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Digoxin Dosing and the Risk of Toxicity in Older Adults With CKD

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Digoxin Dosing and the Risk of Toxicity in Older Adults With CKD

To the Editor:

Digoxin, commonly used to treat heart failure,[1,2] has a narrow therapeutic range and is eliminated primarily by the kidney.[1] To avoid toxicity, digoxin should be started at ≤0.125 mg/d in patients with chronic kidney disease (CKD) (Table S1).[1,2] Reviewing the literature, we found studies of digoxin toxicity in patients with CKD were limited to case reports or focused on patients receiving dialysis (Tables S2-S3). We addressed this knowledge gap by conducting a population-based study of older adults with CKD who were newly prescribed digoxin. We examined digoxin prescribing patterns and 90-day risk of a hospital visit with toxicity in those prescribed >0.125 versus ≤0.125 mg/d.

The data source, design, and methods are given in Item S1.[3] We analyzed linked administrative health care data housed at ICES in Ontario, Canada, where all residents aged ≥65 years have universal prescription drug coverage. The cohort included adults aged ≥66 (to ensure ≥ 1 year of drug coverage) who had an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² and who were newly dispensed oral digoxin from an outpatient pharmacy between January 1, 2008, and December 31, 2019. We excluded patients with evidence of digoxin use within 180 days before the dispense date.

To align with prescribing guidelines (Table S1), we compared patients prescribed >0.125 versus ≤0.125 mg/d digoxin. The primary outcome was time to first hospital admission or an emergency department (ED) visit with toxicity within 90 days of starting digoxin. The secondary outcomes were time to first hospitalization for any reason and all-cause mortality. In a validation study, the algorithm used to identify hospitalization with digoxin toxicity using ICD-9 codes had a sensitivity of 84% (IQR, 71%-93%), a specificity of 99% (IQR, 99%-99%), and a positive predictive value of 57% (IQR, 45%-68%).[4] In this study, we used the corresponding ICD-10 codes and captured patients with digoxin toxicity who visited the ED (diagnostic codes in Table S4).

We used inverse probability of treatment weighting on the propensity score to balance patients in the exposed and reference groups on 151 baseline health indicators (Table S5).[5-7] Weighted hazard ratios (wHR) were obtained using Cox proportional hazards regression, and 95% CI were obtained using bootstrap variance estimators.[8] The proportional hazards assumption was assessed using a time-dependent covariate test and was met for all outcomes. We conducted primary analyses according to the intention-to-treat principle. Death was treated as a censoring event.

In prespecified sensitivity analyses, (1) we restricted the primary outcome to patients hospitalized with digoxin toxicity (excluding ED visits), and (2) we examined potential effect modification by baseline eGFR.

Of 25,698 older adults who initiated digoxin during the study period, 11,755 (46%) had an eGFR < 60 mL/min/1.73 m²: 1,671 (14%) were prescribed >0.125 mg/d and 10,084 (86%) ≤0.125 mg/d (Fig S1). The median dose in each group was 0.25 (IQR, 0.15-0.25) and 0.125 (IQR, 0.06-0.125) mg/d, respectively. Weighting produced well-balanced groups (Table S5; Table 1). The patients largely received digoxin prescriptions from primary care physicians (49%), cardiologists (31%), and internists (8%).

Starting digoxin at >0.125 versus ≤0.125 mg/d was associated with a higher 90-day risk of a hospital admission or an ED visit with toxicity: 149 versus 33 events per 1,000 person-years (wHR, 5.75 [95% CI, 4.00-8.27]). Starting digoxin at >0.125 versus ≤0.125 mg/d was also associated with a higher risk of all-cause hospitalization

Table 1. Baseline Characteristics of Older Adults With CKD Newly Prescribed Digoxin in Ontario, Canada (2008-2019)

