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No difference in bleeding risk between subcutaneous enoxaparin and heparin for thromboprophylaxis in end-stage renal disease

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Enoxaparin, a low-molecular-weight form of heparin, is not approved for use in dialysis patients in the United States, because it is eliminated through the kidneys and could therefore accumulate and cause inadvertent bleeding. Accordingly, it is unknown if enoxaparin is as safe to prescribe as subcutaneous heparin for thromboprophylaxis in patients with chronic renal failure. Here we conducted a retrospective comparative effectiveness study in a large population of chronic maintenance dialysis patients initiated with subcutaneous injections of enoxaparin or heparin for thromboprophylaxis. The primary study end point was hospitalization or death related to bleeding, with a secondary end point of venous thromboembolism. Among 7721 dialysis patients started on subcutaneous enoxaparin or heparin at doses for thromboprophylaxis, the crude rate for bleeding requiring hospitalization or resulting in death was 15.2 (95% confidence interval (CI) 12.7–18.2) events per 100 patient-years in the enoxaparin group, which did not differ from the heparin group in which the crude rate was 16.2 (95% CI 14.0–18.7) events per 100 patient-years. In risk factor–adjusted Poisson models, enoxaparin was not associated with more bleeding in comparison to heparin (risk ratio, 0.98; 95% CI 0.78–1.23). The risk of venous thromboembolism was not associatively worse with enoxaparin (risk ratio, 0.77; 95% CI 0.49–1.22). Thus, in dialysis patients, daily enoxaparin for thromboprophylaxis was not associated with increased serious bleeding or less effective compared to subcutaneous heparin.

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Enoxaparin was approved by the FDA (US Food and Drug Administration) in 1993 for thromboprophylaxis in patients at high risk for deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] Because low-molecular-weight heparin (LMWH) is eliminated primarily through the kidneys, the FDA did not extend enoxaparin approval to patients on dialysis, because the drug could theoretically bioaccumulate and precipitate inadvertent bleeding. Because of its smaller molecular mass, enoxaparin binds less to plasma proteins, macrophages, and endothelial cells, thereby conferring a more reliable dose–response relationship and longer plasma half-life when compared with unfractionated heparin (UFH).[2,3] Studies have indicated that the half-life for enoxaparin approximately doubles when the kidneys fail (glomerular filtration rate <15 ml/min); however, there are insufficient data to determine whether this in fact translates to more clinical bleeding.[4,5] As such, it is currently unknown whether enoxaparin is as safe to prescribe in dialysis patients as subcutaneous heparin, whose elimination does not depend on the kidney.[6]

Studies in the non-chronic kidney disease (CKD) population suggest that LMWH is an equivalent of, if not better than, heparin for thromboprophylaxis. A meta-analysis of 10 randomized controlled trials in non-CKD patients concluded that daily LWMH was 32% more effective than heparin in preventing DVT, without increasing the risk of bleeding.[7] Consequently, therapies such as enoxaparin have become the drug of choice for thromboprophylaxis in general practice, and sometimes enoxaparin is prescribed to dialysis patients as well.[1]

Given that the safety profile of low-dose enoxaparin is uncertain in dialysis, we conducted a comparative effectiveness analysis in dialysis patients on such medications for thromboprophylaxis. We compared the risk of serious bleeding in dialysis patients administered a daily dose of enoxaparin against heparin administered two or three times per day.

RESULTS

A total of 7721 dialysis subjects who were initiated on thromboprophylaxis doses of enoxaparin (daily) or heparin

Table 1a | Prevalence of risk factors for bleeding

Risk factor for bleeding	% Of patients Enoxaparin ($n=2991$)	Heparin ($n=4730$)	*P*-value
Age ≥60 years	67.1	68.0	0.11
Male	43.0	46.3	0.003
Caucasian	71.0	67.0	0.0002
Time on dialysis (<1 year)	49.0	51.3	0.04
Diabetic	41.2	34.0	<0.0001
HTN (>130/80 mm Hg)	53.4	53.0	0.88
Arteriovenous fistula	19.2	23.2	0.62
Catheter	58.0	57.4	
Graft	20.1	17.0	
Peritoneal dialysis	2.7	2.4	
Recent hemorrhage	7.7	10.1	0.0003
Recent PUD	2.1	2.9	0.11
Recent ICU admission	2.8	5.0	<0.0001
Cancer	10.3	10.8	0.46
Thrombocytopenia	1.8	1.8	0.98
Liver disease	5.5	6.2	0.18
Rheumatic disease	4.7	3.7	0.02
Intradialytic heparin >4000 units/treatments	40.5	39.8	0.56
Antiplatelet therapy	42.4	51.1	<0.0001
PPI therapy	72.9	75.0	0.04
Time on drug (days)	135	143	0.41

Abbreviations: HTN, hypertension; ICU, intensive care unit; PPI, proton pump inhibitor; PUD, peptic ulcer disease.

