------|------------------|
| **Age category in y, n (%)** | | |
| 18-44 | 2,838 (4.7) | 771 (4.3) |
| 45-64 | 15,987 (26.5) | 4,310 (24.3) |
| 65-74 | 22,032 (36.5) | 6,026 (33.9) |
| 75-84 | 15,521 (25.7) | 4,981 (28.0) |
| ≥85 | 3,951 (6.5) | 1,675 (9.4) |
| **Female sex, n (%)** | | |
| | 26,734 (44.3) | 10,805 (60.8) |
| **Race, n (%)** | | |
| | 42,132 (69.8) | 10,008 (56.3) |
| **Medicare/Medicaid dual eligible, n (%)** | | |
| | 28,365 (47.0) | 9,600 (54.0) |
| **Body mass index in kg/m², n (%)** | | |
| <18.5 | 1,796 (3.0) | 847 (4.8) |
| 18.5-24.9 | 18,115 (30.0) | 6,068 (34.2) |
| 25-29.9 | 17,476 (29.0) | 4,750 (26.7) |
| ≥30 | 22,501 (37.3) | 5,960 (33.6) |
| **Primary cause of kidney failure, n (%)** | | |
| Diabetes | 31,305 (51.9) | 9,003 (50.7) |
| Hypertension | 18,688 (31.0) | 5,772 (32.5) |
| Glomerulonephritis | 3,143 (5.2) | 817 (4.6) |
| Cystic kidney disease | 894 (1.5) | 182 (1.0) |
| Other | 6,299 (10.4) | 1,989 (11.2) |
| **Catheter at HD initiation, n (%)** | | |
| 37,632 (62.4) | 12,710 (71.6) |
| **≥6 mo since HD initiation, n (%)** | | |
| 17,703 (29.3) | 4,500 (25.3) |
| **Comorbid conditions, n (%)** | | |
| Diabetes | 45,820 (76.0) | 13,775 (77.5) |
| Hypertension | 59,725 (99.0) | 17,634 (99.3) |
| Congestive heart failure | 36,007 (59.7) | 11,559 (65.1) |
| Atherosclerotic heart disease | 33,464 (55.5) | 10,286 (57.9) |
| Other cardiac disease | 27,655 (45.8) | 8,857 (49.9) |
| Cerebrovascular disease | 14,582 (24.2) | 5,539 (31.2) |
| Peripheral vascular disease | 26,552 (44.0) | 8,672 (48.8) |
| Chronic obstructive pulmonary disease | 20,713 (34.3) | 6,909 (38.9) |
| Atrial fibrillation | 9,750 (16.2) | 3,406 (19.2) |
| Liver disease | 4,393 (73) | 1,452 (8.2) |
| Cancer | 8,664 (14.4) | 2,660 (15.0) |
| **Prior acute disease events, n (%)** | | |
| Major bleeding | 1,966 (3.3) | 730 (4.1) |
| Nonmajor clinically relevant bleeding | 945 (1.6) | 331 (1.9) |
| Ischemic stroke | 1,383 (2.3) | 544 (3.1) |
| Myocardial infarction | 4,567 (7.6) | 1,499 (8.4) |
| Venous thromboembolism | 4,130 (6.8) | 1,961 (11.0) |
| Acute limb ischemia | 916 (1.5) | 323 (1.8) |
| **Prescription medications, n (%)** | | |
| Antiplatelet | 9,643 (16.0) | 2,956 (16.6) |
| Statin | 28,226 (46.8) | 7,974 (44.9) |
| Antihypertensive | 31,035 (51.4) | 9,107 (51.3) |
| Antiarrhythmic | 2,104 (3.5) | 696 (3.9) |
| Antidiabetic | 23,358 (38.7) | 6,801 (38.3) |

Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; HD, hemodialysis.

aBody mass index values missing in 579 patients.
was used to identify fatal events. Major bleeding, defined using an adaptation of a claims-based nontraumatic bleeding algorithm, included fatal bleeding, inpatient bleeding accompanied by a blood transfusion, and inpatient bleeding at a critical site. The full algorithm is shown in Table S2. We also defined 2 other bleeding endpoints that additionally considered events treated in the emergency department or observation unit (expanded major bleeding) and events not involving a transfusion, critical site, or death (nonmajor bleeding). Each bleeding outcome included all events (first and recurrent) during follow-up, allowing a maximum of one bleeding event per day.

