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ORIGINAL RESEARCH ARTICLE

Dosing of Direct Oral Anticoagulants in Patients with Moderate Chronic Kidney Disease in US Clinical Practice: Results from the Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF II)

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Background

- All DOACs have partial renal clearance and require dosage adjustments based on renal function or a combination of weight, renal function, age, or concomitant medications.
- Recent data suggested that “overdosing” of DOACs in patients with a renal indication for dose reduction was associated with a higher risk of major bleeding and that underdosing of DOACs was frequent and associated with reduced efficacy.
- Dose adjustment in patients with moderate chronic kidney disease (CKD) are recommended in the current US and European prescribing guidance, but how often this is done in clinical practice remains unclear.

AIM of the study

- to describe patient characteristics among patients with moderate CKD who were appropriately and inappropriately dosed;
- to describe the frequency of inappropriate and appropriate DOAC dosing in patients with AF and moderate CKD as determined by a creatinine clearance (CrCl) of 30–50 mL/min calculated using the Cockcroft–Gault formula;
- to describe clinical outcome event rates by two-level and three-level DOAC dosing.

Methods

- Data from the ORBIT-AF II (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II) registry.
- 1134 patients with CKD and a CrCl 30–50 mL/min.
- Patients with moderate CKD were stratified by DOAC dosing at baseline—appropriate or inappropriate based on the approved US FDA labeling for each agent and assessments of renal function, as well as weight, age, and chronic concomitant medications.

Results (I)

- Overall, 34.5% of patients with moderate CKD treated with DOACs were inappropriately dosed: in particular, 15% (N = 170/1134) were underdosed, 66% (743/1134) were appropriately dosed, and 20% (N = 221/1134) were overdosed according to FDA labeling.
- The median age was 82, 38% were male, and the median CHA2DS2VASC score was 4.
- There were no significant differences in comorbid medical conditions between patients with moderate CKD, irrespective of appropriate or inappropriate dosing of DOACs.

Results (II)

- Inappropriate versus appropriate dosing was associated with higher rates of all-cause mortality (7.64 vs. 7.05 events per 100 patient-years), major bleeding (5.55 vs. 3.65 events per 100 patient-years), and all-cause hospitalization (48.36 vs. 46.31 events per 100 patient-years).
- Underdosing was associated with higher rates of all-cause death, major adverse cardiovascular and neurologic events, cardiovascular death, new-onset heart failure, and cardiovascular hospitalizations.
- Overdosing was associated with major bleeding, all-cause hospitalizations, and bleeding hospitalizations.

Table 3 Event rates by direct oral anticoagulant dosing categories

Outcome	Overall ($N = 1134$)	DOAC dosage	
		Inappropriate ($N = 391$)	Appropriate ($N = 743$)
All-cause death	101; 7.26 (5.97–8.82)	37; 7.64 (5.53–10.54)	64; 7.05 (5.52–9.01)
MACNE	96; 7.10 (5.81–8.67)	29; 6.12 (4.25–8.80)	67; 7.63 (6.00–9.69)
CV death	40; 2.89 (2.12–3.94)	14; 2.92 (1.73–4.93)	26; 2.87 (1.96–4.22)
MI	21; 1.52 (0.99–2.33)	5; 1.04 (0.43–2.50)	16; 1.78 (1.09–2.91)
Stroke/TIA	21; 1.52 (0.99–2.33)	5; 1.04 (0.43–2.49)	16; 1.78 (1.09–2.91)
New-onset HF	25; 2.48 (1.67–3.67)	10; 2.79 (1.50–5.18)	15; 2.31 (1.39–3.82)
Major bleeding	58; 4.31 (3.33–5.57)	26; 5.55 (3.78–8.14)	32; 3.65 (2.58–5.15)
All-cause bleeding	483; 47.03 (43.00–51.43)	174; 48.36 (41.65–56.16)	309; 46.31 (41.42–51.78)
CV hospitalization	277; 23.28 (20.69–26.21)	97; 23.01 (18.84–28.11)	180; 23.43 (20.24–27.13)
Bleeding hospitalization	58; 4.32 (3.34–5.59)	25; 5.36 (3.62–7.93)	33; 3.77 (2.68–5.30)

Data are presented as number of events; rate per 100 patient-years (95% confidence interval)

CV cardiovascular, *DOAC* direct oral anticoagulant, *HF* heart failure, *MACNE* major adverse cardiovascular and neurologic events, *MI* myocardial infarction, *TIA* transient ischemic attack

Table 4 Event rates by three-level direct oral anticoagulant dosing categories

Outcome	Overall ($N = 1134$)	DOAC dosage		
		Underdosed ($N = 170$)	Appropriate ($N = 743$)	Overdosed ($N = 221$)
All-cause death	101; 7.26 (5.97–8.82)	20; 9.99 (6.45–15.49)	64; 7.05 (5.52–9.01)	17; 5.98 (3.72–9.62)
MACNE	96; 7.10 (5.81–8.67)	16; 8.25 (5.06–13.47)	67; 7.63 (6.00–9.69)	13; 4.64 (2.69–7.99)
CV death	40; 2.89 (2.12–3.94)	8; 4.04 (1.73–4.93)	26; 2.87 (1.96–4.22)	6; 2.13 (0.96–4.74)
MI	21; 1.52 (0.99–2.33)	2; 1.01 (0.25–4.02)	16; 1.78 (1.09–2.91)	3; 1.06 (0.34–3.29)
Stroke/TIA	21; 1.52 (0.99–2.33)	2; 1.00 (0.25–4.01)	16; 1.78 (1.09–2.91)	3; 1.06 (0.34–3.29)
New-onset HF	25; 2.48 (1.67–3.67)	6; 4.37 (1.96–9.72)	15; 2.31 (1.39–3.82)	4; 1.81 (0.68–4.82)
Major bleeding	58; 4.31 (3.33–5.57)	10; 5.12 (2.76–9.52)	32; 3.65 (2.58–5.15)	16; 5.85 (3.58–9.54)
All-cause bleeding	483; 47.03 (43.00–51.43)	72; 45.93 (36.40–57.95)	309; 46.31 (41.42–51.78)	102; 50.24 (41.34–61.05)
CV hospitalization	277; 23.28 (20.69–26.21)	40; 22.49 (16.50–30.67)	180; 23.43 (20.24–27.13)	57; 23.39 (18.00–30.40)
Bleeding hospitalization	58; 4.32 (3.34–5.59)	9; 4.36 (2.41–8.89)	33; 3.77 (2.68–5.30)	16; 5.88 (3.60–9.59)

Data are presented as number of events; rate per 100 patient-years (95% confidence interval)

CV cardiovascular, *DOAC* direct oral anticoagulant, *HF* heart failure, *MACNE* major adverse cardiovascular and neurologic events, *MI* myocardial infarction, *TIA* transient ischemic attack

Conclusions

- In routine clinical practice, the prescribing of DOACs in patients with AF and moderate CKD is often inconsistent with drug labeling, with up to one-third of patients being inappropriately dosed.
- While this analysis demonstrates no objective patient characteristics that appeared to drive inappropriate dosing in patients with moderate CKD, drug-specific factors and physician judgment may be central to inappropriate dosing.
- It is possible that decision support interventions in the electronic medical record and a greater awareness of guidelines reccommendations might be able to improve dosing practices.