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Title: Potential pharmacological interactions between oral pulmonary arterial hypertension (PAH) therapies and new oral anticoagulants

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Body: Background Anticoagulation with vitamin-K antagonists is currently recommended in PAH. We aimed to search for potential pharmacological interactions between new oral anticoagulants (NOA) and oral PAH therapies. Methods We reviewed the potential pharmacokinetic and pharmacodynamics drug-drug interactions (DDI), in particularly regarding metabolism and drug transport, with bosentan (B), ambrisentan (A), sildenafil (S), tadalafil (T) and NOA (rivaroxaban, apixaban, dabigatran). Results B is metabolized mainly by hepatic cytochrome P450 (CYP) 3A4, A by uridine 5' diphosphate glucuronyltransferase and to a lesser extent, by CYP3A4 and CYP2C19. The organic anion transport proteins for B and P-glycoprotein for both are probably involved in the transports of these drugs. B, but not A, induces CYP3A4, which is involved in the metabolism of anti-Xa NOA rivaroxaban (30%) and apixaban (50%). Concomitant use of B may reduce their biological efficacy. S and T are also mainly metabolized by CYP3A4, but act as slight CYP3A4 inhibitors. The risk for clinically significant DDI seems low between S or T and anti-Xa NOA. However, in case of PAH-combination therapy, the risk for a decreased concentration might be amplified for anti-Xa NOA. Conversely, an increased risk of myocardial infarction recently evoked with dabigatran, an anti-IIa drug not metabolised by CYP, should preclude its use in PAH. Conclusion DDI may occur in PAH patients receiving NOA and PAH therapies, and potentially amplified in case of combination therapy. In the absence of robust clinical and pharmacological data, NOA are not recommended in PAH.