The definitions for the thrombotic and cardiovascular outcomes (venous thromboembolism, ischemic stroke, myocardial infarction, cardiovascular death, and acute limb ischemia), which have been used previously, are shown in Table S3. Two composite cardiovascular endpoints were also studied: composite 1 (major adverse cardiovascular events) included ischemic stroke, myocardial infarction, and cardiovascular death, and composite 2 included venous thromboembolism, ischemic stroke, myocardial infarction, and acute limb ischemia.

**Statistical Analysis**

Descriptive statistics were used to summarize the patients’ baseline characteristics for each exposure group (AVF and AVG). The patients were followed from the index date until the earliest of the following events: date of the outcome of interest (except for outcomes including recurrent events), death, kidney transplant, switch to a catheter or peritoneal dialysis (if for longer than 30 days), first oral anticoagulant prescription, loss of Medicare coverage, August 31, 2015, or 3 years of follow-up. We estimated the 3-year incidence rates of each outcome of interest, and Poisson regression with robust standard errors was used to estimate incidence rate ratios (IRRs) for AVG users relative to AVF users adjusted for the baseline sociodemographic, clinical, and medication covariates shown in Table 1. Missing values for body mass index category were multiply imputed with 10 datasets using multinomial logistic regression; the results were pooled according to Rubin’s rules. An intention-to-treat framework was used, whereby patients were categorized as AVF or AVG users according to the access used on the index date.

**Subgroup and Sensitivity Analyses**

To examine the robustness of the main findings, the following analyses were conducted: (1) a subgroup analysis of new AV access users who initiated HD with a catheter alone, (2) a sensitivity analysis using inverse probability of treatment (IPT) weighting, and (3) a secondary analysis of prevalent AV access users. The full details of these analyses are described in Item S1.

**RESULTS**

**Baseline Characteristics**

The main cohort (consisting of patients newly using an AV access for maintenance HD, provided they were not using an oral anticoagulant) comprised 78,092 individuals, including 60,329 (77.3%) AVF users and 17,763 (22.7%) AVG users. The mean age was 68.9 ± 12.3 years, 48.1% were women, and 66.8% were White. The baseline characteristics according to the AV access type are shown in Table 1. Use of an AVG was more common among those who were older, women, Black, Medicaid eligible, and normal weight or underweight. Those with comorbid conditions or who had experienced an acute bleeding, thrombotic, or cardiovascular event in the prior year were also more likely to use an AVG. Conversely, AVF and AVG users were largely similar in terms of kidney failure etiology; use of cardiovascular medications; and prevalence of diabetes, hypertension, atherosclerotic heart disease, and cancer.

The mean follow-up period was 1.11 ± 0.98 years among AVF users and 0.94 ± 0.89 years among AVG users. The...
rates of bleeding, thrombotic, and cardiovascular events following the start of using an AV access for HD are shown in Fig 2. Major bleeding was slightly more common in AVG users (incidence rate, 4.5; 95% confidence interval [CI], 4.1-4.8 events per 100 person-years) than in AVF users (incidence rate, 3.9; 95% CI, 3.7-4.0). However, the baseline characteristics-adjusted rate of major bleeding did not differ (IRR, 1.04; 95% CI, 0.93-1.17) for AVG relative to AVF. Similarly, the covariate-adjusted rate of bleeding did not differ for AVG relative to AVF when also considering events treated in the emergency department or observation unit or those with nonmajor bleeding (Fig S1).

**Thrombotic Events in New AV Access Users**

The rate of venous thromboembolism, which includes deep vein thrombosis and pulmonary embolism, was twice as high in AVG users (incidence rate, 4.5; 95% confidence interval [CI], 4.1-4.8 events per 100 person-years) than in AVF users (incidence rate, 3.9; 95% CI, 3.7-4.0). However, the baseline characteristics-adjusted rate of major bleeding did not differ (IRR, 1.04; 95% CI, 0.93-1.17) for AVG relative to AVF. Similarly, the covariate-adjusted rate of bleeding did not differ for AVG relative to AVF when also considering events treated in the emergency department or observation unit or those with nonmajor bleeding (Fig S1).

