Major Bleeding in Hemodialysis Patients

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Background and objectives: Few studies have examined risk factors for hemorrhage in hemodialysis patients. The contribution of warfarin and antiplatelet agent exposure to the incidence of first major bleeding episodes in hemodialysis patients was determined.

Design, setting, participants, & measurements: Retrospective chart review was performed in eligible hemodialysis patients. Incidence rates were determined as the number of first major bleeding events divided by the total exposure time on each treatment combination. Time-dependent covariates and Cox proportional hazard models were used to determine the hazard rate of having a first major bleeding event.

Results: A total of 1028 person-years of exposure were observed from 255 patients with a median follow-up time of 3.6 yr. The incidence rate of major bleeding episodes was 2.5% per person-year. The incidence of major bleeding episodes was 3.1% per person-year of warfarin exposure, 4.4% per person-year of aspirin exposure, and 6.3% per person-year of exposure to the combination of warfarin and aspirin. Compared with patients who were not prescribed warfarin or aspirin, the multivariable hazard ratio for time to first major bleeding event was 3.59 for warfarin, 5.24 for aspirin, and 6.19 for the combination of aspirin and warfarin.

Conclusions: The risk for major bleeding episodes in hemodialysis patients increases significantly while on aspirin and/or warfarin, although warfarin alone did not reach statistical significance. Future studies should evaluate the efficacy of these agents in the secondary prevention of cardiovascular events in this high-risk population.


H emodialysis (HD) patients are generally believed to have an elevated bleeding risk. Bleeding in uremia relates to an acquired defect of primary hemostasis caused by platelet dysfunction and altered platelet–vessel wall interaction (1).

Warfarin and antiplatelet agents such as aspirin increase the frequency of major bleeding. In our single-center study of HD patients, warfarin and aspirin were prescribed to 25 and 37.8% of HD patients, respectively (2). Chronic kidney disease (CKD), defined as a creatinine level >1.5 mg/dl, was identified as a risk factor for warfarin-associated bleeding in one inception cohort study (3). The two randomized, controlled trials (4,5) that investigated the efficacy of low-intensity warfarin for the preservation of vascular access failed to demonstrate a benefit, and one of these studies was terminated early because of an unacceptably high rate of major bleeding episodes in the warfarin-treated group.

In a healthy population at low risk for thrombosis, aspirin is associated with an unacceptably high number of bleeding complications, whereas for those who are at high risk for cardiovascular or cerebrovascular complications, the benefit of aspirin outweighs the risk (6). Randomized, controlled trials (7–9) in the HD population that have evaluated the use of antiplatelet agents for prevention of access thrombosis have shown inconsistent benefit with elevated bleeding events noted, especially in the elderly. To date, no evidence in the HD population exists on the efficacy of either warfarin or antiplatelet agents for the purpose of reduction of cardiovascular events or stroke.

We sought to determine the incidence of and risk factors for a first major bleeding event in a retrospective cohort of HD patients. Specifically, we sought to determine the contribution of exposure to warfarin and antiplatelet agents (aspirin, dipyridamole, and clopidogrel) to the incidence of first major bleeding episode in this population.

Concise Methods

Patients

The Kingston General Hospital (KGH) Renal Program provides care to all patients with ESRD in southeastern Ontario. Eligible patients included all those who were ≥18 yr of age and were receiving long-term outpatient HD therapy at KGH or any one of its affiliated satellite units between January 2002 and January 2004. Follow-up began on the date of initiation of HD therapy. Patients were excluded from the study only when they met any of the following criteria: Had received HD for <3 mo, were transferred into the program, had previous renal transplantation, or had previous peritoneal dialysis (PD). Follow-up was continued until April 1, 2006, with patients censored at date of death, transfer out of center, renal transplantation, or transfer to PD.

