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Direct Oral Anticoagulant Dose Selection: Challenging Cases

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Synopsis

Direct oral anticoagulants (DOACs) are given in fixed doses without routine laboratory monitoring of their anticoagulant effect based on the results of pivotal phase III trials. In some of these trials, patients were randomly allocated to receive a higher or lower dose of a DOAC, whereas in others, most patients were given a standard dose and only a subset deemed to be at risk of drug accumulation was given a lower dose. Treatment guidelines recommend dosing DOACs according to the way that they were tested in the trials, but for some patients the optimal dosing remains uncertain. One example is patients with atrial fibrillation who are thought to have an unacceptably high risk of bleeding but do not meet the guideline criteria for dose reduction. A second is patients with venous thromboembolism who have completed 3 to 6 months of anticoagulation and are eligible for extended treatment with a standard or reduced dose of DOAC. In this review we present a case-based approach to DOAC dose selection in these two settings.

Treatment with a vitamin K antagonist (VKA) such as warfarin requires dose adjustment according to the results of laboratory monitoring of the international normalized ratio (INR). Unlike VKAs, direct oral anticoagulants (DOACs) are given in fixed doses without routine laboratory monitoring, which simplifies treatment. In several pivotal DOAC trials, the dose was reduced in selected patients who were deemed to be at risk of drug accumulation because of advanced age, low body weight, impaired renal function, or concomitant use of potent p-glycoprotein inhibitors. Guidelines recommend that DOACs should be dosed according to the manner that they were tested in the clinical trials, but clinicians often prescribe reduced doses of a DOAC even when the criteria for dose reduction are not met (i.e., “off-label” dose reduction) because they are concerned about the risk of bleeding. Patients who receive “off-label” reduced doses of DOACs have higher rates of thromboembolism and mortality than those who receive recommended doses [1, 2], suggesting that off-label dosing should be avoided. However, in some cases optimal dose selection remains uncertain. We present a case-based approach to DOAC dose selection in patients for whom the guidelines do not provide clear guidance.

Case 1: An 89-year-old male is referred for a second opinion regarding anticoagulant therapy for atrial fibrillation (AF). His CHADS₂ score is 5 (age >75, hypertension, diabetes, prior stroke) and you estimate that his annual risk of stroke is 10-15%. Rivaroxaban was stopped three months earlier after he was hospitalized with a second episode of major bleeding from the lower gastrointestinal (GI) tract which required transfusion of four units of packed red blood cells. Upper GI endoscopy and capsule endoscopy were unremarkable, but colonoscopy demonstrated moderately severe diverticular disease, which was assumed to be the source of bleeding. Anticoagulation was not restarted because of concerns about the risk of further GI bleeding, and he was discharged on aspirin 81 mg once daily. On examination he is in AF with a pulse of 80, blood pressure is 128/76 (on treatment) and weight is 69 kilograms. Serum creatinine is 115 µmol/L and estimated creatinine clearance is 38 mL/min.

Randomized trial evidence and guideline recommendations

Atrial fibrillation (AF) affects more than 10% of persons over the age of 80 and is a common preventable cause of stroke. The risk of stroke in patients with AF increases steeply with age and in

the presence of additional risk factors (e.g., hypertension, diabetes, heart failure, prior stroke).

Treatment with a vitamin K antagonist (VKA) or aspirin reduces the risk of stroke by 64% and 22%, respectively [3]. Direct oral anticoagulants (DOACs) are at least as effective as VKAs for stroke prevention in patients with AF but are associated with lower rates of life-threatening and fatal bleeding. In the only large, randomized trial directly comparing a DOAC to aspirin, apixaban was more effective for stroke prevention and associated with a similar risk of major bleeding [4].

AF treatment guidelines recommend using the lower dose of dabigatran in the elderly and in patients with moderate chronic kidney disease, and recommend that the factor Xa inhibitors, apixaban, rivaroxaban and edoxaban, be dosed according to the way that they were tested in the phase III trials (Table 1) [5, 6, 7].

