Anticoagulation therapy and selection: impact of weight

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Weight issues

• Worldwide obesity has nearly tripled since 1975

• Older adults – living longer – low body weight

• Drug dosing issues arise
Clearance and Volume of Distribution

\[ t_{1/2} = \frac{0.693 \times Vd}{Cl} \]
What can we learn from traditional anticoagulants?

- Warfarin
- UFH
- LMWH
PHARMAEOEPIDEMIOLOGY

Trends in the prescription of novel oral anticoagulants in UK primary care

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Keywords atrial fibrillation, oral anticoagulants, pharmacoepidemiology, prescription patterns, venous thromboembolism
Figure 1
Rates of new use of oral anticoagulants (OAC) in the UK Clinical Practice Research Datalink, from 2009 to 2015. NOAC, novel oral anticoagulants; VKA, vitamin K antagonists

Figure 2
Rates of new use of individual novel oral anticoagulants (NOAC) in the UK Clinical Practice Research Datalink, from 2009 to 2015
Real-world vs. trial patients

- RCTs vary in their inclusiveness due to:
  - Underrepresentation e.g. ethnic minority groups
  - Application of exacting inclusion/exclusion criteria
- The study population becomes a small subset of the target population, which raises concerns as to whether it is valid to apply the results of the trial to the wider target population

Subjects

- Patient non-participation
- Not invited to participate (administrative oversight or practitioner preference)
- Centre/doctor non-participation (not invited/declined)
CLINICAL COMMUNICATION TO THE EDITOR

Monitoring of Apixaban in a Super Obese Patient

To the Editor:

Direct oral anticoagulants (DOACs) are considered advantageous compared to vitamin K antagonists in eligible atrial fibrillation patients. Increased body weight is associated with 30% lower exposure to standard doses of DOACs, raising concerns about adequate dosing in obese patients. A mass spectrometric method observed apixaban concentrations were initially found at the lower margin of the expected on-therapy range but increased over time, while body weight continuously decreased (Table).

A 2-compartment pharmacokinetic model (MwPharm++, Mediware, Prague, Czech Republic) was developed based on concentration data in healthy obese volunteers (≥120 kg). Pharmacokinetic parameters were fitted to observed apixaban plasma concentrations. The derived apixaban elimination half-life was 9.8 hours and thus was comparable to that reported by Upreti et al. in the high body weight group.

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https://doi.org/10.1007/s11239-019-01857-2

Effects of body mass index on the safety and effectiveness of direct oral anticoagulants: a retrospective review

Jared Netley1, Kris Howard1, William Wilson2

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Abstract

Background The International Society on Thrombosis and Haemostasis recommends avoiding the use of direct oral anticoagulants (DOACs) in patients with a body mass index (BMI) greater than 40 kg/m² or weight greater than 120 kg.

Hypothesis Higher BMI is associated with altered pharmacokinetics which may affect the safety and effectiveness for DOACs.

https://doi.org/10.1007/s11239-019-01857-2
PK summary of DOACs

Heidbuchel H et al, Europace 2013;15:625
What does the SSC from ISTH say?

• Appropriate standard dosing of the DOACs in patients with a BMI less than or equal to 40 kg m$^2$ and weight less than or equal to 120 kg for VTE treatment, VTE prevention, and prevention of ischemic stroke and systemic arterial embolism in non-valvular AF.

• DOACs should not be used in patients with a BMI of > 40 kg m$^2$ or a weight of > 120 kg, because there are limited clinical data available for patients at the extreme of weight, and the available PK/PD evidence suggests that decreased drug exposures, reduced peak concentrations and shorter half-lives occur with increasing weight, which raises concerns about underdosing in the population at the extreme of weight.

• If DOACs are used in a patient with a BMI of > 40 kg m$^2$ or a weight of > 120 kg, we suggest checking a drug-specific peak and trough level (anti-FXa for apixaban, edoxaban, and rivaroxaban; ecarin time or dilute thrombin time with appropriate calibrators for dabigatran; or mass spectrometry drug level for any of the DOACs). If the level falls within the expected range, continuation of the DOAC seems reasonable. However, if the drug-specific level is found to be below the expected range, we suggest changing to a VKA rather than adjusting the dose of the DOAC.
Rivaroxaban population PK model from King’s – Barsam Model

The impact of body weight on rivaroxaban pharmacokinetics

Sarah J. Barsam MA¹ | Jignesh P. Patel PhD¹,² | Lara N. Roberts MD¹ | Venu Kavarthapu MBBS³ | Raj K. Patel MD¹ | Bruce Green DClinPharm⁴ | Roopen Arya PhD¹
What is Population PK modelling?

