Non-vitamin K antagonist oral anticoagulants and major bleeding-related fatality in patients with atrial fibrillation and venous thromboembolism: a systematic review and meta-analysis

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Abstract
Objective
Non-vitamin K antagonist oral anticoagulants (NOACs) are efficacious and safe antithrombotic drugs but the non-availability of an antidote for potential fatal haemorrhagic events is clinically perceived as a strong limitation. We aimed at evaluating the risk of haemorrhage-related fatalities associated with NOACs in patients requiring long-term anticoagulation.

Methods
MEDLINE, Cochrane Library and Web of Science databases were searched in November 2014 for atrial fibrillation (AF) or venous thromboembolism (VTE) phase III randomised controlled trials (RCT) comparing NOACs with vitamin K antagonists (VKAs) or low molecular weight heparin (LMWH) followed by VKAs. Pooled OR and 95% CIs were estimated through meta-analysis. Heterogeneity was assessed with the I² test.

Results
Eleven studies were included: 5 on AF and 6 on VTE. A total of 100,324 patients were evaluated in 4 rivaroxaban, 3 dabigatran, 2 apixaban and 2 edoxaban studies. NOAC-treated patients had a 47% odds reduction compared with VKA (OR 0.53; 95% CI 0.42 to 0.68; I²=0%; 3 events avoided per 1000 patients) and 64% odds reduction compared with LMWH–VKA (OR 0.36; 95% CI 0.15 to 0.84; I²=0%; 1 event avoided per 1000 patients) regarding fatal bleeding risk. Case fatality due to major bleeding was lower in NOAC-treated patients both in AF (OR 0.68; 95% CI 0.48 to 0.96; I²=37%; 1 death avoided per 39 major bleedings) and VTE (OR 0.54; 95% CI 0.22 to 1.32; I²=0%) patients. AF survivors of major bleeding events treated with NOACs had lower mortality compared with patients treated with VKAs (OR 0.57; 95% CI 0.45 to 0.73; I²=0%; 78 events avoided per 1000 survivors to major bleeding).

Conclusions
These data suggest that NOACs decrease the risk of fatality cases related to major bleeding events, particularly in AF patients. These results support the safety profile of NOACs even without having a widely available drug-specific antidote.