**Cardiovascular Events in New AV Access Users**

There was evidence that use of an AVG relative to an AVF was associated with slightly increased rates of ischemic stroke (adjusted IRR, 1.10; 95% CI, 0.99-1.22), myocardial infarction (adjusted IRR, 1.05; 95% CI, 0.98-1.12), and cardiovascular death (adjusted IRR, 1.09; 95% CI, 1.01-1.16), although the CIs were wide. There was no evidence of an association between the access type and acute limb ischemia events. The access type also showed a weak association with major adverse cardiovascular events (adjusted IRR, 1.07; 95% CI, 1.02-1.13) and a modest association with the cardiovascular composite endpoint, including ischemic stroke, myocardial infarction, venous thromboembolism, and critical limb ischemia (adjusted IRR, 1.24; 95% CI, 1.19-1.29) (Fig S1). The latter access type association was likely primarily driven by venous thromboembolism.

**New AV Access Users Who Initiated HD With a Catheter Alone**

In the main cohort, there were 32,665 new AV access users whose access was placed after initiating HD with a catheter alone. In this subgroup, covariate-adjusted associations of access type with the main study outcomes (Table S4) were consistent with the findings from the overall cohort (Fig 2).

**Sensitivity Analysis Using Inverse Probability Weighting**

In the main cohort, a sensitivity analysis using IPT weighting was conducted. Before IPT weighting, there were numerous baseline characteristics with standardized differences of >10% comparing AVF and AVG users; conversely, after IPT weighting, observed covariates were balanced between the 2 groups (standardized differences ≤2.2%) (Table S5). IRRs for the main study outcomes using the IPT weighted approach (Table S6) were nearly identical to the findings using regression adjustment (Fig 2).

**Outcomes in Prevalent AV Access Users**

A total of 27,607 prevalent AV access users, for whom a new index date was randomly chosen 0-5 years after the
original index date, were included in the secondary analysis. The baseline characteristics of patients included in the secondary analysis are shown in Table S7. Consistent with the findings of the main cohort, the covariate-adjusted IRR for venous thromboembolism was 1.77 (95% CI, 1.57-1.99) for AVG relative to AVF (Fig 3). There was no evidence of associations of access type with other outcomes (Figs 3 and S1).

**DISCUSSION**

In this large, nationwide study of new users of an AV access for maintenance HD, we found that using an AVG, compared with using an AVF, was associated with a 1.7-fold higher rate of venous thromboembolism. This association was also observed among patients who originally initiated HD with a catheter alone, prevalent AV access users, and after excluding patients with a history of venous thromboembolism. Conversely, differences in the rates of major bleeding, ischemic stroke, myocardial infarction, cardiovascular death, and critical limb ischemia were generally small or nonexistent between AVF and AVG users.

While it is well known that the rates of bleeding and thromboembolic events are much higher in patients receiving maintenance HD than in the general population,1-10,13-17 relatively few studies have compared the rates of these outcomes by AV access type in patients receiving maintenance HD. Of the few studies on the rates of major bleeding in maintenance HD overall, most have focused on oral anticoagulant users. In an international study, patients requiring maintenance HD and not using oral anticoagulants, aspirin, or antiplatelet medications had a major bleeding rate of 4.9 events per 100 person-years.32 In a Canadian study, patients initiating maintenance dialysis (80% undergoing HD, 20% undergoing peritoneal dialysis, and 12% receiving warfarin) had a rate of major hemorrhage of 5.3 events per 100 person-years.33 These rates of major bleeding were similar, but slightly higher, than those in the present study, which might be explained by the inclusion of HD catheter or anticoagulant users. These studies did not report on bleeding according to the access type.

In another Canadian study, patients using an AV access for maintenance HD experienced venous thromboembolism at a rate of 2.8 events per 100 person-years,10 which is lower than that in the present study. However, in this latter study, it is unclear how many patients were using oral anticoagulants, which would decrease the rate of thrombosis.

