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Oral anticoagulant switching in patients with atrial fibrillation: a scoping review

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Kimberlyn McGrail,3,4 Peter S Loewen1,2

ABSTRACT

Introduction Oral anticoagulants (OACs) prevent stroke in patients with atrial fibrillation (AF). Several factors may cause OAC switching.

Objectives To examine the phenomenon of OAC switching in patients with AF, including all available evidence; frequency and patterns of switch, clinical outcomes, adherence, patient-reported outcomes, reasons for switch, factors associated with switch and evidence gaps.

Design Scoping review.

Data sources MEDLINE, Embase and Web of Science, up to January 2022.

Results Of the 116 included studies, 2/3 examined vitamin K antagonist (VKA) to direct-acting OAC (DOAC) switching. Overall, OAC switching was common and the definition of an OAC switch varied across. Switching from VKA to dabigatran was the most prevalent switch type, but VKA to apixaban has increased in recent years. Patients on DOAC switched more to warfarin than to other DOACs. OAC doses involved in the switches were hardly reported and patients were often censored after the first switch. Switching back to a previously taken OAC (frequently warfarin) occurred in 5%–21% of switchers.

The risk of ischaemic stroke and gastrointestinal bleeding in VKA to DOAC switchers compared with non-switchers was conflicting, while there was no difference in the risk of other types of bleeding. The risk of ischaemic stroke in switchers from DOAC versus non-switchers was conflicting. Studies evaluating adherence found no significant changes in adherence after switching from VKA to DOAC, however, an increase in satisfaction with therapy was conflicting. Studies evaluating adherence found no significant changes in adherence after switching from VKA to DOAC, however, an increase in satisfaction with therapy were reported. Reasons for OAC switch, and factors associated with OAC switch were mostly risk factors for stroke and bleeding. Clinical outcomes, adherence and patient-reported outcomes were sparse for switches from DOACs.

Conclusions OAC switching is common in patients with AF and patients often switch back to an OAC they have previously been on. There are aspects of OAC switching that have received little study, especially in switches from DOACs.

INTRODUCTION

Atrial fibrillation (AF) is a chronic condition in which the electrical activity in the atria are rapid and chaotic.1 AF increases the risk of thromboembolic stroke by threefold to fivefold, and oral anticoagulants (OACs) reduce this risk by approximately 66%.1 Several OAC drugs exist for patients with AF, including vitamin K antagonists (VKAs; eg, warfarin), which were the mainstay of anticoagulation therapy before 2010, and direct-acting oral anticoagulants (DOACs; eg, dabigatran, rivaroxaban, apixaban and edoxaban) which were approved for AF stroke prevention over the last 12 years around the world.1,2 Since then, DOAC prescribing in AF has increased, while warfarin use has dropped.3–6 Attributes of individual OACs, patient factors and prescriber factors may predispose patients with AF to switching between OACs over time.3–6 Broadly, a switch is a change from one drug to another drug that has the same indication with a minimal temporal gap between them.

Safety and effectiveness attributes of OACs and patient comorbidities may contribute to OAC switches. For example, clinical trials have shown DOACs have better or similar stroke or systemic embolism prevention efficacy than VKAs.7–13 Compared with warfarin, the risk of major bleeding is significantly lower for dabigatran and apixaban, and lower with apixaban than dabigatran or rivaroxaban.7–13 VKAs do not require dosage adjustment in patients with renal dysfunction, but do require frequent international normalised ratio (INR) monitoring and have more food and dietary restrictions than DOACs.8–12 14–15 Factors that may contribute to OAC switching may be categorised as: (1) clinical factors...
such as suboptimal response, convenience/adherence concerns, safety worries; (2) patient-related factors such as cost concerns, drug coverage availability; and (3) prescriber preferences, including availability of a new drug or emergence of guidelines recommending certain drugs. For all of the above reasons, switching between OACs may be common among patients with AF who are prescribed OACs.