Risk Factor Identification

Demographic data and information on comorbid conditions were abstracted (G.J.H. and R.M.P.) from review of the KGH inpatient and
outpatient chart and the outpatient HD record. KGH is the regional center for all HD patients who require admission to hospital. These records include all details of hospital admissions and outpatient consultation visits and the results of all laboratory tests and diagnostic imaging. Comorbid conditions were defined on the basis of their presence on the day of HD initiation. All patients received 4 h of dialysis therapy thrice weekly using a Fresenius (Ogden, UT) F80 high-flux dialyzer.

Demographic data included age, gender, and cause of CKD (diabetes, renovascular disease, or other). Comorbid conditions were defined according to the original description by Charlson et al. (10). Renal disease was not considered, given its presence in all patients. The Charlson comorbidity index (CCI) was calculated for each patient. The CCI assigns 1 point for history of coronary artery disease, congestive heart failure, peripheral vascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease, and diabetes without end-organ damage; 2 points for hemiplegia, diabetes with end-organ damage, tumor without metastases, leukemia, lymphoma, and multiple myeloma; 3 points for moderate or severe liver disease; and 6 points for metastatic solid tumor or acquired immunodeficiency syndrome. For every decade >40 yr of age, 1 point was added to the score. The medication flow sheet in the outpatient HD chart was reviewed for nonsteroidal anti-inflammatory drug prescription. Start and end dates for warfarin, aspirin, dipyridamole, or clopidogrel were determined for each patient by review of the medication flow sheets in the outpatient HD chart. The indication for the use of warfarin was determined from the international normalized ratio (INR) flow sheet in the patient’s outpatient HD medical record.

Outcome Definition
First episode of a major bleeding event was obtained by reviewing the KGH inpatient and outpatient chart and the outpatient HD record (R.M.P. and G.J.H.). Patients were considered to have experienced a major bleeding event when it was the indication for their hospitalization, the bleed occurred in either the central nervous system or the retroperitoneum, or the patient required at least 2 units of packed red blood cells. Whether the patient was taking warfarin, aspirin, dipyridamole, or clopidogrel at the time of the major bleeding event was determined from the medical chart. Data collection was done exclusively through medical chart review without the use of coded hospital records.

Statistical Analyses
Only the first major bleeding event per patient was counted in this analysis. Exposure time was counted as time from start of HD to the earliest of first major bleeding event, transfer, or data collection. Exposure time to warfarin and aspirin was determined from dates obtained from the outpatient HD chart. The date of first HD was selected as the start date of exposure when the patient was taking warfarin and/or aspirin at initiation of HD.

Two approaches were used to assess the risk factors for having a first major bleeding event. Because it is difficult to test thoroughly model assumptions with a small number of events, we confirmed our conclusions by using two analysis approaches that make very distinct assumptions. The first approach compared incidence rates of the major bleeding events by each combination of warfarin and antiplatelet agents. The rate was estimated as the number of first major bleeding events divided by the total exposure time on each treatment combination. Rate ratios comparing rates on each treatment combination with the time on no warfarin, aspirin, Persantine, or clopidogrel was then calculated. Exact confidence intervals (CI) of the rates, asymptotic approximate CI of the rate ratios, and exact test comparing each rate with the referent group were then estimated by assuming that the major bleed events followed a Poisson distribution when pooled across patients.

The second analytic approach used the Cox proportional hazards model to examine the effect of the patient characteristics (age, gender, CCI, and cause of HD) and use of warfarin and antiplatelet agents on the hazard rate of having a first major bleeding event. Time-dependent covariates were used to assess how present use of warfarin, aspirin, dipyridamole, or clopidogrel affected the hazard rate of having a major bleeding event. For this analysis, major bleeding events were considered to have occurred on a treatment when the bleed occurred either while the patient was receiving the treatment or within 30 d of cessation of the treatment. The proportional hazards assumption was confirmed by testing the significance of time-dependent interactions between each covariate and the log of time.