Table 1: Guideline Recommendations for DOAC Dosing in Atrial Fibrillation

Anticoagulant	Usual Dosing (CCS, ACC/AHA, ESC)	Dose Reduction Criteria
Dabigatran	150 mg twice daily	CCS: 110 mg twice daily if age >80, or age >75 with other bleeding risk factors including CrCl 30-50 mL/min). Consider 110 mg twice daily if CrCl 30-49 mL/min ACC/AHA: 75 mg twice daily if CrCl 15-30 mL/min ESC: 110 mg twice daily if age >80, concomitant use of verapamil or increased bleeding risk
Rivaroxaban	20 mg once daily	CCS: 15 mg once daily if CrCl 30-49 mL/min ACC/AHA: 15 mg once daily if CrCl 15-50 mL/min ESC: 15 mg once daily if CrCl 15-49

		mL/min
Apixaban	5 mg twice daily	CCS: Consider 2.5 mg twice daily if >2/3 criteria including age >80, weight <60 kg or Cr >133 µmol/L ACC/AHA: 2.5 mg twice daily if >2/3 criteria including age >80, weight <60 kg or Cr >133 µmol/L ESC: 2.5 mg twice daily if >2/3 criteria including age >80, weight <60 kg or Cr >133 µmol/L
Edoxaban	60 mg once daily	CCS: 30 mg once daily if CrCl 30-49 mL/min Consider 30 mg once daily if weight <60 kg or concomitant p-gp inhibitor therapy except amiodarone or verapamil ACC/AHA: 30 mg once daily if CrCl 15-50 mL/min ESC: 30 mg once daily if CrCl 15-50 mL/min, weight <60 kg, or concomitant use of dronedarone, cyclosporin, erythromycin or ketoconazole

ACC, American College of Cardiology; AHA, American Heart Association; CCS, Canadian Cardiovascular Society; Cr, creatinine; CrCl, creatinine clearance; ESC, European Society of Cardiology; kg, kilogram; mg, milligram; mL, millilitre; p-gp, p-glycoprotein.

Clinical practice

While 50% of patients in the RE-LY trial were randomly assigned the lower dose of dabigatran, only 5%, 21% and 25% of patients in factor Xa inhibitor trials received a reduced dose of apixaban, rivaroxaban and edoxaban, respectively, according to pre-specified criteria [8, 9]. In contrast to the

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trials, between 24-39% of patients with AF prescribed a DOAC in the community receive a reduced dose, and of these as many as 42% do not meet guideline criteria for dose reduction [10, 11]. The most common reason for off-label DOAC dose reduction is concern about the risk of bleeding because of advanced age, reduced renal function, frequent falls, previous bleeding, and concomitant antiplatelet therapy [11, 12].

Off-label dosing

Off-label DOAC dose reduction potentially exposes patients with AF to an increased risk of stroke because of inadequate anticoagulation and should only be considered when there are no alternatives. Prior to considering the use of off label DOAC dosing, clinicians should address potentially modifiable risk factors for bleeding, including uncontrolled hypertension, concomitant use of antiplatelet or non-steroidal anti-inflammatory drugs, and excessive alcohol intake. Another potential alternative to off label DOAC dose reduction is left atrial appendage closure [13].

In patients who remain at high risk of bleeding and who do not qualify for left atrial appendage closure, we prefer using a reduced dose of DOAC (even if off-label) over aspirin (which is relatively ineffective for stroke prevention and does not confer a lower risk of major bleeding) or no treatment.

Table 2 provides examples of the types of patients in whom off-label dose reduction of DOACs should be avoided, as well examples of patients in whom it may be reasonable. Off-label dose reduction should be avoided if done only because a patient is elderly, has had prior falls or has experienced minor bleeding. Minor bleeding (e.g., self limiting epistaxis) does not require interruption of anticoagulation and most patients who experience major bleeding should resume standard dose anticoagulation once the bleed has stopped and the underlying cause has been identified and addressed (e.g., GI bleeding due to peptic ulcer disease that is treated with a proton pump inhibitor; subarachnoid hemorrhage treated with coiling of ruptured aneurysm).