We do not know of a previous study reporting on venous thromboembolism separately for AVF and AVG users. It is unclear whether the higher rate of venous thromboembolism we observed among AVG users, relative to AVF users, was due to differences in the background rates of thrombotic events in those selected for AVG placement rather than AVF (given inherent differences in the vasculature between these groups) or was caused by unique properties of the AVGs not shared by the AVFs. We originally hypothesized that the presence of an AVG, which as a prosthetic implant would likely be
prothrombotic relative to an AVF, may be associated with thrombotic events. Virchow’s triad (ie, stasis due to access stenosis, endothelial injury due to shear stress, and activation of coagulation due to the presence of synthetic graft material) has been invoked as a reason why AVGs are particularly prothrombotic, therefore, it is plausible that the presence of an AVG could have an association with thrombotic events systemically.

Unsurprisingly, the AVG users in this study generally had a higher burden of adverse risk factors at baseline. This may indicate that residual confounding, if present, could be a source of bias toward more favorable outcomes among AVF users. However, given the magnitude of the association (a 74% higher rate of venous thromboembolism in AVG users after statistical adjustment for baseline covariates) and the general absence of associations for the other endpoints in this study, residual confounding is unlikely to completely explain the key finding. One explanation may be specifically related to access thrombosis, which is more common among AVG users than among AVF users. Procedural interventions for managing access thrombosis can, in rare cases, dislodge a clot and cause an adverse event such as a pulmonary embolism. However, these emboli are nearly always asymptomatic because of their very small particle size, making it unlikely that they would be recognized and diagnosed. Alternatively, while we cannot rule out the possibility that some access thromboses are miscoded as deep vein thrombosis in the claims record, this seems to be an uncommon occurrence based on another study.

Numerous observational studies have compared the risk of cardiovascular events according to the access type. In a systematic review and meta-analysis, there was a lack of evidence supporting the association of the use of an AVG relative to an AVF with the risk of major cardiovascular events (relative risk, 1.07; 95% CI, 0.95–1.21). This estimate is highly consistent with the small IRRs for the ischemic stroke, myocardial infarction, and cardiovascular death outcomes (point estimates, 1.05–1.10) among new access users in the present study. In contrast to the relatively large association observed for venous thromboembolism, the weak associations for cardiovascular disease events may be explained by residual confounding.

Our findings are potentially important when physicians and other providers work with patients to select the optimal access for HD. Current guidelines are based on the principle of obtaining “the right access, in the right patient, at the right time, for the right reasons.” It appears, at least in the case of older patients, that neither the risk of major bleeding nor major cardiovascular events are important factors in this calculus. However, a nearly 2-fold increase in the risk of venous thromboembolism associated with the use of AVGs provides a basis for discussion about the risks incurred by AVG users compared with AVF users when attempting to select an optimal access for a given patient.

This study has limitations. First, this analysis included only patients treated with HD via a functioning AV access. However, it is also important to consider the risks faced by patients starting from the creation of the access, particularly because AVFs have higher rates of maturation failure and longer times to cannulation. For instance, in patients close to dialysis initiation, particularly the elderly, placement of an AVG as opposed to an AVF may be considered a catheter-sparing strategy. A second limitation is that the scope of outcomes considered provides an incomplete picture of the risks facing AV access users. While this analysis was primarily concerned with assessing bleeding, thrombotic, and cardiovascular events, the risk of a variety of other serious clinical outcomes should be considered when choosing a vascular access. Beyond the known differences in the risk of access complications, observational evidence also suggests that the risk of all-cause mortality and fatal infection may be higher among AVG users than among AVF users. Third, as is the case in all observational studies, residual confounding is likely present. Because there may be unmeasured characteristics, such as small caliber blood vessels, that are more common in patients who receive AVGs and that may contribute to the thrombosis risk, randomized trials will be needed to confirm whether the observed association is causal. Fourth, this study included Medicare fee-for-service beneficiaries with Part D coverage who were not receiving oral anticoagulation; as such, the results may not be generalizable to other kidney failure populations.