One previous systematic review on this topic was limited to VKA to DOAC switching (dabigatran and rivaroxaban mainly) and included a small number of studies, all from early in the DOAC era. The other systematic review focused only on DOAC to DOAC switches, examined only the frequency of switching and included only five (mostly older) studies. Finally, a narrative review including 39 studies, though valuable, did not report on patients with more than one switch, switchbacks or outcomes such as quality of life and adherence.

This scoping review aimed to overcome the limitations of previous reviews by holistically examining the phenomenon of OAC switching in patients with AF by including all available evidence on the topic. Specific objectives were: (1) to determine switching characterisation (types and patterns of switching) and frequency, (2) to determine clinical outcomes in switchers compared with non-switchers, (3) to determine switching’s effects on adherence and patient-reported outcomes, (4) to identify reasons for switching and factors associated with switching and (5) to identify evidence gaps about OAC switching.

METHODS
This was a scoping review using the Arksey and O’Malley framework and the Joanna Briggs Institute statement on the conduct of scoping reviews. Reporting in this manuscript follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-extension for Scoping Reviews standards. A scoping review was chosen because there are aspects of OAC switching in AF that have not been previously addressed in systematic or scoping reviews and the included evidence was expected to be heterogeneous in study designs and outcomes reported.

Research question
The Joanna Briggs Institute ‘Population and Concept’ strategy was used to frame the research question. The population was patients with AF on OAC therapy, the concept was the phenomenon of OAC switching. A switch was defined as a change from a patient’s prescribed OAC to another OAC for the same indication. The overarching research question was: what is the available evidence on OAC switching in patients with AF? with the specific objectives stated above.

Inclusion/exclusion criteria
This review included observational studies involving patients ≥18 years with AF in which the phenomenon of switching between OACs was observed. Studies that stated the OACs involved were included. Studies with a mixed population of other OAC indications were included if patients with AF’s data were distinctly reported.

The exclusion criteria were guidelines/guidance on switching, position papers, management plans, protocols, commentary, opinion papers, conference proceedings, critical appraisals, pilot studies and studies reporting only switching from VKA to VKA. Studies on switching after ablation or cardioversion were also excluded since OAC changes in these situations are usually dictated by protocols and guidelines rather than clinician or patient factors. Non-English and duplicate articles were excluded.

Literature sources and search strategy
MEDLINE, Embase and Web of Science were searched from inception to January 2022. A search strategy was developed with the help of an academic librarian. Medical Subject Headings and search terms were combined with Boolean operators (AND, OR) to refine the searches (online supplemental appendix A, tables A1-A3). References in included studies were scanned for additional candidate studies.

Studies that emerged from the three databases were screened to remove duplicates. Title and abstract screening were done separately by two reviewers. Candidate studies were advanced to full-text review for further screening of eligibility according to the inclusion and exclusion criteria. A third reviewer intervened when agreement could not be reached.

After the literature searches were conducted the outcomes reported in eligible studies were reported and composed into a set of outcomes of interest for organising the results.

Data extraction and analyses
For included articles, one reviewer extracted data and entered them into Microsoft Excel. The accuracy of extracted data was checked by a second reviewer. Extracted data included study title, authors, year of publication, study demography, country of study, population size and characteristics, study period, follow-up duration, switch definition and switch outcomes reported. Results are presented narratively with the organisation of findings into outcomes of interests (see table 1).

Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS
We included 116 studies. Figure 1 shows the PRISMA flow diagram of the screening process.

Description of included studies
Characteristics of the included studies are in table 2. Most of the included studies were conducted in North America. The majority were conducted in the USA, followed by Canada and European countries. The number of switchers ranged from 15 to 3,864, with 1,294 patients specifically reported from 12 studies.

The mean age of switchers was 71 years, range 50–100 years. The mean duration of follow-up was 1.8 years, range 0.7–13 years. The most commonly used OACs were dabigatran (n = 602) and rivaroxaban (n = 228). The most common reasons for switching were related to adherence and patient-reported outcomes (n = 21) and type of OAC (n = 19). The most common switching outcomes were drug-related adverse effects (n = 37), followed by switching back to the OAC they were switched from (n = 15).

