

## MINI REVIEW

# Effectiveness and safety of direct oral anticoagulants in atrial fibrillation patients switched from vitamin K antagonists: A systematic review and meta-analysis

Maja Hellfritsch<sup>1</sup> | Kasper Adelborg<sup>2,3</sup> | Per Damkier<sup>4,5</sup> | Søren Paaske Johnsen<sup>2,6</sup> | Jesper Hallas<sup>1</sup> | Anton Pottegård<sup>1</sup> | Erik Lerkevang Grove<sup>7,8</sup>

<sup>1</sup>Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark

<sup>2</sup>Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

<sup>3</sup>Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark

<sup>4</sup>Department of Clinical Chemistry and Pharmacology, Odense University Hospital, Odense, Denmark

<sup>5</sup>Department of Clinical Research, University of Southern Denmark, Odense, Denmark

<sup>6</sup>Department of Clinical Medicine, Aalborg University and Aalborg University Hospital, Aalborg, Denmark

<sup>7</sup>Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark

<sup>8</sup>Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark

### Correspondence

Maja Hellfritsch, Clinical Pharmacology and Pharmacy, University of Southern Denmark, J.B. Winsløvs Vej 19, 2, DK-5000 Odense C, Denmark.  
Email: mmhellfritsch@health.sdu.dk

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### Abstract

A substantial proportion of atrial fibrillation patients initiating direct oral anticoagulants (DOAC) are vitamin K antagonists (VKA)-experienced, for example switchers from VKA to DOAC. With this study, we aimed to summarize available evidence on the effectiveness and safety of DOAC vs VKA in real-life VKA-experienced atrial fibrillation patients. We searched EMBASE, MEDLINE and Cochrane Library systematically for English-language studies indexed any time before October 2018. We included studies of VKA-experienced atrial fibrillation patients initiating DOAC therapy, with continued VKA therapy as comparator. Outcomes included arterial thromboembolism and bleeding. When appropriate, meta-analysis was performed by calculating pooled, weighted and adjusted hazard ratios (aHR) with 95% confidence intervals (CI). Eight cohort studies comparing VKA-experienced DOAC (dabigatran or rivaroxaban) users with continued VKA users were included. When comparing DOAC to VKA, an increased risk of ischaemic stroke and myocardial infarction was found for dabigatran (pooled aHR of 1.61 [95% CI 1.19-2.19,  $I^2 = 65\%$ ] and 1.29 [95% CI 1.10-1.52,  $I^2 = 0\%$ ], respectively), but not for rivaroxaban. The use of dabigatran in VKA-experienced users was associated with an increased risk of gastrointestinal bleeding (pooled aHR 1.63 [95% CI 1.36-1.94,  $I^2 = 30\%$ ]), but a decreased risk of intracranial bleeding (pooled aHR 0.45 [95% CI 0.32-0.64,  $I^2 = 0\%$ ]). In conclusion, the use of dabigatran in prior VKA users in clinical practice was associated with a slightly increased risk of arterial thromboembolism and gastrointestinal bleeding, but a decreased risk of intracranial bleeding. Importantly, observational studies of real-life VKA-experienced oral anticoagulant users may be confounded by the reason for switching.

### KEYWORDS

anticoagulation treatment, atrial fibrillation, meta-analysis, pharmacoepidemiology, thromboembolism

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## 1 | INTRODUCTION

Direct oral anticoagulants (DOAC: dabigatran, rivaroxaban, apixaban and edoxaban) were introduced from 2010 and onwards as alternatives to vitamin K antagonists (VKA, *eg* warfarin) for stroke prevention in patients with atrial fibrillation (AF). In four large randomized clinical trials (RCT),<sup>1-4</sup> DOACs were equally or more effective to warfarin while conferring a similar or lower risk of bleeding. As DOACs also provide a more convenient therapy, their use has rapidly increased in AF patients.<sup>5,6</sup> A substantial proportion of AF patients initiating DOAC therapy are previous VKA users and thereby not naïve to oral anticoagulant therapy.<sup>7</sup> The majority of these ‘VKA-experienced’ DOAC users are ongoing VKA users switching to DOAC therapy.

Evidence from RCTs on the efficacy of DOACs in patients previously exposed to VKA is conflicting. For dabigatran, rivaroxaban and apixaban, the treatment effect relative to warfarin did not differ between VKA-naïve and VKA-experienced patients.<sup>8-10</sup> In contrast, while edoxaban showed superior efficacy to warfarin in VKA-naïve trial participants in the ENGAGE AF trial, VKA-experienced participants had no benefit of edoxaban relative to warfarin with regard to the risk of ischaemic stroke and systemic embolism.<sup>11</sup> Also, the two RCTs comparing the thrombin inhibitor ximelagatran to warfarin in AF patients differed in the number of VKA-experienced trial participants included.<sup>12,13</sup> Consequently, the trials reached different conclusions regarding the relative efficacy; the trial with the highest number of VKA-experienced trial participants showed the lowest benefit of ximelagatran relative to warfarin.<sup>14</sup>

The benefits of DOACs *vs.* warfarin demonstrated in RCTs<sup>15</sup> have been confirmed in several large cohorts of real-life new users of oral anticoagulants.<sup>16,17</sup> However, compared to such VKA-naïve oral anticoagulant initiators, VKA-experienced initiators, including switchers from VKA to DOAC, have already ‘survived’ the risks associated with being exposed to AF as well as anticoagulation for the first time.<sup>18,19</sup> The fact that they are still eligible for oral anticoagulant therapy may influence the treatment benefit of DOACs *vs.* VKA in clinical trials as well as in clinical practice. Based on an overall aim of exploring the potential risks and benefits associated with switching from VKA to DOAC, the objective of this systematic review and meta-analysis was to summarize current evidence concerning the comparative effectiveness and safety of DOACs *vs.* VKA in VKA-experienced real-life anticoagulant users with AF.

## 2 | MATERIAL AND METHODS

This systematic review and meta-analysis is reported according to the ‘Meta-analyses of Observational Studies in Epidemiology’ (MOOSE) reporting guidelines.<sup>20</sup>

### 2.1 | Data sources and searches

Based on search terms indicating (a) AF, (b) treatment with DOAC, (c) treatment with VKA and (d) drug switching, we performed a systematic search in electronic bibliographic databases, including MEDLINE, EMBASE and Cochrane Library's Database of Systematic Reviews. As we aimed for a high sensitivity, only one further restriction—English-language studies—was applied to the literature search. We searched for studies indexed any time before 15 October 2018. The literature search was performed by one reviewer (MH) and planned in collaboration with and supervised by a health science librarian. The detailed search strategy is provided in Table S1. Further, we hand-searched reference lists of relevant reviews identified in the search.

