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Major Bleeding Rates in an International Cohort of Patients With End-Stage Kidney Disease

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INTRODUCTION

An estimated 2.5 million patients worldwide were being treated for end-stage kidney disease (ESKD) in 2016.[1] The vast majority of patients with ESKD are treated with hemodialysis (HD, ∼89%) and peritoneal dialysis (PD); however, patterns of HD and PD vary internationally.[2] Patients with ESKD who are on dialysis have been observed to be at increased risk of major bleeding likely due to multiple factors;[3] however, the epidemiology of bleeding in different ESKD subgroups is not well-described. We aimed to determine rates of overall and cause-specific major bleeding events in patients with ESKD overall and by key characteristics, including HD versus PD, region, demographics, and comorbidities.

Data were obtained from the Dialysis Outcomes and Practice Patterns Study (DOPPS) and the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS), which are both international prospective cohort studies of patients receiving chronic HD or PD, respectively.[2,4] We assessed event rates for major bleed types (Supplementary Methods), including a composite of death or hospitalization due to any bleeding event, and the most frequently reported cause-specific bleeding (i.e., gastrointestinal [GI] or vascular access bleeding leading to hospitalization, and death due to hemorrhagic stroke).

RESULTS

A total of 38,466 patients were included: 32,396 receiving HD (84%) and 6070 receiving PD (16%). On average, patients were aged 64 years (SD, 15 years), 14% were aged ≥80 years, and 61% were male (Supplementary Table S1). Although over half (58%) had a history of cardiovascular disease, only 9% were on an oral anticoagulant and 9% were on an antiplatelet (excluding aspirin) in patients with prescription data available (n = 32, 901).

The overall rates for the composite outcome of hospitalization or death due to any bleeding event were similar in the HD (DOPPS) and PD (PDOPPS) cohorts: 4.5 (95% confidence interval [CI]: 4.4–4.7 and 4.4 (95% CI: 4.0–4.9) per 100 person-years, respectively (Figure 1). In both cohorts, bleeding rates were higher if patients had a prior history of bleeding; were aged ≥80 years; or had a history of any cardiovascular disease, including atrial fibrillation, cerebrovascular disease, atherothrombotic disease, or other cardiovascular disease. Minimal differences were observed by the history of diabetes.

The highest cause-specific event rate was for nonfatal GI bleeding, at 2.3 (95% CI: 2.1–2.4) and 2.0 (95% CI: 1.7–2.4) per 100 patient-years in the HD and PD cohorts, respectively (Table 1). In both HD and PD cohorts, subgroups with the highest event rates for nonfatal GI bleeding were similar to those for the composite bleeding endpoint. However, North America had the highest rates of hospitalizations due to GI bleeding at 3.1 (95% CI: 2.6–3.5) and 3.8 (95% CI: 3.0–4.7) per 100 patient-years for the HD and PD cohorts, respectively. Australia-New Zealand had the highest rates for the composite end point, at 5.9

