DOAC drug interactions management resource

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Background
Over the past decade, direct oral anticoagulants (DOACs; apixaban, dabigatran, edoxaban and rivaroxaban) have offered many advantages over traditional therapy with warfarin ± low-molecular-weight heparins (LMWHs). The DOACs have established dosing without the need for coagulation monitoring as well as a quick onset (C$_{\text{max}}$ at 1-4 hours) and offset (half-lives ranging from 9-14 hours for patients with normal renal function), thereby eliminating the need for bridging with LMWHs (Figure 1).$^{1-5}$ Moreover, DOACs have fewer drug-drug interactions (DDIs) relative to warfarin; however, as the use of DOACs continues to increase in clinical practice, more information surrounding DOAC DDIs is necessary to make timely clinical decisions.

Pathways relevant to DOAC DDIs encompass the cytochrome P450 system (focusing on 3A4), as well as the P-glycoprotein (P-gp) transport system. Rivaroxaban and apixaban are substrates for P-gp and (in part) metabolized by CYP 3A4. Subsequently, rivaroxaban and apixaban DDIs must strongly affect both P-gp and CYP 3A4; the clinician should ensure a patient is not on 2 concomitant drugs that affect CYP 3A4 and P-gp separately, as these combined DDIs could cause significant changes in DOAC concentrations. In contrast, dabigatran and edoxaban are affected only by strong inhibitors/inducers of P-gp, as they lack metabolism by the CYP enzyme. The P-gp impact is within the gastrointestinal tract; hence, to minimize the P-gp DDI, dabigatran or edoxaban may be administered 2 hours prior to the interacting agent.$^4$ Notably, all DOACs have a component of renal elimination (dabigatran > edoxaban > rivaroxaban > apixaban), and while progressive renal dysfunction will result in elevated DOAC concentrations, this elimination is not a direct mechanism of DDIs.$^{2,5}$

At this time, there is limited clinical pharmacokinetic (PK)/pharmacodynamic (PD) data to quantify the clinical impact of specific DOAC DDIs. DDIs of this nature (i.e., P-gp or CYP 450) are highly variable because of the timing of the induction/inhibition turnover as well as the strength (mild, moderate or strong) of the interaction.$^6$ In addition, there is inherent inter-subject variability of 30% for concentrations of dabigatran, edoxaban and apixaban, with rivaroxaban reaching 40% for PK parameters.$^9$ In addition, reported ranges of DOAC concentrations assessed in subgroups of clinical trials demonstrate variability in peak/trough ratios of nearly 1.6-fold.$^{2-5}$ With this in mind, DDIs that alter DOAC concentrations of 30% to 40% often still result in DOAC concentrations falling within these reported concentration ranges. Subsequently, when regulators consider providing advice surrounding DDIs, within the context of high PK/PD variability, general recommendations are often to avoid these combinations; specifically, regulators contraindicate DOACs for DDIs with inducing agents (for fear of thrombotic events) and recommend use with caution and assess other factors that may warrant avoidance when an inhibitor is the interacting culprit.

Limited, if any, data provide a comparison of DDIs between the DOACs. Unique to edoxaban are recommendations for dose reduction (from 60 to 30 mg daily) in the presence of P-gp inhibitors (except amiodarone and verapamil), with certain drugs listed based on clinical trial protocols or product monograph content.$^{5,10}$ As the front-line clinician continues to manage more complex clinical scenarios with consideration of DOAC use, a summary of available literature specific to DOAC DDIs is necessary, given there may be no or conflicting information for drug interactions. As such, our purpose is to provide a tool that differentiates DDIs across the 4 DOACs specific to agents commonly prescribed for patients with cardiovascular disease, with a description of available data to support the same.

Development of the practice tool
To create the practice tool, a systematic approach was used to collate data from both product monographs and peer-reviewed
literature available for DDIs with the DOACs. As conflicting information was identified across multiple sources, we streamlined our approach. First, a general table of drugs known to be CYP 3A4 and P-gp inhibitors and inducers was created using data from LexiComp and was cross-checked using the Food and Drug Administration (FDA) database where inconsistencies arose.11,12 Following this, all possible medication interactions were entered into the Lexi-Interact database—the one most commonly used by our clinical pharmacists.13 As most information was general in nature and based on a theoretical interaction, a formal search of the literature was then completed using the OVID database searching both MEDLINE (back to 1946) and Embase (back to 1974) on May 14, 2021, using the following search strategy: search term 1: “Dabigatran or Pradaxa or Apixaban or Eliquis or Rivaroxaban or Xarelto or Edoxaban or Lixiana or DOAC* or direct oral acting anticoagulant* or NOAC* or novel oral acting anticoagulant*” and search term 2: “Drug interaction* or Drug-drug interaction* or medication interaction*”. A total of 182 articles were identified and included if they demonstrated area under the curve (AUC) data or any clinical evidence (either drug concentrations or clinical outcomes) of a DDI. Among included articles, citations were also reviewed for relevant literature. Based on available data, recommendations for concomitant use with a DOAC (Table 1) were classified as follows:

