

Intra-Individual Variability of Direct oral Anticoagulant Plasma Concentrations in Frail Nursing-Home Residents

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Abstract:

Direct oral anticoagulants are generally prescribed without routine laboratory monitoring, but exposure may be less predictable in frail nursing-home residents. This case series describes intra-individual variability in serial peak direct oral anticoagulant plasma concentrations in four frail nursing-home residents with atrial fibrillation, each treated with a different direct oral anticoagulant. Peak concentrations were measured 2 – 4 hours after dosing during routine nursing-home blood testing and interpreted against expected on-therapy ranges. Across 23 peak concentrations, 10 measurements (43%) were outside the expected range, with nine above and one below. Coefficients of variation ranged from 15.3% to 61.0%. Changes in estimated glomerular filtration rate or other clinical characteristics did not consistently explain the observed variability. These findings suggest that direct oral anticoagulant exposure in frail nursing-home residents may be clinically variable and support further prospective evaluation of selective concentration assessment and dose adjustment strategies.

Key words: direct oral anticoagulants; nursing-home residents; frailty; pharmacokinetics; therapeutic drug monitoring; atrial fibrillation; polypharmacy

Abbreviations

AF: atrial fibrillation; **CDL:** Central Diagnostic Laboratory; **CV:** coefficient of variation; **DOAC:** direct oral anticoagulant; **eGFR:** estimated glomerular filtration rate; **EPR:** electronic patient record; **INR:** International Normalized Ratio; **P-gp:** P-glycoprotein; **VKA:** vitamin K antagonist; **VTE:** venous thromboembolism.

Introduction

Direct oral anticoagulants (DOACs) have largely replaced vitamin K antagonists (VKAs) for thrombosis prevention in patients with atrial fibrillation (AF) and for the treatment and prevention of venous thromboembolism (VTE) [1-3]. Unlike VKAs, which require frequent International Normalized Ratio (INR) monitoring, DOACs have more predictable pharmacokinetic and pharmacodynamic profiles, allowing fixed dosing without routine laboratory testing [3].

However, frail older adults, particularly those living in nursing homes, are often underrepresented in pivotal clinical trials of DOACs [4-7]. This population is characterized by multimorbidity, polypharmacy (including the use of CYP3A4 and P-glycoprotein (P-gp) modulators), altered body composition and fluctuating renal function, all of which can influence drug exposure and may also affect DOAC plasma concentrations (hereafter, DOAC concentrations) [8-11]. As a result, DOAC pharmacokinetics may be less predictable in this group, raising concerns about the reliability of standardized dosing recommendations.

Intra-individual variability in DOAC concentrations remains poorly characterised, in part because routine laboratory monitoring is not recommended in current practice [3]. Available longitudinal studies in general cohorts suggest that intra-individual variability is often modest, but these data largely do not include frail nursing-home residents [12, 13]. In contrast, a study in acutely hospitalised frail older adults reported substantial intra-individual variability in DOAC concentrations [14], but

whether similar patterns occur in long-term institutional care remains uncertain. Accordingly, the aim of this case series was to describe intra-individual variability in serial peak DOAC concentrations in four frail nursing-home residents with atrial fibrillation, each treated with a different DOAC, and to explore whether observed variability could be explained by renal function, documented intercurrent clinical changes, or strong CYP3A4/P-gp inhibitors or inducers.

Methods

Within the DOAC-FRAIL study, nursing-home residents receiving a DOAC were prospectively enrolled. Serial DOAC concentrations were collected during routine care to characterise intra- and inter-individual variability. For this case series, a descriptive analysis was performed on serial peak DOAC concentrations from four residents, each using a different type of DOAC.

One resident for each DOAC type was selected a priori using predefined, outcome-independent rules. Within each DOAC type, residents with ≥ 2 peak DOAC concentrations on different dates were first identified to permit estimation of intra-individual variability. From these, the resident with the greatest number of repeated peak DOAC concentrations was selected. If counts were equal, tie-breakers were applied in the following order: (i) data completeness, defined as availability of dosing and sampling times for all DOAC concentrations and non-missing key clinical variables (serum creatinine, eGFR, intercurrent illness and medication changes) across the sampling interval. Thereafter, (ii) the case that reached its highest number of measurements earlier in calendar time.

All residents lived in nursing homes with standardised care, including fixed medication times, nurse-supervised administration and consistent daily routines. Blood was drawn two to four hours post-dose (peak DOAC concentrations) alongside routine tests. Blood sampling occurred as part of routine nursing-home blood testing or during evaluation of intercurrent illness or clinical instability. The clinical indication for each routine blood draw was extracted from the medical record where documented. Assays were performed in the Central Diagnostic Laboratory (CDL) of the Maastricht University Medical Centre+ (MUMC+) using validated, drug-specific methods [15]. Factor Xa inhibitors (apixaban, edoxaban and rivaroxaban) were measured using a chromogenic anti-factor Xa assay, and dabigatran concentrations were measured using diluted thrombin time (Hemoclot) [15].