Table 1b | Prevalence of risk factor for bleeding by prophylaxis regime

Risk factor for bleeding	% Of patients Enoxaparin ($n=2991$)	Heparin ($n=4730$)	*P*-value
Age ≥60 years[a]	67.1	68.0	0.11
Male[a]	43.0	46.3	0.003
Caucasian[a]	71.0	67.0	0.0002
Time on dialysis (<1 year)[a]	49.0	51.3	0.04
Diabetic[a]	41.2	34.0	<0.0001
HTN (>130/80 mm Hg)[a]	53.4	53.0	0.88
Arteriovenous fistula[a]	19.2	23.2	0.62
Catheter	58.0	57.4	
Graft	20.1	17.0	
Peritoneal dialysis	2.7	2.4	
History of thrombosis	8.5	6.7	0.005
Recent orthopedic surgery	14.2	8.9	<0.0001
Recent high- or moderate-risk surgery	2.1	2.4	0.39
Recent amputation	5.1	8.7	<0.0001
Recent ischemic stroke	3.8	4.7	0.06
Recent CHF admission	13.4	15.1	0.04
Recent COPD admission	4.1	4.8	0.15
Recent trauma	0.4	0.6	0.07
Immobile	5.1	9.8	<0.0001
Cancer	10.3	10.8	0.46
Obesity	28.0	30.0	0.07
Inflammatory bowel disease	0.4	0.5	0.42
Active pregnancy	0.03	0.1	0.38
EPO 8000 units/treatment	44.1	47.9	0.001
Estrogen therapy	2.3	1.1	<0.0001
Time on drug (days)	135	143	0.41

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; EPO, erythropoietin; HTN, hypertension.
[a]These variables are repeated from panel (a).

(b.i.d.–t.i.d.) were identified for the study. On average, enoxaparin patients received 135 days of therapy, which was statistically not different from the heparin patients in whom the duration of treatment was 143 days ($P=0.41$). Clinically, enoxaparin patients were more likely to be Caucasian, diabetic, and have undergone postorthopedic surgery, whereas heparin patients were more likely to be immobile and prescribed antiplatelet medications (Table 1a and b).

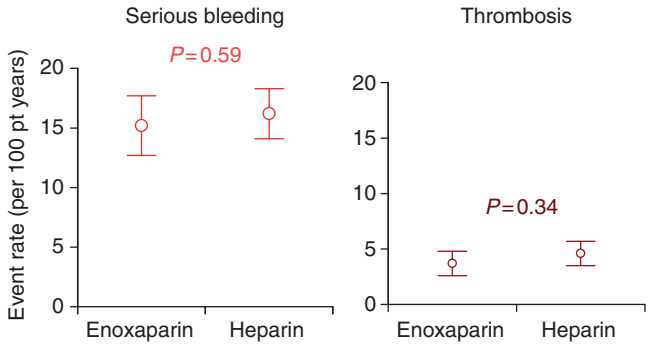

Figure 1 | Crude thrombosis and bleeding rate in end-stage renal disease (ESRD) patients initiated on subcutaneous enoxaparin or heparin for thromboprophylaxis. Unadjusted rates with 95% confidence intervals were calculated using Poisson regression. pt, patient.

During the study period, there were 309 bleeding events and 83 thrombosis events among the study cohort. The crude rate for bleeding requiring hospitalization or resulting in death was 15.2 (95% CI 12.7–18.2) events per 100 patient-years in the enoxaparin group and 16.2 (95% CI 14.0–18.7) events per 100 patient-years in the heparin group (see Figure 1). These rates were not significantly different from each other ($P=0.59$). Similarly, the crude rate for thrombosis was not statistically different between enoxaparin and heparin (3.7 vs. 4.6; $P=0.34$).

After risk factor adjustment, the standardized rate for bleeding was 16.9 events per 100 patient-years (95% confidence interval (CI) 12.9–22.3) among enoxaparin patients and 17.2 events per 100 patient-years (95% CI 13.5–22.0) among heparin patients. Statistically, enoxaparin was associated with equivalence to heparin in terms of bleeding risk (risk ratio (RR) = 0.98; 95% CI 0.78–1.23; *P*-for-equivalence = 0.02). For thrombosis, enoxaparin was associatively noninferior to heparin (RR = 0.77; 95% CI 0.49–1.22; $P=0.04$ for noninferiority) at preventing thromboembolism. See Table 2 and Supplementary Appendix B.

In dose–response analyses, patients administered standard-dose enoxaparin for normal renal function (31–60 mg per day, $n=1422$) had a standardized bleeding rate of 17.6 events per 100 patient-years (12.6–24.4), whereas patients with a dose reduction for moderate CKD (30 mg per day, $n=1569$) had a standardized bleeding rate of 16.3 events per 100 patient-years (11.7–22.8). These bleeding rates were not statistically different ($P=0.71$) from each other, nor was the cumulative dose of enoxaparin different in patients who had a bleeding event versus those who did not (5499 vs. 4967 mg; $P=0.13$). In comparison with heparin, the RR for bleeding with low-dose enoxaparin was 0.95 (95% CI