- **Green**: No interaction or clinically nonsignificant interaction—no effect on pharmacokinetics
- **Green/yellow**: Use together with caution; limited data suggest either increased major bleeding or altered drug concentrations
- **Yellow**: Use with caution as either:
  - a theoretical/documented interaction that would affect DOAC concentration,
  - product monograph recommendation to use with caution, or
  - for edoxaban, recommendation to reduce dose (signified with ↓ dose)
- **Yellow/red**: Concomitant use is not recommended; limited data may support use
- **Red**: Avoid combination, may use only if DOAC concentrations are assessed as either:
  - theoretical/documented interaction that affects DOAC concentration or
  - product monograph recommendation to avoid or contraindicate, implies expected drug concentrations exceed the observed and acceptable variability

Inclusion of all actual or potential DDIs with DOACs was beyond the scope of our tool. As this tool was created for use by practitioners within an anticoagulation clinic having a thrombosis/cardiology-based practice, herbal supplements and drug
**TABLE 1** DOAC drug interaction tool

| Antiarrhythmic agents | Substrate | DDI mechanism                                      | R  | A  | D  | E   |
|-----------------------|-----------|---------------------------------------------------|----|----|----|-----|
| Amiodarone            | 3A4       | Moderate 2C9 inhibitor Weak 3A4, 2D6 inhibitor P-gp inhibitor | 1  | 2  | 3  | 4   |
| Dronedarone           | 3A4       | Moderate 3A4 inhibitor P-gp inhibitor              | 5  | 6  | 7  | 8  ↓ dose |
| Propafenone           | 3A4, 2D6  | P-gp inhibitor                                     | 9  | 10 | 11 | 12 |
| Quinidine             | 3A4, P-gp | Weak 3A4 inhibitor P-gp inhibitor                  | 13 | 14 | 15 | 16 ↓ dose |

| Antibacterial agents  | Substrate | DDI mechanism                                      | R  | A  | D  | E   |
|-----------------------|-----------|---------------------------------------------------|----|----|----|-----|
| Azithromycin          | 3A4       | P-gp inhibitor                                     | 17 | 18 | 19 | 20 |
| Ciprofloxacin         | P-gp      | Strong 1A2 inhibitor Moderate 3A4 inhibitor        | 21 | 22 | 23 | 24 |
| Clarithromycin        | 3A4       | Strong 3A4 inhibitor P-gp inhibitor                | 25 | 26 | 27 | 28 |
| Erythromycin          | 3A4, P-gp | Moderate 3A4 inhibitor P-gp inhibitor              | 29 | 30 | 31 | 32 ↓ dose |
| Rifampicin            | P-gp      | Strong 3A4, 2C19 inducer Weak 2C9, 1A2 inducer P-gp inducer | 33 | 34 | 35 | 36 |

| Antidepressants       | Substrate | DDI mechanism                                      | R  | A  | D  | E   |
|-----------------------|-----------|---------------------------------------------------|----|----|----|-----|
| SSRI                  | Pharmacodynamic      | 37 | 38 | 39 | 40 |
| SNRI                  | Pharmacodynamic      | 41 | 42 | 43 | 44 |

| Antiepileptic agents  | Substrate | DDI mechanism                                      | R  | A  | D  | E   |
|-----------------------|-----------|---------------------------------------------------|----|----|----|-----|
| Carbamazepine         | 3A4, 2C8  | Strong 3A4 inducer Weak 2C9/1A2 inducer P-gp inducer | 45 | 46 | 47 | 48 |
| Phenobarbital         | 2C19, 2C9 | Strong 3A4 inducer Weak 2C9/1A2 inducer 2C19/2C9 substrate | 49 | 50 | 51 | 52 |
| Phenytoin             | 2C19, 2C9, 3A4 | Strong 3A4 inducer Weak 1A2 inducer P-gp inducer | 53 | 54 | 55 | 56 |
| Other                 | (lamotrigine, levetiracetam, valproic acid) | 57 | 58 | 59 | 60 |

| Antiplatelet agents   | Substrate | DDI mechanism                                      | R  | A  | D  | E   |
|-----------------------|-----------|---------------------------------------------------|----|----|----|-----|
| Aspirin               | 2C9       | Pharmacodynamic                                    | 61 | 62 | 63 | 64 |
| Clopidogrel           | 2C19, 3A4 | Moderate 2C8 inhibitor Pharmacodynamic             | 65 | 66 | 67 | 68 |
| Ticagrelor            | 3A4       | P-gp inhibitor Pharmacodynamic                     | 69 | 70 | 71 | 72 |