America and Europe, with the USA and Denmark being the most represented countries. VKA to DOAC switch was reported in 67% of the included studies. Ten studies reported on patients with more than one switch. Detailed characteristics of included studies are in online supplemental appendix A, tables A4 and

Table 1 Outcomes of interest from the scoping review of OAC switching in AF

<table>
<thead>
<tr>
<th>Outcome categories</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switching characterisation and frequency</td>
<td>➤ Definitions of OAC switch. ➤ Frequency of OAC switch. ➤ Switch types (the 'switched-from' and 'switched-to' OAC). ➤ Switch patterns (switching sequences with more than one switch type). ➤ Switchbacks. ➤ Timing of switch.</td>
</tr>
<tr>
<td>Adherence and patient-reported outcome measures before and after switching</td>
<td>➤ Adherence. ➤ Quality of life. ➤ Satisfaction.</td>
</tr>
<tr>
<td>Factors associated with switches, reasons for switching</td>
<td>➤ Clinical factors, patient-related factors and prescriber-related factors.</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; OAC, oral anticoagulants.

Table 2 Characteristics of included studies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%) of 116 studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country of study</strong></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>32 (27.6)</td>
</tr>
<tr>
<td>Denmark</td>
<td>11 (9.5)</td>
</tr>
<tr>
<td>Multicountry/multicontinental</td>
<td>11 (9.5)</td>
</tr>
<tr>
<td>Germany</td>
<td>7 (6.0)</td>
</tr>
<tr>
<td>Canada</td>
<td>7 (6.0)</td>
</tr>
<tr>
<td>Japan</td>
<td>7 (6.0)</td>
</tr>
<tr>
<td>France</td>
<td>6 (5.2)</td>
</tr>
<tr>
<td>UK</td>
<td>6 (5.2)</td>
</tr>
<tr>
<td>Italy</td>
<td>5 (4.3)</td>
</tr>
<tr>
<td>Netherlands</td>
<td>4 (3.5)</td>
</tr>
<tr>
<td>Australia</td>
<td>4 (3.5)</td>
</tr>
<tr>
<td>Others*</td>
<td>16 (13.7)</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td></td>
</tr>
<tr>
<td>Retrospective cohort</td>
<td>75 (64.7)</td>
</tr>
<tr>
<td>Prospective cohort</td>
<td>28 (24.1)</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>9 (7.8)</td>
</tr>
<tr>
<td>Qualitative†</td>
<td>9 (7.8)</td>
</tr>
<tr>
<td>Mixed methods‡</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Case-crossover</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Pre–post</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td><strong>Year of publication</strong></td>
<td></td>
</tr>
<tr>
<td>2019–2021</td>
<td>53 (45.7)</td>
</tr>
<tr>
<td>2017–2018</td>
<td>34 (29.3)</td>
</tr>
<tr>
<td>2015–2016</td>
<td>19 (16.4)</td>
</tr>
<tr>
<td>2013–2014</td>
<td>10 (8.6)</td>
</tr>
<tr>
<td><strong>Type of switch described‡</strong></td>
<td></td>
</tr>
<tr>
<td>VKA to DOAC</td>
<td>78 (67.2)</td>
</tr>
<tr>
<td>DOAC to VKA</td>
<td>70 (60.3)</td>
</tr>
<tr>
<td>DOAC to DOAC</td>
<td>53 (45.7)</td>
</tr>
<tr>
<td><strong>Studies that included all four DOACs</strong></td>
<td>11 (9.5)</td>
</tr>
<tr>
<td><strong>Multiple switches described</strong></td>
<td>8 (6.9)</td>
</tr>
</tbody>
</table>

*Greece, Hong Kong, Korea (2), Malaysia, Norway, Scotland, Spain (2), Sweden (2), Switzerland (2), Stockholm, Taiwan, China.
†Qualitative studies counts have been captured in other observational study types.
‡Prospective/cross-sectional, retrospective/cross-sectional.
§Some studies had one or more of the types of switches. DOACs, direct-acting oral anticoagulants; VKA, vitamin K antagonists.
A5. References for the included studies are in online supplemental appendix A.