### 2.2 | Study selection

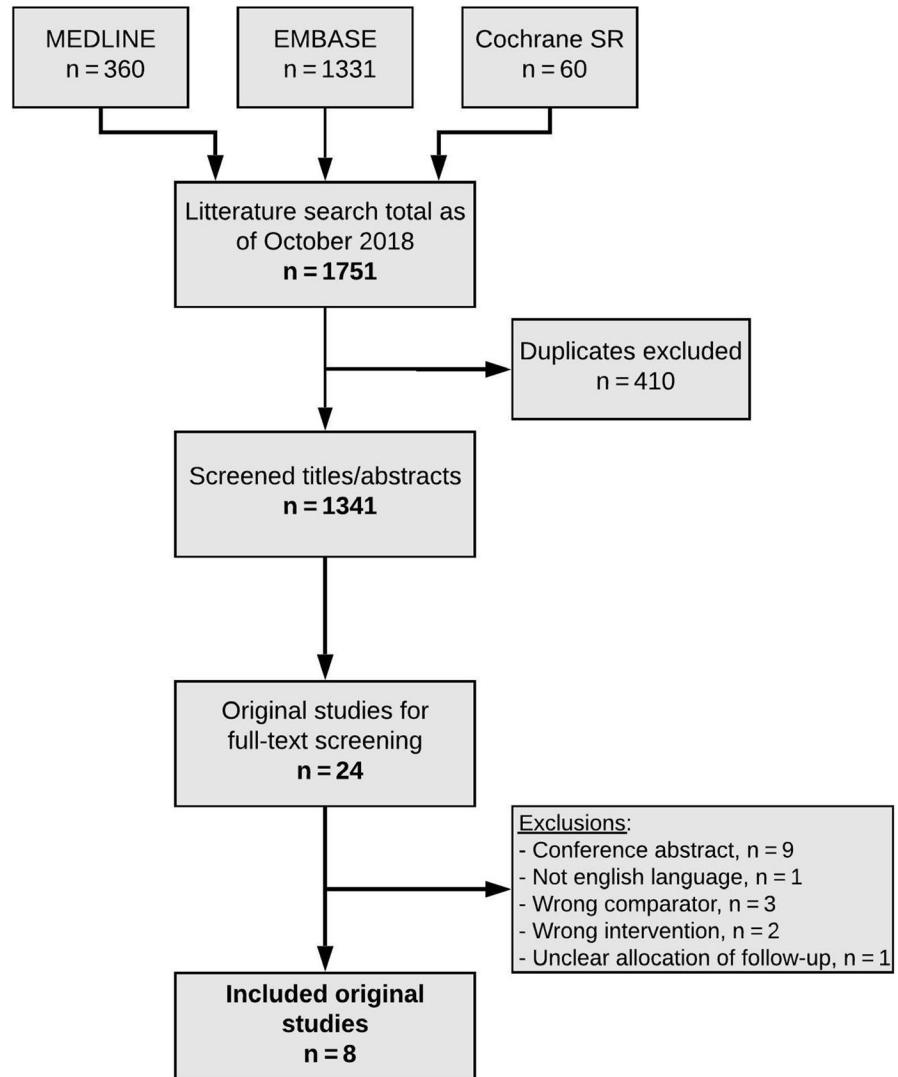
Using Covidence, titles and abstracts of articles containing all four types of search terms were screened by two independent reviewers (MH and KA). Full text was obtained and screened for all abstracts that appeared to meet the eligibility criteria. Studies on AF patients were considered eligible if they compared the risk of outcomes in VKA-experienced DOAC initiators to the risk in patients continuing VKA treatment (‘VKA-experienced VKA users’). Outcomes included arterial thromboembolic events (myocardial infarction and ischaemic stroke  $\pm$  transient ischaemic attack and/or systemic embolism), specific and non-specific bleeding events (gastrointestinal bleeding, intracranial bleeding and any bleeding), and all-cause mortality. Thus, an eligible study could be a study comparing the risk of ischaemic stroke in AF patients who switched from VKA to DOAC to the risk in AF patients who remained on VKA therapy. To avoid inclusion of results potentially biased by immortal time,<sup>21</sup> we required that switchers had been followed from the date of the switch in potentially eligible cohort studies. We only included peer-reviewed original work. Differences in eligibility assessment of studies were resolved by consensus among the reviewers.

### 2.3 | Data extraction and quality assessment

Data extraction was performed independently by two reviewers. Using a standardized data collection form, we collected data on relevant study characteristics, study population and the clinical outcomes of interest. Any data discrepancy was resolved by referring to the original study.

To evaluate the risk of bias in the included studies, we used ‘the Newcastle-Ottawa Scale for assessing the quality of non-randomized studies’ modified to fit this specific meta-analysis (Table S2). In observational cohort studies, this scale evaluates cohort selection (four items), comparability

**FIGURE 1** Flow chart of the study selection



of cohorts (two items) and outcome assessment (three items) by assigning points to each category.<sup>22</sup> For each category, a maximum of one point per item can be assigned, yielding a point maximum of nine. A high number of points indicate a low risk of bias. The quality assessment was also performed independently by two assessors. Any disagreement was resolved by consensus.

## 2.4 | Data synthesis

Results for each of the outcomes of interest were stratified by type of DOAC initiated and summarized. Also, for each specific outcome, we explored the possibility of performing meta-analysis. Meta-analysis could be performed if (a) two or more studies within a DOAC strata reported on a specific outcome and (b) the between-study statistical heterogeneity was below 65% as expressed by the  $I^2$ -statistics.<sup>23</sup> If fulfilled, we combined point estimates to calculate the pooled weighted estimate of the outcome in VKA-experienced users of DOAC vs VKA

using a random-effect model based on the inverse variance method.<sup>24</sup>

## 2.5 | Other

The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.<sup>25</sup> All analyses were performed using Stata Release 15.0 (StataCorp).

## 3 | RESULTS

Our search strategy yielded 1751 potentially relevant studies (Figure 1). After exclusion of 410 duplicates, 1341 titles and abstracts were assessed for eligibility. A total of 24 original articles were selected for full-text review, of which eight studies fulfilled the criteria for inclusion in the systematic review.<sup>26-33</sup> Reasons for exclusions for the other 16 studies are specified in Table S3.