(continued)
### Table 1 (continued)

| Azole antifungal agents | Substrate | DDI mechanism | R  | A  | D  | E  |
|-------------------------|-----------|---------------|----|----|----|----|
| Fluconazole             |           |               | 73 | 74 | 75 | 76 |
| Itraconazole            | 3A4       |               | 77 | 78 | 79 | 80 |
| Ketoconazole            | 3A4       |               | 81 | 82 | 83 | 84 |
| Posaconazole            | 3A4       |               | 85 | 86 | 87 | 88 |
| Voriconazole            | 2C19      |               | 89 | 90 | 91 | 92 |

| Beta-blockers           | Substrate | DDI mechanism | R  | A  | D  | E  |
|-------------------------|-----------|---------------|----|----|----|----|
| Carvedilol              |           | P-gp inhibitor | 93 | 94 | 95 | 96 |
| Other (atenolol, bisoprolol, labetalol, metoprolol, nadolol, propranolol, sotalol, timolol) | 97 | 98 | 99 | 100 |

| Cardiotonic glycosides  | Substrate | DDI mechanism | R  | A  | D  | E  |
|-------------------------|-----------|---------------|----|----|----|----|
| Digoxin                 | 3A4, P-gp |               | 101| 102| 103| 104|

| Immunosuppressants      | Substrate | Inhibitor | R  | A  | D  | E  |
|-------------------------|-----------|-----------|----|----|----|----|
| Cyclosporine            | 3A4, P-gp | Weak 3A4/2C9 inhibitor | 105| 106| 107| 108↓ dose |
| Tacrolimus              | 3A4, P-gp | P-gp inhibitor | 109| 110| 111| 112|

| Lipid-lowering agents   | Substrate | DDI mechanism | R  | A  | D  | E  |
|-------------------------|-----------|---------------|----|----|----|----|
| Lovastatin              | 3A4, P-gp |               | 113| 114| 115| 116|
| Simvastatin             | 3A4, P-gp |               | 117| 118| 119| 120|
| Other (atorvastatin, rosuvastatin, fluvastatin, pravastatin) | 121 | 122 | 123 | 124 |

| Nonsteroidal anti-inflammatory drugs | Substrate | DDI mechanism | R  | A  | D  | E  |
|-------------------------------------|-----------|---------------|----|----|----|----|
| Naproxen                            | 2C9, 1A2  | Pharmacodynamic | 125| 126| 127| 128|
| Other (ibuprofen, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam) | 129 | 129 | 129 | 129 |

(continued)
### TABLE 1 (continued)

| Proton pump inhibitors | Substrate | DDI mechanism | R  | A  | D  | E  |
|------------------------|-----------|---------------|----|----|----|----|
| Esomeprazole           | 3A4, 2C19 | Weak 2C19 inhibitor | Increase gastric pH | 130 | 131 | 132 | 133 |
| Omeprazole             | 3A4, 2C19 | Weak 2C19 inhibitor | Increase gastric pH | 134 | 135 | 136 | 137 |
| Pantoprazole           | 3A4, 2C19 | Increase gastric pH | | 138 | 139 | 140 | 141 |
| Other (dexlansoprazole, lansoprazole, rabeprazole) | | Increase gastric pH | | 142 | 143 | 144 | 145 |

| Selective Calcium Channel Blockers | Substrate | Inhibitor | R  | A  | D  | E  |
|-----------------------------------|-----------|-----------|----|----|----|----|
| Diltiazem                         | 3A4, 2C9, P-gp | Moderate 3A4 inhibitor | | 146 | 147 | 148 | 149 |
| Verapamil                         | 3A4, 1A2, 2C9, P-gp | Moderate 3A4 inhibitor Weak 1A2 inhibitor P-gp inhibitor | | 150 | 151 | 152 | 153 |
| Other (felodipine, nifedipine, amlodipine) | | | | 154 | 155 | 156 | 157 |

Numbers in this table refer to interaction details described below.
Disclaimer: To the best of our knowledge, the data in the table are an accurate summary of the published data up to July 2021. See full disclaimer at the end of the article.

- No interaction or clinically nonsignificant interaction—no effect on pharmacokinetics
- Use together with caution; limited data suggest either increased major bleeding or altered drug concentrations
- Use with caution as either:
  - a theoretical/docummented interaction that would affect DOAC concentration yet in an allowable quantity,
  - product monograph recommendation to use with caution or
  - for edoxaban, recommendation to reduce dose (signified with ↓ dose)
- Concomitant use is not recommended; limited data may support use
- Avoid combination, may use only if DOAC concentrations are assessed as either:
  - theoretical/docummented interaction that affects DOAC concentration or
  - product monograph recommendation to avoid or contraindicate implying expected drug concentrations due to the interaction exceed the observed and acceptable variability

DOAC, direct oral anticoagulant; DDI, drug-drug interaction; R, rivaroxaban; A, apixaban; D, dabigatran; E, edoxaban; P-gp, P-glycoprotein; MB, major bleeding; GIB, gastrointestinal bleeding; PM, product monograph; ICH, intracerebral haemorrhage; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor.