**Definitions of OAC switch**

‘Switch’ was the most common term used for the phenomenon under study with 115 (99.1%) of studies using it. ‘Shift’, ‘remote VKA use’, ‘VKA-experienced’, ‘prior VKA use’, ‘change’, ‘crossover’ and ‘transition’ were also used with similar meanings.

Definitions of an OAC switch varied. Most studies did not explicitly define an OAC switch and therefore did not specify the permissible gap between the two OACs, making it difficult to distinguish between a switch and a discontinuation. Online supplemental appendix B, table B1 depicts definitions found. There were 14 unique definitions among studies containing them. A permissible gap of 1 year between OACs was the most common (18 studies). Interestingly, an OAC switch was also called discontinuation and/or non-persistence in 16 studies.42–57

**Frequency of OAC switch**

**Frequency of VKA to DOAC switch**

OAC switching frequency varied depending on the OAC switch type, the length of follow-up, the baseline population (prevalent or incident OAC users) and the timeline of the study period. Warfarin to dabigatran switches were the most reported, followed by VKA to rivaroxaban.18 60 62 75 77–82 Frequencies of VKA to DOAC switching ranged from 2% to 56% over periods ranging from 0.3 years to 5.5 years.6 16 18 43 44 48 54 60 62 63 66 68 71 73–75 77 80 81 83–105 Of the ‘switched to’ OACs, some studies observed higher VKA to rivaroxaban switch rates compared with VKA to dabigatran switching (58% vs 40%, 65 53% vs 20%, 106 41% vs 36%).60 62 80 106 Other studies that depicted the ‘switched to’ OACs can be found in figure 2. Switching from VKA to edoxaban was only reported in a few studies.88 92 96 Table 3 shows the range of proportions of patients switching from VKA to each DOAC.

Between 2011 and 2013 the rank-ordered switching frequency from VKA was to dabigatran, rivaroxaban and apixaban (54%, 26% and 19.8%, respectively), however, in 2015 this order reversed to apixaban, rivaroxaban and dabigatran (45%, 45% and 10%, respectively).77 Two other studies reported a similar flip in the switching trend within a 5-year period (2010–2015).6 87 Sciria et al reported an increase over time (2010–2016) in the switch from VKA to DOAC.98 Overall, switching from VKA to DOAC was common, with highest frequencies reported for switches to dabigatran and rivaroxaban. However, there was a reported increase in switch from VKA to apixaban compared with the earlier DOACs over time.

**Frequency of DOAC to VKA switch and DOAC to DOAC switch**

Patients on dabigatran and rivaroxaban were more likely to switch to a VKA or another DOAC than to apixaban, especially in the first year after DOAC initiation.19 25 51 81 107–110 Olimpieri et al reported an increased likelihood of switching from dabigatran (OR 4.73, 95% CI 4.07 to 5.51), rivaroxaban (OR 1.80, 95% CI 1.53 to 2.12) or edoxaban (OR 1.54, 95% CI 1.13 to 2.08) than from apixaban.81 Warfarin was the most switched-to OAC (29%–79%).25 46 47 53 60 62 63 66 68 71 73–75 80 81 83–105 The reported frequency of switch from DOAC ranged from 2% to 33% over periods ranging from 0.3 years to 5.5 years.16 19 23 25 43 45–53 48 54 56 60 62 63 66 68 71 73–75 77 80 81 83–105 107–127 Brown et al reported an increase in switch frequency from DOACs over time.111 Hellfritzsch et al reported that 10%, 14% and 17% of DOAC initiators switched in the first, second and third year of follow-up, respectively.25 Of the studies that reported switch frequency from apixaban, 1% to 16% of apixaban-treated patients switched to another OAC within a year of study.18 19 25 29 51 81 87 108 109 118 De Caterina et al reported that one in three switches from DOAC were from apixaban, while 8% of edoxaban initiators were switched from DOAC, with more switching from
rivaroxaban and apixaban than dabigatran (rivaroxaban 42%, apixaban 32%, dabigatran 26%).