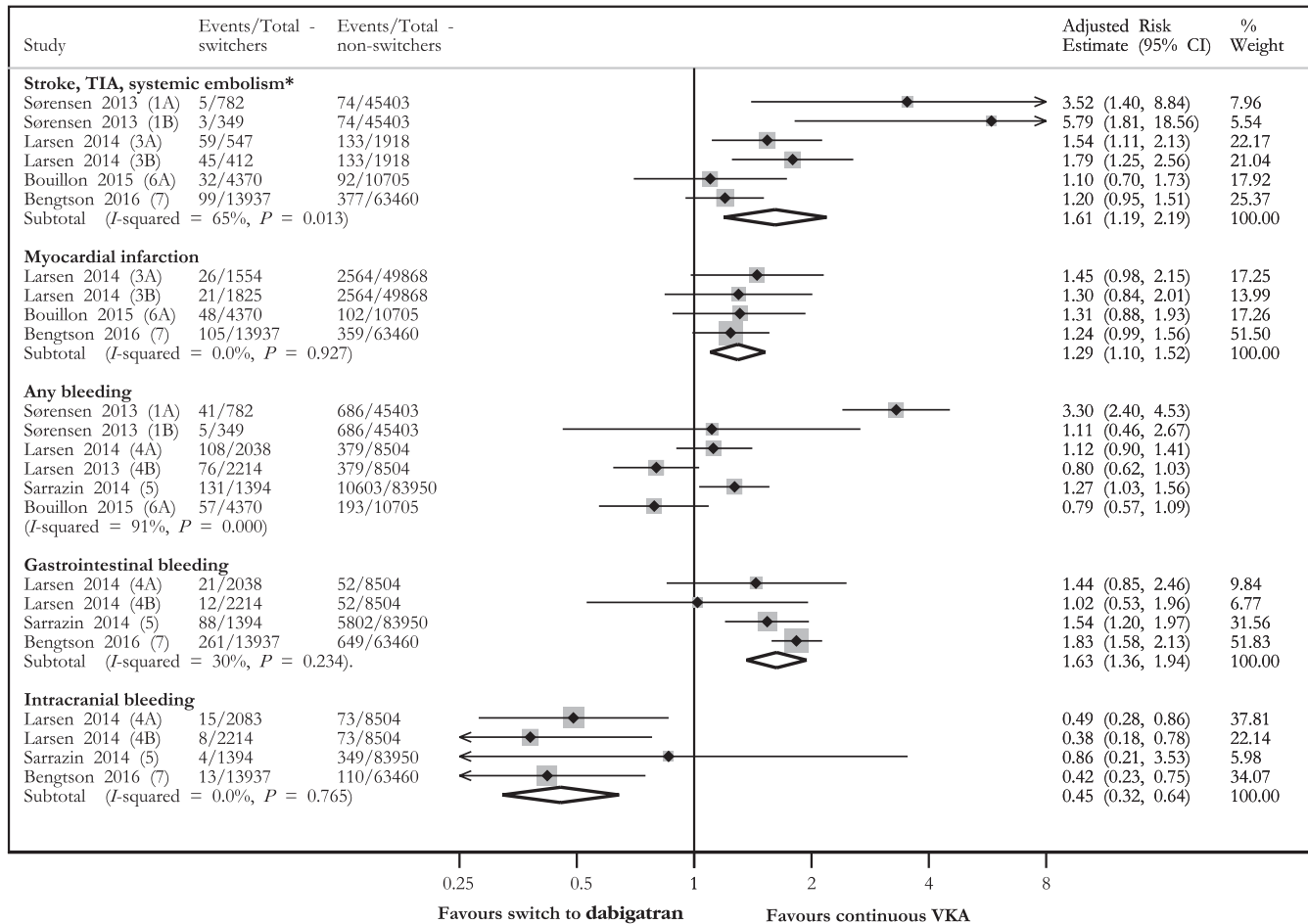
**TABLE 1** Characteristics of the included studies of VKA-experienced oral anticoagulant users with atrial fibrillation

No.	First author and year of publication	Design and setting	DOAC type (exposure)	VKA type (comparator)	Sample size (n DOAC/ n VKA)	Outcome(s) of interest	Age, y (DOAC/VKA) <sup>a</sup>	Follow-up, mo <sup>b</sup>
1	Sørensen, 2013 <sup>27</sup>	Cohort study, Danish nationwide healthcare databases	Dabigatran 110 mg (1A) Dabigatran 150 mg (1B)	Warfarin	782/ 349/ 45 403	Combined: ischaemic stroke, TIA and SE. Any bleeding	73.8 (9.9) for all	Up to 4 months
2	Larsen, 2014 <sup>32</sup>	Cohort study, Danish nationwide healthcare databases	Dabigatran 110 mg (5A) Dabigatran 150 mg (5B)	Warfarin	1554/ 1825/ 49 868	MI	82 (77-86)/ 69 (64-74)/ 75 (68-81)	Mean: 16 (SD 4.6)
3	Larsen, 2014 <sup>29</sup>	Cohort study, Danish nationwide healthcare databases	Dabigatran 110 mg (3A) Dabigatran 150 mg (3B)	Warfarin	547/ 412/ 1918	Combined: ischaemic stroke, TIA	82 (78-86)/ 70 (65-74)/ 75 (69-82)	Mean: 12.6 (SD 4.5)
4	Larsen, 2014 <sup>31</sup>	Cohort study, Danish nationwide healthcare databases	Dabigatran 110 mg (4A) Dabigatran 150 mg (4B)	Warfarin	2,038/ 2,214/ 8,504	Any bleeding, GI bleeding, ICB	82 (77-86)/ 69 (64-73)/ 74 (67-81)	Mean: 13.2 (SD 6.1)
5	Sarrazin, 2014 <sup>30</sup>	Cohort study, Veterans Affairs Health System (US)	Dabigatran	Warfarin	1394/ 83 950	Any bleeding, ICB, GI bleeding All-cause mortality	69.7 (9.0)/ 74.4 (10.1)	Up to 15 mo
6	Bouillon, 2015 <sup>26</sup>	Cohort study, French national health insurance databases	Dabigatran (6A) Rivaroxaban (6B)	VKA (fludione, warfarin, acenocoumarol)	6705/ 10 705	Ischaemic stroke, MI Any bleeding	75 (67-82)/ 75 (67-82)	Median: 10 (IQR 9.8-10)
7	Bengtson, 2016 <sup>28</sup>	Cohort study, US Healthcare claims databases	Dabigatran	Warfarin	13 937/ 63 460	Ischaemic stroke, MI GI bleeding, ICB.	70.9 (11.3)/ 71.5 (11.4)	Median: 15
8	Norby, 2017 <sup>33</sup>	Cohort study, US Healthcare claims databases	Rivaroxaban	Warfarin	11 845/ 43 904	Ischaemic stroke, MI GI bleeding, ICB.	71.2 (12.1)/ 71.4 (12.0)	Mean: 12

Abbreviations: DOAC, direct oral anticoagulant; GI, gastrointestinal; ICB, intracranial bleeding; MI, myocardial infarction; SE, systemic embolism; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

<sup>a</sup>Reported as either the mean followed by the standard deviation in parenthesis or as the median followed by the interquartile range in parenthesis.