	Unweighted Data (N = 11,755) by Digoxin Dose			Weighted Data (N = 3,342)[a] by Digoxin Dose		
	>0.125 mg/d (n = 1,671)	≤0.125 mg/d (n = 10,084)	Std Diff[b]	>0.125 mg/d (n = 1,671)	≤0.125 mg/d (n = 1,671)	Std Diff[b]
Demographics						
Women	852 (51.0%)	5,884 (58.3%)	15%	852 (51.0%)	855 (51.2%)	0%
Age, y	79.6 ± 7.7	81.8 ± 8	29%	79.6 ± 7.7	79.6 ± 3.0	1%
Residence						
Urban	1,458 (87.3%)	8,843 (87.7%)	1%	1,458 (87.3%)	1,457 (87.2%)	0%
Rural	213 (12.7%)	1,241 (12.3%)	1%	213 (12.7%)	214 (12.8%)	0%
Long-term care	83 (5.0%)	626 (6.2%)	5%	83 (5.0%)	85 (5.1%)	0%
Income quintile[c]						
1 (lowest)	320 (19.2%)	2,017 (20.0%)	2%	320 (19.2%)	321 (19.2%)	0%
2	363 (21.7%)	2,188 (21.7%)	0%	363 (21.7%)	363 (21.7%)	0%
3 (middle)	313 (18.7%)	2,050 (20.3%)	4%	313 (18.7%)	312 (18.7%)	0%
4	341 (20.4%)	1,921 (19.0%)	4%	341 (20.4%)	341 (20.4%)	0%
5 (highest)	334 (20.0%)	1,908 (18.9%)	3%	334 (20.0%)	334 (20.0%)	0%
Kidney Function						
eGFR, mL/min/1.73 m²,[d]	47.5 ± 10.0	44.6 ± 10.8	28%	47.5 ± 10.0	47.4 ± 3.9	1%
eGFR category						
<30 mL/min/1.73 m²	114 (6.8%)	1,133 (11.2%)	15%	114 (6.8%)	106 (6.4%)	2%
30-<45 mL/min/1.73 m²	450 (26.9%)	3,476 (34.5%)	17%	450 (26.9%)	470 (28.1%)	3%
<45-60 mL/min/1.73 m²	1,107 (66.2%)	5,475 (54.3%)	24%	1,107 (66.2%)	1,095 (65.5%)	1%
Digoxin Prescriber						
General practitioner	815 (48.8%)	4,886 (48.5%)	1%	815 (48.8%)	815 (48.8%)	0%
Cardiologist	525 (31.4%)	3,162 (31.4%)	0%	525 (31.4%)	521 (31.2%)	0%
Internist	145 (8.7%)	793 (7.9%)	3%	145 (8.7%)	148 (8.9%)	1%
Nephrologist	21 (1.3%)	69 (0.7%)	6%	21 (1.3%)	22 (1.3%)	0%
Other	47 (2.8%)	290 (2.9%)	1%	47 (2.8%)	46 (2.8%)	0%
Missing	118 (7.1%)	884 (8.8%)	6%	118 (7.1%)	118 (7.1%)	0%
Comorbidities[e]						
Atrial fibrillation or flutter	577 (34.5%)	4,413 (43.8%)	19%	577 (34.5%)	585 (35.0%)	1%
Congestive heart failure	838 (50.1%)	6,063 (60.1%)	20%	838 (50.1%)	837 (50.1%)	0%
COPD	591 (35.4%)	3,744 (37.1%)	4%	591 (35.4%)	592 (35.4%)	0%
Diabetes	448 (26.8%)	2,355 (23.4%)	8%	448 (26.8%)	449 (26.9%)	0%
Hypothyroidism	176 (10.5%)	1,195 (11.9%)	4%	176 (10.5%)	174 (10.4%)	0%
Hypertension	1,505 (90.1%)	9,130 (90.5%)	1%	1,505 (90.1%)	1,508 (90.2%)	0%
Modified CCI[f]	2.8 (1.5)	3.2 (1.7)	22%	2.8 (1.5)	2.8 (0.6)	0%

(Continued)

Table 1 (Cont'd). Baseline Characteristics of Older Adults With CKD Newly Prescribed Digoxin in Ontario, Canada (2008-2019)

