**Bleeding risk in patients treated with aspirin vs. direct oral anticoagulants at doses approved for atrial fibrillation:**

**Systematic review and meta-analysis of randomized controlled trials**

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**Abstract**

**Background and purpose:** A considerable proportion of patients with atrial fibrillation (AF) are still treated with aspirin despite current guidelines which do not recommend its use anymore. The level of evidence supporting a beneficial of aspirin compared to control/placebo for stroke prevention in AF is weak, being based on a single, prematurely terminated randomized controlled trial (RCT). These recommendations could be strengthened by the results of recent large RCTs in non-AF populations which compared aspirin vs. direct oral anticoagulant (DOACs) at doses approved for AF. We performed a systematic review and meta-analysis of bleeding outcomes in RCTs which compared aspirin vs. DOACs at doses approved for AF.

**Methods:** We searched PubMed and Scopus for phase-III RCTs of aspirin vs. DOACs at doses approved for AF (inception to 28/05/2019). The outcomes assessed were major-, intracranial-, gastrointestinal-, clinically-relevant-non-major- and fatal bleeding. We performed two subgroup analyses: one per patient population i.e. AF/non-AF population, and one per DOAC used. We also performed a meta-regression to assess the association with patient age.

**Results**: In 4 eligible trials (20,440 patients) comparing DOACs vs. aspirin, the ORs were as follows: for major bleeding, 1.55 (95%CI:0.99-2.45, relative-risk-reduction:55%, absolute-risk-reduction:0.6%, number-needed-to-harm:170) with moderate heterogeneity between AF/non-AF subgroups and large heterogeneity between different DOACs; and for intracranial bleeding, 1.48 (95%CI:0.71-3.10) with moderate heterogeneity between AF/non-AF subgroups and large heterogeneity between different DOACs. For gastrointestinal bleeding, the OR was 1.26 (95%CI:0.86-1.85) with no heterogeneity between subgroups; and for clinically-relevant-non-major bleeding, 1.42 (95%CI:1.18-1.70, relative-risk-reduction:40.2%, absolute-risk-reduction:0.9%, number-needed-to-harm:113) with low heterogeneity between AF/non-AF subgroups and large heterogeneity between different DOACs. Age at study recruitment was not a predictor of the magnitude of the OR for all bleeding outcomes.

**Conclusions**: The present meta-analysis and meta-regression does not provide support for the use of aspirin over DOACs in AF patients. Accordingly, the level of evidence of the related recommendations should be upgraded, which in turn may reduce further the proportion of AF patients treated with antiplatelets.

**Key words:** oral anticoagulation; aspirin; atrial fibrillation; non-vitamin-K antagonist oral anticoagulants; stroke prevention; bleeding; safety

**Disclosures**

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**Introduction**

Aspirin was recommended in the past as an alternative to oral anticoagulation for the prevention of thromboembolism in patients with atrial fibrillation (AF) and a CHA2DS2-VASc score of 1[1](#_ENREF_1). The AVERROES trial (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) was the first large randomized controlled trial of a non-vitamin-K-antagonist oral anticoagulant (NOAC, also called direct oral anticoagulant, DOAC) vs. aspirin in an AF population and showed no significant difference in major bleeding between apixaban and aspirin[2](#_ENREF_2). Current guidelines do not recommend the use of aspirin for stroke prevention[3-5](#_ENREF_3). The supposed beneficial effect of aspirin compared to placebo/control is supported by a single RCT which was prematurely terminated, with marked internal heterogeneity for the aspirin effect between anticoagulation-eligible and anticoagulation-ineligible patients [SPAF trial 1991].

A considerable proportion of AF patients worldwide are still treated with aspirin[6-15](#_ENREF_6). The phase-II GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation) investigators reported a global mean percentage of 11% aspirin-prescribed patients at baseline in newly diagnosed AF[15](#_ENREF_15). Of note, 20% of AF-patients with a CHA2DS2VASc score 1 and 10% of patients at high risk for ischemic stroke were treated with aspirin5. These high use of aspirin has been attributed to a perceived lower hemorrhagic risk of aspirin compared to oral anticoagulants. The GARFIELD-AF study (Global Anticoagulant Registry in the FIELD-Atrial Fibrillation) demonstrated increasing antiplatelet use with each increase in HAS-BLED score points[16](#_ENREF_16).

