We were interested to read the report by Chin\textsuperscript{1} recently published in this journal, suggesting that some patients may benefit from dose adjustment of non-vitamin K antagonist oral anticoagulants (NOACs), otherwise referred to as direct oral anticoagulants (DOACs). We would like to report a small case series that provides evidence for selective dose adjustment and/or measurement of NOACs, in particular dabigatran.

The World Health Organization (WHO) Global Database of Individual Case Safety Reports ("VigiBase") holds reports of suspected adverse drug reactions collected worldwide through the WHO Program for International Drug Monitoring.\textsuperscript{2} A previous investigation of reports of thromboembolic events associated with dabigatran in VigiBase\textsuperscript{3} included a literature search, which identified four published case reports of dabigatran plasma concentrations below the expected "within therapy range" (representing the generally reported range of values identified in patients on such therapy in clinical trials). VigiBase was therefore searched for similar reports of low plasma concentrations. It is acknowledged, however, that the information provided in VigiBase is heterogeneous (i.e., it originates from multiple sources [different countries and types of reporters] and the amount of information given, as well as the likelihood that the medicine caused the adverse reaction, may vary from case to case). Two of the published reports and 12 additional reports of this unexpected effect were identified, originating from five countries.

While specific target therapeutic ranges for dabigatran plasma concentrations have not been validated, "within therapy" ranges identifying values that are typically seen in treated patients have been described. Thus, "expected" trough and peak dabigatran plasma levels after intake of approved dosages for atrial fibrillation are around 61 to 143 and 117 to 275 ng/mL, respectively, for 150 mg twice a day and 43 to 102 and 85 to 200 ng/mL, respectively, for 110 mg twice a day.\textsuperscript{4} Chin calculated an optimal trough range of 30 to 130 ng/mL after constructing a combined risk versus trough concentration model for a typical patient based on data from the RE-LY (Randomized Evaluation of Long-term anticoagulant therapy) trial.\textsuperscript{1}

\textbf{Table 1} shows the details of the four published case reports. Patients 1 and 2 had embolic stroke while taking dabigatran.\textsuperscript{5,6} Peak and trough plasma concentrations were measured thereafter using Hemoclot, a commercially available dilute thrombin time (dTT) assay, following witnessed intake. Patients 3 and 4 did not have thromboembolic events.\textsuperscript{7,8} Patient 3 had a lower than expected activated partial thromboplastin time (aPTT) shortly after starting dabigatran, so that peak concentrations at two dose levels were quantified, using Hemoclot, following confirmed intake after 31 days of treatment. Patient 4, who had undergone gastric bypass surgery, had trough concentrations quantified because another patient with gastric bypass developed a cardioembolic stroke on dabigatran and was found to have lower than expected aPTT values. The doses of dabigatran administered were appropriate for all four patients, especially after the dose increase in patient 3 who had normal
Published reports for dabigatran and below expected within therapy (or unexpectedly low) plasma concentrations

Table 1  Published reports for dabigatran and below expected within therapy (or unexpectedly low) plasma concentrations

