Supplementary Tables

# Non-vitamin K Antagonist Oral Anticoagulant Use in Patients with Renal Impairment

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**Supplemental Table S1:** NOAC indications for major markets

| | Dabigatran | | | | Apixaban | | | | Edoxaban | | | | Rivaroxaban | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AF | VTE | OS | ACS | AF | VTE | OS | ACS | AF | VTE | OS | ACS | AF | VTE | OS | ACS |
| Canada | ✓ | ✓ | ✓ | - | ✓ | ✓ | ✓ | - | ✓ | ✓ | - | - | ✓ | ✓ | ✓ | - |
| US | ✓ | ✓ | ✓ | - | ✓ | ✓ | ✓ | - | ✓ | ✓ | - | - | ✓ | ✓ | ✓ | - |
| EU | ✓ | ✓ | ✓ | - | ✓ | ✓ | ✓ | - | ✓ | ✓ | - | - | ✓ | ✓ | ✓ | ✓ |
| Japan | ✓ | - | - | - | ✓ | ✓ | - | - | ✓ | ✓ | ✓ | - | ✓ | ✓ | - | - |

ACS: acute coronary syndrome; AF: atrial fibrillation; OS: orthopedic surgery; VTE: venous thromboembolism.

## Supplemental Table S2: NOAC Dose Recommendations for AF in Major Jurisdictions

| Drug | Canada | United States | Europe |
|---|---|---|---|
| Dabigatran | • Recommended dose 150 mg BID<br>• Patients ≥80 years or those at higher risk of bleeding, including elderly ≥75 years with ≥1 bleeding risk factor: recommended dose 110 mg BID<br>• Contraindicated if eCrCl <30 mL/min | • CrCl >30 mL/min: 150 mg BID<br>• CrCl 15-30 mL/min: 75 mg BID<br>• Not recommended if CrCl <15 mL/min or on dialysis | • Recommended dose 150 mg BID<br>• Patients ≥80 years or who receive concomitant verapamil: recommended dose 110 mg BID<br>• Contraindicated if CrCl <30 mL/min |
| Apixaban | • Recommended dose 5 mg BID<br>• Patients with at least 2 of the following: ≥80 years, body weight ≤60 kg, or sCr ≥133 µmol/L (1.5 mg/dL): recommended dose 2.5 mg BID<br>• No dosing recommendation for CrCl 15-24 mL/min<br>• Not recommended if CrCl <15 mL/min | • Recommended dose 5 mg BID<br>• Patients with at least 2 of the following: ≥80 years, body weight ≤60 kg, or sCr ≥133 µmol/L (1.5 mg/dL): recommended dose 2.5 mg BID<br>• Not recommended if CrCl <15 mL/min | • Recommended dose 5 mg BID<br>• Patients with at least 2 of the following: ≥80 years, body weight ≤60 kg, sCr ≥133 µmol/L (1.5 mg/dL): recommended dose 2.5 mg BID<br>• Patients with CrCl 15-29 mL/min: recommended dose 2.5 mg BID<br>• Not recommended if CrCl <15 mL/min, or in patients undergoing dialysis |
| Edoxaban | • Recommended dose 60 mg OD<br>• In patients with moderate renal impairment (CrCl 30-50 mL/min), weight ≤60 kg, or concomitant use of P-gp inhibitors (except amiodarone and verapamil) recommended dose is 30 mg OD<br>• Not recommended in patients with CrCl <30 mL/min | • CrCl >50 to ≤ 95 mL/min: 60 mg OD<br>• CrCl 15-50 mL/min: 30 mg OD<br>• Not recommended/avoid use if CrCl >95 mL/min | • Recommended dose 60 mg OD<br>• Patients with ≥1 of the following: CrCl 15-50 mL/min, body weight ≤60 kg, concomitant use of P-gp inhibitors (ciclosporin, dronedarone, erythromycin, or ketoconazole): recommended dose 30 mg OD<br>• Not recommended if CrCl <15 mL/min or on dialysis |
| Rivaroxaban | • Recommended dose 20 mg OD<br>• CrCl 30-49 mL/min: 15 mg OD<br>• Not recommended if CrCl <30 mL/min | • Recommended dose 20 mg OD<br>• CrCl 15-50 mL/min: 15 mg OD<br>• Avoid use if CrCl <15 mL/min | • Recommended dose 20 mg OD<br>• CrCl 15-49 mL/min: 15 mg OD<br>• Not recommended if CrCl <15 mL/min |