Clinical data were extracted from the electronic patient record (EPR). To evaluate intra-individual variability, coefficients of variation (CV) for peak DOAC concentrations were calculated. In line with previously reported intra-individual CVs for DOAC concentrations, values around 15 – 35% are often observed in general cohorts [13, 14, 16]. In this context, CVs above this upper bound were interpreted as indicating pronounced intra-individual variability. Peak DOAC concentrations were interpreted against the expected on-therapy ranges for AF reported by Douxfils et al. [17], given that AF was the indication for DOAC therapy in all four cases.

The DOAC-FRAIL study was approved by the Medical Ethics Review Committee azM/UM (METC 2021-2945-A-2) and written informed consent was obtained from all participants or their legal representatives.

Case Series

Across 23 peak DOAC concentrations obtained under standardised nursing-home conditions, 10 out of 23 measurements (43.0%) fell outside the expected on-therapy range (9 above and 1 below). Figure 1 provides a longitudinal overview of serial peak DOAC concentrations and corresponding eGFR values for each case. In each panel, the DOAC concentration is plotted against the expected on-therapy peak range for atrial fibrillation, allowing visual assessment of whether repeated measurements remained within, above, or below the expected range over time.

Case 1 (apixaban)

A woman in her early 90s (58 kg) with AF received apixaban 5 mg twice daily. After the eighth measurement, the dose was reduced to 2.5 mg twice daily in accordance with dose-reduction criteria. In total, ten peak DOAC concentrations were collected between 9 July 2024 and 15 May 2025. Most routine blood draws were performed for periodic monitoring of renal function and volume status, including during recovery from a suspected lower respiratory tract infection/pneumonia and follow-up of fluid overload. Eight peak DOAC concentrations on the full dose ranged from 137 to 454 ng/mL and, after dose reduction, two peak DOAC concentrations were 152 and 103 ng/mL (Figure 1A). Measurements 1, 5 and 7 were above the expected on-therapy range, whereas the remaining measurements were within the expected on-therapy range. The intra-individual variability of peak DOAC concentrations was 47.1%, expressed as the CV. Across the sampling interval, eGFR ranged from 21 to 44 mL/min/1.73 m². The highest peak DOAC concentration occurred alongside the highest eGFR (measurement 1), while the lowest eGFR coincided with an in-range peak DOAC concentration (measurement 9).

Case 2 (edoxaban)

A 96-year-old woman (54 kg) with AF received edoxaban 30 mg once daily. Seven peak DOAC concentrations were obtained, ranging from 98 to 226 ng/mL (Figure 1B). Routine blood draws were performed for periodic monitoring. Out-of-range values were observed at measurements 4, 5 and 7, whereas all other measurements were within the expected on-therapy range. Peak DOAC concentrations showed a CV of 33.6%, reflecting intra-individual variability across measurements. During the measurement period, eGFR ranged from 22.9 to 38 mL/min/1.73 m². The highest peak DOAC concentration was recorded at measurement 7, when eGFR was also highest. In contrast, the lowest eGFR (measurement 3) was accompanied by a peak DOAC concentration within the expected on-therapy range. Over time, peak DOAC concentrations increased as eGFR gradually declined. When eGFR improved, peak DOAC concentrations initially moved towards the expected on-therapy range before increasing again.

Case 3 (rivaroxaban)

A 78-year-old man with AF received rivaroxaban 20 mg once daily. Routine blood draws were performed for periodic monitoring. Four peak DOAC concentrations were measured, ranging from 312 to 1011 ng/mL (Figure 1C). Measurement 1 was within the expected on-therapy range, whereas measurements 2, 3 and 4 were above the expected on-therapy range. Across the four measurements, the coefficient of variation (CV) for peak DOAC concentrations was 61.0%. During the measurement period, eGFR ranged from 71 to 82.6 mL/min/1.73 m². As shown in Figure 1C, measurement 1 had the highest eGFR and a peak DOAC concentration within the expected on-therapy range. Thereafter (measurements 2 – 4), peak DOAC concentrations increased while eGFR declined slightly and remained within a relatively narrow range.