Recently, three large randomized controlled trials in non-AF populations compared aspirin vs. DOACs at doses which are approved for AF [17](#_ENREF_17), [18](#_ENREF_18), [19](#_ENREF_19). These studies provide further data about the safety profile of DOACs vs. aspirin and could be used to strengthen the level of evidence of the recommendations about the safety of antiplatelets in patients with AF.

In this context, we performed a systematic review and meta-analysis of randomized controlled trials which compared aspirin vs. a DOAC at doses approved for AF and reported bleeding outcomes.

**Methods**

This systematic review with meta-analysis was conducted in accordance with the Preferred Reporting of Systematic Review and Meta-Analysis (PRISMA) statement and was registered at the PROSPERO registry (CRD42019125520) [20](#_ENREF_20).

*Search strategy and inclusion criteria*

We searched PubMed (all fields) and Scopus (title-abstract-key words) without language restriction between first available date and 28/05/2019 for full-text articles of randomized controlled trials comparing aspirin with a DOAC regardless of the indication. The search items were: (DOAC OR DOAC OR new oral anticoagulant OR direct oral anticoagulant OR novel oral anticoagulant OR non-vitamin-K antagonist oral anticoagulant OR NOAC OR thrombin antagonist OR Xa inhibitor OR apixaban OR rivaroxaban OR dabigatran OR edoxaban) AND (aspirin OR acetylsalicylic acid) AND (randomized controlled trial) AND (bleeding OR hemorrhage OR haemorrhage). According to prespecified criteria, eligible studies for the meta-analysis had to be phase-III RCT of aspirin vs. a DOAC. We excluded trials that investigated DOACs at a dose that is not approved for AF.

*Outcomes, data extraction and assessment of risk of bias*

The outcomes assessed were major-, intracranial-, gastrointestinal-, clinically relevant non-major- and fatal bleeding. Data extraction was performed independently by the first and the last author using prespecified forms including information about the study design, eligibility criteria, number of patients, duration of follow-up and outcomes. An assessment of the risk of bias was done by the same investigators with the use of the Cochrane Collaboration’s tool focusing on sequence generation, allocation concealment, blinding, addressing incomplete outcome data, selective reporting and presence of other bias. Any discrepancy or uncertainty was resolved by consensus or discussion among all authors.

*Statistical analysis*

All analyses were performed on the intention-to-treat principle. Pooled results are presented as odds-ratios (OR) and 95% confidence intervals (CI), which were calculated for each outcome using the random-effects method. The mean effect size and CIs of individual studies were illustrated with forest plots. Statistical heterogeneity between trials was assessed by the I2 index and considered as low, moderate or large for I2 levels of 0-25%, 25%-50% and >50% respectively. We calculated differences in relative risk [relative risk reduction (RRR) or increase (RRI)], absolute risk [absolute risk reduction (ARR) or increase (ARI)] and numbers-needed-to-harm (NNH) to have an additional outcome. In pooled outcomes with substantial heterogeneity, we pre-specified two exploratory subgroup analyses: one per patient population i.e. AF and non-AF population, and one per DOAC used. Differences in pooled effect sizes between subgroups were compared with a test of interaction (Cochran’s Q test). Also, we performed a random-effects meta-regression to estimate the contribution of the participants’ mean age to the overall heterogeneity of bleeding outcomes.

All analyses were performed with the Review Manager 5 (RevMan) version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Meta-regression was conducted with STATA package, version 11.1 (StataCorp, College Station, Texas USA).

**Results**

The initial literature search in databases yielded 1161 potentially eligible articles, of which 4 met the inclusion criteria (Supplemental Figure 1) [17](#_ENREF_17), [21](#_ENREF_21), [18](#_ENREF_18), [19](#_ENREF_19). The main characteristics of the 4 trials included in the meta-analysis are summarized in the supplemental Table 1. The DOACs tested in these trials were apixaban, dabigatran and rivaroxaban; there was no eligible trial of edoxaban. The median duration of follow-up ranged between 11 and 19 months. We did not identify any major risk of bias (supplemental Figure 2).

Among 20,440 patients included in the meta-analysis, 10,219 (50.0%) were allocated to a DOAC [2,695 (26.4%) to dabigatran; 2,808 (27.5%) to apixaban; 4,716 (46.1%) to rivaroxaban] and 10,221 (50.0%) to aspirin.