<sup>b</sup>Reported as the mean potentially followed by the standard deviation in parenthesis and/or as the median potentially followed by the interquartile range in parenthesis. Some studies only provide the length of the study period.



**FIGURE 2** Dabigatran vs VKA. Risk of arterial thromboembolism and bleeding for dabigatran vs VKA in VKA-experienced oral anticoagulant users with atrial fibrillation. Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist. \* The ischaemic stroke outcome was based on studies reporting ischaemic stroke alone or in combination with transient ischaemic attack and/or systemic embolism. The conditions included in the outcome in each of the studies are specified in Table 1

### 3.1 | Characteristics of the included studies

Characteristics and methodological details of the included studies are provided in Table 1 and Table S4, respectively. All included studies were observational cohort studies exploring the comparative effectiveness and/or safety of dabigatran or rivaroxaban and VKA in VKA-experienced AF patients. Warfarin was the only studied VKA in all but one study that also included fluindione and acenocoumarol.<sup>26</sup> The studies were heterogeneous with regard to several methodological characteristics. The definition of VKA experience, and thereby likely also the proportion of DOAC initiators switched directly from VKA, varied between the included studies (Table S4). Duration of follow-up was reported differently across studies and varied from 'up to four months' in Sørensen et al to a median follow-up of 15 months (interquartile range not provided) in Bengtson et al.<sup>27,28</sup>

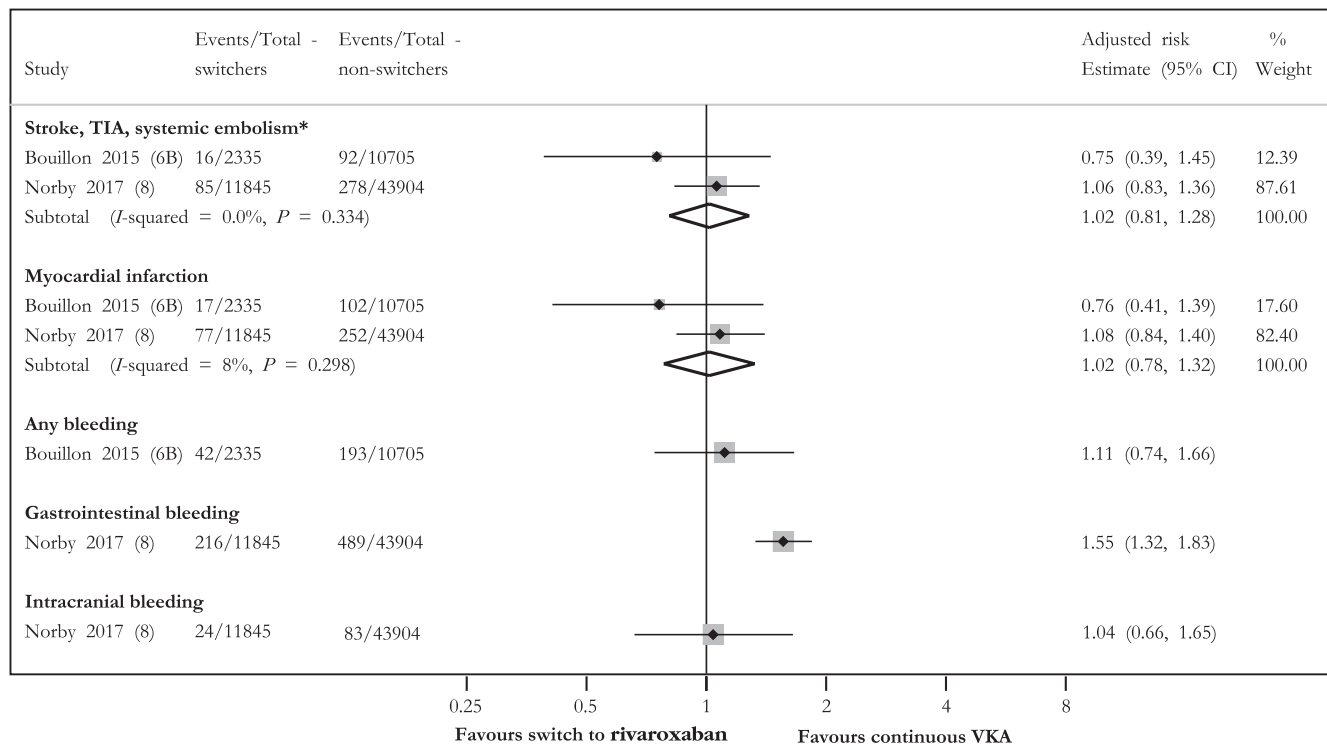
In all studies, the risk of bias was assessed to be either low or moderate, with a range of 6-9 points and a mean score of

7.3 (Table S5). The items leading to risk of bias were similar across studies with the most common reasons being that the study was performed in a subgroup of AF patients, did not consider incident outcomes only and/or did not account for the quality of VKA therapy before or after start of follow-up.

The results for the individual outcomes in VKA-experienced users can be found for dabigatran in Figure 2 and for rivaroxaban in Figure 3. Of note, some of the included studies provided stratified risk estimates only (stratified by DOAC dose or type, specified in Table 1) and could therefore contribute with more than one estimate in a combined analysis.