**Interaction details:**

1. Rivaroxaban: no ↑ in MB (ROCKET-AF clinical trial\(^{1,14}\)); ↑ MB (3 retrospective cohorts\(^{1,13}\)); predicted ↑ in rivaroxaban area under the curve (AUC) by 37% (in silico study\(^{18}\)).
2. Apixaban: ↓ MB compared with warfarin independent of amiodarone use (subanalysis of ARISTOLE\(^{13}\)); ↑ MB (2 retrospective cohorts\(^{1,13}\)); apixaban 5 mg bid + amiodarone 200 mg daily with hemopericardium (1 case report\(^{12}\)); probable ↑ AUC by 30% and C\(_{\text{max}}\) by 40%\(^{3}\).
3. Dabigatran: ↑ MB (1 retrospective cohort\(^{17}\)); dabigatran 75 mg bid + amiodarone 200 mg daily with rectal bleeding – ↑ renal function with dabigatran trough concentration at 5600 ng/mL (1 case report\(^{11}\)); single dose of amiodarone 600 mg ↑ AUC by 60% and C\(_{\text{max}}\) by 50%\(^{5}\).
4. Edoxaban: single dose of edoxaban 60 mg and amiodarone 400 mg daily × 4 days with ↑ in AUC by 40% and C\(_{\text{max}}\) by 66% (clinical trial in 30 healthy volunteers\(^{5,22}\)).
5. Rivaroxaban: ↑ overall bleeding and GIB (2 retrospective cohorts\(^{17,23}\)); + no ↑ MB (1 retrospective cohort\(^{13}\)); PM not recommended\(^{2}\).
6. Apixaban: no ↑ overall bleeding (1 retrospective cohort\(^{23}\)); no ↑ MB (2 retrospective cohorts\(^{15,24}\)); ↑ overall bleeding (1 retrospective cohort\(^{13}\)); probable ↑ in AUC by 30% and C\(_{\text{max}}\) by 40% (based on diltiazem\(^{15}\)).
7. Dabigatran: ↑ GIB (1 retrospective cohort\(^{17}\)); no ↑ MB (1 retrospective cohort\(^{17}\)); single and multiple doses of dronedarone 400 mg ↑ AUC by 114%-136% and C\(_{\text{max}}\) by 87%-125%\(^{4}\).
8. Edoxaban: single dose of edoxaban 60 mg and dronedarone 400 mg twice daily × 7 days with ↑ in AUC by 46% and C\(_{\text{max}}\) by 66% (clinical trial in 34 healthy volunteers\(^{5,22}\)).
9. Rivaroxaban: no anticipated drug interaction
10. Apixaban: no anticipated drug interaction
11. Dabigatran: no clinical data—theoretical interaction\(^{4}\)
12. Edoxaban: no clinical data—oretical interaction
13. Rivaroxaban: no anticipated drug interaction
14. Apixaban: no anticipated drug interaction
15. Dabigatran: dabigatran 150 mg bid + dextromethorphan 20 mg/ quinidine 10 mg bid resulting in lower GIB in a patient with acute kidney injury and ↑ thrombin time despite several doses of idarucizumab (1 case report); ↑ in AUC by 53%—product monograph recommends separating administration of dabigatran by at least 2 hours before quinidine
16. Edoxaban: single dose of edoxaban 60 mg and quinidine 300 mg × 2 days, ↑ in AUC by 77% and C max by 85% (clinical trial in 42 healthy volunteers)
17. Rivaroxaban: no anticipated drug interaction
18. Apixaban: no anticipated drug interaction
19. Dabigatran: no clinical data—oretical interaction
20. Edoxaban: no clinical data—ethical interaction
21. Rivaroxaban: no anticipated drug interaction
22. Apixaban: no anticipated drug interaction
23. Dabigatran: no anticipated drug interaction
24. Edoxaban: no anticipated drug interaction
25. Rivaroxaban: ↑ MB compared with either azithromycin or no clarithromycin use (1 elderly cohort); no difference when used for Helicobacter pylori treatment combined erythromycin and clarithromycin (1 retrospective cohort); rivaroxaban 20 mg daily + clarithromycin 500 mg twice daily resulting in ICH and rivaroxaban trough concentration of 537 ng/mL (1 case report); single dose of rivaroxaban 10 mg daily and clarithromycin 500 mg twice daily ↑ AUC by 50% and C max by 40% (clinical trial in 16 healthy volunteers)
26. Apixaban: ↑ MB compared with azithromycin use (1 cohort study); ↑ MB when used for H. pylori treatment combined erythromycin and clarithromycin (1 retrospective cohort); ↑ MB when used for H. pylori treatment combined erythromycin and clarithromycin (1 retrospective cohort); single dose of dabigatran 300 mg and 500 mg clarithromycin twice daily ↑ AUC by 49% and C max by 60% (clinical trial in 10 healthy volunteers); coadministration of 500 mg bid clarithromycin with dabigatran ↑ in AUC by 19% and C max by 15%
27. Edoxaban: no clinical data—ethical interaction
28. Rivaroxaban: ↓ MB when used for H. pylori treatment combined erythromycin and clarithromycin (1 retrospective cohort); erythromycin 500 mg tid and rivaroxaban ↑ in AUC by 30%
29. Apixaban: ↓ MB when used for H. pylori treatment combined erythromycin and clarithromycin (1 retrospective cohort)
30. Dabigatran: ↓ MB when used for H. pylori treatment combined erythromycin and clarithromycin (1 retrospective cohort)
31. Apixaban: ↓ MB compared with those on apixaban alone (cohort study); ↑ MB risk with DOAC + SSRI vs no SSRI
32. Dabigatran: ↑ MB with DOACs, a secondary analysis with individual DOACs found statistically significant interaction of rivaroxaban with SSRI (1 case-control study); ↑ MB with dabigatran and warfarin with SSRI vs without (drug information manufacturer)
33. Edoxaban: theoretical ↑ MB risk (not in other DOAC studies)
34. Rivaroxaban: no DDI studies done, yet potential ↑ risk of MB identified in case reports and epidemiological studies—ethical impact