In this observational study of Medicare beneficiaries newly using an AV access for maintenance HD, the rate of venous thromboembolic events, adjusted for patient case-mix, was roughly 70% higher among AVG users than among AVF users. Conversely, there were generally no marked differences in the rates of major bleeding or other cardiovascular outcomes, including ischemic stroke, myocardial infarction, cardiovascular death, or peripheral vascular disease, according to the access type. These findings should be considered as part of the risk calculus involved when choosing a vascular access for the maintenance HD population.

**SUPPLEMENTARY MATERIAL**

**Figure S1:** Rates and multivariable-adjusted incidence rate ratios of composite bleeding and cardiovascular outcomes in patients using an arteriovenous access for hemodialysis.

**Figure S2:** Rates of major bleeding and venous thromboembolism by arteriovenous access type and time since starting the use of an arteriovenous access for hemodialysis.

**Item S1:** Supplementary Methods.

**Table S1:** Definitions for Comorbid Conditions.

**Table S2:** Algorithm for Major Bleeding.

**Table S3:** Algorithms for Thrombotic and/or Cardiovascular Events.

**Table S4:** Incidence Rate Ratios for Bleeding, Thrombosis, and Cardiovascular Outcomes in New AV Access Users who Initiated HD With a Catheter and Later had an AV Access Placed.

**Table S5:** Baseline Characteristics of Patients With HD by Access Type in the Main Cohort (New AV Access users) Before and After IPT Weighting.
Table S6: Incidence Rate Ratios for Bleeding, Thrombosis, and Cardiovascular Outcomes in the Main Cohort (New AV Access Users) Using an IPT Weighted Analysis.

Table S7: Baseline Characteristics in Patients With HD by Access Type in Secondary Cohort (Prevalent AV Access Users).

ARTICLE INFORMATION

Authors’ Full Names and Academic Degrees: Nicholas S. Roetker, PhD, MS, Haifeng Guo, MS, Dena Rosen Ramey, ABD, Ciaran J. McMullan, MB, BCH, BAO, G. Brandon Atkins, MD, PhD, and James B. Wetmore, MD, MS

Authors’ Affiliations: Chronic Disease Research Group, Hennepin Healthcare Research Institute, Minneapolis, Minnesota (NSR, HG, JBW); Merck & Co, Inc, Kenilworth, New Jersey (DRR, CJM, GBA); and Division of Nephrology, Hennepin County Medical Center and Department of Medicine, University of Minnesota, Minneapolis, Minnesota (JBW).

Address for Correspondence: Nicholas S. Roetker, PhD, MS, Chronic Disease Research Group, Hennepin Healthcare Research Institute, 701 Park Ave, Suite S2.100, Minneapolis, MN 55415. Email: nick.roetker@cdrgr.org

Authors’ Contributions: Research idea and study design: NSR, DRR, CJM, GBA, and JBW; data acquisition: NSR and HG; data analysis/interpretation: NSR, HG, DRR, CJM, GBA, and JBW; statistical analysis: NSR and HG; supervision or mentorship: DRR and JBW. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Support: This study was funded by Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, New Jersey. The authors employed by the funder (Rosen Ramsey, McMullan, and Dr Atkins) had a role, jointly with the other coauthors, in the study design, interpretation of the study findings, drafting of the manuscript, and the decision to submit the manuscript for publication.

Financial Disclosure: Dr Roetker receives grant/research support to Chronic Disease Research Group from Amgen, the Centers for Disease Control and Prevention, and the National Institutes of Health. Dr Wetmore has been a consultant for Aurinia and Reata and receives grant/research support from Chronic Disease Research Group from Amgen, the Centers for Disease Control and Prevention, and the National Institutes of Health (National Institute of Diabetes and Digestive and Kidney Diseases), OPKO, Merck, Relypsa, Genentech, Bristol-Myers Squibb, and ACADIA. Rosen Ramsey, McMullan, and Dr Atkins are employed by the funder of this study. Guo has no relevant financial interests.

Acknowledgements: The authors thank Chronic Disease Research Group colleague Mary Van Beusekom, MS, ELS, for manuscript editing.

Disclaimer: The data reported here have been supplied by the US Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government.

Peer Review: Received October 8, 2021. Evaluated by 2 external peer reviewers, with direct editorial input from the Statistical Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form February 14, 2022.

