

# DOAC drug interactions and risk of major bleeding

**Overview of:** Zhang Y, Souverein PC, Gardarsdottir H. Risk of major bleeding among users of direct oral anticoagulants combined with interacting drugs: a population-based nested case-control study. *Br J Clin Pharmacol* 2020;86:1150–4.

## Key learning points

- ▶ Several drugs can interact with direct oral anticoagulants (DOACs) through altering their absorption or elimination, or by independently increasing the risk of major bleeds.
- ▶ This case–control study found that drugs that affect the pharmacokinetics of DOACs were not associated with an increased risk of major bleeds.
- ▶ Antiplatelet drugs and selective serotonin reuptake inhibitors (SSRIs) were associated with an increase in the risk of major bleeds when taken with a DOAC.

A nested case–control study found that use of antiplatelet drugs and selective serotonin reuptake inhibitors (SSRIs) with direct oral anticoagulants (DOACs) was associated with an increased risk of major bleeds requiring hospital admission.<sup>1</sup>

## Overview

This case–control study used data from the UK Clinical Practice Research Datalink linked to Hospital Episode Statistics to study the incidence of major bleeds in people aged 18 years or older taking DOACs with other medicines known to interact with them.<sup>1</sup> Interacting drugs were classed as pharmacokinetic (PK)-interacting drugs (inhibitors of cytochrome p450 3A4 [CYP3A4] or P-glycoprotein [P-gp]) or pharmacodynamic (PD)-interacting drugs that also increase the risk of bleeding. Some drugs result in both PK and PD interactions but were classed as PD-interacting drugs (naproxen, clopidogrel, ticagrelor and diclofenac).

The study identified 23 492 patients aged over 18 years who started a DOAC between 2008 and 2015. Of these, 393 people had a first hospital admission for a major bleed (a composite of gastrointestinal, intracranial or other symptomatic bleeding in a critical area or organ).<sup>1</sup> These cases were matched to 1494 controls. Cases and controls had a mean age of 79 years, 62% were men and most used DOACs to reduce the risk of stroke in atrial fibrillation.

PK-interacting drugs were used by 45.0% of cases and 51.2% of controls, with the most frequently prescribed drugs being simvastatin, atorvastatin and digoxin. There was no increased risk of major bleeds in people who used PK-interacting drugs alongside DOACs (adjusted OR [OR] 0.77;

95% CI 0.53 to 1.10). By contrast, concurrent use of drugs that have PD interactions with DOACs was associated with an increased risk of bleeding (adjusted OR 1.92, 95% CI 1.40 to 2.66). The most frequently used PD-interacting drugs were antiplatelet drugs (adjusted OR 2.01, 95% CI 1.29 to 3.11) and SSRIs (adjusted OR 1.68, 95% CI 1.10 to 2.59). The most commonly used antiplatelet drug was aspirin (8.1% of cases and 4.4% of controls).

## Context

DOACs are absorbed via P-gp and their elimination involves CYP3A4.<sup>1</sup> The summary of product characteristics for each DOAC includes details of possible PK interactions that may occur with concomitant use of drugs that inhibit and induce CYP3A4 and P-gp as well as details of PD interactions with drugs such as anticoagulants, antiplatelets, SSRIs and NSAIDs. A *Drug Safety Alert* published by the Medicines and Healthcare products Regulatory Agency advised healthcare professionals that some drug interactions with DOACs increase the risk of bleeding.<sup>2</sup> It included advice that strong inhibitors of P-gp or CYP3A4 (or both) increase circulating levels of DOACs and therefore may not be recommended or may require DOAC dose reduction. It also advised that DOACs should not be taken with other anticoagulants.

There is limited published data on the effect of concomitant medicines on the pharmacokinetics and pharmacodynamics of DOACs.<sup>3</sup> A study of 115 362 patients who had newly started a DOAC found that a bleeding event occurred in 7001 people (6.1%) of whom 3971 also received a drug with potential to interact with the DOAC.<sup>3</sup> The most common PD interactions were

associated with NSAIDs (1612), antiplatelet drugs (1490) and SSRIs (497). The most common PK interactions were associated with diltiazem (808), amiodarone (564), fluconazole (195), clarithromycin (164) and verapamil (141). Among the 2283 patients with a major bleeding event, 1508 were taking a drug with potential to interact with the DOAC. The risk of major bleeding events increased by around 3.6-fold in DOAC users who were taking two or more potentially interacting drugs.

This study provides further data on drug interactions with DOACs and highlights the need to remain vigilant for both pharmacokinetic and pharmacodynamic interactions.

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## References

- 1 Zhang Y, Souverein PC, Gardarsdottir H, *et al*. Risk of major bleeding among users of direct oral anticoagulants combined with interacting drugs: a population-based nested case-control study. *Br J Clin Pharmacol* 2020;86:1150–64.
- 2 Medicines and Healthcare products Regulatory Agency. Direct-Acting oral anticoagulants (DOACs): reminder of bleeding risk, including availability of reversal agents. *Drug Safety Update* 2020;13:1.
- 3 Lee JY, Oh I-Y, Lee J-H, *et al*. The increased risk of bleeding due to drug-drug interactions in patients administered direct oral anticoagulants. *Thromb Res* 2020;195:243–9.

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