	Unweighted Data (N = 11,755) by Digoxin Dose			Weighted Data (N = 3,342)[a] by Digoxin Dose		
	>0.125 mg/d (n = 1,671)	≤0.125 mg/d (n = 10,084)	Std Diff[b]	>0.125 mg/d (n = 1,671)	≤0.125 mg/d (n = 1,671)	Std Diff[b]
Healthcare Visits or Tests[g]						
Primary care visits	14.2 ± 13.0	16.4 ± 15.0	15%	14.2 ± 13.0	14.2 ± 5.1	0%
ED visits	1.1 ± 1.8	1.4 ± 1.9	13%	1.1 ± 1.8	1.1 ± 0.7	0%
Hospitalizations	0.4 ± 0.9	0.6 ± 1.0	18%	0.4 ± 0.9	0.4 ± 0.3	0%
Medication Use[h]						
Other antiarrhythmic	79 (4.7%)	591 (5.9%)	5%	79 (4.7%)	77(5%)	0%
ACEI	558 (33%)	3,550 (35%)	4%	558 (33%)	587 (35%)	4%
ARB	365 (21.8%)	2,061 (20.4%)	1%	365 (21.8%)	343 (20.5%)	3%
β-Blockers	961 (57.5%)	6,037 (59.9%)	5%	961 (57.5%)	982 (58.8%)	3%
Calcium channel blocker	582 (34.8%)	3,426 (34.0%)	2%	582 (34.8%)	571 (34.2%)	1%
Loop diuretics	781 (46.7%)	5,228 (51.8%)	10%	781 (46.7%)	773 (46.2%)	1%
Thiazide diuretics	207 (12.4%)	1,162 (11.5%)	3%	207 (12.4%)	211 (12.6%)	1%
Potassium-sparing diuretics	233 (13.9%)	1,454 (14.4%)	1%	233 (13.9%)	236 (14.1%)	1%
Spironolactone	195 (11.7%)	1,273 (12.6%)	3%	195 (11.7%)	201 (12.0%)	1%
Clarithromycin	41 (2.5%)	206 (2.0%)	3%	41 (2.5%)	41 (2.5%)	0%
Azithromycin	62 (3.7%)	370 (3.7%)	0%	62 (3.7%)	68 (4.0%)	2%
Nitrates	203 (12.1%)	1,514 (15.0%)	8%	203 (12.1%)	205 (12.2%)	0%
Laboratory Test Values[i]						
UACR available	466 (27.9%)	2,810 (27.9%)	0%	466 (27.9%)	465 (27.8%)	0%
Baseline UACR category						
Missing	1,205 (72.1%)	7,274 (72.1%)	0%	1,205 (72.1%)	1,207 (72.2%)	0%
<30 µg/mg	248 (14.8%)	1,409 (14.0%)	2%	248 (14.8%)	241 (14.4%)	1%
30-300 µg/mg	166 (9.9%)	1,093 (10.8%)	3%	166 (9.9%)	173 (10.4%)	2%
>300 µg/mg	52 (3.1%)	308 (3.1%)	0%	52 (3.1%)	50 (3.0%)	1%

Values given as count (percentage) or mean ± standard deviation. Unless otherwise specified, baseline characteristics were assessed on the date the patient filled the digoxin prescription (cohort entry date). Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCI, Charlson comorbitidy index; COPD, chronic obstructive pulmonary disease; ED, emergency department; eGFR, estimated glomerular filtration rate; Std Diff, standardized difference; UACR, urinary albumin-creatinine ratio.
[a]Weighted using inverse probability of treatment weighting based on propensity scores. The propensity score was estimated using multivariable logistic regression with 129 covariates chosen a priori. Patients in the reference group were weighted as [Propensity score/(1 − Propensity score)].[5-7] This method produces a weighted pseudo-sample of patients in the reference group with the same distribution of measured covariates as the exposure group.[5,6]
[b]The difference between the groups divided by the pooled SD; a value greater than 10% is interpreted as a meaningful difference.
[c]Income was categorized into fifths of average neighborhood income on the cohort entry date; missing data on this variable (0.2%) were recoded as the middle quintile.
[d]The most recent eGFR in the 365-day period before cohort entry date (including that date), calculated using the CKD-EPI creatinine equation. Race information was not available in data sources and all patients were assumed not to be African Canadian (who represented <5% of the Ontario population in 2006).
[e]Baseline comorbidities were assessed in the 5-year period before the cohort entry date.
[f]Presence of CKD is a variable in the CCI, which automatically results in all individuals receiving a minimum score of 2.
[g]In the 12-month period before the cohort entry date.
[h]In the 120-day period before the cohort entry date (the Ontario Drug Benefit program dispenses a maximum 100-day supply). Some of these medications may have been discontinued after the initiation of digoxin.
[i]Most recent laboratory test values in the 1-to-365–day period before cohort entry date.