<table>
<thead>
<tr>
<th>Patient number/Publication</th>
<th>Sex/Age</th>
<th>Dose (mg)</th>
<th>Duration of dabigatran use</th>
<th>Time to dabigatran measurement</th>
<th>Indication</th>
<th>Concomitant drugs</th>
<th>Thrombotic, ischemic or embolic events</th>
<th>Dabigatran concentration method</th>
<th>Dabigatran concentration</th>
<th>aPTT</th>
<th>Comments and other potential contributors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Breuer et al, 2013</td>
<td>M/48</td>
<td>150 mg b.i.d</td>
<td>~31 d</td>
<td>28 and 31 d</td>
<td>AF paroxysmal</td>
<td>Omeprazole</td>
<td>Cerebral infarction, embolic</td>
<td>Hemoclot</td>
<td>Trough not detectable day of stroke, 10 h post dose 48% advanced intake for 3 d, peak 50 ng/mL at 4 h</td>
<td>Not reported</td>
<td>Weight 153 kg, BMI 44.4, creatinine clearance 163 mL/min</td>
</tr>
<tr>
<td>2. Douvy et al, 2014</td>
<td>F/81</td>
<td>110 mg b.i.d</td>
<td>Not stated</td>
<td>3 mo</td>
<td>AF</td>
<td>Pantoprazole, Lercanidipine, Gadimine, Metoprolol, Tramiparone, HydroChlorothiazide, Furosemide, Diclofenac mononitrate</td>
<td>Dysarthria, facial palsy with AF, presumed diagnosis of cardioembolic stroke of cerebral artery</td>
<td>Hemoclot</td>
<td>Peak and trough concentrations, 2 and 12 h after witnessed administration, 31 and 21 ng/mL</td>
<td>Normal at dabigatran trough</td>
<td>Short-gut syndrome following surgery for embolic mesenteric ischemia, SNP affecting liver carboxylesterase and P-glycoprotein, GFR 37-45 mL/min</td>
</tr>
<tr>
<td>3. Sargento-Freitas et al, 2014</td>
<td>F/70</td>
<td>110 mg b.i.d</td>
<td>31 d</td>
<td>31 d</td>
<td>AF, acute ischemic stroke, occlusion terminal segment right internal carotid artery</td>
<td>Lorazeepam, Mitrazapine, Furosemide, Fluoxetine, Simvastatin, Bisoprolol, Ramipril, Digoxin, Omeprazole</td>
<td>None</td>
<td>Hemoclot</td>
<td>Peak concentrations after confirmed intake (ng/mL): 1) 40.6 at 31 d, 110 mg b.i.d, 2) 41.9 at 5 d, 150 mg b.i.d, 3) 45.0 at 7 d, 150 mg b.i.d, interacting medicines stopped</td>
<td>Normal 7 h after dose in hospital, and at each point when dabigatran concentrations measured</td>
<td>Creatinine clearance 65 mL/min</td>
</tr>
<tr>
<td>4. Lee et al, 2013</td>
<td>F/67</td>
<td>Dose not stated</td>
<td>9 mo</td>
<td>9 mo</td>
<td>AF</td>
<td>Pantoprazole</td>
<td>None</td>
<td>Hemoclot</td>
<td>Trough concentration 21 ng/mL</td>
<td>Not measured</td>
<td>Roux-en-Y gastric bypass</td>
</tr>
</tbody>
</table>

Abbreviations: aPTT, activated partial thromboplastin time; AF, atrial fibrillation; b.i.d., twice a day; BMI, body mass index; GFR, glomerular filtration rate; SNP, single nucleotide polymorphism.

Overall dabigatran concentrations (Table 1) were well below or near the expected within therapy range or were too low to be quantified. Eight of the patients had cerebral or venous thromboembolic events, occurring between 3 and 270 days after starting dabigatran. Dabigatran concentrations were below the within therapy range or were too low to be quantified in 12 of the patients. The method used was not stated in the remaining four. Two of these reported a concentration too low to be detectable. Unlike previous studies, the patients had cerebral or venous thromboembolic events. In the two cases, the patients were taking dabigatran for 21 or 22 days. One had a glomerular filtration rate of 37 to 43 mL/min and one had a glomerular filtration rate of 40.6 at 31 d, 110 mg b.i.d, 2) 41.9 at 5 d, 150 mg b.i.d, 3) 45.0 at 7 d, 150 mg b.i.d, interacting medicines stopped. The method used was not stated in the remaining four. Two of these reported a concentration too low to be detectable.
Pantoprazole and atorvastatin have each been shown to reduce dabigatran exposure by approximately 20%. However, the high proportion of proton pump inhibitor (PPI) users in this case series may reflect background use. Dabigatran etexilate has low oral bioavailability. Genetic variants decreasing conversion of dabigatran etexilate to active dabigatran by liver carboxylesterase and influencing intestinal p-glycoprotein activity may account for a 15% decrease in

### Table 2 Characteristics of patients in 16 published and VigiBase reports of below expected within therapy dabigatran plasma concentrations