35. Apixaban: apixaban coadministered with SSRI/SSRI did not show a significant ↑ MB compared with those on apixaban alone (cohort study); ↑ MB risk with DOAC + SSRI vs no SSRI
36. Dabigatran: ↑ MB compared with those on apixaban alone (cohort study); ↑ MB risk with DOAC + SSRI vs no SSRI
37. Rivaroxaban: ↑ MB risk (not in other DOAC studies)
38. Rivaroxaban: rivaroxaban 20 mg/day + carbamazepine 900 mg/ day with reduced rivaroxaban concentration <20 ng/mL with recurrent venous thrombembolism (VTE; case report); PE after total knee replacement taking rivaroxaban 10 mg/day + carbamazepine 600 mg bid without rivaroxaban concentration (case report); avoid use
39. Dabigatran: dabigatran 150 mg bid + carbamazepine dose not specified yielded reduced dabigatran concentration of <30 ng/mL (2 case reports); avoid use
40. Edoxaban: edoxaban 60 mg/day + carbamazepine 400 mg/day with peak apixaban concentration 94 ng/mL (case report); apixaban 5 mg bid + carbamazepine 400 mg/day with peak apixaban concentration 110 ng/mL and trough 64 ng/mL—concentrations higher than while not taking carbamazepine (case report); tiration of carbamazepine with apixaban 5 mg bid + carbamazepine 800 mg/day had apixaban trough concentration 30 ng/mL; peak 114 ng/mL, apixaban 10 mg bid + carbamazepine 1000 mg/day with repeat trough/peak of 41/99 ng/mL (case report); avoid use
41. Rivaroxaban: rivaroxaban 150 mg bid + phenytoin or phenobarbital had cardioembolic stroke after 3 months (no dabigatran concentration; 1 case report)
42. Rivaroxaban: no anticipated drug interaction
43. Rivaroxaban: rivaroxaban 15 mg bid + phenytoin or phenobarbital had cardioembolic stroke after 3 months (no dabigatran concentration; 1 case report)
44. Rivaroxaban: no anticipated drug interaction
45. Rivaroxaban: rivaroxaban 20 mg daily + dextromethorphan 20 mg/ dextromethorphan 20 mg bid with repeat trough/peak of 41/99 ng/mL (case report); avoid use
46. Rivaroxaban: rivaroxaban 20 mg bid + carbamazepine 400 mg/day with reference range edoxaban of peak 199 ng/mL after 2 weeks and 236 ng/mL after 4 weeks (1 case report); avoid use
47. Rivaroxaban: rivaroxaban 150 mg bid + phenytoin or phenobarbital had cardioembolic stroke after 3 months (no dabigatran concentration; 1 case report)
48. Rivaroxaban: rivaroxaban 150 mg bid + phenytoin or phenobarbital had cardioembolic stroke after 3 months (no dabigatran concentration; 1 case report)
49. Rivaroxaban: no anticipated drug interaction
50. Rivaroxaban: rivaroxaban 20 mg daily + dextromethorphan 20 mg/ dextromethorphan 20 mg bid with clinical improvement and thrombin time >180 seconds 4 hours postdose (1 case report); avoid use
51. Dabigatran: dabigatran + phenytoin or phenobarbital resulted in median corrected trough steady state >3 standard deviations below cohort mean (1 cohort study); dabigatran 150 mg bid + "low-dose phenobarbital" had cardioembolic stroke after 3 months (no dabigatran concentration; 1 case report)
52. Edoxaban: no anticipated drug interaction
53. Rivaroxaban: rivaroxaban 15 mg bid + phenytoin or phenobarbital had cardioembolic stroke after 3 months (no dabigatran concentration; 1 case report)
54. Rivaroxaban: rivaroxaban 20 mg bid + dextromethorphan 20 mg/ dextromethorphan 20 mg bid with repeat trough/peak of 41/99 ng/mL (case report); avoid use
55. Dabigatran: dabigatran + phenytoin or phenobarbital resulted in median corrected trough steady state >3 standard deviations below cohort mean (1 cohort study); dabigatran 150 mg bid + phenytoin or phenobarbital had cardioembolic stroke after 3 months (no dabigatran concentration; 1 case report)
56. Rivaroxaban: rivaroxaban 20 mg bid + dextromethorphan 20 mg/ dextromethorphan 20 mg bid with clinical improvement and thrombin time >180 seconds 4 hours postdose (1 case report); avoid use
57. Rivaroxaban: rivaroxaban 20 mg bid + dextromethorphan 20 mg/ dextromethorphan 20 mg bid with repeat trough/peak of 41/99 ng/mL (case report); avoid use
58. Rivaroxaban: rivaroxaban 150 mg bid + phenytoin or phenobarbital had cardioembolic stroke after 3 months (no dabigatran concentration; 1 case report)
59. Rivaroxaban: rivaroxaban 20 mg bid + dextromethorphan 20 mg/ dextromethorphan 20 mg bid with repeat trough/peak of 41/99 ng/mL (case report); avoid use
60. Rivaroxaban: rivaroxaban 20 mg bid + dextromethorphan 20 mg/ dextromethorphan 20 mg bid with repeat trough/peak of 41/99 ng/mL (case report); avoid use
61. Rivaroxaban: ↑ MB; no clinically significant pharmacokinetic (PK) interaction with aspirin 500 mg
62. Rivaroxaban: ↑ MB; no clinically significant PK interaction with aspirin 325 mg
63. Rivaroxaban: ↑ MB; no PK data available
64. Rivaroxaban: ↑ MB; coadministration of aspirin 100 mg or 325 mg and edoxaban ↑ AUC by 32% and C max by 35%
65. Rivaroxaban: ↑ MB; clopidogrel 75 mg daily + single dose of rivaroxaban had no effect on PK
66. Rivaroxaban: ↑ MB, no changes in PK with clopidogrel 75 mg daily
101. Rivaroxaban: no mutual PK interactions between digoxin and posaconazole, voriconazole; retrospective cohort15; potential ↑ rivaroxaban concentration by 160%2