Results
A total of 1028 person-years of exposure were observed from 255 patients (see Table 1 for patient characteristics). A total of 109 patients were excluded for the following reasons: Transfer from another dialysis program (n = 15), previous PD (n = 59), previous transplantation (n = 25), and recovery of renal function within 3 mo of initiation of HD therapy (n = 35). The mean age of the included patients was 62.1 ± 16.4 yr (range 16 to 92), and 39% were female. Eighty-three (33%) of the patients had diabetes. The mean CCI was 5.0 ± 2.5 (range 2 to 16). No patient was prescribed nonsteroidal anti-inflammatory drugs.

The median follow-up time was 3.6 yr. During this exposure time, 26 patients had a major bleeding event, yielding an incidence rate of 2.5% (95% CI 1.7 to 3.7%) per person-year. Only one bleeding event occurred in the central nervous system, and the remainder occurred in the gastrointestinal (GI) tract.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>mean ± SD 62.1 ± 16.4 range 16.0 to 92.0</td>
</tr>
<tr>
<td>CCI</td>
<td>mean ± SD 5.0 ± 2.5 range 2.0 to 16.0</td>
</tr>
<tr>
<td>Gender (n [%])</td>
<td>female 99 (39.0) male 156 (61.0)</td>
</tr>
<tr>
<td>Renal failure cause (n [%])</td>
<td>diabetes 83 (33.0) renovascular disease 62 (24.0) glomerulonephritis 43 (17.0) urologic 29 (11.4) PCKD 11 (4.3) multiple myeloma 10 (3.9) unknown 6 (2.4) other 11 (4.3)</td>
</tr>
</tbody>
</table>

CCI, Charlson comorbidity index; PCKD, polycystic kidney disease.
patient took dipyridamole for 3.7 yr and did not have a bleeding event. One of the 34 patients who took clopidogrel for a total of 46 person-years had a major bleeding event, but it did not occur while taking clopidogrel. Thus, because of the limited exposure of this cohort to either dipyridamole or clopidogrel and because no events occurred while exposed to either of these medications, they are not considered further in this analysis.

Table 2 provides the incidence rate of major bleeding episodes while on each combination of aspirin and warfarin. Rate ratios comparing each treatment combination with the time not on aspirin or warfarin are provided. Each treatment combination has a higher incidence rate than the reference value of time on no aspirin or warfarin therapy, but not all differences are statistically significant. It should be noted with this small number of events that some estimates may be imprecise, and the approximate 95% CI for the rate ratios may be inaccurate; however, the exact 95% CI for the incidence rates and the P values are based on the exact distributions and will be accurate assuming that events conform to a Poisson distribution.

Table 2 provides results from the Cox proportional hazards model. Only treatment combination remained significant at P < 0.1 in the multivariable model; however, because of the small number of events, power is limited to assess the significance of covariates. The estimated effect of treatment combination is similar to that obtained by the incidence rate approach, regardless of adjustment for covariates. Older patients were more likely to sustain a bleed, but the effect of age diminished after adjustment for the other covariates and warfarin and aspirin use. Cause of renal failure (including diabetes) and higher CCI were not associated with major bleeding events.

There were 13 upper GI bleeds and 12 lower GI bleeds. Eleven upper GI bleeds related to inflammatory conditions of the GI tract, including gastric or duodenal ulcers, gastritis, duodenitis, and esophagitis. Cause of the lower GI bleeds included hemorrhoids (n = 2), ischemic colitis (n = 2), diverticular disease (n = 2), angiodysplasia (n = 1), polyp (n = 1), and unknown (n = 4). In one patient only, the major bleed occurred at an INR outside the acceptable range for any indication (5.1). In the remaining patients, the INR at the time of the bleed ranged from 1.3 to 2.6.

Discussion

The results of this study indicate that the overall frequency of major bleeding events in HD patients in our center was 2.5% per person-year. The overwhelming majority of major bleeding episodes originated from the GI tract. The frequency of major bleeding events increased to 3.1% per person-year of warfarin exposure, 4.4% per person-year of aspirin exposure, and 6.3% per person-year of exposure to the combination of warfarin and aspirin.

