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Reconsideration of Interactions Between Direct Oral Anticoagulants and Calcineurin Inhibitors

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From the first published guidelines on the use of direct oral anti-coagulants (DOACs) in non-valvular atrial fibrillation in 2013 up to the latest updates in 2018 (1), DOAC interactions with other drugs have been one of the important challenges in their prescribing. Given the rapid increase in the number of solid organ transplant recipients, the need for anticoagulant therapy among transplant patients is on the rise. Based on in vivo studies (2, 3) and clinical reviews (4, 5) on concomitant administration of calcineurin inhibitors (CNIs) and DOACs, reassessing the color coding indicating the severity of interactions in the guidelines (1) seems to be necessary. The use of midazolam as a human Cytochrome P450 3A (CYP3A) probe has shown that cyclosporine inhibits CYP3A more strongly than tacrolimus, while there was no significant difference in CYP3A inhibition between tacrolimus and the control group (2). The same pattern of inhibition is seen with the P-glycoprotein (P-gp) pathway (3). Hence, cyclosporine may be considered as a moderate to strong P-gp inhibitor and moderate CYP3A inhibitor while tacrolimus could be regarded as a mild to moderate P-gp and mild CYP 3A inhibitor. Based on current data, higher rivaroxaban exposure and risk of bleeding has been reported when concomitantly used with cyclosporine. However, coadministration of cyclosporine with apixaban increased apixaban exposure only modestly within its therapeutic range. Dabigatran is not metabolized by CYP3A, however, clinical experiences and reports on CNIs plus dabigatran regimen are limited and inconclusive (3,4).

On the other hand, the competitive effect of DOACs on CNI metabolism can be easily overcome by blood level monitoring of the CNIs about 5 to 7 days after DOAC initiation (6) .

In conclusion, given the acceptable safety of DOACs when coadministered with tacrolimus- which is the more frequently used CNI among transplant patients- DOACs may be considered as a convenient anticoagulant in this population. We suggest three revisions to the CNI-DOAC drug interactions in the EHRA 2018 guidelines:

i) considering higher level of caution regarding concomitant use of cyclosporine and rivaroxaban (i.e., changing the yellow color to orange), ii) considering lower level of caution for concomitant administration of tacrolimus and apixaban (i.e., changing the orange color to yellow); and iii) considering lower level of caution for concomitant administration of tacrolimus and apixaban (i.e., changing the orange color to yellow).

Reconsiderations of the severity and color coding of CNI-DOAC interactions are illustrated in Table 1.

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Table 1. calcineurin inhibitors (CNIs) and direct oral anti-coagulants (DOACs) interactions.

Calcineurin inhibitors	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Cyclosporine	**Strong to Moderate** P-gp inhibition **Moderate** CYP3A4 inhibition CYP3A4/P-gp competition	R	Y	R	O
Tacrolimus	**Mild to moderate** P-gp inhibition **Mild** CYP3A4 inhibition CYP3A4/P-gp competition	R	Y	R	Y

- "Y" - Yellow: Caution is needed in case of polypharmacy or in the presence of ≥2 bleeding risk factors.
- "O" - Orange: Consider dose adjustment or different DOAC.
- "R" - Red: Contraindicated / not recommended.

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