**Supplemental Table S3**: NOAC Dose Recommendations for VTE in Major Jurisdictions

| Drug | Canada | United States | Europe |
|---|---|---|---|
| Dabigatran | • Recommended dose 150 mg BID following 5-10 days with parenteral anticoagulant<br>• Patients ≥80 years or those at higher risk of bleeding, including elderly ≥75 years with ≥1 bleeding risk factor: recommended dose 110 mg BID<br>• Contraindicated if eCrCl <30 mL/min | • CrCl >30 mL/min: 150 mg BID, after 5-10 days of parenteral AC<br>• Not recommended if CrCl ≤30 mL/min or on dialysis<br>• Avoid co-administration of dabigatran and P-gp inhibitors in patients with CrCl <50 mL/min | • Recommended dose 150 mg BID following Tx with a parenteral AC for at least 5 days<br>• Patients ≥80 years or who receive concomitant verapamil, recommended dose 110 mg BID<br>• Contraindicated if CrCl <30 mL/min |
| Apixaban | • 10 mg BID x 7 days, then 5 mg BID<br>• Continued prevention of recurrent DVT and PE following at least 6 months of Tx for DVT or PE: 2.5 mg BID<br>• Use with caution if eCrCl 15-29 mL/min<br>• Not recommended if CrCl <15 mL/min | • 10 mg BID x 7 days, then 5 mg BID<br>• Reduction in the risk of recurrence of DVT and PE following at least 6 months of treatment for DVT or PE: 2.5 mg BID<br>• Not Recommended if CrCl <15 mL/min | • Tx of DVT/PE: 10 mg BID x 7 days, then 5 mg BID<br>• Prevention of recurrent DVT and/or PE following completion of 6 months of Tx for DVT or PE: 2.5 mg BID<br>• To be used with caution if CrCl 15-29 mL/min<br>• Not recommended if CrCl <15 mL/min, or in patients undergoing dialysis |
| Edoxaban | • Recommended dose 60 mg OD following initial use of a parenteral anticoagulant for 5-10 days<br>• Patients with moderate renal impairment (CrCl 30-50 mL/min), weight ≤60 kg, or concomitant use of P-gp inhibitors (except amiodarone and verapamil) recommended dose is 30 mg OD | • Recommended dose 60 mg OD following 5-10 days of initial therapy with a parenteral anticoagulant<br>• Patients ≤60 kg or CrCl 15-50 mL/min or using certain P-gp inhibitors: 30 mg OD<br>• Not recommended/avoid use if CrCl >95 mL/min | • Recommended dose 60 mg OD following at least 5 days of parenteral anticoagulant<br>• Patients with ≥1 of the following: CrCl 15-50 mL/min, ≤60 kg, concomitant use of P-gp inhibitors (ciclosporin, dronedarone, erythromycin, or ketoconazole): recommended dose 30 mg OD<br>• Not recommended if CrCl <15 mL/min or on dialysis |
| Rivaroxaban | • 15 mg BID x 21 days, then 20 mg OD<br>• Not recommended if CrCl <30 mL/min | • 15 mg BID x 21 days, then 20 mg OD<br>• Avoid use if CrCl <30 mL/min | • 15 mg BID x 21 days, then 20 mg OD<br>• CrCl 15-49 mL/min same as above. Consider dose reduction if risk of bleeding outweighs the risk of recurrent DVT and PE (then 15 mg BID x 21 days, then 15 mg OD)<br>• Not recommended if CrCL <15 mL/min |

**Supplemental Table S4: First ischemic stroke rates and outcomes in NOAC trials by renal function subgroup – FDA analysis**

| Drug, Trial | CrCl (mL/min) | First Stroke/SSE Rates (%/yr) | | Hazard Ratio NOAC vs. Warfarin |
|---|---|---|---|---|
| | | NOAC | Warfarin | |
| Dabigatran 150 mg, RE-LY | >50 to <80 | 0.94 | 1.22 | 0.77 |
| | ≥80 | 0.61 | 0.72 | 0.84 |
| Apixaban, ARISTOTLE | >50 to <80 | 0.77 | 0.89 | 0.87 |
| | ≥80 | 0.69 | 0.51 | 1.35 |
| Edoxaban 60/30 mg, ENGAGE AF | >50 to <80 | 1.21 | 1.49 | 0.81 |
| | ≥80 | 1.02 | 0.73 | 1.40 |
| Rivaroxaban, ROCKET-AF | >50 to <80 | 1.39 | 1.70 | 0.82 |
| | ≥80 | 0.94 | 0.87 | 1.07 |

Adapted from: FDA. Cardiovascular and Renal Drugs Advisory Committee Edoxaban NDA 206316. Statistical Considerations, ENGAGE AF Trial. 2014. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM421612.pdf.