- Andrassy and Eschenfelder, 1996
Objective

To develop a pharmacokinetic model for rivaroxaban, based on real-world patients, specifically focusing on the impact of patients’ body weight on rivaroxaban pharmacokinetics.

Method

• Subjects had up to 3 rivaroxaban concentrations measured during a single dosing period (trough, 1 and 3 hours post dose).

• Population pharmacokinetic analyses was conducted to develop a rivaroxaban model, which was subsequently evaluated.
Sampling

• Up to three measurements:
  – 1 hour post dose
  – 3 hours post dose
  – 24 hours post dose
Rivaroxaban – Barsam Model

**TABLE 1** Demographic information on the patients recruited

<table>
<thead>
<tr>
<th>Patient demographics (n = 101)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean range)</td>
<td>52 (20-86)</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>58/42</td>
</tr>
<tr>
<td>Body weight, kg (mean ± SD)</td>
<td>88.0 (23.4)</td>
</tr>
<tr>
<td>&lt;50 kg (%)</td>
<td>2</td>
</tr>
<tr>
<td>50-100 kg (%)</td>
<td>81</td>
</tr>
<tr>
<td>&gt;100 kg (%)</td>
<td>17</td>
</tr>
<tr>
<td>Lean body weight, kg (mean ± SD)</td>
<td>57.0 (11.3)</td>
</tr>
<tr>
<td>BMI, kg/m² (%)</td>
<td></td>
</tr>
<tr>
<td>16-18.49</td>
<td>1</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>27</td>
</tr>
<tr>
<td>25-29.9</td>
<td>32</td>
</tr>
<tr>
<td>30-34.9</td>
<td>21</td>
</tr>
<tr>
<td>35-39.9</td>
<td>14</td>
</tr>
<tr>
<td>≥40</td>
<td>6</td>
</tr>
<tr>
<td>Creatinine clearance, (%)</td>
<td></td>
</tr>
<tr>
<td>&gt;80 mL/min</td>
<td>67</td>
</tr>
<tr>
<td>50-79 mL/min</td>
<td>25</td>
</tr>
<tr>
<td>30-49 mL/min</td>
<td>7.8</td>
</tr>
<tr>
<td>&lt;30 mL/min</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Breadth of rivaroxaban levels obtained with respect to weight
Rivaroxaban – Barsam Model

Weight on its own is not a good predictor of rivaroxaban clearance

Renal function computed by the Cockcroft–Gault equation was found to be a significant covariant explaining rivaroxaban clearance

\[ CL = \text{POPCL} \times \left(\frac{\text{CrCL}}{79}\right)^{0.434} \]

Further studies with larger numbers in the subgroups of interest are required to confirm findings
Victoria Speed’s model - ongoing

913 individual patients, 1108 PK samples

Data collected from Anticoagulation clinics at King’s Denmark Hill and The Princess Royal University Hospital

Rivaroxaban levels and laboratory data taken during routine practice and remaining covariate data collected from case note review
### Victoria Speed’s Model

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Patients (n = 913)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEX (%)</td>
<td>Male: 522 (57.2), Female: 391 (42.8)</td>
</tr>
<tr>
<td>AGE (mean (SD))</td>
<td>67.03 (15.00)</td>
</tr>
<tr>
<td>WT (mean (SD))</td>
<td>85.75 (23.07)</td>
</tr>
<tr>
<td>WTCat (%)</td>
<td>&lt;50kg: 30 (3.3), 50kg-100kg: 668 (73.2), 100kg-150kg: 209 (22.9), &gt;150kg: 6 (0.7)</td>
</tr>
<tr>
<td>LBW (mean (SD))</td>
<td>55.80 (13.10)</td>
</tr>
<tr>
<td>BMI (mean (SD))</td>
<td>29.67 (7.01)</td>
</tr>
<tr>
<td>BMICat (%)</td>
<td>Underweight: 19 (2.1), Healthy Weight: 231 (25.3), Overweight: 282 (30.9), Obese: 185 (20.3), Severly Obese: 122 (13.4), Morbidly Obese: 74 (8.1)</td>
</tr>
<tr>
<td>CABW (mean (SD))</td>
<td>91.47 (43.81)</td>
</tr>
<tr>
<td>CLBW (mean (SD))</td>
<td>59.51 (26.71)</td>
</tr>
<tr>
<td>DIAG (%)</td>
<td>Atrial Fibrillation: 629 (68.9), Other: 17 (1.9), VTE: 267 (29.2)</td>
</tr>
<tr>
<td>HF (%)</td>
<td>Heart failure: 142 (15.6), No heart failure: 771 (84.4)</td>
</tr>
</tbody>
</table>