Patients with AF in whom off-label DOAC dose reduction may be reasonable include those with recurrent major bleeding where the underlying cause is unknown or cannot be adequately treated or

those at high risk of life-threatening bleeding who do not have other modifiable risk factors for bleeding and in whom left atrial appendage closure may not be a suitable option. The decision of whether to start or re-initiate anticoagulation in such patients and the choice of agent and dose can be challenging. Observational data suggest that re-initiation of anticoagulation in patients admitted to hospital with major bleeding reduces the risk of thrombosis and mortality at the cost of an increase in recurrent bleeding [14]. However, these data are difficult to interpret because patients at highest risk of recurrent bleeding are unlikely to have been re-started on anticoagulation. Clinicians must therefore weigh the risk of thrombosis against the risk of recurrent bleeding to determine the best approach. In Table 3, we summarize factors that should be considered when evaluating this balance.

Table 2: Off-Label direct oral anticoagulant dose reduction in patients with atrial fibrillation

Examples of patients in whom off-label dose reduction should be avoided	Recommendation
Advanced age	Suggest no off-label dose reduction; the net benefit of guideline recommended anticoagulation is magnified in the elderly.
Frequent falls	Suggest no off-label dose reduction; need to fall frequently on warfarin for risk to exceed benefit [15] and DOACs lower ICH risk as compared to warfarin.
Minor bleeding	Suggest no off-label dose reduction; minor bleeding (e.g., bruising, self-limited epistaxis, hemorrhoidal bleeding) not requiring medical attention does not predict major bleeds [16].

Examples of patients in whom off-label dose reduction might be considered	Recommendation
<p>Recurrent major bleeding:</p> <ul style="list-style-type: none"> • GI tract with no source identified • Angiodysplastic lesions in the GI tract when control measures have failed • Diverticular disease where surgery is not possible • Urinary tract in patients with post radiation hemorrhagic cystitis • Epistaxis requiring hospitalization and transfusion 	<p>Consider resuming anticoagulation at off-label reduced DOAC doses in patients at increased thrombosis risk.</p>
<p>High risk of life-threatening bleeding</p> <ul style="list-style-type: none"> • High risk esophageal or gastric varices with preventative measures in place (e.g., banding, beta blockers) • Previous deep ICH in patients with adequate control of underlying risk factors including hypertension • Severe thrombocytopenia (platelets 25-50) 	

DOAC, direct oral anticoagulant; GI, gastrointestinal; ICH, intracranial haemorrhage

Table 3: Risk factors for thrombosis and bleeding in patients with atrial fibrillation or venous thromboembolism

<p>Examples of patients with AF at very high risk of stroke or systemic embolism:</p> <ul style="list-style-type: none"> • CHADS₂ >4 • Valvular AF (mechanical valve and/or moderate-severe mitral stenosis) • Transient ischemic attack or ischemic stroke within the past 3 months
<p>Examples of patients with a history of VTE at very high risk of recurrent thrombosis:</p> <ul style="list-style-type: none"> • VTE within the past 3 months • History of recurrent VTE after anticoagulation is stopped

- Triple positive antiphospholipid antibody syndrome*
- Heparin-induced thrombocytopenia within 3 months
- Active cancer with history of cancer-associated thrombosis

Examples of patients at very high bleeding risk:

- Multiple risk factors for bleeding (e.g., extreme age, advanced kidney disease)
- Thrombocytopenia (platelets less than 50)
- Unresected gastrointestinal tumours
- Angiodysplasia
- Severe colitis
- Lobar ICH secondary to cerebral amyloid angiopathy
- Recurrent ICH

*DOACs are less effective than warfarin in patients in patients with antiphospholipid antibody syndrome

Approach to case

You consider the patient's risk of stroke (10-15% per year) and of recurrent major GI bleeding (exact risk uncertain but definitely "high"). He does not have modifiable risk factors for bleeding and is not a candidate for left atrial appendage closure. Anticoagulation is highly effective for stroke prevention in AF, and apixaban reduced the risk of stroke by more than 50% compared with aspirin without increasing GI bleeding [4]. Furthermore, compared to warfarin, apixaban did not increase the risk of GI bleeding, including in the elderly [17]. While off-label reduced dosing of apixaban is unproven, it offers the potential for superior stroke protection compared with aspirin and is likely to be safer than higher doses. Based on age, renal function and weight, your patient does not meet guideline recommendations for apixaban dose reduction but in consultation with your patient, you decide to prescribe apixaban at a dose of 2.5 mg twice daily with the expectation that this will provide superior stroke protection without increasing the risk of recurrent GI bleeding compared with aspirin. You organize follow up in 3 months to re-assess apixaban dosing.