There are few data on the incidence or frequency of major bleeding episodes in patients who require HD, although the risk is generally believed to be higher than that for nonuremic individuals because of the associated platelet dysfunction. When one considers observational studies that provided a definition for major bleeding episodes, the incidence of major bleeding episodes in HD patients who were not taking anticoagulants ranged between 0.025 and 0.11 events per person-year (11,12). Recognizing the limitations in attempting to compare different patient populations, the overall incidence rate that we have reported (0.025 major bleeding events per person-year) is identical to the rate reported in the observational study of Biggers et al. (11).

In patients without exposure to warfarin or antiplatelet agents, the rate was 0.008 events per person-year. Randomized, controlled trials that compared low-intensity warfarin with placebo for prevention of either graft or venous catheter thrombosis did not encounter any major bleeding episodes in the control arms within the follow-up time of these studies (4,13). Comparative bleeding rates in similarly high-risk individuals can be gleaned from the control groups of randomized, controlled trials of warfarin prophylaxis in atrial fibrillation (AF). In the pooled analysis of five major trials, the risk for major hemorrhage was 1% in control patients (14).

The frequency of warfarin-associated bleeding in this observational study of HD patients was 3.1% per person-year in patients who were not concurrently prescribed an antiplatelet agent. Two observational cohort studies and two case series involving hypercoagulable patients evaluated full-intensity anticoagulation in HD patients (11,12,15,16). The incidence of major bleeding episodes ranged from 0.1 to 0.54 events per

Table 2. Incidence rate analysis by treatment combination

<table>
<thead>
<tr>
<th>Treatment Combination</th>
<th>Contributed Patients</th>
<th>Person-Years</th>
<th>Major Bleeds</th>
<th>IR (Exact 95% CI)</th>
<th>Rate Ratio (Approximate 95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>178</td>
<td>518.9</td>
<td>4</td>
<td>0.8% (0.2 to 2.0%)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Warfarin only</td>
<td>89</td>
<td>159.1</td>
<td>5</td>
<td>3.1% (1.0 to 7.3%)</td>
<td>4.1 (1.1 to 15.2)</td>
<td>0.076</td>
</tr>
<tr>
<td>Aspirin only</td>
<td>107</td>
<td>271.7</td>
<td>12</td>
<td>4.4% (2.3 to 7.7%)</td>
<td>5.7 (1.8 to 17.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Aspirin + warfarin</td>
<td>50</td>
<td>79.0</td>
<td>5</td>
<td>6.3% (2.1 to 14.8%)</td>
<td>8.2 (2.2 to 30.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Total</td>
<td>255</td>
<td>1027.9</td>
<td>26</td>
<td>2.5% (1.7 to 3.7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aCI, confidence interval; IR, incidence rate.
*bThe same patient may contribute to multiple treatment combinations because patients may change their treatment over time. For example, the 178 patients in the none combination suggests that 178 patients were on no treatment at some time during follow-up, but these same patients may have received treatment at other times during follow-up.
*cThis CI is asymptotically approximate and may not be accurate for this small sample.
person-year of exposure with between 10 and 77% of bleeding episodes occurring when the INR was above the target range. Two studies evaluated low-intensity anticoagulation (target INR 1.4 to 1.9) for the prevention of HD access thrombosis (4,13). The one randomized, placebo-controlled trial was discontinued early because of a clinically important increase in major bleeding episodes in the patients who were randomly assigned to warfarin. In addition, the point estimate for effectiveness of warfarin suggested that it was inferior to placebo (4).

In a meta-analysis of observational studies of anticoagulant-related bleeding in the high-risk general population, the mean frequency of major bleeding episodes during warfarin therapy from 25 inception cohort studies with a total of 4318 patients was 3.0% per person-year (95% CI 2.5 to 3.4%), a value similar to the rate reported in this study (17); however, the CI identified in our study indicate that the risk could be as high as 7.3% in HD patients, limiting comparisons. One hundred percent of the major bleeding episodes in the patients who were taking warfarin were associated with aspirin exposure results in a bleeding frequency of 4.4% per person-year. Both the rate ratio and the hazard rate for first major bleed for patients who were taking aspirin exceeded that of warfarin alone, although none of the differences was statistically significant (all P > 0.2). Of the 17 major bleeding episodes that occurred in patients who were exposed to aspirin, eight were upper GI bleeds, seven were lower GI bleeds, and one was an intracerebral hemorrhage. Comparative bleeding rates can be obtained from randomized, controlled trials that were performed in the general population with AF. In a meta-analysis of antiplatelet therapy for preventing stroke in patients with nonvalvular AF, the rate of major bleeding episodes that were associated with aspirin was <1% per year.