### 3.2 | Comparative effectiveness of DOAC vs. VKA in VKA-experienced AF patients

With the exception of the high rate of ischaemic stroke reported for AF patients using oral anticoagulants for secondary prevention in Larsen et al,<sup>29</sup> crude incidence rates for arterial thromboembolic outcomes only varied slightly between studies (Table S6). Most studies reporting on the risk of ischaemic stroke for



**FIGURE 3** Rivaroxaban vs VKA. Risk of arterial thromboembolism and bleeding for rivaroxaban vs VKA in VKA-experienced oral anticoagulant users with atrial fibrillation. Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant VKA, vitamin K antagonist. \* The ischaemic stroke outcome was based on studies reporting ischaemic stroke alone or in combination with transient ischaemic attack and/or systemic embolism. The conditions included in the outcome in each of the studies are specified in Table 1

dabigatran vs VKA in VKA-experienced users found either no or a slightly increased risk. As the only study, Sørensen et al found a substantially increased risk. The meta-analysis yielded a combined adjusted HR of the ischaemic stroke risk in VKA-experienced dabigatran initiators of 1.61 (95% confidence interval [CI] 1.19-2.19,  $I^2 = 65\%$ ) when compared to continued VKA use. Also, the risk of myocardial infarction was slightly increased among VKA-experienced dabigatran users compared to continued VKA users in all studies reporting on this outcome (pooled adjusted HR 1.29; 95% CI 1.10-1.52,  $I^2 = 0\%$ ). Both studies reporting on the risk of arterial thromboembolic events in VKA-experienced rivaroxaban initiators found no increased risk of either ischaemic stroke (pooled adjusted HR 1.02; 95% CI 0.81-1.28,  $I^2 = 0\%$ ) or myocardial infarction (pooled adjusted HR 1.02; 0.78-1.32,  $I^2 = 8\%$ ) when compared to continued VKA users.

### 3.3 | Comparative safety of DOAC vs VKA in VKA-experienced AF patients

Crude incidence rates for any bleeding and gastrointestinal bleeding varied markedly between studies with the highest rates reported in the studies by Sørensen et al and Sarrazin et al (Table S6).<sup>27,30</sup> Intracranial bleeding rates were low in all study cohorts (0.20-0.69/100 person-years

and 0.21-0.71/100 person-years in DOAC and VKA cohorts, respectively). Meta-analysis could be allowed only for the comparative safety of dabigatran vs VKA in VKA-experienced users for the outcomes gastrointestinal bleeding and intracranial bleeding. The studies reporting on the comparative risk of any bleeding in VKA-experienced users showed point estimates close to 1.0 with 95% CIs overlapping or almost overlapping unity irrespective of DOAC type. The only exception was the subgroup of VKA-experienced patients on reduced dose dabigatran in Sørensen et al,<sup>27</sup> for whom there was an adjusted pooled HR for any bleeding of 3.30 (95% CI 2.40-4.53) compared to continuous VKA users. Also, the risk of gastrointestinal bleeding was higher in VKA-experienced dabigatran users than in patients kept on VKA therapy (pooled adjusted HR 1.63; 95% CI 1.36-1.94,  $I^2 = 30\%$ ). A similar association was found for rivaroxaban in Norby et al (HR 1.55; 95% CI 1.32-1.83).<sup>33</sup> The risk of intracranial bleeding was reduced in VKA-experienced users of dabigatran (pooled adjusted HR of 0.45; 95% CI 0.32-0.64,  $I^2 = 0\%$ ), but not rivaroxaban (HR 1.04; 95% CI 0.66-1.65 in Norby et al),<sup>33</sup> when compared to continued VKA users.

All-cause mortality in VKA-experienced oral anticoagulant users was only reported in the study by Sarrazin et al,<sup>30</sup> which found an odds ratio of 0.76 (95% CI 0.49-1.17) when

comparing VKA-experienced dabigatran users to continued VKA users.

## 4 | DISCUSSION

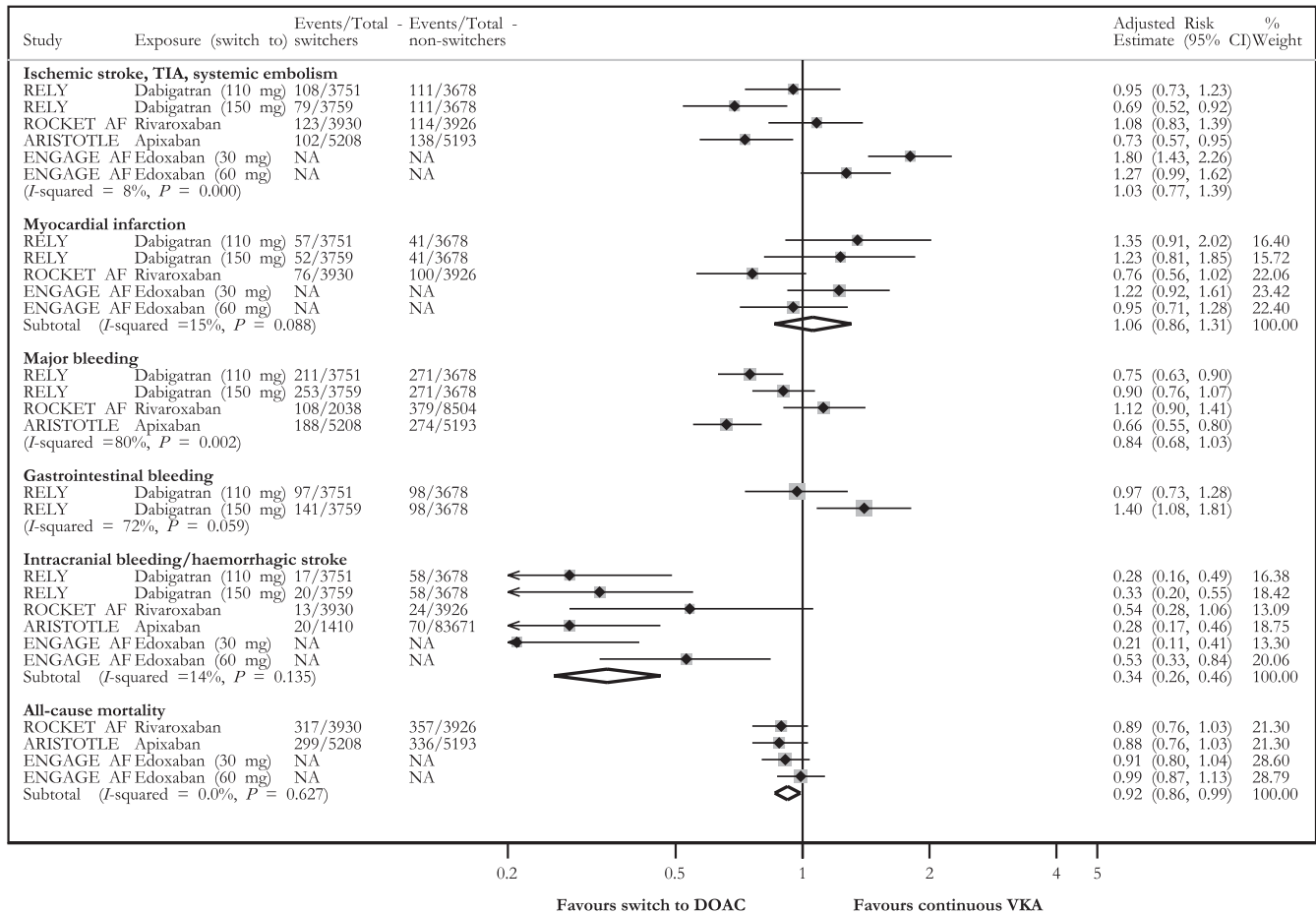
This systematic review and meta-analysis of observational studies of VKA-experienced AF patients had three main findings concerning the effectiveness and safety of DOAC therapy when compared to continued VKA use. Firstly, the use of dabigatran, but not rivaroxaban, was associated with an increased risk of arterial thromboembolism. Secondly, prior VKA users switched to dabigatran or rivaroxaban had an increased risk of gastrointestinal bleeding. Thirdly, the risk of intracranial bleeding was lower in VKA-experienced dabigatran users than in continued VKA users.