102. Rivaroxaban: no anticipated drug interaction

103. Rivaroxaban: no anticipated drug interaction per PM4

104. Edoxaban: no mutual PK interactions between digoxin and posaconazole, voriconazole; retrospective cohort15; potential ↑ Cmax by 70%2

105. Rivaroxaban: rivaroxaban 20 mg → dose-individualized oral regimen of cyclosporine ↑ AUC by 47% and Cmax by 104% (clinical trial in 12 healthy volunteers2); no ↑ MB (retrospective cohort15); mean for trough rivaroxaban concentration 131.7 ng/mL with cyclosporine compared with mean for trough rivaroxaban concentration 20.3 ng/mL with tacrolimus (cohort study in 9 patients after liver transplant, 5 received cyclosporine and 4 received tacrolimus13); all but 2 patients (both with renal dysfunction) had trough rivaroxaban concentration <137 ng/mL (upper limit of reported range; prospective observational study in 11 patients with orthostatic heart transplant, 8 received cyclosporine and 3 received tacrolimus13); no ↑ MB (dabigatran n = 9, rivaroxaban n = 17, apixaban n = 1, cyclosporine n = 2, tacrolimus n = 25; retrospective observational study12)

106. Apixaban: single dose of apixaban 10 mg and cyclosporine 100 mg daily × 3 days ↑ AUC by 20% and Cmax by 43% (clinical trial in 12 healthy volunteers15); ↑ in MB (retrospective cohort15)

107. Dabigatran: ↑ in MB (retrospective cohort14); no ↑ MB among combined DOACs (dabigatran n = 9, rivaroxaban n = 17, apixaban n = 1, cyclosporine n = 2, tacrolimus n = 25) yet both MBs were taking dabigatran (retrospective observational study12); may be expected to ↑ systemic exposure to dabigatran and should be used with caution (theoretical)

108. Edoxaban: cyclosporine 500 mg with a single dose of edoxaban 60 mg ↑ edoxaban AUC by 73% and Cmax by 74% (clinical trial in 33 healthy volunteers8)

109. Rivaroxaban: No bleeding or thrombotic events, trough rivaroxaban concentration of 30-63 ng/L and peak rivaroxaban concentration of 134-449 ng/mL with limited variability in the 25th to 75th percentile range (prospective observational study in 8 renal transplant patients with stable renal function treated with tacrolimus = everolimus15); mean for trough rivaroxaban concentration 131.7 ng/mL with cyclosporine compared with mean for trough rivaroxaban concentration 20.3 ng/mL with tacrolimus (cohort study in 9 patients after liver transplant, 5 received cyclosporine and 4 received tacrolimus13); all but 2 patients (both with renal dysfunction) had trough rivaroxaban concentration <137 ng/mL (upper limit of reported range; prospective observational study in 11 patients with orthostatic heart transplant, 8 received cyclosporine and 3 received tacrolimus13); no ↑ MB (dabigatran n = 9, rivaroxaban n = 17, apixaban n = 1, cyclosporine n = 2, tacrolimus n = 25; retrospective observational study12)