<table>
<thead>
<tr>
<th>Characteristics (no. of patients with information)</th>
<th>Number or range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (15)</td>
<td>Males/females</td>
</tr>
<tr>
<td>Age (y) (12)</td>
<td>Median (range)</td>
</tr>
<tr>
<td>Indication (12)</td>
<td>AF/flutter</td>
</tr>
<tr>
<td></td>
<td>AF and DVT</td>
</tr>
<tr>
<td></td>
<td>DVT/PE</td>
</tr>
<tr>
<td>Daily dose (12)</td>
<td>150 mg bd/110 mg b.i.d</td>
</tr>
<tr>
<td>Time from dabigatran start to measurement (d) (10)</td>
<td>Median (range)</td>
</tr>
<tr>
<td>Thrombotic/embolic/ischemic events (8)</td>
<td>CVA (one with ventricular clot)</td>
</tr>
<tr>
<td></td>
<td>TIA</td>
</tr>
<tr>
<td></td>
<td>DVT/PE</td>
</tr>
<tr>
<td>Compliance recorded (6)</td>
<td>Witnessed intakea</td>
</tr>
</tbody>
</table>

**Potential contributors to low plasma concentrations**

- Weight (4)  
  - BMI obese (44.7, 35.6) | 2 |
  - Obese                   | 1 |
  - Weight > 100 kg         | 1 |
- Major GI surgery (3)     
  - Short-gut syndrome      | 1 |
  - Gastric bypass surgery  | 2 |
- Potentially interacting medicines (8) 
  - PPIs                    | 7 |
  - Atorvastatin            | 1 |
- Patients with multiple potential contributors to low dabigatran concentrations (5) 
  - Short-gut syndrome, genotypes, PPI | 1 |
  - BMI 44.7, high creatinine clearance, PPI | 1 |
  - Atorvastatin, PPI       | 1 |
  - Weight 110 kg, PPI      | 1 |
  - Gastric bypass, PPI     | 1 |
- No. with no recorded potential contributors to low dabigatran concentrations | 6 |

**Laboratory measurements**

- Lower than expected coagulation parameters (6)  
  - aPTT | 6 |
- Dabigatran measurement method (12) 
  - dTT assays (Hemoclot 9) | 12 |
- Dabigatran plasma concentrations (ng/mL) (16) 
  - Peak and trough (5)  
    - Trough | 0–21 |
    - Peak    | 0–50  |
  - Peak alone (1) | 40.6 and 41.9 |
  - Trough alone (3) | 0–21 |
  - Peak or trough not stated (7) | 0–43 |

Abbreviations: aPTT, activated partial thromboplastin time; BMI, body mass index; CVA, cerebrovascular accident; dTT, dilute thrombin time; DVT, deep vein thrombosis; GI, gastrointestinal; PPI, proton pump inhibitor; PE, pulmonary embolism; TIA, transient ischemic attack.

aConcentrations measured at 2 and 12 hours post dose (four patients); after 3 days concentration measured 2 hourly for peak level (one patient); peak levels at 110 mg bd, 31 days and 150 mg bd, 5 days (one patient).
dabigatran bioavailability (►Table 1, patient 2). Decrease in gastric acidity due to the use of PPIs and major upper gastrointestinal disorders may also contribute to reduced absorption. Body weight greater than 100 kg influenced trough levels in the RE-LY study. Because dabigatran is predominantly excreted by the kidneys, glomerular hyperfiltration associated with severe obesity may contribute to low plasma concentrations.

Though it is appropriate to tailor dose to patient characteristics where possible, our series of case reports supports the need for trials in which dabigatran concentrations are measured at the time of thrombotic events, ideally followed by testing after witnessed intake where measured concentrations are low. Investigation is needed into the potential pathways leading to very low plasma concentrations including a combined effect of multiple covariates.

Our data support Chin’s suggestion that thrombin inhibition should be appropriately measured more frequently than currently recommended, especially after dabigatran is initiated, after a dose change and when there are changing patient characteristics. The frequency would still be considerably less than that required for vitamin K antagonist monitoring. Anticoagulants continue to be one of the major causes of drug-related serious morbidity and death. The lower risk of cerebral bleeding with dabigatran compared with warfarin and its equivalence in other respects is encouraging. By identifying patients who may need finer dose adjustments or do not respond well to dabigatran, and elucidating the causes, we have an even greater opportunity to achieve badly needed improvements in outcomes with only a small loss of convenience regarding testing.