**Adherence of Direct oral anticoagulants in patients with atrial fibrillation: meta-analysis and systematic review**

*Subo Emanuel, Riyaz Kaba, Gregory Y.H. Lip, Ben Field, Simon de Lusignan*

**Citation**

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**Review question**

In people with atrial fibrillation to what extend does adherence (or persistence) affect clinical outcomes, with a focus on all-cause mortality, stroke and bleeding ?

Abstract

Atrial Fibrillation (AF) is the leading and most preventable cause of embolic stroke. It is directly responsible for approximately 20-30% of all strokes. One in twenty patients over the age of 65 years with AF are expected to suffer a stroke each year i.e. those with AF are at 5-6 times greater risk of stroke (Wolf *et al.*, 2012). This increases to one in five patients over the age of 80 years, with 25% of all strokes in patients aged 80-89 years being associated with AF. Of note, AF-related strokes are associated with increased mortality, morbidity, disability, and a longer inpatient stay. Patients with AF related strokes have disability with cortical deficit (aphasia), severe limb weakness, reduced alertness and are often bedridden at admission (Stewart *et al.*, 2002).

The World Health Organisation defines adherence as “the extent to which a person’s behaviour, taking medication, following a diet, and /or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.”

Most frequently adherence to therapy is limited by the complexity of the regimen (the number of medicines and the frequency of administration), and failure of a patient and/or their relatives to understand the importance of compliance. We reviewed if there are factors which affect adherence and persistence such CHA2DS2VASc score, which is commonly used for clinical estimating the risk of stroke in patients with non-valvular atrial fibrillation(Lip al 2010)

Adherence (and persistence) to direct oral anticoagulants (DOACs) is an essential element of anticoagulation effectiveness and can be related to the outcomes of long-term therapy as discussed above.. However, despite these DOACs offering some potential advantages over vitamin K antagonists, information on adherence and clinical outcomes based on real-world data are still limited.

The goal of this meta-analysis and systemic review is to identify any distinct characteristics of patients with AF who received initial anticoagulation therapy with warfarin versus those who received DOACs.

**Searches**

Electronic searches will be conducted using the following major medical databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Science Citation Index, BIOSIS Previews and LILACS without language or date restrictions. Search strategies designed for the MEDLINE scoping searches will be adapted to run on other databases. In addition, information on studies in progress, unpublished research or research reported in the grey literature will be sought from a range of relevant databases and trial registers including www.clinicaltrials.gov. Additional studies, including unpublished and grey literature, will be identified by screening reference list of retrieved studies and relevant review articles, contacting drug manufacturers, internet searches, and by searching trial registers

The search included a combination of the following MESH and keyword searches:

atrial fibrillation, oral anticoagulant, direct acting oral anticoagulant, factor Xa inhibitor,pradaxa,xarelto,eliquis,lixiana,edoxaban,rivaroxaban,dabigatran,apixaban,bleeding,stroke,gastrointestinal bleeding, intracranial haemorrhage, medication adherence, medication non adherence patient compliance, patient noncompliance ,drug persistence, drug nonpersistence

**Condition or domain being studied**

In comparison to warfarin, non-vitamin K antagonist oral anticoagulants (DOACs) have the advantages of ease of dosing, fewer drug interactions, and lack of need for ongoing monitoring. We sought to evaluate whether these advantages translate to improved adherence and whether adherence is associated with improved outcomes in patients with atrial fibrillation.

**Participants/population**

Patients affected by non-valvular AF treated with DOACs. All participants on direct oral anticoagulants for other reasons than AF such as deep venous thrombosis, pulmonary embolism, and mechanical valves. Any information not relevant to primary care was excluded and competing risks are not considered.

**Intervention(s), exposure(s)**

Adherence and/ persistence related to direct oral anticoagulants

**Comparator(s)/control**

Non-adherence and/nonpersistence related to direct oral anticoagulants

**Main outcome(s)**

**Primary endpoints**

Clinical outcomes, including all-cause mortality, stroke, and bleeding.

***\* Measures of effect***

All clinical outcomes, including all-cause mortality, strokes and bleeding during follow-up periods.

**Additional outcome(s)**

We will also measure if there are any factors associated with poor or good medication adherence to DOACs such as age,sex,ethnicity CHA2DS2VASc score, type of anticoagulant treatment, prior exposure to warfarin.

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***Measures of effect***

All outcomes above will be looked up during follow-up

**Inclusion Criteria:**

All participants with AF on DOACs.

**Exclusion Criteria**

All participants on direct oral anticoagulants for other reasons than AF such as deep venous thrombosis, pulmonary embolism, and mechanical valves. Any information not relevant to primary care was excluded and competing risks are not considered.

**Data extraction (selection and coding)**

Study selection will be performed in accordance with PRISMA guidelines.

The study selection will be performed in multiple phases. In the first phase, potentially relevant studies will be obtained by combined searches of electronic databases using the above-mentioned selected keywords. Then, studies not in English language, with no abstract/full text available or not involving humans, were excluded. In the second phase, studies will be reviewed and excluded by study typology; thus, letters, editorials, case reports, cross-sectionals, reviews, meta-analysis, and comments were excluded. The third phase consisted of a detailed analysis of full-text articles to assess whether they addressed the specific study question and if they provided necessary data for the analysis.

For each study we will collect the following information: authors, year of publication, study typology, number of participants included, percentage of males, age, CHA2DS2VASc score, prevalence of any factors affecting adherence , type of anticoagulant treatment, prior exposure to warfarin, follow-up (year), number of events during follow-up.

**Risk of bias (quality) assessment**

The presence of publication bias was evaluated by using the funnel plots.

Quality assessment will be performed independently and blindly by two researchers according to the “Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies” developed by the National Heart, Lung, and Blood Institute (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). According to the answers obtained from a specific list of 14 questions, the studies will be divided into high, medium, and low quality.

Two physicians independently will screen the titles and abstracts of manuscripts identified through the database searches to identify studies potentially eligible for further assessment. Controversies will be resolved by a third investigator.

**Strategy for data synthesis**

Meta-analysis for each endpoint (primary and additional) will be performed separately based on both linear fixed and random effects, using the logarithm of hazard ratios (HR) as outcome

Additionally, meta-regression analysis will be performed for age, sex, CHA2DS2VASc scoring, chronic kidney disease, diabetes, previous myocardial infarction, duration of treatment, heart failure. Results of meta-regression will also be summarized by means of bubble plots, with bubbles proportional to the inverse variance of each study and trends estimated through non-parametric local polynomial regression.

The statistical analysis was performed using R and the metaphor package.

The average difference was used for the summarization of meta-analytic effect by the random-effect model.

**Analysis of subgroups or subsets**

We will perform meta-regression analysis according to sex, age, CHA2DS2VASc scoring, prior myocardial infarction, chronic kidney disease, heart failure and diabetes mellitus.

**Discussion:**

This will be one of the first meta-analysis and systematic review of adherence of DOACs in AF which will have primary care management at the forefront. The main importance is that It will fulfil the needs in primary care management where DOACs are commenced and are now the first line anticoagulant treatment for stroke prevention of AF.Thus the findings from this study will aid primary care to place special weight and attention where required to be given to factors which affect adherence and persistence and hence prevent stroke and bleeding.

References :

Lip GYH et al (2010) ” Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation”.Chest.137(2)263-72.doi:10.1378/chest.09-1584

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Wolf, P. A. *et al.* (2012) ‘Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The fiamingham Study’, *Neurology*. doi: 10.1212/wnl.28.10.973.

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