- **Age range between 19 and 96, 191 >80 years old**
- **Nearly 1/4 of patients weigh in excess of 100kg, 74 patients with a BMI over 40, 69 patients with a weight over 125kg**
Victoria Speed’s Model
Victoria Speed’s model – early findings

• Analysis still ongoing

• Early analysis confirms findings from Sarah’s work

• CrCl seems to be the covariate that describes exposure to rivaroxaban
Victoria Speed’s model – early findings

PK Parameter Estimates according to BMI (CLEARANCE)

- Clearance (L/H)
- BMI category
  - Underweight
  - Overweight
  - Obese
  - Morbidly Obese

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Victoria Speed’s model – early findings

PK Parameter Estimates according to CABW (CLEARANCE)

CrCL category (using actual bodyweight)
What does this mean for the other DOACs?

Heidbuchel H et al, Europace 2013;15:625
What target to aim for?

International Council for Standardization in Haematology (ICSH) Recommendations for Laboratory Measurement of Direct Oral Anticoagulants

Robert C. Gosselin¹  Dorothy M. Adcock²  Shannon M. Bates³  Jonathan Douxfils⁴  Emmanuel J. Favaloro⁵  Isabelle Gouin-Thibault⁶  Cecilia Guillermo⁷  Yohko Kawai⁸  Edelgard Lindhoff-Last⁹  Steve Kitchen¹⁰
**What target to aim for?**

Table 2: Expected peak and trough DOAC concentrations in patients treated for stroke prevention in NVAF or treatment of PE/VTE.

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Stroke prevention in NVAF</td>
<td>Stroke prevention in NVAF</td>
<td>Stroke prevention in NVAF</td>
<td>Stroke prevention in NVAF</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>150 mg bid</td>
<td>150 mg bid</td>
<td>20 mg qd</td>
<td>20 mg qd</td>
</tr>
<tr>
<td><strong>Peak concentration, ng/mL</strong></td>
<td>175&lt;sup&gt;a&lt;/sup&gt; (117–275)</td>
<td>175&lt;sup&gt;a&lt;/sup&gt; (117–275)</td>
<td>249&lt;sup&gt;b&lt;/sup&gt; (184–343)</td>
<td>270&lt;sup&gt;b&lt;/sup&gt; (189–419)</td>
</tr>
<tr>
<td><strong>Trough concentration, ng/mL</strong></td>
<td>91&lt;sup&gt;a&lt;/sup&gt; (61–143)</td>
<td>60&lt;sup&gt;a&lt;/sup&gt; (39–95)</td>
<td>44&lt;sup&gt;b&lt;/sup&gt; (12–137)</td>
<td>26&lt;sup&gt;b&lt;/sup&gt; (6–87)</td>
</tr>
</tbody>
</table>

Abbreviations: bid, twice daily; IQR, interquartile range; NVAF, non-valvular atrial fibrillation; PE, pulmonary embolism; qd, once daily; VTE, venous thromboembolism.

Notes: Other approved indications for DOACs include secondary prevention of PE/VTE, and post hip and knee replacement, which may have alternative dosing strategies. Additionally, changes in doses may occur after initiation phase of DOAC treatment. Consultation of regional DOAC labeling information is required before interpreting or using these peak and trough DOAC concentration data.

<sup>a</sup>Mean (25th–75th percentile).
<sup>b</sup>Mean (5th–95th percentile).
<sup>c</sup>Median (5th–95th percentile).
<sup>d</sup>Median (1.5 x IQR).
<sup>e</sup>Median (IQR).
Final thoughts

• The weight story is not as clear cut as one might expect

• For rivaroxaban, weight on its own is not a good predictor of clearance

• Need to consider each DOAC individually – same may not be true for other agents

• When in doubt, measure activity as per ISTH
Factor Xa inhibition

Monitoring of Apixaban in a Super Obese Patient

To the Editor:

Direct oral anticoagulants (DOACs) are considered advantageous compared to vitamin K antagonists in eligible atrial fibrillation patients.\textsuperscript{1} Increased body weight is associated with 30\% lower exposure to standard doses of DOACs, raising concerns about adequate dosing in obese patients.\textsuperscript{2,3} Mass spectrometric method.\textsuperscript{4} Observed apixaban concentrations were initially found at the lower margin of the expected on-therapy range but increased over time, while body weight continuously decreased (Table).