*Major bleeding*

During the total follow-up period, there were 318 major bleeding events. The rate was 1.8% (189 events) in DOAC-assigned patients and 1.3% (129 events) in aspirin-assigned patients (OR: 1.55, 95%CI:0.99-2.45, RRI:55%, ARI:0.6%, NNH:170), with large heterogeneity between studies (I2: 68%). The ORs for the AF and the non-AF population were 1.12 (95%CI:0.73-1.73) and 1.81 (95%CI:0.94-3.48) respectively, with moderate heterogeneity in-between (I2: 30.1%) (figure 1, panel A).

Compared with aspirin, the ORs were 1.12 (95%CI:0.73-1.73) for apixaban, 1.21 (95%CI:0.86-1.69) for dabigatran and 2.64 (95%CI:1.68-4.16, RRI:162%, ARI:0.9%, NNH:112) for rivaroxaban, with large heterogeneity between the DOAC used (I2: 78.1%) (figure 1, panel B).

*Intracranial bleeding*

During the total follow-up period, there were 118 intracranial bleeding events. The rate was 0.6% (66 events) in DOAC-assigned patients and 0.5% (52 events) in aspirin-assigned patients (OR: 1.48, 95%CI:0.71-3.10). There was significant heterogeneity between studies (I2: 62%). The ORs for the AF and the non-AF population were 0.84 (95%CI:0.38-1.88) and 1.76 (95%CI:0.64-4.82) respectively, with low heterogeneity in-between (I2: 20.6%) (figure 2, panel A).

Compared with aspirin, the ORs were 0.84 (95%CI:0.38-1.88) for apixaban, 1.00 (95%CI:0.61-1.64) for dabigatran and 3.85 (95%CI:1.56-9.46, RRI:285%, ARI:0.3%, NNH:277) for rivaroxaban, with large heterogeneity between the DOAC used (I2: 68.3%) (figure 2, panel B).

*Gastro-intestinal bleeding*

During the total follow-up period, there were 109 gastrointestinal bleeding events. The rate was 0.60% (61 events) in DOAC-assigned patients and 0.47% (48 events) in aspirin-assigned patients (OR:1.26, 95%CI:0.86-1.85). There was no sign of heterogeneity between studies (I2: 0%). The ORs for the AF and the non-AF population were 0.85 (95%CI:0.39-1.84) and 1.44 (95%CI:0.92-2.24) respectively, with low heterogeneity (I2: 24.9%) (figure 3, panel A).

Compared with aspirin, the ORs were 0.85 (95%CI:0.39-1.84) for apixaban, 1.23 (95%CI:0.70-2.16) for dabigatran and 1.84 (95%CI:0.91-3.72) for rivaroxaban, with no heterogeneity between the DOAC used (I2: 4.0%) (figure 3, panel B).

*Clinically relevant non-major bleeding*

During the total follow-up period, there were 538 clinically relevant non-major bleeding events. The rate was 3.1% (314 events) in DOAC-assigned patients and 2.2% (224 events) in aspirin-assigned patients (OR:1.42, 95%CI:1.18-1.70, RRI:40.2%, ARI:0.9%, NNH:113). There was low heterogeneity between studies (I2: 9%). The ORs for the AF and the non-AF population were 1.14 (95%CI:0.85-1.54) and 1.58 (95%CI:1.27-1.96) respectively, with large heterogeneity in-between (I2: 66.6%) (figure 4, panel A).

Compared with aspirin, the ORs were 1.14 (95%CI:0.85-1.54) for apixaban, 1.73 (95%CI:1.17-2.55, RRI: 70.7%, ARI: 1.1%, NNH: 93) for dabigatran and 1.52 (95%CI:1.17-1.96, RRI: 50.1%, ARI: 1.0%, NNH: 95) for rivaroxaban, with moderate heterogeneity between the DOAC used (I2: 39.2%) (figure 4, panel B).

*Fatal bleeding*

During the total follow-up period, there were 24 fatal bleeding events. The rate was 0.10% (10 events) in DOAC-assigned patients and 0.14% (14 events) in aspirin-assigned patients (OR:0.76, 95%CI:0.24-2.45). There was low heterogeneity between studies (I2: 30%). The ORs for the AF and the non-AF population were 0.66 (95%CI:0.19-2.35) and 0.85 (95%CI:0.12-6.10) respectively, with no heterogeneity in-between (I2: 0%) (figure 5, panel A).