Some limitations should be addressed. Firstly, this meta-analysis was based on observational evidence alone and is susceptible to the limitations inherent to this type of research most importantly the potential for confounding. As an example, only few of the included studies had information on the quality of VKA therapy in study participants, which could thereby not be accounted for in their analyses. Secondly, the validity of the pooled estimates of the meta-analyses may be limited by important clinical and methodological differences between studies as well as by the risk of duplicate data. Several of the included studies were based on Danish AF patients. Although these studies focused on different subgroups of patients, different outcomes, and had different study periods, this might have given Danish observations undue weight. Thirdly, the risk of switching-related complications is highly dependent on the transition regimen employed.<sup>34</sup> As such, differences between study results could, in part, be explained by varying compliance with the recommended switching procedures. However, none of the studies included in the present systematic review and meta-analysis provided information on this issue. Finally, as most studies were on dabigatran and performed in Western Europe or the United States, generalization of our findings to other DOACs and to populations with other demographics and standards of care, including anticoagulant control,<sup>35</sup> should be made with caution.

As the only study, Sørensen et al found use of dabigatran in VKA-experienced users to be associated with a markedly higher risk of ischaemic stroke than continued use of VKA.<sup>27</sup> Although the contribution of this ‘outlier’ study to the meta-analysis was limited due to the low number of events, the pooled estimate for the ischaemic stroke outcome should be interpreted with caution. The higher risk in this specific study could be due to chance. Alternatively, it could also be explained by the study being based on the very first months of dabigatran use following market entry. Studies based on this period alone are likely especially susceptible to bias due to channelling of dabigatran to frail or high-risk

patients who have previously failed or been found unsuitable for VKA therapy.<sup>36</sup> Further supporting the presence of residual confounding by frailty in the study is the finding of a higher bleeding risk in dabigatran users on reduced dose than on standard dose, which contrasts with RCT findings<sup>1</sup> as well as with pharmacological reasoning. Also, as the study by Sørensen et al had the shortest follow-up time (‘up to four months’) of all the included studies, their results could reflect an increased risk of complications in the early period following oral anticoagulant switching corresponding to the observations immediately after start and termination of the DOAC trials.<sup>34,37-40</sup> Such potential early risks may be outweighed by potential benefits of DOAC use over time, which could explain that the associations receded towards unity in studies with longer follow-up. Unfortunately, the low number of included studies did not allow us to meaningfully explore this issue further.

For most outcomes, there was agreement between our findings and the results concerning VKA-experienced patients in the randomized controlled trials RELY (Randomized Evaluation of Long-Term Anticoagulation Therapy) and ROCKET AF (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) (the results of these subgroup analyses are provided for context in Figure 4).<sup>8,9</sup> However, while dabigatran reduced the risk of ischaemic stroke and systemic embolism in the VKA-experienced stratum of RELY,<sup>8</sup> none of the studies included in our review were able to confirm this trial finding in a real-world setting. In all studies, the risk of ischaemic stroke was higher among VKA-experienced dabigatran users than among patients staying on VKA. A similar discrepancy was, however, not observed between the rivaroxaban strata of our systematic review and meta-analysis and the results from ROCKET AF.<sup>9</sup> Although our finding may reflect a true difference in the relative stroke risk in VKA-experienced users according to study setting and DOAC type, the collective findings could also be explained by other mechanisms. We propose two such alternative interpretations. Firstly, consistent with prior reports on the adherence to DOACs in real-world patients,<sup>41</sup> our findings could reflect suboptimal adherence to especially dabigatran in clinical practice. A second possible explanation is the selection performed by physicians in clinical practice when choosing to switch some VKA-treated patients to DOAC and others to stay on VKA. In the Dresden non-VKA oral anticoagulants Registry,<sup>42</sup> patients maintained on VKA therapy were less likely than patients switched to DOAC to have a history of stroke and unstable INRs, both of which are important predictors of stroke on VKA therapy.<sup>43</sup> This clinical selection process therefore channels VKA users likely to perform poorly on VKA to the DOAC group (ie the exposed group in observational



**FIGURE 4** VKA-experienced strata of the randomized clinical trials. Forest plots and meta-analyses (if  $I^2 \leq 65\%$ ) of the risk of arterial thromboembolism, bleeding, and all-cause mortality in the VKA-experienced strata of the randomized clinical trials comparing DOAC to VKA in patients with atrial fibrillation. Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist; RELY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ENGAGE AF, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation

studies) and users likely to perform well on VKA therapy to the VKA group (ie the comparator group). Supportive of this explanation is the fact that the rates of ischaemic stroke among continued VKA users in the included observational studies (Table S6) were consistently lower than the corresponding rates in VKA-experienced trial participants in the warfarin arm (0.45/100PY-1.15/100PY vs 1.47/100 PY-2.09/100PY). The observed association between switching from VKA to dabigatran and risk of ischaemic stroke may reflect a low stroke risk among patients selected to stay on VKA therapy rather than an increased stroke risk following switching to dabigatran. Importantly, if such selective prescribing (or, more precisely, selective switching) is an important driver of our results, it would not be appropriate to conclude on differences in treatment effect between groups due to the risk of residual confounding. The rivaroxaban strata of our meta-analysis were overall in accordance with the results from ROCKET AF.<sup>9</sup> A

potential explanation of the inconsistent findings between dabigatran and rivaroxaban may be that the study contributing with the highest number of switchers to rivaroxaban<sup>33</sup> had the highest degree of confounder control of all included studies.