A 2-compartment pharmacokinetic model (MwPharm++, Mediware, Prague, Czech Republic) was developed based on concentration data in healthy obese volunteers (\textgtr= 120 kg).\textsuperscript{5} Pharmacokinetic parameters were fitted to observed apixaban plasma concentrations. The derived apixaban elimination half-life was 9.8 hours and thus was comparable to that reported by Upreti et al.\textsuperscript{5} in the high body weight
Relationship between body mass index and outcomes in patients with atrial fibrillation treated with edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial

Giuseppe Boriani\textsuperscript{1}, Christian T. Ruff\textsuperscript{2}, Julia F. Kuder\textsuperscript{2}, Minggao Shi\textsuperscript{3}, Hans J. Lanz\textsuperscript{4}, Howard Rutman\textsuperscript{3}, Michele F. Mercuri\textsuperscript{3}, Elliott M. Antman\textsuperscript{2}, Eugene Braunwald\textsuperscript{2}, and Robert P. Giugliano\textsuperscript{2*}

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Effects of body mass index on the safety and effectiveness of direct oral anticoagulants: a retrospective review

Jared Netley1 · Kris Howard1 · William Wilson2

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Abstract

Background The International Society on Thrombosis and Haemostasis recommends avoiding the use of direct oral anticoagulants (DOACs) in patients with a body mass index (BMI) greater than 40 kg/m² or weight greater than 120 kg.

Hypothesis Higher BMI is associated with altered pharmacokinetics which may affect the safety and effectiveness for DOACs.

Methods Data was collected on 2450 patients taking DOACs in a tertiary institution. Medications, lifestyle factors,
<table>
<thead>
<tr>
<th></th>
<th>Apixaban (n = 181)</th>
<th>Warfarin (n = 209)</th>
<th>Composite (n = 390)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age at prescription date (yrs)</strong></td>
<td>61.7</td>
<td>61.7</td>
<td>61.7</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>45.8</td>
<td>46.6</td>
<td>46.2</td>
</tr>
<tr>
<td>≥ 50</td>
<td>37 (20.4%)</td>
<td>46 (22.0%)</td>
<td>83 (21.3%)</td>
</tr>
<tr>
<td><strong>Male, n(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, n(%)</td>
<td>46 (25.4%)</td>
<td>48 (23.5%)</td>
<td>94 (24.1%)</td>
</tr>
<tr>
<td>Black, n(%)</td>
<td>74 (40.9%)</td>
<td>92 (44.0%)</td>
<td>166 (42.6%)</td>
</tr>
<tr>
<td>Other, n(%)</td>
<td>61 (33.7%)</td>
<td>69 (33.0%)</td>
<td>130 (33.3%)</td>
</tr>
<tr>
<td><strong>AC Indication</strong>¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF, n(%)</td>
<td>124 (68.5%)</td>
<td>124 (59.3%)</td>
<td>248 (63.6%)</td>
</tr>
<tr>
<td>VTE, n(%)</td>
<td>58 (32.0%)</td>
<td>88 (42.1%)</td>
<td>146 (37.4%)</td>
</tr>
<tr>
<td><strong>Stroke Rate, n(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF, n(%)</td>
<td>1 (0.8%)</td>
<td>3 (2.4%)</td>
<td>4 (1.6%)</td>
</tr>
<tr>
<td>VTE, n(%)</td>
<td>1 (1.7%)</td>
<td>1 (1.1%)</td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td><strong>Recurrent VTE, n(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All, n(%)</td>
<td>15 (8.3%)</td>
<td>25 (12%)</td>
<td>40 (10.3%)</td>
</tr>
<tr>
<td>Major *, n(%)</td>
<td>1 (0.6%)</td>
<td>9 (4.3%)</td>
<td>10 (2.6%)</td>
</tr>
</tbody>
</table>

* *p*-value < 0.05.

¹AC indication sums to > 100% due to patients with dual indications

Yun Choi et al. Blood 2017;130:1105