110. Apixaban: single dose of apixaban 10 mg and tacrolimus 5 mg daily × 3 days ↓ AUC by 22% and Cmax by 13% (clinical trial in 12 healthy volunteers15)

111. Dabigatran: no ↑ MB among combined DOACs (dabigatran n = 9, rivaroxaban n = 17, apixaban n = 1, cyclosporine n = 2, tacrolimus n = 25) yet both MBs were taking dabigatran (retrospective observational study12); may be expected to ↑ systemic exposure to dabigatran and should be used with caution (theoretical)

112. Edoxaban: no data—theoretical, P-gp inhibitor per FDA1,12

113. Rivaroxaban: no anticipated drug interaction

114. Apixaban: no anticipated drug interaction

115. Dabigatran: ↑ MB compared with other statins (case-control study14)

116. Edoxaban: no anticipated drug interaction

117. Rivaroxaban: no anticipated drug interaction

118. Apixaban: no anticipated drug interaction

119. Dabigatran: ↑ MB compared with other statins (case-control study14)

120. Edoxaban: no anticipated drug interaction

121. Rivaroxaban: no anticipated drug interaction, PM notes no drug interaction with atorvastatin1

122. Apixaban: no anticipated drug interaction

123. Dabigatran: no anticipated drug interaction, ↓ in AUC by 20% of dabigatran when coadministered with atorvastatin1

124. Edoxaban: no anticipated drug interaction, ↓ in AUC and Cmax by 15% of edoxaban when coadministered with atorvastatin1

125. Rivaroxaban: ↑ MB; coadministration of naproxen and rivaroxaban did not affect rivaroxaban PK; no clinically relevant prolongation of bleeding time observed when 500 mg naproxen was preadministered 24 hours before concomitant administration of single doses of rivaroxaban 15 mg8
126. Apixaban: ↑ MB; single dose of 500 mg naproxen led to ↑ in AUC by 50% and 60% ↑ in C\text{max} of apixaban (recommends no dose adjustment but use caution)

127. Dabigatran: ↑ MB

128. Dabigatran: ↑ MB; coadministration of naproxen and apixaban did not affect edoxaban PK, ↑ bleeding time relative to either alone

129. Diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam—no PK data, pharmacodynamic interaction suspected

130. Rivaroxaban: no anticipated drug interaction

131. Apixaban: no anticipated drug interaction

132. Dabigatran: concurrent proton pump inhibitor (PPI) administration ↓ trough dabigatran concentration and peak dabigatran concentration by 33% than without coadministration (clinical trial in 35 patients with nonvalvular atrial fibrillation [NVAF] 14 lansoprazole, 14 rabeprazole, 6 esomeprazole); coadministration of PPIs with dabigatran ↓ AUC by 12.5% (PK analysis of RE-LY trial)

133. Edoxaban: single dose of edoxaban and esomeprazole 40 mg once daily × 5 days had no effect on the AUC of edoxaban but the C\text{max} by 33%—no dose modification is necessary

134. Rivaroxaban: single dose of rivaroxaban and multiple doses of omeprazole, geometric means for AUC and C\text{max} were within 80%-125% range (clinical trial in 22 healthy volunteers); coadministration of rivaroxaban and omeprazole did not affect rivaroxaban PK [(2)]

135. Apixaban: no anticipated drug interaction

136. Dabigatran: concurrent PPI administration ↓ trough dabigatran concentration and peak dabigatran concentration by 50% than without coadministration (prospective observational study in 31 hospitalized patients 9 omeprazole 10 pantoprazole 12 no PPI); coadministration of PPIs with dabigatran ↓ AUC by 12.5% (PK analysis of RE-LY trial)

137. Edoxaban: no anticipated drug interaction

138. Rivaroxaban: no anticipated drug interaction

139. Apixaban: no anticipated drug interaction

140. Dabigatran: concurrent PPI administration ↓ trough dabigatran concentration and peak dabigatran concentration by 50% than without coadministration (prospective observational study in 31 hospitalized patients 9 omeprazole 10 pantoprazole 12 no PPI); coadministration of PPIs with dabigatran ↓ AUC by 12.5% (PK analysis of RE-LY trial)

141. Edoxaban: no anticipated drug interaction

142. Rivaroxaban: no anticipated drug interaction

143. Apixaban: no anticipated drug interaction

144. Dabigatran: concurrent PPI administration ↓ trough dabigatran concentration and peak dabigatran concentration by 33% than without coadministration (clinical trial in 35 patients with NVAF 14 lansoprazole, 14 rabeprazole, 6 esomeprazole); coadministration of PPIs with dabigatran ↓ bioavailability AUC by 12.5% (PK analysis of RE-LY trial)

145. Edoxaban: no anticipated drug interaction

146. Rivaroxaban: rivaroxaban + diltiazem was not associated with ↑ bleeding (retrospective cohort); no ↑ MB (retrospective cohort); no ↑ in overall bleeding in patients treated with verapamil or diltiazem vs amiodipine or metoprolol with rivaroxaban (retrospective cohort)