Case 2: A 66-year-old female presents with pleuritic chest pain, normal electrocardiogram and chest x-ray, and an elevated troponin. Computed tomography pulmonary angiogram demonstrates pulmonary embolism (PE) with an extensive bilateral thrombus burden and an enlarged right ventricle. She is treated with intravenous heparin for 48 hours and is then transitioned to rivaroxaban 15 mg twice daily for 21 days, followed by 20 mg once daily. She weighs 118 kg, has a body mass index of 42 kg/m², a creatinine of 65 µmol/L and a creatinine clearance of 140 mL/min. She returns for review at six months and reports complete resolution of symptoms. Echocardiogram shows normal right-sided heart function. You evaluate her as being at high risk of recurrent venous thromboembolism (VTE) and recommended extended treatment with oral anticoagulation. What dose of DOAC do you recommend?

Randomized trial evidence and guideline recommendations

VTE, which includes deep vein thrombosis (DVT) and PE, affects 1-2 per 1000 persons each year and has a lifetime risk of 8% after age 45. DVT is associated with a 20 to 50% incidence of post-thrombotic syndrome and PE is associated with a 0.1 to 4% incidence of chronic thromboembolic pulmonary hypertension (CTEPH). Between one third and one half of all events are unprovoked, which are associated with a 10% risk of recurrence at 1 year and 25% at 5 years if anticoagulation treatment is discontinued [18, 19]. Extended anticoagulation reduces the risk of recurrent VTE by 80-90% but is associated with an increased risk of bleeding [20].

Aiming to reduce the risk of bleeding with extended treatment for VTE, two randomized controlled trials, AMPLIFY-EXT [21] and EINSTEIN-CHOICE [22], examined the use of reduced dose DOACs. Both trials included patients who had completed an initial 6 to 12 months of anticoagulation and in whom there was equipoise with respect to extended treatment; patients at high risk of recurrent thrombosis or bleeding were excluded. The proportion of patients with unprovoked VTE in AMPLIFY-EXT was 92% and in EINSTEIN CHOICE was 41%. In AMPLIFY-EXT, both apixaban 5 mg twice daily and 2.5 mg twice daily compared with placebo reduced recurrent VTE or all-cause death. In EINSTEIN-CHOICE, both rivaroxaban 20 mg once daily and 10 mg once daily compared with ASA 100 mg once daily reduced recurrent symptomatic VTE or unexplained death in which PE

could not be ruled out. Neither trial demonstrated a difference in efficacy or safety between the two DOAC doses but were also not powered to show this. Dabigatran and edoxaban have not been tested at reduced doses for extended treatment of VTE.

Treatment guidelines suggest extended anticoagulation after unprovoked VTE in patients who are not at high bleeding risk [23, 24, 25] and indicate that consideration should be given to use of the reduced dose or apixaban or rivaroxaban (Table 4). However, they do not identify which patients should receive a reduced dose.

Table 4: Guideline Recommendations for DOAC Dosing for Extended Secondary VTE

Prevention

Guideline	Dose Reduction Recommendation
ACCP (2016) [23]	No recommendation.
ESC (2019) [24]	If extended oral anticoagulation is decided after PE in a patient without cancer, a reduced dose of apixaban (2.5 mg twice daily) or rivaroxaban (10 mg once daily) should be considered after 6 months of therapeutic anticoagulation.
ASH (2020) [25]	For patients with DVT and/or PE who have completed primary treatment and will continue with a DOAC for secondary prevention, the ASH guideline panel suggests using standard dose DOAC or lower dose DOAC.