Table 2. Risk of Digoxin Toxicity in Older Adults With CKD Starting a New Prescription for Digoxin at >0.125 Versus ≤0.125 mg/d

	Unweighted				Weighted[a]				
	No. Events (%) by Digoxin Dose		No. Events per 1,000 Person-Years by Digoxin Dose		No. Events (%) by Digoxin Dose		No. Events per 1,000 Person-Years by Digoxin Dose		
	>0.125 mg/d (n = 1,671)	≤0.125 mg/d (n = 10,084)	>0.125 mg/d	≤0.125 mg/d	>0.125 mg/d (n = 1,671)	≤0.125 mg/d (n = 1,671)	>0.125 mg/d	≤0.125 mg/d	wHR (95% CI)
Primary Outcome									
Hospital admission or ED visit with digoxin toxicity[b]	58 (3.5)	79 (0.8)	148.6	33.0	58 (3.5)	10 (0.6)	148.6	25.0	5.75 (4.00-8.27)
Secondary Outcomes									
All-cause hospitalization[b]	324 (19.4)	1,874 (18.6)	900.9	853.0	324 (19.4)	269 (16.1)	900.9	727.6	1.23 (1.11-1.37)
All-cause mortality	83 (5.0)	593 (5.9)	207.6	246.3	83 (5.0)	79 (4.7)	207.6	196.3	1.06 (0.84-1.33)
Additional Outcome									
Hospital admission with digoxin toxicity[b]	52 (3.1)	63 (0.6)	132.4	26.3	52 (3.1)	8 (0.5)	132.4	20.0	6.43 (4.28-9.66)

Reference group: digoxin dose ≤0.125 mg/d. Abbreviations: ED, emergency department; wHR, weighted hazard ratio.
[a]Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on indicators of baseline health.[5-7] The propensity score was estimated as described in the notes to Table 1. We obtained wHR and 95% CI using a Cox proportional hazards regression, and 95% CI were obtained using a bootstrap variance estimator.[8] The proportional hazards assumption was assessed using a time-dependent covariate test and was met for all outcomes. Death was treated as a censoring event.
[b]Death censored.

but not all-cause mortality (Table 2). The results were consistent when the primary outcome was restricted to a hospital admission with digoxin toxicity (Table 2). There was no statistical evidence of effect modification by baseline eGFR (Table S6). The results of a post hoc sensitivity analysis examining sepsis as a negative outcome are in Table S7.

Our study has limitations. First, while the Cockcroft-Gault equation, expressed in mL/min, is commonly used to guide drug dosing, this equation requires information on body weight, which was unavailable. However, the US Kidney Disease Education program indicates that GFR equations that express results in mL/min/1.73 m^2 or mL/min are both appropriate to adjust drug doses in most adults, and these measures tend to be similar in patients with advanced CKD (Item S2).[9] Second, we were unable to assess intake of foods that may influence digoxin absorption. Third, serum digoxin levels were not available, so we could not corroborate whether a hospital visit with toxicity was accompanied by elevated serum digoxin. Fourth, we were unable to study patients with milder toxicity who did not visit a hospital; therefore, the incidence of digoxin toxicity may be underestimated in this study.

In summary, we found that 46% of older adults who initiated digoxin had CKD, and 14% were prescribed a higher than recommended dose (>0.125 mg/d). The 90-day risk of toxicity was nearly 6 times higher in those who started digoxin at >0.125 versus ≤0.125 mg/d.

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Supplementary Material

Supplementary File (PDF)

Figure S1; Items S1-S2; Tables S1-S7.

Article Information

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