147. Apixaban: no ↑ in MB (retrospective cohort); no ↑ in overall bleeding in patients treated with verapamil or diltiazem vs amiodipine or metoprolol with apixaban (retrospective cohort); diltiazem 360 mg daily + apixaban led to ↑ in AUC by 40% and C\text{max} by 30%; no dose adjustment required, use with caution

148. Dabigatran: ↑ in overall bleeding in patients treated with verapamil or diltiazem vs amiodipine or metoprolol (retrospective cohort); no ↑ in MB (retrospective cohort)

149. Edoxaban: no anticipated drug interaction

150. Rivaroxaban: concurrent verapamil + rivaroxaban ↑ AUC by 40% (clinical trial in 27 volunteers with normal or mildly impaired renal function); no ↑ in overall bleeding in patients treated with verapamil or diltiazem vs amiodipine or metoprolol with rivaroxaban (retrospective cohort); no ↑ in MB (retrospective cohort); ↑ in MB and ICH across both rivaroxaban and warfarin (analysis of data from clinical trial ROCKET AF)

151. Apixaban: no ↑ in overall bleeding in patients treated with verapamil or diltiazem vs amiodipine or metoprolol with apixaban (retrospective cohort); no ↑ MB (retrospective cohort)

152. Dabigatran: ↑ in overall bleeding in patients treated with verapamil or diltiazem vs amiodipine or metoprolol with dabigatran (retrospective cohort); no ↑ MB (retrospective cohort); coadministration of 150 mg dabigatran once daily with verapamil (120 mg bid or 240 mg) resulted in variable ↑ of dabigatran AUC by 20%-150% and C\text{max} by 10%-180% depending on the timing (1 hour prior, concurrently, 2 hours after, steady state) of administration and the formulation (immediate or extended release) of verapamil used. Simultaneous initiation of treatment with dabigatran and verapamil should be avoided at all times. In all cases, to minimize potential interaction, dabigatran should be given at least 2 hours before verapamil. Use caution

153. Edoxaban: single dose of edoxaban 60 mg + extended release verapamil 240 mg daily for 11 days ↑ the AUC and C\text{max} by 53% (clinical trial in 34 healthy volunteers)

154. Rivaroxaban: no anticipated drug interaction

155. Apixaban: no anticipated drug interaction

156. Dabigatran: no anticipated drug interaction

157. Edoxaban: no anticipated drug interaction

classes such as (but not limited to) hormonal agents, monoclonal antibodies, tyrosine kinase inhibitors, intercalating agents and antimitotic agents were excluded, given they are not commonly encountered in our practice. As DDIs most relevant to the DOACs involve either P-gp or CYP 3A4, we also identified if potentially interacting medications were substrates of these pathways and to what extent (mild, moderate, severe). In doing so, we allow the clinician to extrapolate the potential impact that an inducer/inhibitor may have on these drug concentrations.

**Clinical management of DOAC DDIs**

To effectively manage a potential/actual DDI with a DOAC, the clinician should consider individual patient characteristics and how these may have an impact on anticipated DOAC concentrations. For patients prescribed anticoagulants, the clinician should assess the risk of clotting vs bleeding to provide a basis for comfort in having the patient’s anticipated DOAC concentration on the higher vs lower end. Risk for clotting is specific to the indication for anticoagulant use; for some indications, validated risk scores are available (e.g., CHADS\textsubscript{2} score for nonvalvular atrial fibrillation), whereas for others, such as venous thromboembolism, clinical factors such as the proximity/extensiveness of the clot are more helpful. Specific to bleeding risk, the clinician should contemplate factors that encompass patient history of bleeding, diseases of note (e.g., esophageal varices, diffuse diverticulitis) or drugs increasing risk (e.g., concomitant antplatelet therapy). Knowledge of renal dysfunction and the impact on DOAC concentration should also be integrated into this assessment. Once done, the clinician should extrapolate a preference for having the DOAC concentration on the high end (assuming clot risk trumps bleeding risk) or the low end (assuming the opposite).
Conclusion
This tool has been developed to assist clinicians in making decisions surrounding DOAC use. The clinician is encouraged to review the basis of the recommendation with available literature described, all drugs being administered and renal function to gauge the overall impact on DOAC concentration. With this in mind, clinical judgement should dictate practice.

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Disclaimer: To the best of our knowledge, the data in the tool are an accurate summary of the published data as of July 2021. The data were reviewed by all authors with recommendations put forth based on predefined criteria. Clinicians are encouraged to routinely assess information with drug interaction–checking tools and literature that may be new. This material is intended for general information only and is provided on an “as is,” “where is” basis. Although reasonable efforts were made to confirm the accuracy of the information, the authors do not make any representation or warranty, express, implied or statutory, as to the accuracy, reliability, completeness, applicability or fitness for a particular purpose of such information. This material is not a substitute for the advice of a qualified health professional. The authors expressly disclaim all liability for the use of these materials and for any claims, actions, demands or suits arising from such use.

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