ACCP, American College of Chest Physicians; ESC, European Society of Cardiology; ASH, American Society of Hematology

Reduced DOAC dosing

In Table 5, we propose an approach to DOAC dose selection in patients with unprovoked VTE being considered for extended treatment after an initial 3 to 6 months of anticoagulation. In most of these patients, we favour the use of a reduced DOAC dose but in selected patients we prefer maintaining standard doses. We acknowledge that in the absence of high-quality evidence, our approach is based

on expert opinion, considering the expected benefits and risks of using a reduced compared with standard dose of apixaban or rivaroxaban.

We recommend continuing standard dose of DOAC in patients with another indication for anticoagulation (e.g., AF) and in those who have experienced recurrent VTE on a reduced dose DOAC. Patients whose index VTE event was limb or life-threatening (e.g., phlegmasia, PE with hemodynamic compromise) should also continue standard dose DOAC treatment; patients whose initial event was a symptomatic PE are 3 times more likely to present with another PE as compared to those who initially present with a proximal DVT [26]. We also recommend that if treated with DOACs, patients with PE complicated by CTEPH should be continued on standard dose anticoagulation given the risk and consequences of further worsening in pulmonary arterial pressures and right ventricular failure should they experience recurrent PE. We note that DOACs are increasingly used in treatment of CTEPH, but that they have not been formally evaluated in randomized trials [27]. Similarly, patients with severe post thrombotic syndrome after DVT should be continued on standard dose anticoagulation to ensure optimal prevention of subsequent DVTs which may further worsen PTS symptoms and quality of life. We note that ipsilateral DVT recurrence is associated with a 4-6 times increased risk of post-thrombotic syndrome (PTS) [28]. Patients with active cancer and VTE are at particularly high risk of recurrence and were excluded from trials of DOAC dose reduction. We recommend continuing anticoagulation at standard dose for extended treatment in these patients pending the results of EVE randomized controlled trial comparing apixaban 5 mg twice daily with 2.5 mg twice daily for secondary VTE prevention in patients with cancer associated VTE [29]. Emerging evidence indicates that DOACs are effective for prevention of recurrent VTE in patients with body weight over 120 kg or BMI over 40 [30]. However, we recommend avoiding dose reduction in these patients because they were poorly represented in AMPLIFY-EXT and EINSTEIN-CHOICE.

Table 5: Recommendations for DOAC Dosing in Extended treatment of VTE

Patients who should continue standard dose for secondary prevention:

- Another indication for anticoagulation (e.g., AF)
- Previous recurrence on reduced dose DOAC

- Limb or life-threatening index event (e.g., phlegmasia, PE with hemodynamic compromise)
- Chronic thromboembolic pulmonary hypertension
- Severe post-thrombotic syndrome
- Active cancer
- Body weight >120 kg or BMI >40 kg/m²

Patients appropriate for dose reduction for secondary prevention:

- Patients not meeting above criteria
- High bleeding risk (Table 3)

Approach to case:

You consider the severity of the original PE event, the risk of recurrence, and the risk of bleeding.

Although your patient had evidence of right heart dysfunction and elevated troponin levels at presentation, she was not hemodynamically unstable. However, her event was unprovoked, and you calculate her HERDOO2 score to be 2 based on her BMI of 42 kg/m² and age of 66 indicating a high risk of recurrence [31], and you note that she does not have risk factors for bleeding. You decide that she is a good candidate for continuing a standard dose of rivaroxaban for extended treatment of VTE. In discussion with the patient, you elect to continue her on rivaroxaban 20 mg once daily and counsel her on the importance of taking this medication with food to ensure adequate absorption. You plan for annual review.

Conclusion

DOACs are the anticoagulant of choice for most patients with AF or VTE. Pivotal phase III trials have established effective and safe dosing in these populations but have not always informed the use of reduced doses. DOAC dosing choices presented in this review are informed by considerations of the pharmacology of DOACs, evidence for dose reduction in other clinical settings, and clinical experience. Additional randomized comparisons are needed to inform optimal dosing of DOACs in

patients with AF in whom concern about bleeding is a barrier to standard dosing, and in patients with VTE being considered for extended anticoagulation.

Author Contributions

S. Carlin and J. W. Eikelboom contributed equally to the critical writing and revising of intellectual content of the manuscript. Both authors approved the final manuscript version for publication.

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