REFERENCES

1. Sood P, Sinson GP, Cohen EP. Subdural hematomas in chronic dialysis patients: significant and increasing. Clin J Am Soc Nephrol. 2007;2(6):956-969.

2. Olesen JB, Lip GY, Kamper AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med. 2012;367(7):625-635.

3. Yang JY, Lee TC, Montez-Rath ME, et al. Trends in acute nonvariceal upper gastrointestinal bleeding in dialysis patients. J Am Soc Nephrol. 2012;23(3):495-506.

4. Sood P, Kumar G, Nanchal R, et al. Chronic kidney disease and end-stage renal disease predict higher risk of mortality in patients with primary upper gastrointestinal bleeding. Am J Nephrol. 2012;35(3):216-224.

5. Sakhija A, Schold JD, Kumar G, Katanz I, Navaneethan SD. Nontraumatic subarachnoid hemorrhage in maintenance dialysis hospitalizations: trends and outcomes. Stroke. 2014;45(1):71-76.

6. Ocak G, Noordzij M, Rookmaaker MB, et al. Mortality due to bleeding, myocardial infarction and stroke in dialysis patients. J Thromb Haemost. 2018;16(10):1953-1963.

7. Tvet DP, Hypolite IO, Hsieh P, et al. Chronic dialysis patients have high risk for pulmonary embolism. Am J Kidney Dis. 2002;39(5):1011-1017.

8. Ocak G, van Stralen KJ, Rosendaal FR, et al. Mortality due to pulmonary embolism, myocardial infarction, and stroke among incident dialysis patients. J Thromb Haemost. 2012;10(12):2484-2493.

9. Wang IK, Shen TC, Muo CH, Yen TH, Sung FC. Risk of pulmonary embolism in patients with end-stage renal disease receiving long-term dialysis. Nephrol Dial Transplant. 2017;32(8):1386-1393.

10. Molnar AO, Bota SE, McArthur E, et al. Risk and complications of venous thromboembolism in dialysis patients. Nephrol Dial Transplant. 2018;33(5):874-880.

11. Lutz J, Menke J, Sollinger D, Schinzel H, Thurnel K. Haemostasis in chronic kidney disease. Nephrol Dial Transplant. 2014;29(1):29-40.

12. Cozzolino M, Mangano M, Stucchi A, Ciceri P, Conte F, Galassi A. Cardiovascular disease in dialysis patients. Nephrol Dial Transplant. 2018;33(suppl 3):iii28-iii34.

13. O’Hare A, Johansen K. Lower-extremity peripheral arterial disease among patients with end-stage renal disease. J Am Soc Nephrol. 2001;12(12):2838-2847.

14. Seliger SL, Gillen DL, Longstreth WT Jr, Kestenbaum B, Stehman-Breen CO. Elevated risk of stroke among patients with end-stage renal disease. Kidney Int. 2003;64(2):603-609.

15. Reinecke H, Brand E, Mesters R, et al. Dilemmas in the management of atrial fibrillation in chronic kidney disease. J Am Soc Nephrol. 2009;20(4):705-711.

16. Chertow GM, Liu J, Monda KL, et al. Epoetin alfa and outcomes in dialysis amid regulatory and payment reform. J Am Soc Nephrol. 2016;27(10):3129-3138.

17. O’Lone E, Kelly PJ, Masson P, et al. Incidence of ischaemic heart disease in men and women with end-stage kidney disease: a cohort study. Heart Lung Circ. 2020;29(10):1517-1526.

18. Pavord S, Myers B. Bleeding and thrombotic complications of kidney disease. Blood Rev. 2011;25(6):271-278.

19. Ribic C, Crowther M. Thrombosis and anticoagulation in the setting of renal or liver disease. Hematology Am Soc Hematol Educ Program. 2016;2016(1):188-195.

20. Boccardo P, Remuzzi G, Galbusera M. Platelet dysfunction in renal failure. Semin Thromb Hemost. 2004;30(5):579-589.

21. Vinhas J, Barreto C, Assuncao J, Parreira L, Vaz A. Treatment of anaemia with erythropoiesis-stimulating agents in patients with chronic kidney disease does not lower mortality and may increase cardiovascular risk: a meta-analysis. Nephron Clin Pract. 2012;121(3-4):c95-c101.
22. Ellingson KD, Palekar RS, Lucero CA, et al. Vascular access hemorrhages contribute to deaths among hemodialysis patients. *Kidney Int*. 2012;82(6):686-692.