Case 4 (dabigatran)

An 85-year-old woman with AF received dabigatran 110 mg twice daily. Blood testing was requested for renal function and electrolyte monitoring, including follow-up after initiation of spironolactone. Two peak DOAC concentrations were measured (87 ng/mL and 70 ng/mL) (Figure 1D). Measurement 1 was within the expected on-therapy range, whereas measurement 2 was below the expected on-therapy range. For peak DOAC concentrations, intra-individual variability was quantified by a CV of 15.3%. During the measurement period, eGFR ranged from 46.7 to 60 mL/min/1.73 m².

Across cases, approximately 12-15 oral medicines were used; no systemic strong CYP3A4 or P-gp inhibitors or inducers were documented.

Serial peak DOAC levels in four frail nursing-home residents

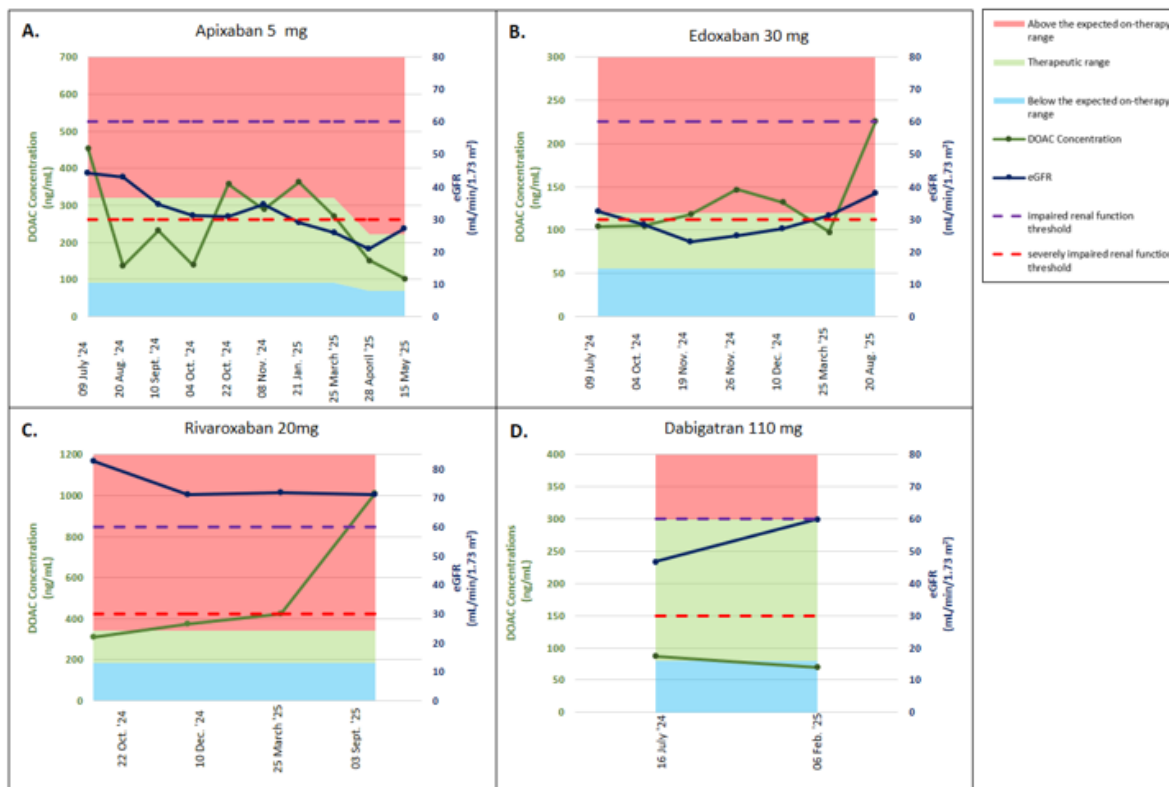


Figure 1: Serial peak DOAC levels over time in four frail nursing-home residents treated with apixaban, edoxaban, rivaroxaban or dabigatran for AF.

Each panel represents one case. Horizontal reference lines or shaded areas indicate the expected on-therapy peak range for AF for the corresponding DOAC and dose. Points outside the expected range indicate out-of-range DOAC levels. Across 23 peak DOAC levels, 10 were outside the expected on-therapy range, including nine above and one below. CVs ranged from 15.3% to 61.0%, indicating variable degrees of intra-individual fluctuation between cases.

Discussion

This case series provides a detailed characterisation of intra-individual variability in DOAC concentrations in a nursing-home population. Almost half (43%) of all DOAC concentrations measured were outside the expected on-therapy range. CVs ranged from 15.3% to 61.0%, with two cases above the upper end commonly reported in general outpatient cohorts (15%-35%) [13, 14, 16]. Together, these findings suggest that fixed DOAC dosing may not consistently result in expected on-therapy ranges in frail nursing-home residents. Longitudinal data on DOAC concentrations in nursing-home residents appear limited and available longitudinal studies in frail older adults have largely focused on hospitalised populations rather than long-term care [2, 14]. Even with standardised administration, peak DOAC concentrations shifted repeatedly between on-therapy and out-of-range values.