Whereas aspirin prolongs the bleeding time in normal volunteers, the effect is exaggerated in CKD (9); however, few studies have evaluated aspirin-associated bleeding risk in HD patients (9,20,21). In addition to the effect on bleeding time, two distinct cyclooxygenase-1 mechanisms contribute to the increased risk for upper GI bleeding: The dosage-independent inhibition of thromboxane A2-mediated platelet aggregation and the dosage-dependent inhibition of the prostaglandin H synthase–mediated cytoprotection in the gastric mucosa (6). Thus, in addition to its effect on platelet function, aspirin may directly cause gastric erosions (9). All eight upper GI bleeds that were sustained by the HD patients who were taking aspirin were taking the medication for access preservation. There is no evidence supporting the use of warfarin for this indication in HD patients, suggesting that 50% of the major bleeding episodes that were encountered in this study could potentially be eliminated by avoiding this practice.

In considering aspirin, the results of this study indicate that aspirin exposure results in a bleeding frequency of 4.4% per person-year. Both the rate ratio and the hazard rate for first major bleed for patients who were taking aspirin exceeded that of warfarin alone, although none of the differences was statistically significant (all P > 0.2). Of the 17 major bleeding episodes that occurred in patients who were exposed to aspirin, eight were upper GI bleeds, seven were lower GI bleeds, and one was an intracerebral hemorrhage. Comparative bleeding rates can be obtained from randomized, controlled trials that were performed in the general population with AF. In a meta-analysis of antiplatelet therapy for preventing stroke in patients with nonvalvular AF, the rate of major bleeding episodes that were associated with aspirin was <1% per year.

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**Table 3. Analysis of time to first bleed by Cox proportional hazards model**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate Model</td>
<td></td>
<td>Multivariate Model</td>
<td></td>
</tr>
<tr>
<td>Age (per decade)</td>
<td>1.36 (1.03 to 1.80)</td>
<td>0.031</td>
<td>1.03 (0.99 to 1.06)</td>
<td>0.011</td>
</tr>
<tr>
<td>Female</td>
<td>1.39 (0.64 to 3.00)</td>
<td>0.405</td>
<td>1.40 (0.62 to 3.12)</td>
<td>0.418</td>
</tr>
<tr>
<td>CCI (per point)</td>
<td>1.06 (0.92 to 1.22)</td>
<td>0.416</td>
<td>0.93 (0.76 to 1.13)</td>
<td>0.454</td>
</tr>
<tr>
<td>Cause of renal failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>–</td>
<td>0.452</td>
<td>–</td>
<td>0.406</td>
</tr>
<tr>
<td>diabetes</td>
<td>1.78 (0.72 to 4.44)</td>
<td>0.214</td>
<td>1.82 (0.60 to 5.49)</td>
<td>0.290</td>
</tr>
<tr>
<td>renovascular</td>
<td>1.54 (0.56 to 4.25)</td>
<td>0.404</td>
<td>0.85 (0.29 to 2.48)</td>
<td>0.771</td>
</tr>
<tr>
<td>Treatment combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>not on either</td>
<td>–</td>
<td>0.009</td>
<td>–</td>
<td>0.036</td>
</tr>
<tr>
<td>on warfarin only</td>
<td>3.91 (1.05 to 14.63)</td>
<td>0.043</td>
<td>3.59 (0.95 to 13.60)</td>
<td>0.061</td>
</tr>
<tr>
<td>on aspirin only</td>
<td>5.81 (1.87 to 18.02)</td>
<td>0.002</td>
<td>5.24 (1.64 to 16.79)</td>
<td>0.005</td>
</tr>
<tr>
<td>on both warfarin and aspirin</td>
<td>8.22 (2.20 to 30.68)</td>
<td>0.002</td>
<td>6.19 (1.60 to 23.97)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*aThe treatment combination is modeled as a time-dependent covariate, so the corresponding hazard ratios estimate the magnitude of the increase in the hazard rate while on these treatments rather than the increased hazard rate for individuals who ever took these combinations.