23. Jose MD, Marshall MR, Read G, et al. Fatal dialysis vascular access hemorrhage. *Am J Kidney Dis*. 2017;70(4):570-575.

24. Brown RS. Barriers to optimal vascular access for hemodialysis. *Semin Dial*. 2020;33(6):457-463.

25. Lok CE, Huber TS, Lee T, et al. KDOQI clinical practice guideline for vascular access: 2019 update. *Am J Kidney Dis*. 2020;75(4)(suppl 2):S1-S164.

26. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2018 Annual Data Report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2019;73(3)(suppl 1):A7-A8.

27. Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant use. *Pharmacoepidemiol Drug Saf*. 2011;20(6):560-566.

28. Graham DJ, Reichman ME, Wernecke M, et al. Stroke, bleeding, and mortality risks in elderly Medicare beneficiaries treated with dabigatran or rivaroxaban for nonvalvular atrial fibrillation. *JAMA Intern Med*. 2016;176(11):1662-1671.

29. Agarwal S, Pitcavage JM, Sud K, Thakkar B. Burden of readmissions among patients with critical limb ischemia. *J Am Coll Cardiol*. 2017;69(15):1897-1908.

30. Lutsey PL, Zakai NA, MacLehose RF, et al. Risk of hospitalised bleeding in comparisons of oral anticoagulant options for the primary treatment of venous thromboembolism. *Br J Haematol*. 2019;185(5):903-911.

31. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. Wiley; 1987. doi:10.1002/9780470316696

32. Sood MM, Larkina M, Thumma JR, et al. Major bleeding events and risk stratification of antithrombotic agents in hemodialysis: results from the DOPPS. *Kidney Int*. 2013;84(3):600-608.

33. Sood MM, Bota SE, McArthur E, et al. The three-year incidence of major hemorrhage among older adults initiating chronic dialysis. *Can J Kidney Health Dis*. 2014;1:21.

34. Allon M. A patient with recurrent arteriovenous graft thrombosis. *Clin J Am Soc Nephrol*. 2015;10(12):2255-2262.

35. Calderon K, Jhaveri KD, Mossey R. Pulmonary embolism following thrombolysis of dialysis access: is anticoagulation really necessary? *Semin Dial*. 2010;23(5):522-525.

36. Ravani P, Palmer SC, Oliver MJ, et al. Associations between hemodialysis access type and clinical outcomes: a systematic review. *J Am Soc Nephrol*. 2013;24(3):465-473.

37. Lee T, Thamer M, Zhang Y, Zhang Q, Allon M. Outcomes of elderly patients after predialysis vascular access creation. *J Am Soc Nephrol*. 2015;26(12):3133-3140.
Is the use of an arteriovenous graft associated with more complications than an arteriovenous fistula?

| Methods and Cohort | Exposure | Findings |
|--------------------|----------|----------|
| Observational cohort study | AV graft | Adjusted IRR 1.74 (1.63 - 1.85) |
| USRDS registry database | N = 17,763 | Adjusted IRR 1.04 (0.93 - 1.17) |
| HD patients with AV vascular access | AV fistula | Adjusted IRR 1.09 (1.01 - 1.16) |
| 2010 - 2015 | | |

**Venous thromboembolism**

**Major bleeding**

**Cardiovascular death**

AV graft associated with increased risk of venous thromboembolism and potentially a small increased risk of cardiovascular death as compared to an AV fistula.

**Conclusion:** Use of an AVG, relative to an AVF, in HD is associated with increased risk of venous thromboembolism. Given recent guidelines emphasizing selection of the "right access" for the "right patient," the results of this study should potentially be considered as one additional factor when selecting the optimal access for HD.

**Reference:** Roetker NS, Guo X, Ramsey DR et al. Association of arteriovenous graft versus fistula and risk of major bleeding, thrombosis, and cardiovascular events in hemodialysis patients: a cohort study. Kidney Medicine, 2022.

Visual Abstract by Denise Arelano, MD