Renal function is a recognised determinant of DOAC exposure, as all DOACs undergo renal elimination to some extent, most prominently dabigatran and to a lesser extent factor Xa inhibitors [18, 19]. In older adults, renal function may fluctuate during intercurrent illness, dehydration or heart failure, potentially affecting DOAC concentrations [10, 18-20]. In the present case series, renal function was often reduced and varied within residents, but eGFR changes were not consistently paralleled by changes in peak DOAC concentrations. This suggests that renal function may have contributed to exposure, but was unlikely to be the sole factor associated with the observed intra-individual variability. Because samples were obtained during routine nursing-home blood

testing, mainly for monitoring renal function, electrolytes or volume status, and occasionally during intercurrent illness, these data reflect real-world practice. However, the heterogeneous indications and opportunistic timing of sampling limit firm conclusions about the extent to which renal function explained out-of-range concentrations.

Polypharmacy is highly prevalent in nursing-home residents [21]. Concomitant medicines may influence DOAC pharmacokinetics through CYP3A4 enzymes and P-gp pathways [10]. Across the four cases, polypharmacy was substantial (approximately 12-15 oral medicines per case), yet no systemic strong CYP3A4 or P-gp inhibitors or inducers were documented. Variability in peak DOAC concentrations nevertheless persisted, suggesting that contributors beyond recognised strong drug-drug interactions may be important in this setting.

Besides renal function and drug-drug interactions, frailty and liver disease may also influence DOAC levels in older adults. Eidam et al. reported higher dose-normalised apixaban trough levels in older adults with performance-based frailty [22]. Furthermore, liver disease remains a clinically relevant context for DOAC use. Mostly, because hepatic clearance is important in drug metabolism. Nevertheless, evidence in moderate-to-severe liver disease is limited [23]. In the present case series, liver function was not systematically recorded. Therefore, hepatic dysfunction could not be assessed as a potential contributor to the observed variability.

Age-related physiological change may be one explanation for the variability observed in these cases. In older adults, reductions in lean mass and total body water, increases in fat mass and age-related changes in gastrointestinal function and hepatic clearance can alter DOAC distribution and handling [10, 20]. Across the four residents, peak DOAC concentrations at a fixed prescribed dose shifted over time between within expected on-therapy range and outside the expected on-therapy range measurements despite standardised administration. This intra-individual variation may reflect age associated and frailty associated changes in

absorption, distribution and clearance that can vary over time in nursing-home residents. Episodes of acute illness may further contribute, as clinical instability can transiently alter pharmacokinetics and has previously coincided with unexpected DOAC concentration shifts in the DOAC-FRAIL pilot study [2].

Strengths of this case series are the availability of serial peak DOAC concentrations in nursing-home residents under standardised administration and measurement with validated drug-specific assays, a setting for which longitudinal data are scarce. Limitations are the small sample size and the use of peak-only measurements, which precludes assessment of trough exposure and overall exposure. Because samples were obtained as part of routine nursing-home monitoring and sometimes during intercurrent illness, the measurements reflect real-world practice. This context enhances clinical relevance but limits inference regarding prevalence of out-of-range concentrations and their direct association with bleeding or thrombotic events.

Recent evidence indicates that DOAC concentrations below and above the expected on-therapy range are associated with increased risks of thromboembolic events and bleeding, respectively [24]. In this context, intra-individual variability in frail nursing-home residents is clinically relevant because it may increase the likelihood of excursions into ranges associated with harm.

Conclusion

This case series suggests that peak DOAC concentrations may vary substantially over time in frail nursing-home residents, even under standardised medication administration. The observed variability was not consistently explained by renal function or documented systemic strong CYP3A4/P-gp inhibitors or inducers. Prospective studies in frail older adults, including nursing-home residents, are needed to determine whether selective concentration assessment and dose adjustment can improve the safety and precision of DOAC therapy in this population.

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Conflict of Interest Statement

Daan Teerds: No conflicts of interest to disclose.

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Analysis and interpretation of data: Daan Teerds, Irme S. Franssen, Dave Hellenbrand, Yvonne Henskens, Fabienne J.H. Magdelijns.

Drafting of the manuscript: Daan Teerds.

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Supervision: Fabienne J.H. Magdelijns.

All authors approved the final version and agree to be accountable for all aspects of the work.

Data Availability Statement

The data underlying this article are not publicly available because they contain individual-level clinical information from frail nursing-home residents. De-identified data may be made available by the corresponding author upon reasonable request and subject to applicable privacy and ethical restrictions.

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