If a high quality of VKA therapy in the comparison groups of the included studies is indeed the explanation of our findings of an increased risk of ischaemic stroke in switchers from VKA to DOAC, they can be viewed as consistent with the TTR (ie time spent in the therapeutic interval) stratified results of RELY. These demonstrated that a high quality of VKA therapy reduces the efficacy benefit of dabigatran vs VKA, whereas the lower risk of intracranial bleeding is consistent across levels of TTR.<sup>35</sup> As guidelines support switching from VKA to DOAC at TTR levels below 70%,<sup>44</sup> it seems likely that patients kept on VKA therapy, despite the availability of DOACs, would perform well on VKA therapy, as observed in the included studies. As such, we consider our



results concerning AF patients staying on VKA as overall reassuring and supportive of the selection performed by physicians when choosing which patients should not be switched to DOAC therapy in clinical practice. Also, in a recent small Dutch RCT,<sup>45</sup> AF patients with high TTR levels on VKA therapy randomized to continued VKA therapy had comparable 1-year risks of arterial thromboembolism and bleeding to patients randomized to switch to a DOAC (mainly apixaban). Thus, this trial, as well as the results of the current review, supports that a satisfactory effectiveness and safety of oral anticoagulant therapy can likely be expected if choosing to continue VKA in AF patients presenting with high TTR levels.

Despite searching for references published up until October 2018, no eligible studies addressing the comparative effectiveness and/or safety of neither apixaban nor edoxaban vs. VKA in VKA-experienced AF patients were identified. Although these drugs had a later market entry than dabigatran and rivaroxaban, the use of especially apixaban among AF patients is extensive.<sup>6,46,47</sup> Further, in a recent register-based drug utilization study, we showed that 16% of all AF patients initiating apixaban during the period of June 2016 to June 2017 in Denmark switched directly from VKA.<sup>48</sup> In the VKA-experienced stratum of the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, the risks of ischaemic stroke, major bleeding and intracranial bleeding were significantly lower in the apixaban arm than in the warfarin arm.<sup>10</sup> Although these results are reassuring, patients using apixaban may be especially susceptible to switching-related risks, as apixaban has become the preferred anticoagulant among the eldest, most frail and comorbid AF patients.<sup>49,50</sup> Thus, studies exploring the risks and benefits associated with use of apixaban in VKA-experienced patients in clinical practice including switching from VKA to apixaban are highly warranted.

#### 4.1 | Conclusion

Consistent with trial findings, the use of DOAC in VKA-experienced AF patients from everyday clinical settings was associated with a lower risk of intracranial bleeding (dabigatran) and an increased risk of gastrointestinal bleeding (dabigatran and rivaroxaban) when compared to patients kept on VKA. In contrast with trial findings, observational studies did not support that switching from VKA to dabigatran is associated with a lower risk of ischaemic stroke than non-switch. Whether this reflects an excess risk of events in VKA-experienced dabigatran users/switchers from VKA to dabigatran or rather that patients staying on VKA therapy in clinical practice have a low risk of ischaemic stroke needs to be explored further. In future studies, special attention needs to be paid to potential confounding from the underlying reasons for switching to DOAC

therapy or not, which have likely affected the results of current observational studies.

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#### CONFLICT OF INTEREST

MH reports speaker honorarium from Bristol-Myers Squibb (BMS) and Pfizer and travel grants from LEO Pharma. KA and PD declare no conflicts of interest. SPJ reports speaker honorarium from BMS, Pfizer, Bayer and Boehringer-Ingelheim (BI), participation in advisory board meetings for BMS, Pfizer, and Bayer and previous research funding from BMS and Pfizer. JH and AP report participation in research projects funded by BI with funds paid to the institution where they were employed (no personal fees). ELG has received speaker honoraria or consultancy fees from AstraZeneca, Bayer, BI, BMS, MSD, Pfizer and Roche.

#### REFERENCES

1. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361:1139-1151.
2. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365:883-891.
3. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med.* 2011;364:806-817.
4. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369:2093-2104.
5. Huisman MV, Rothman KJ, Paquette M, et al. Antithrombotic treatment patterns in patients with newly diagnosed nonvalvular atrial fibrillation: the GLORIA-AF registry, phase II. *Am J Med.* 2015;128(1306-1313):e1.
6. Haastrup SB, Hellfritsch M, Rasmussen L, Pottegård A, Grove EL. Use of non-vitamin K antagonist oral anticoagulants 2008–2016: a Danish nationwide cohort study. *Basic Clin Pharmacol Toxicol.* 2018;123:452-463.
7. Pokorney SD, Granger CB. Should patients on vitamin K antagonists be treated differently? *Eur Heart J.* 2015;36:1431-1433.
8. Ezekowitz MD, Wallentin L, Connolly SJ, et al. Dabigatran and warfarin in vitamin K antagonist-naïve and -experienced cohorts with atrial fibrillation. *Circulation.* 2010;122:2246-2253.
9. Mahaffey KW, Wojdyla D, Hankey GJ, et al. Clinical outcomes with rivaroxaban in patients transitioned from vitamin K antagonist therapy: a subgroup analysis of a randomized trial. *Ann Intern Med.* 2013;158:861-868.
10. Garcia DA, Wallentin L, Lopes RD, et al. Apixaban versus warfarin in patients with atrial fibrillation according to prior warfarin use: results from the apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation trial. *Am Heart J.* 2013;166:549-558.