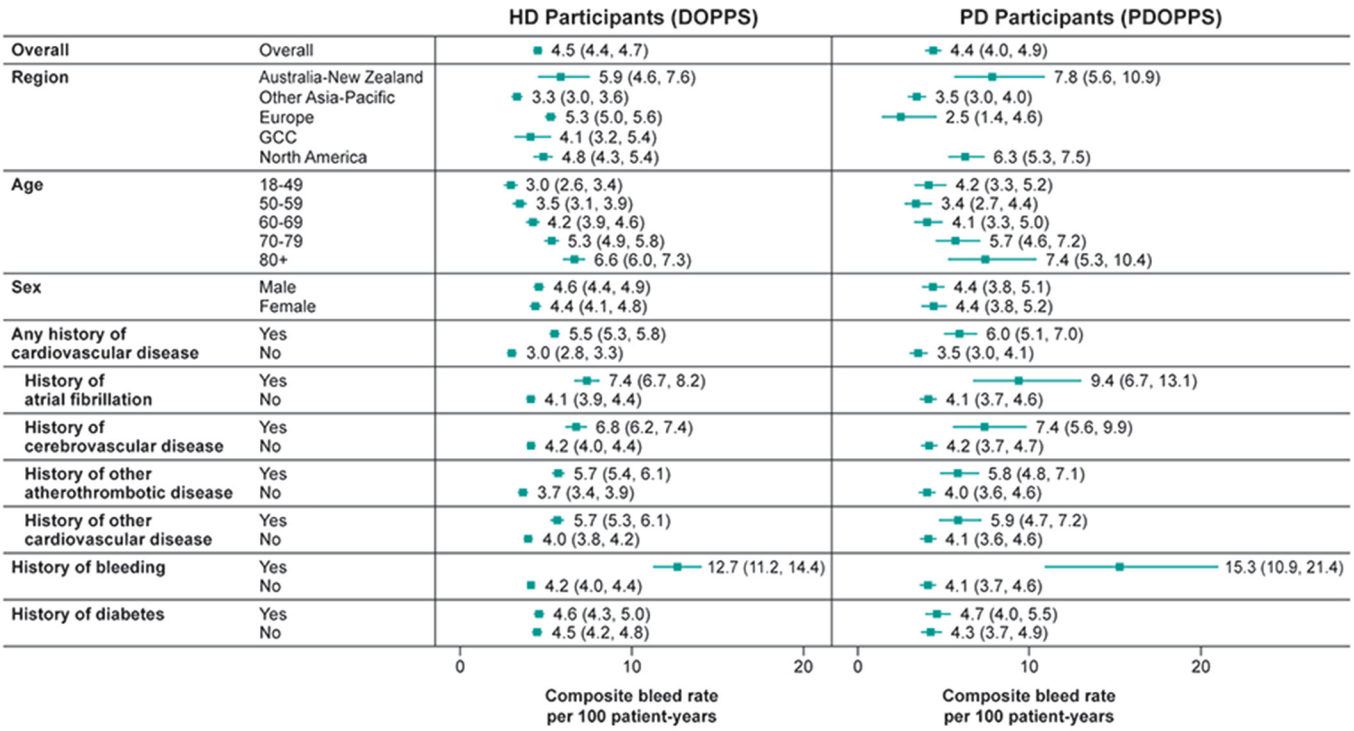

Figure 1. Composite major bleed rate in HD and PD. (a) The composite major bleed end point comprised any nonfatal bleeding event that resulted in hospitalization and any bleeding event that resulted in death. Nonfatal bleeding events that resulted in hospitalization included epistaxis, subdural hematoma, cerebral hemorrhage, evacuation of hematoma, abnormal bleeding, hemoptysis, hematuria, and vascular access bleeding. Any bleeding event that resulted in death included gastrointestinal hemorrhage, hemorrhage from vascular access, hemorrhage from ruptured vascular aneurysm, hemorrhage from surgery, and other hemorrhage. DOPPS, Dialysis Outcomes and Practice Patterns Study; HD, hemodialysis; PD, peritoneal dialysis; PDOPPS, Peritoneal Dialysis Outcomes and Practice Patterns Study.

(95% CI: 4.6–7.6) and 7.8 (95% CI: 5.6–10.9) per 100 patient-years for HD and PD cohorts, respectively. In the HD cohort, rates of hospitalization for vascular access bleeding were 3 to 4 times lower than for hospitalization caused by GI bleeding but followed a similar pattern across subgroups (Table 1).

Rates of death due to hemorrhagic stroke were similar in the HD and PD cohorts, respectively: 0.4 (95% CI: 0.4–0.5) and 0.3 (95% CI: 0.2–0.5) per 100 patient-years. Regional heterogeneity in rates of death due to hemorrhagic stroke, showed highest rate among patients living in the Other Asia-Pacific region in the HD cohort and in Australia-New Zealand in the PD cohort.

DISCUSSION

In this large, observational dataset of over 38,000 patients receiving dialysis, rates of hospitalization or death due to bleeding were approximately 4% to 5% per year, most frequently caused by GI bleeding, and were similar in patients receiving HD or PD. Subgroups with the highest bleeding rates had a prior history of bleeding, older age, and comorbid cardiovascular disease. There were geographic differences in bleeding rates as well as the use of HD versus PD.

In this population of patients, bleeding rates varied minimally by dialysis modality, which contrasts with results of other recent studies.[3,5] A Taiwanese study found higher risk of subdural hematoma in the HD cohort than in the PD cohort (adjusted hazard ratio: 1.6; 95% CI: 1.2–2.3).[5] Another study in the Netherlands showed that bleeding risk for patients on HD compared with PD increased 1.5-fold (95% CI: 1.0–2.2) based on adjusted results.[3] However, these studies were conducted in a single population, and while we assessed bleeding rates by region, rates could vary substantially by practice patterns and country, neither of which were included in DOPPS or PDOPPS.

