Risk of drug-induced liver injury with the new oral anticoagulants: systematic review and meta-analysis

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Authors
Caldeira D, Barra M, Santos AT, Abreu D, Pinto FJ, Ferreira JJ, Costa J

Abstract
Objective
In recent years, safety alerts have been made warning of the risk of serious drug-induced liver injury (DILI) caused by cardiovascular drugs. The new oral anticoagulants (NOACs) have now reached the market. However, safety concerns have been raised about their hepatic safety. Therefore we aimed to evaluate NOAC liver-related safety.

Methods
Systematic review and meta-analysis of phase III randomised controlled trials (RCTs). Medline and CENTRAL were searched to September 2013. Reviews and reference lists were also searched. Two reviewers independently searched for studies and retrieved data estimates. Primary outcome was DILI (transaminases elevations >3× upper limit of normal (ULN) with total bilirubin >2× ULN). NOACs were compared against any control group. Random-effects meta-analysis was performed, and pooled estimates were expressed as relative risk (RR) and 95% CI heterogeneity was evaluated with I² test.

Results
Twenty-nine RCTs evaluating 152 116 patients (mean follow-up of 16 months) were included. All RCTs were rated as having low risk of bias. NOAC were not associated with an increased risk of DILI (RR 0.90, 95% CI 0.72 to 1.13, I²=0%). Similar results were obtained for individual NOAC (rivaroxaban, apixaban, dabigatran, darexaban, edoxaban) and considering the different control groups (vitamin K antagonists, low molecular weight heparin (LMWH) and placebo). The risk of transaminases elevations (>3×ULN) was lower among NOAC-treated patients, in particular in comparison with LMWH-treated patients (RR 0.71, 95% CI 0.59 to 0.85; I²=27%)"