Overall, switching from DOACs was common with VKA being the most switched to OAC. Within 1 year of follow-up, up to 16% of apixaban-treated patients switched to another OAC. Figure 3A–C depict how patients switched from DOACs. Patients on apixaban switched more to VKA and rivaroxaban, patients on dabigatran switched more to VKA and rivaroxaban, while patients on rivaroxaban switched more to VKA and apixaban. Online supplemental appendix B, table B2 shows the proportions of patients switching from each DOAC to other OACs.

Patterns of OAC switching and switchbacks

Few of the included studies (7%) reported on patients who experienced more than one switch. Manzoor et al reported that 71% of switches from DOAC were in patients with two or more switch events. Switchback was sparsely evaluated in the included studies. Warfarin was the OAC most frequently switched back within 1 year of being on a DOAC. Hellfritzsch et al found switching back to VKA more common for DOAC initiators with previous VKA experience than for DOAC initiators without it (14% vs 9%) in the first year of DOAC use. Hale et al reported that 13% of patients that switched to a DOAC switched back to warfarin, with 54% occurring within the first 6 months. Alcusky et al reported that 13%–21% of patients who switched between OAC classes switched back to their original OAC during 2011 and 2012, which dropped to 8%–11% during 2013–2016. Kjerpeseth et al and Ferroni et al reported 20% of switchers switched back to their original OAC. Two studies reported 5% of warfarin to DOAC switchers switched back to warfarin, 61% of which occurred within 6 months.

Overall, switching back to a previously taken OAC were observed, with switching back to warfarin being the most frequent.

Time to switch

Analyses of time to switch were reported in eight studies, mostly for switching from DOAC (table 4). Longer time to switch was observed with older OACs like the VKAs and dabigatran compared with the newer OACs. There is no report on the time to switch from edoxaban.

Kjerpeseth et al reported that in incident users of DOAC, patients on dabigatran had a shorter time to first switch compared with apixaban.

Clinical outcomes in switchers compared with non-switchers

Eighteen studies reported on clinical outcomes in switchers (mostly switchers from VKA to DOAC) compared with non-switchers (online supplemental appendix B, table B3). Compared with VKA non-switchers, switchers from VKA to DOAC showed conflicting results on the risk of ischaemic stroke/transient ischaemic attack (TIA) / systemic embolism and the risk of gastrointestinal (GI) bleeding, that is, depending on the study, the risk was higher, lower or not different. However, of the studies that evaluated the risk of any bleeding, major bleeding, intracranial hemorrhage (ICH) and myocardial infarction (MI), there was no difference in risk.

The risk of ischaemic stroke/TIA/systemic embolism in DOAC switchers was conflicting compared with DOAC users who did not switch. Hale et al reported a significant association between switching (either from VKA to DOAC or from DOAC to VKA) and clinical outcomes compared with non-switchers (adjusted risk ratio (RR) for switches of 2.24, 95% CI 1.46 to 3.45 for stroke and systemic embolism; RR 1.41, 95% CI 1.04 to 1.91 for major bleeding; and RR 1.54 95% CI 1.29 to 1.85 for net clinical harm).
Table 4 Time to switch from incident OAC