11. O'Donoghue ML, Ruff CT, Giugliano RP, et al. Edoxaban vs. warfarin in vitamin K antagonist experienced and naive patients with atrial fibrillation†. *Eur Heart J*. 2015;36:1470-1477.
12. Olsson SB. Executive Steering Committee of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet*. 2003;362:1691-1698.
13. Albers GW, Diener H-C, Frison L, et al. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA*. 2005;293:690-698.
14. Hylek EM, Frison L, Henault LE, Cupples A. Disparate stroke rates on warfarin among contemporaneous cohorts with atrial fibrillation: potential insights into risk from a comparative analysis of SPORTIF III versus SPORTIF V. *Stroke*. 2008;39:3009-3014.
15. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955-962.
16. Potpara TS, Lip G. Postapproval observational studies of non-vitamin K antagonist oral anticoagulants in atrial fibrillation. *JAMA*. 2017;317:1115-1116.
17. Larsen TB, Skjøth F, Nielsen PB, Kjældgaard JN, Lip G. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ*. 2016;353:i3189.
18. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation*. 2007;115:2689-2696.
19. DiMarco JP, Flaker G, Waldo AL, et al. Factors affecting bleeding risk during anticoagulant therapy in patients with atrial fibrillation: observations from the atrial fibrillation follow-up investigation of rhythm management (AFFIRM) study. *Am Heart J*. 2005;149:650-656.
20. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA*. 2000;283:2008-2012.
21. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol*. 2008;167:492-499.
22. Ottawa Hospital Research Institute. [Internet]. [cited 2019 Mar 19]. Available from: [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)
23. Higgins J, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
24. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.
25. Tveden-Nyborg P, Bergmann TK, Lykkesfeldt J. Basic & clinical pharmacology & toxicology policy for experimental and clinical studies. *Basic Clin Pharmacol Toxicol*. 2018;123:233-235.
26. Bouillon K, Bertrand M, Maura G, Blotière P-O, Ricordeau P, Zureik M. Risk of bleeding and arterial thromboembolism in patients with non-valvular atrial fibrillation either maintained on a vitamin K antagonist or switched to a non-vitamin K-antagonist oral anticoagulant: a retrospective, matched-cohort study. *Lancet Haematol*. 2015;2:e150-159.
27. Sørensen R, Gislason G, Torp-Pedersen C, et al. Dabigatran use in Danish atrial fibrillation patients in 2011: a nationwide study. *BMJ Open*. 2013;3(5):e002758.
28. Bengtson L, Lutsey PL, Chen LY, MacLehose RF, Alonso A. Comparative effectiveness of dabigatran and rivaroxaban versus warfarin for the treatment of non-valvular atrial fibrillation. *J Cardiol*. 2017;69:868-876.
29. Larsen TB, Rasmussen LH, Gorst-Rasmussen A, Skjøth F, Lane DA, Lip G. Dabigatran and warfarin for secondary prevention of stroke in atrial fibrillation patients: a nationwide cohort study. *Am J Med*. 2014;127:1172-1178.
30. Vaughan Sarrazin MS, Jones M, Mazur A, Chrischilles E, Cram P. Bleeding rates in Veterans Affairs patients with atrial fibrillation who switch from warfarin to dabigatran. *Am J Med*. 2014;127:1179-1185.
31. Larsen TB, Gorst-Rasmussen A, Rasmussen LH, Skjøth F, Rosenzweig M, Lip G. Bleeding events among new starters and switchers to dabigatran compared with warfarin in atrial fibrillation. *Am J Med*. 2014;127:650-656.
32. Larsen TB, Rasmussen LH, Gorst-Rasmussen A, et al. Myocardial ischemic events in 'real world' patients with atrial fibrillation treated with dabigatran or warfarin. *Am J Med*. 2014;127:329-336.
33. Norby FL, Bengtson LGS, Lutsey PL, et al. Comparative effectiveness of rivaroxaban versus warfarin or dabigatran for the treatment of patients with non-valvular atrial fibrillation. *BMC Cardiovasc Disord*. 2017;17:238.
34. Ruff CT, Giugliano RP, Braunwald E, et al. Transition of patients from blinded study drug to open-label anticoagulation: the ENGAGE AF-TIMI 48 trial. *J Am Coll Cardiol*. 2014;64:576-584.
35. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet*. 2010;376:975-983.
36. Schneeweiss S, Gagne JJ, Glynn RJ, Ruhl M, Rassen JA. Assessing the comparative effectiveness of newly marketed medications: methodological challenges and implications for drug development. *Clin Pharmacol Ther*. 2011;90:777-790.
37. Granger CB, Lopes RD, Hanna M, et al. Clinical events after transitioning from apixaban versus warfarin to warfarin at the end of the apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial. *Am Heart J*. 2015;169:25-30.
38. Patel MR, Hellkamp AS, Lokhnygina Y, et al. Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: analysis from the ROCKET AF trial (rivaroxaban once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *J Am Coll Cardiol*. 2013;61:651-658.
39. Mahaffey KW, Hellkamp AS, Patel MR, et al. End of study transition from study drug to open-label vitamin K antagonist therapy: the ROCKET AF experience. *Circ Cardiovasc Qual Outcomes*. 2013;6:470-478.
40. Caldeira D, Costa J, Ferreira JJ, Pinto FJ. Thromboembolic risk in the initiation, switch and interruption/re-initiation of oral anticoagulants: do newcomers improve outcomes? Insights from a meta-analysis of RCTs. *Int J Cardiol*. 2014;177:117-119.

41. Obamiro KO, Chalmers L, Bereznicki L. A Summary of the literature evaluating adherence and persistence with oral anticoagulants in atrial fibrillation. *Am J Cardiovasc Drugs*. 2016;16:349-363.
42. Michalski F, Tittl L, Werth S, et al. and outcome of vitamin K antagonist-treated patients with atrial fibrillation not switched to novel oral anticoagulants. Results from the Dresden NOAC registry. *Thromb Haemost*. 2015;114:1076-1084.
43. Björck F, Renlund H, Lip G, Wester P, Svensson PJ, Själander A. Outcomes in a warfarin-treated population with atrial fibrillation. *JAMA Cardiol*. 2016;1:172-180.
44. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893-2962.
45. van Miert J, Kooistra H, Veeger N, Westerterp A, Piersma-Wichers M, Meijer K. Choosing between continuing vitamin K antagonists (VKA) or switching to a direct oral anticoagulant in currently well-controlled patients on VKA for atrial fibrillation: a randomised controlled trial (GAINN). *Br J Haematol*. 2019. <https://doi.org/10.1111/bjh.15856>. [Epub ahead of print]
46. Urbaniak AM, Strøm BO, Krontveit R, Svanqvist KH. Prescription patterns of non-vitamin K oral anticoagulants across indications and factors associated with their increased prescribing in atrial fibrillation between 2012–2015: a study from the Norwegian prescription database. *Drugs Aging*. 2017;34:635-645.
47. van den Heuvel JM, Hövels AM, Büller HR, et al. NOACs replace VKA as preferred oral anticoagulant among new patients: a drug utilization study in 560 pharmacies in the Netherlands. *Thromb J*. 2018;16:7.
48. Pottegård A, Grove EL, Hellfritsch M. Use of direct oral anticoagulants in the first year after market entry of edoxaban: a Danish nationwide drug utilization study. *Pharmacoepidemiol Drug Saf*. 2018;27:174-181.
49. Gundlund A, Staerk L, Fosbøl EL, et al. Initiation of anticoagulation in atrial fibrillation: which factors are associated with choice of anticoagulant? *J Intern Med*. 2017;282:164-174.
50. Kjerpeseth LJ, Ellekjaer H, Selmer R, Ariansen I, Furu K, Skovlund E. Risk factors for stroke and choice of oral anticoagulant in atrial fibrillation. *Pharmacoepidemiol Drug Saf*. 2018;27:176-177.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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