In general, patients aged ≥80 years had the highest fatal and nonfatal bleed rates compared to other age groups with the exception that patients on PD who were aged ≥80 years had the lowest rate of death due to hemorrhagic stroke compared to other age groups. Consistent with other studies,[6,7] in general, patients with and without diabetes had similar rates of hospitalizations due to GI bleeds and deaths due to hemorrhagic stroke in both dialysis cohorts, though patients on HD without comorbid diabetes had higher rates of hospitalizations due to vascular access bleeds versus those with diabetes. These observations among elderly patients receiving

Table 1. Top nonfatal and fatal cause-specific major bleeding events[a]

	Hemodialysis (DOPPS) n = 32,396			Peritoneal dialysis (PDOPPS) n = 6070	
Patient group	Hospitalization due to GI bleed	Hospitalization due to vascular access[b]	Death due to hemorrhagic stroke	Hospitalization due to GI bleed	Death due to hemorrhagic stroke
Overall	2.26 (2.13–2.40)	0.59 (0.52–0.67)	0.42 (0.37–0.48)	2.01 (1.72–2.35)	0.32 (0.22–0.45)
Region					
Australia-New Zealand	2.74 (1.90–3.94)	1.21 (0.70–2.08)	0.19 (0.06–0.60)	3.29 (1.98–5.45)	0.53 (0.17–1.65)
Other Asia-Pacific	1.58 (1.39–1.79)	0.29 (0.22–0.39)	0.58 (0.48–0.70)	1.24 (0.96–1.60)	0.41 (0.28–0.61)
Europe	2.53 (2.33–2.76)	0.83 (0.72–0.96)	0.39 (0.32–0.48)	0.69 (0.22–2.14)	–
Gulf Cooperative Council (GCC)	1.79 (1.21–2.64)	0.28 (0.11–0.75)	0.39 (0.17–0.87)	–	–
North America	3.06 (2.64–3.53)	0.46 (0.32–0.67)	0.17 (0.09–0.31)	3.76 (3.01–4.69)	0.12 (0.04–0.36)
Age category (yr)					
18–49	1.17 (0.95–1.45)	0.44 (0.31–0.63)	0.35 (0.24–0.50)	1.43 (0.97–2.10)	0.30 (0.14–0.63)
50–59	1.66 (1.40–1.98)	0.40 (0.28–0.57)	0.43 (0.31–0.59)	1.38 (0.94–2.03)	0.34 (0.17–0.68)
60–69	2.17 (1.92–2.46)	0.59 (0.47–0.75)	0.36 (0.27–0.47)	1.89 (1.40–2.56)	0.39 (0.22–0.70)
70–79	2.77 (2.49–3.08)	0.64 (0.51–0.80)	0.47 (0.37–0.59)	3.23 (2.39–4.35)	0.24 (0.09–0.64)
≥80	3.40 (2.98–3.88)	0.88 (0.68–1.14)	0.53 (0.39–0.72)	3.88 (2.44–6.16)	0.17 (0.02–1.23)
Sex					
Male	2.28 (2.11–2.47)	0.55 (0.47–0.65)	0.45 (0.38–0.53)	2.11 (1.72–2.58)	0.32 (0.20–0.51)
Female	2.23 (2.02–2.47)	0.65 (0.54–0.78)	0.37 (0.30–0.47)	1.87 (1.46–2.41)	0.32 (0.18–0.54)
Disease history					
Any cardiovascular					
Yes	2.79 (2.60–3.00)	0.69 (0.60–0.79)	0.50 (0.43–0.59)	2.96 (2.38–3.67)	0.43 (0.26–0.72)
No	1.44 (1.27–1.62)	0.44 (0.35–0.55)	0.29 (0.22–0.37)	1.46 (1.16–1.84)	0.26 (0.16–0.42)
Atrial fibrillation					
Yes	3.94 (3.45–4.51)	0.86 (0.65–1.14)	0.61 (0.45–0.83)	4.20 (2.57–6.85)	0.63 (0.20–1.95)
No	2.01 (1.87–2.16)	0.55 (0.48–0.63)	0.39 (0.34–0.46)	1.85 (1.56–2.19)	0.31 (0.21–0.45)
Cerebrovascular					
Yes	3.08 (2.69–3.52)	0.80 (0.61–1.04)	0.75 (0.58–0.96)	3.40 (2.24–5.16)	0.64 (0.27–1.53)
No	2.12 (1.98–2.27)	0.56 (0.49–0.64)	0.36 (0.31–0.42)	1.88 (1.59–2.23)	0.29 (0.20–0.43)
Other atherothrombotic					
Yes	3.05 (2.81–3.30)	0.71 (0.60–0.83)	0.45 (0.37–0.55)	3.49 (2.70–4.52)	0.35 (0.16–0.73)
No	1.68 (1.53–1.84)	0.51 (0.43–0.60)	0.40 (0.33–0.47)	1.60 (1.31–1.95)	0.31 (0.21–0.47)
Other cardiovascular					
Yes	2.81 (2.55–3.09)	0.73 (0.61–0.88)	0.50 (0.41–0.62)	2.65 (1.93–3.62)	0.44 (0.22–0.87)
No	1.99 (1.83–2.15)	0.52 (0.45–0.61)	0.38 (0.32–0.45)	1.86 (1.55–2.23)	0.29 (0.19–0.44)
Bleeding[c]					
Yes	8.74 (7.54–10.1)	0.87 (0.56–1.37)	0.55 (0.33–0.93)	8.13 (5.19–12.8)	0.65 (0.16–2.61)
No	1.96 (1.83–2.10)	0.58 (0.51–0.66)	0.41 (0.36–0.48)	1.82 (1.53–2.15)	0.31 (0.21–0.44)
Diabetes					
Yes	2.50 (2.28–2.74)	0.49 (0.40–0.60)	0.44 (0.36–0.54)	2.04 (1.61–2.59)	0.41 (0.25–0.65)
No	2.09 (1.93–2.28)	0.67 (0.57–0.77)	0.41 (0.34–0.48)	1.98 (1.61–2.45)	0.25 (0.15–0.43)