<table>
<thead>
<tr>
<th>Study</th>
<th>Switch type</th>
<th>Mean follow-up for time to switch data (days)</th>
<th>Time to switch (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manzoor et al&lt;sup&gt;19&lt;/sup&gt;</td>
<td>DOAC to warfarin</td>
<td>183.0–730 (range)</td>
<td>118.0 (median), IQR 41.0–287.0</td>
</tr>
<tr>
<td></td>
<td>DOAC to DOAC</td>
<td></td>
<td>309.5 (median), IQR 119.0–552.0</td>
</tr>
<tr>
<td>Maura et al&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Dabigatran to other DOACs</td>
<td>365.0</td>
<td>90 (median)</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban to other DOACs</td>
<td></td>
<td>46 (median)</td>
</tr>
<tr>
<td>Zhou et al&lt;sup&gt;124&lt;/sup&gt;</td>
<td>Dabigatran to other OACs</td>
<td>180.0</td>
<td>74.1 (mean), SE 51.4</td>
</tr>
<tr>
<td>Dhamane et al&lt;sup&gt;102&lt;/sup&gt;</td>
<td>Warfarin to other OACs</td>
<td>892.0 (SD 543.7)</td>
<td>211.0 (mean), SD 301.3</td>
</tr>
<tr>
<td></td>
<td>Dabigatran to other OACs</td>
<td>939.3 (SD 566.4)</td>
<td>208.0 (mean), SD 299.6</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban to other OACs</td>
<td>799.7 (SD 524.4)</td>
<td>198.0 (mean), SD 279.4</td>
</tr>
<tr>
<td></td>
<td>Apixaban to other OACs</td>
<td>605.0 (SD 410.5)</td>
<td>154.0 (mean), SD 213.6</td>
</tr>
<tr>
<td>Rivera-Caravaca et al&lt;sup&gt;43&lt;/sup&gt;</td>
<td>VKA to DOAC</td>
<td>751.9 (IQR 368.65–1073.1)</td>
<td>730.0 (median), IQR 255.5–1058.5</td>
</tr>
<tr>
<td>Ruigómez et al&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Switch from DOAC</td>
<td>365.0</td>
<td>120.0 (mean), SD 90.0</td>
</tr>
<tr>
<td>Martinez et al&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Switch from VKA</td>
<td>693.5 (SD 401.5)</td>
<td>220 (median)</td>
</tr>
<tr>
<td></td>
<td>Switch from DOAC</td>
<td></td>
<td>58 (median, observed for a shorter time window)</td>
</tr>
</tbody>
</table>

DOAC, direct-acting oral anticoagulant; IQR, interquartile range; OACs, oral anticoagulants; SD, standard deviation; SE, standard error; VKA, vitamin K antagonist.

However, there was no distinction if these outcomes occurred before or after the switch.

Bellin et al reported no difference in bleeding rates between switchers from VKA to DOAC and non-switchers while also reporting a lower risk of cardiovascular events (HR 0.5; 95% CI 0.3 to 0.9) and bleeding (HR 0.5; 95% CI 0.3 to 1.0; p=0.0419) after switching than before switching.60 Compared with non-switchers, Yaghi et al found no association between OAC class switches (either VKA to DOAC or DOAC to VKA) and the risk of recurrent ischaemic events (HR 0.41, 95% CI 0.12 to 1.33) or ICH (HR 1.47, 95% CI 0.29 to 7.50).133

In a case-crossover study, switching from VKA to DOAC was associated with an increased short-term (30 day) risk of ischaemic stroke (OR 1.74, 95% CI 1.21 to 2.51), any bleeding (OR 1.42, 95% CI 1.13 to 1.79), GI bleeding (OR 1.72, 95% CI 1.24 to 2.40) and death (OR 1.81, 95% CI 1.56 to 2.09), while switching from DOAC to VKA was associated with increased 30-day risk of death (OR 1.68, 95% CI 1.16 to 2.43).26 These associations became stronger over time when the analysis was extended to a 60-day risk of death.26

Manzoor et al reported a significant reduction in the number of strokes and major bleeds post-switch from DOAC than pre-switch (stroke/TIA 1% vs 3%, major bleed 1.7% vs 2.1%).19 Chan et al also reported that the best (positive) net reduction of the annual intracranial event was found in VKA to dabigatran switchers with a high CHA2DS2-VASc stroke risk score (congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age ≥74, and sex category (female)) and poor time in therapeutic range (TTR).57