*bGlobal test for cause of renal failure. Subsequent tests are compared with referent.

*Global test for treatment combination. Subsequent tests are compared with referent.
rin in this study were inflammatory conditions of the gastric or duodenal mucosa.

Individual studies and meta-analyses of trials of antiplatelet therapy in the general population concluded that, in high-risk patients, the absolute benefit of aspirin therapy outweighs the risk for bleeding. To the best of our knowledge, no long-term, randomized, controlled trials have evaluated the efficacy of aspirin for cardiovascular or stroke prophylaxis in an HD population; however, given the burden of disease, the National Kidney Foundation has recommended giving aspirin (75 to 325 mg/d) to HD patients who have or are at high risk for developing cardiovascular disease. Although antiplatelet therapy might prevent serious vascular events in the HD population, the risk for bleeding may be such that the benefit is counter-balanced by the absolute excess in bleeding events.

The results of this study indicate that the combination of warfarin and aspirin results in the highest incidence of major bleeding episodes in HD patients. Two other studies performed to date in HD patients indicated that combination therapies pose a high bleeding risk. In the placebo-controlled, randomized, controlled trial that evaluated low-intensity anticoagulation with warfarin on polytetrafluoroethylene graft patency (4), all five patients who were randomly assigned to warfarin and had a major bleeding episode were concurrently taking an antiplatelet agent. The randomized, double-blind, placebo-controlled trial to determine the efficacy of the combination of aspirin and clopidogrel in the prevention of graft thrombosis (7) was discontinued early because of the significantly increased risk for bleeding among patients who were receiving the combination compared with patients who were receiving placebo.

No major bleeding episode occurred during the 46 person-years of clopidogrel exposure. There are no comparative studies in HD patients. The number of years of exposure to clopidogrel in this study is insufficient to speculate on comparative safety.

The results of this study suggest that the avoidance of warfarin for the indication of prevention of access thrombosis would reduce the incidence of major bleeding episodes in HD patients. Aspirin is associated with a high incidence of major bleeding episodes in HD patients, a rate that seems considerably higher than rates observed in the general population. Finally, the data indicate that the combination of warfarin and aspirin is associated with highest risk in HD patients and probably should be avoided if possible.

There are weaknesses to this study. Although all tertiary care and hospitalizations were provided by a single center, it is conceivable that a major bleeding episode may have occurred without documentation in either the medical record or dialysis unit record. Given that we considered major bleeding episodes only, we believe that the impact of this would be small. Also, we did not address whether patients had major bleeding episodes before the initiation of HD therapy. We acknowledge the potential data limitations of any retrospective study. Finally, the small number of events limits the precision of our estimates and the power to detect significant predictors.

Conclusions
The risk for major bleeding episodes per year of exposure was 0.8, 3.1, 4.4, and 6.3% in HD patients while taking neither warfarin nor aspirin, taking warfarin alone, taking aspirin alone, or taking the combination of warfarin and aspirin, respectively. The overwhelming majority (25 of 26) of major bleeding episodes were GI in origin. Advancing age was associated only with the increased risk for major bleeding episodes before adjustment for covariates and warfarin and aspirin use. Given that the absolute benefit of either warfarin or antiplatelet agents is offset against their associated bleeding risk, randomized, controlled trials are necessary to evaluate the efficacy and the safety of these agents in the secondary prevention of cardiovascular events in this high-risk population.

Disclosures
None.

References


