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Letter to the Editor

Are direct oral anticoagulants effective in reducing systemic embolism in patients with atrial fibrillation? A systematic review and meta-analysis of the literature

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Dear Sir,

Atrial fibrillation (AF) is the most prevalent sustained heart arrhythmia. It is the most important clinical risk factor for systemic embolism (SE) and is regarded to be the cause of stroke in up to one fourth of cases [1]. However, since stroke is much more prevalent than SE in patients with AF, the latter is not considered to be a main single outcome parameter in AF trials. As a consequence, the majority of trials on the role of anticoagulants in AF patients have focused over stroke prevention, and SE has been included only as a part of composite end-points. Thus, the superiority of warfarin compared to antiplatelet agents in preventing non-cerebral embolism has been proven only in a recent meta-analysis [2]. European and US guidelines currently recommend oral anticoagulants over antiplatelet agents for stroke prevention in AF, and these indications are thought to be applicable also for prevention of SE.

Recently, a number of randomized controlled trials (RCTs) and meta-analyses have shown that direct oral anticoagulants (DOACs) are at least as effective and safe as compared to VKAs in AF patients. Furthermore, DOACs have several potential advantages in comparison to VKAs, including a wider therapeutic window at fixed dosing regimens and minimal and manageable food and drug interactions with no requirement for routine monitoring favoring their use in place of VKAs. However, evidence on their efficacy in reducing the incidence of SE is more limited. Thus, we performed a systematic review and meta-analysis of the literature to clarify this issue.

After having prospectively developed a protocol that specified objectives, criteria for study selection and outcome evaluations, and statistical methods, Medline and Embase databases were searched from inception to September 2014 without any language restriction and using medical subject headings and text words (an example of the search strategy is available in appendix). We supplemented our research searching in the www.clinicaltrials.gov web site to identify unpublished trials. We included only *phase-III* RCTs evaluating the efficacy and safety of DOACs in comparison to VKAs in patients with non-valvular AF. For each selected study, we analyzed data regarding the incidence of SE only. Pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated with a random effects model using Review Manager (Rev-Man; version 5.1 for Windows; Oxford, UK; The Cochrane Collaboration, 2011). Subsequently, we repeated our analysis excluding low dose DOACs arms (e.g dabigatran 110 mg *two times a day*, edoxaban 30 mg *once a day*). The appropriateness of pooling data across the studies was assessed with the use of the Cochran Q and the I2 test for heterogeneity.

After abstracts and full text evaluation, four studies for a total of 71,390 patients were included in our systematic review [3–6]. *Research on www.clinicaltrials.gov did not reveal any unpublished trial.* General characteristics of included studies were summarized in Table 1. Three studies compared factor Xa inhibitors (rivaroxaban, apixaban and edoxaban), and one thrombin inhibitor (dabigatran), to VKAs. In all the included studies, the primary efficacy end-point was a composite of stroke (both ischemic and hemorrhagic) and SE; the mean follow-up was quite similar among the studies (about 2 years). Conversely, the definition of SE was quite different in the four trials and was detailed in Table 1. SE occurred in 92 of 42,247 patients (0.22%) in the DOACs' group, and in 83 of 29,143 (0.28%) in the VKAs' group. Thus, the use of DOACs was associated with a non-significant reduction in the occurrence of SE compared to VKAs with a significant heterogeneity among

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Table 1
General characteristics of included studies and the definition of systemic embolism in the four trials.

Study	Inclusion criteria	Exclusion criteria	Study drug	Primary endpoint	Enrolled patients, n and mean follow-up	Study	Systemic embolism definition
RE-LY 2009	Patients with AF and at least one of the following: previous stroke or transient ischemic attack, left ventricular ejection fraction of less than 40%, NYHA class II and aged at least 75 years or an age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease	Severe heart-valve disorder, stroke within 14 days or severe stroke within 6 months before screening, a condition that increased the risk of hemorrhage, a creatinine clearance of less than 30 ml/min, active liver disease, and pregnancy	Dabigatran 110 or 150 mg twice daily	A composite of stroke or systemic embolism	18,113 2 year FU	RE-LY 2009	Acute vascular occlusion of an extremity or organ, documented by means of imaging, surgery, or autopsy
ROCKET-AF 2011	patients with AF with a history of stroke, transient ischemic attack, or systemic embolism or at least two of the following risk factors: heart failure or a left ventricular ejection fraction of 35% or less, hypertension, an age of 75 years or more, or diabetes mellitus	Valvular or transient AF, active internal bleeding, history of or condition associated with increased bleeding risk, sustained uncontrolled hypertension, severe, disabling stroke, indication for anticoagulant therapy for a condition other than AF; treatment with aspirin >100 mg daily or aspirin in combination with thienopyridines study; calculated CLCR <30 ml/min, known significant liver disease	Rivaroxaban 15 or 20 mg once daily	Composite of stroke (ischemic or hemorrhagic) and systemic embolism	14,264 707 day FU	ROCKET-AF 2011	In the presence of atherosclerotic peripheral arterial disease, the diagnosis of embolism required angiographic demonstration of abrupt arterial occlusion.
ARISTOTLE 2011	patients with AF or flutter and at least one of the following: age of at least 75 years; previous stroke, transient ischemic attack, or systemic embolism; symptomatic heart failure within the previous 3 months or left ventricular ejection fraction of no more than 40%; diabetes mellitus; hypertension requiring pharmacologic treatment.	Atrial fibrillation due to a reversible cause, moderate or severe mitral stenosis, conditions other than atrial fibrillation that required anticoagulation, stroke within the previous 7 days, a need for aspirin at a dose of >165 mg a day or for both aspirin and clopidogrel, and severe renal insufficiency (serum creatinine level of >2.5 mg/dl or calculated creatinine clearance of <25 ml/min)	Apixaban 2.5 or 5 mg twice daily	Stroke or systemic embolism	18,201 1.8 year FU	ARISTOTLE 2011	Systemic embolism required a clinical history consistent with an acute loss of blood flow to a peripheral artery (or arteries) supported by evidence of embolism from surgical specimens, autopsy, angiography, vascular imaging, or other objective testing.
ENGAGE AF-TIMI 18 2013	Patients with AF and a score of 2 or higher on the CHADS2 risk assessment	AF due to a reversible disorder; estimated creatinine clearance of less than 30 ml/min; high risk of bleeding; use of dual antiplatelet therapy; moderate-to-severe mitral stenosis; other indications for anticoagulation therapy; acute coronary syndromes, coronary revascularization, or stroke within 30 days before randomization	Edoxaban 30 or 60 mg once daily	Time to the first adjudicated stroke (ischemic or hemorrhagic) or systemic embolic event	21,105 2.8 years FU	ENGAGE AF TIMI 18 2013	An arterial embolism resulting in clinical ischemia, excluding the CNS, coronary and pulmonary arterial circulation