Compared with aspirin, the ORs were 0.66 (95%CI:0.19-2.35) for apixaban, 0.17 (95%CI: 0.02-1.38) for dabigatran and 2.37 (95%CI:0.42-13.21) for rivaroxaban, with moderate heterogeneity between the DOAC used (I2: 45%) (figure 5, panel B).

*The effect of age on outcomes of DOAC-assigned patients compared with aspirin-assigned*

Age at study recruitment was not a predictor of the magnitude of the OR of the comparison between DOACs and aspirin for all bleeding outcomes: major bleeding: OR=0.976 (95%CI: 0.701-1.36) per year of age; intracranial bleeding OR=0.986 (95%CI 0.605-1.61) per year of age; clinically relevant non-major bleeding OR=0.985 per year of age (95% CI 0.896-1.08) (figure 6).

**Discussion**

In this meta-analysis of 4 RCTs and 20,440 patients, we found no significant difference between patients assigned to aspirin or DOAC at doses approved for AF for the outcomes of major-, intracranial and fatal bleeding. There was a higher rate of clinically relevant non-major bleedings and a trend for more major bleedings in DOAC-assigned patients compared with aspirin-assigned. Still, the clinical significance of these associations are limited, as it would require 113 and 170 patients respectively to be treated with a DOAC rather than aspirin to have one more event`. The risk of bleeding was not associated with the age of the patient or the specific DOAC used.

The evidence supporting aspirin for stroke prevention is weak [ref] and recent studies in elderly patients using warfarin [refs] or DOACs [refs] do not support the effectiveness nor safety of aspirin. A considerable proportion of patients with AF continue to be treated with antiplatelets [6-15](#_ENREF_6), especially patients who are older or are considered frail. Indeed, the present meta-analysis shows a similar safety profile between aspirin and DOACs without any interaction with age. These findings could support the upgrade of the level of evidence of the related recommendations and potentially facilitate the further reduction of the proportion of AF patients who still receive antiplatelet treatment.

*Strengths and Limitations*

The present study is limited by the inherent shortcomings of most meta-analyses like differences in the selection criteria, definitions of comorbidities, outcomes and length of follow-up. In addition, two of the included trials were prematurely terminated[18](#_ENREF_18), [21](#_ENREF_21). Also, another limitation is that much of the evidence which is included in the present meta-analysis has to be considered as indirect, given that three of the four included trials studied non-AF populations. Still, we argue that this indirectness does not bias our conclusions significantly for two reasons: firstly, there was low or no heterogeneity between the AF and the non-AF populations for the three of the five outcomes assessed (intracranial- gastrointestinal- and fatal bleeding). Second, for the other two outcomes (major- and clinically relevant non-major bleeding) for which heterogeneity was present between the AF and the non-AF population, the comparison of bleeding risk in the non-AF population favored aspirin. Hence, if the aforementioned indirectness indeed biased the overall results and conclusions, this would be against DOACs, which means that the true estimate of the safety profile of DOACs against aspirin in a population that would be free of indirectness-bias (i.e. a purely AF population) would have been even more favorable.

In conclusion, this meta-analysis does not provide any support for the use of aspirin over DOACs in patients with AF. Accordingly, the level of evidence of the related recommendations could be upgraded, which in turn may reduce further the proportion of AF patients who are treated with antiplatelets.

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**Figure 1:** Forest plot of the effect of DOACs compared to aspirin on major bleeding per patient population (panel A) and DOAC studied (panel B).

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**Figure 2:** Forest plot of the effect of DOACs vs. aspirin on intracranial bleeding per patient population (panel A) and DOAC studied (panel B).

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**Figure 3:** Forest plot of the effect of DOACs vs. aspirin on gastrointestinal bleeding per patient population (panel A) and DOAC studied (panel B).

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**Figure 4:** Forest plot of the effect of DOACs vs. aspirin on clinically relevant non-major bleeding per patient population (panel A) and DOAC studied (panel B).

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**Figure 5:** Forest plot of the effect of DOACs vs. aspirin on fatal bleeding per patient population (panel A) and DOAC studied (panel B).

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**Figure 6:** Bubble plot with random-effects meta-regression line for the association of age with the logOR risk of major bleeding (panel A), intracranial bleeding (panel B) and clinically relevant non-major bleeding (panel C) between DOACs and aspirin.