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Title: Direct oral anticoagulants halve thromboembolic events following cardioversion of atrial fibrillation compared to warfarin: A meta-analysis of randomized trials

Short title: DOACs for cardioversion of atrial fibrillation

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Key Words: Atrial fibrillation; cardioversion; anticoagulation; NOAC; warfarin; stroke; mortality.

Abbreviations

AF	Atrial fibrillation
CV	Cardiovascular
CI	Confidence interval
DOAC	Direct oral anticoagulant
MI	Myocardial infarction
I^2	Heterogeneity between trials
SE	Systemic embolus
VKA	Vitamin K antagonist oral anticoagulant

Cardioversion of symptomatic atrial fibrillation (AF) is commonly used to restore sinus rhythm, both acutely and as part of a long-term rhythm control strategy.(1) This approach is associated with a risk of stroke, however the efficacy of direct oral anticoagulants (DOACs) compared to vitamin K antagonists (VKA) for prevention of thromboembolism is unclear. We performed a meta-analysis of trials that have randomized AF patients undergoing cardioversion to DOAC or VKA. An online search was performed of PubMed and the Cochrane library, in addition to manual screening. We used an intention-to-treat approach with a fixed-effects model. Our aim was to provide clinicians with a clear understanding of which anticoagulation strategy provides the safest outcome for AF patients undergoing cardioversion.

The search identified 124 studies, of which three prospective trials met inclusion criteria.(2-4) In total, 5203 patients were included in this analysis, 2850 randomized to DOAC and 2353 to VKA. Mean age was 65 years (SD 11), female patients accounted for 32%, and the CHA_2DS_2-VASc score was ≥2 in over 70% of patients. All three trials required treatment with the allocated anticoagulant prior to cardioversion, and in VKA patients, parenteral heparin was used to bridge warfarin therapy until an international normalized ratio ≥2.0 was achieved. Around half of patients had early cardioversion guided by imaging (mainly transesophageal echocardiography). Study treatment after cardioversion was continued for 28-42 days, with 30-day safety follow-up. The risk of bias in these trials was low, apart from potential performance bias due to the open-label designs.

Primary outcome: The composite of stroke, systematic embolism, myocardial infarction and cardiovascular death occurred in 12/2850 (0.42%) patients randomized to a DOAC versus 23/2353 (0.98%) to VKA (Figure). DOAC therapy considerably reduced primary outcome events compared to VKA, with a pooled risk ratio of 0.42, 95% CI 0.21-0.86, a p-value of 0.017, and no heterogeneity between trials (I^2=0%, p=0.84).

Secondary outcomes: Stroke and systemic embolism occurred in 5/2850 (0.18%) in DOAC patients versus 13/2353 (0.55%) randomized to VKA; the pooled risk ratio was 0.33, 95% CI 0.12-0.91, with a p-value of 0.032 and no heterogeneity between trials (I^2=7.5%, p=0.34). There were no significant differences between NOAC and VKA in all-cause mortality (risk ratio 0.58, 95% CI 0.22-1.52, p=0.27) or major bleeding (risk ratio 0.61, 95% CI 0.28-1.34, p=0.22), however both point estimates were consistent with the benefit seen for other outcomes (Figure).

Our analysis suggests that DOAC therapy should be considered the default approach for cardioversion of AF, with half the rate of thromboembolic events compared to anticoagulation with warfarin. Warfarin and other VKA should be restricted to those patients who are not eligible for DOAC therapy, for example those with mechanical heart valves, moderate to severe mitral stenosis or severe chronic kidney disease. We demonstrate the safety of DOAC therapy in patients with newly initiated oral anticoagulation, including those requiring rapid cardioversion with imaging guidance, and those undergoing cardioversion after three weeks of anticoagulation. Due to the short onset of action and the predictable dosing of DOACs, clinicians can commence a DOAC immediately without the need for parenteral heparin.(1)

This meta-analysis is limited by the nature of the trials included, which only studied the short-term effects of anticoagulation. None of the trials were individually powered for clinical outcomes, although the power for our pooled analysis was >0.99 for the stroke-related composite outcomes. Over 90% of patients underwent electrical cardioversion, and although there is no *a priori* reason to suspect a difference with pharmacological cardioversion, data in this context are scarce. Further studies are needed to address the remaining gaps in evidence, including the identification of those at risk of adverse events despite oral anticoagulation, and the optimal timing of both anticoagulants and cardioversion to minimize stroke risk. In combination with integrated approaches to AF care and stratification of therapy (5), the routine use of DOACs for cardioversion can improve safety for patients undergoing cardioversion.

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Figure: Meta-analysis of DOAC versus VKA for cardioversion of AF