CI, confidence interval; DOPPS, Dialysis Outcomes and Practice Patterns Study; GCC, Gulf Cooperation Council; GI, gastrointestinal; PDOPPS, Peritoneal Dialysis Outcomes and Practice Patterns Study.
[a]Data is reported as event rates per 100 patients-years (95% CI).
[b]Vascular access for hemodialysis via catheter, fistula, or graft.
[c]History of hospitalization due to any bleeding.

PD and patients without diabetes in the HD cohort are unexpected and highlight the need for further research.

A prior history of bleeding was also associated with higher rates of subsequent bleeding. This observation has been made in other cardiovascular populations where bleeding history is included in risk scores for treatment with more potent agents.[8] The observation that such history is also associated with higher rates of bleeding in patients receiving dialysis suggests that such risk scores may extend to the dialysis population to assist in identifying patients who would benefit from strategies that lower bleeding risk.

In this context, the observation that bleeding rates were increased approximately 2-fold among those with a history of atrial fibrillation, as well as any cardiovascular disease, underscores the complexity and unmet need for patients receiving dialysis who have atrial fibrillation or other comorbid cardiovascular conditions associated with high thrombotic risk, where the benefit-risk of currently available antithrombotic therapies is unclear. Novel approaches to reducing thrombotic risk with a more favorable safety profile are

needed. In this study, utilization of anticoagulant or antiplatelet (excluding aspirin) therapies was low overall. Aspirin use was not included because the drug utilization data for this study were based on prescription records, and most aspirin use is over the counter, thus aspirin use would be significantly underestimated in prescription records. However, further investigation is required to examine the utilization pattern of antithrombotic therapies in the subgroups of the study sample with a history of atrial fibrillation or any cardiovascular disease; and is the subject of a forthcoming manuscript.

Event rates described and compared between groups are crude, often in limited sample size, and do not reflect associations independent of other patient characteristics (or each other) and should be interpreted with caution. We can speculate that some of the observed differences by geographic setting might be related to differences in the source patient populations and/or in local clinical practice. For example, oral anticoagulants might be prescribed with varying doses or international normalized ratio measurement targets, which impact the subsequent risk of bleeding.[6] Finally, DOPPS and PDOPPS include different countries over differing time periods, which should be considered when drawing comparisons.

Overall, the observations of this large dataset of patients receiving dialysis highlights that impactful bleeding events leading to hospitalization or death are frequent regardless of HD or PD and are associated with regional variation, age, prior history of bleeding, and comorbid cardiovascular disease. The use of antithrombotic agents overall in patients receiving dialysis was low. The majority of bleeds were GI in etiology and not related to dialysis access. Because the factors associated with the highest rates of bleeding are also associated with the risk of severe thrombotic events, these data highlight the unmet need for strategies to reduce thrombotic risk with a more favorable safety profile than currently available agents.

DISCLOSURE

AK, MG, and CA are employees of Arbor Research Collaborative for Health, which administers the DOPPS and PDOPPS studies. CRC, LDB, DRR, GBA, and IB are employees of Merck & Co., Inc., Rahway, NJ, USA.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Table S1. Baseline patient characteristics.

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