Feng et al examined healthcare usage for switchers versus non-switchers and found switching from warfarin to DOACs was significantly associated with fewer inpatient, emergency room and outpatient visits and lower non-drug expenditure overall compared with non-switchers.64

Overall, clinical outcomes were mostly reported for VKA to DOAC switches. The findings on the risk of ischaemic stroke/TIA/systemic embolism in switchers from VKA to DOAC (including risk of GI bleeding), and in switchers from DOAC, compared with non-switchers were conflicting. However, there was no difference in the risk of any bleeding, major bleeding, ICH or MI in VKA to DOAC switchers compared with non-switchers.

**Patient-reported outcomes**

Patient-reported outcomes in included studies were limited to VKA to DOAC switches. Using the Perception of Anti-Coagulant Treatment Questionnaire (PACT-Q2) for convenience, burden and satisfaction with therapy, and the European Quality of Life 5 Dimensions 5 Level Version (EQ-5D-5L) descriptive system for health-related quality of life, De Caterina et al reported that patients with AF who switched from VKA to DOAC more often reported bruising, mobility problems and dissatisfaction with their anticoagulation therapy before switching compared with non-switchers.66

Improved treatment convenience and satisfaction on the PACT-Q2 scale occurred more often in patients who had switched from VKA to dabigatran than in non-switchers in a 1-year prospective observational study.56 61 134 135 Coleman et al reported a significant improvement in the Anti-Clot Treatment Scale (ACTS) satisfaction with burden and...
benefits of OACs scores, 3 months after patients switched from VKA to rivaroxaban. Hanon et al also reported a significant persistent improvement in ACTS burden and benefit scores at baseline, 1, 3 and 6 months post-switch from VKA to rivaroxaban than baseline (burden (46.5, 53.6, 54.9, 54.7, respectively), benefit (10.4, 10.7, 10.9, 10.8, respectively)). The effect size at baseline compared with 3 months was large (0.89) for the burden score and small (0.16) for the benefit score. A 3-month improvement in ACTS burden scores but not benefit scores were reported in two studies that looked at switch to rivaroxaban and apixaban from VKA. The improvement in ACTS burden subscale was sustained until the 6-month (end of follow-up) in the study on a switch to rivaroxaban. Engelberger et al reported a significant increase in satisfaction 3 months after switches from VKA to DOAC compared with baseline, the level of which was similar to VKA-naïve DOAC users.

The patient-reported outcomes generally found an improvement in convenience or satisfaction (with burden or benefit) in VKA to DOAC switches compared with non-switchers.

Adherence following OAC switches
Pre-switch versus post-switch adherence to OAC was reported in five studies mostly of VKA to DOAC switches. The 3 months post-switch, self-reported adherence to rivaroxaban was significantly higher than in the 4 weeks before a switch from VKA, with a significant reduction in the number of patients with AF forgetting to take their medication before a switch from VKA, with a significant reduction in adherence following OAC switches. However, reported factors were mostly unadjusted while 11 studies adjusted for potential confounders.

Factors associated with OAC switching
Thirty-two (27.6%) studies reported on factors associated with OAC switching. However, reported factors were mostly unadjusted while 11 studies adjusted for potential confounders.

VKA to DOAC switch
From studies that adjusted for confounders, Park et al observed the risk of a VKA to DOAC switch in patients with a history of stroke/thromboembolism/TIA to be higher than the risk in those without a history (HR 1.36, 95% CI 1.25 to 1.48). Being female was also associated with a switch in the study. Switching from VKA to DOAC was significantly more likely per 1-point increase in CHA2DS2-VASc score (OR 1.09, 95% CI 1.08 to 1.10) and more likely per 1-point increase in HAS-BLED (Hyperension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage) major bleeding risk score (OR 1.12, 95% CI 1.10 to 1.13). Potpara et al found an HAS-BLED score ≥3 (OR 2.24, 95% CI 1.17 to 4.28) to be an independent predictor of a switch from VKA to DOAC.

Fosbol et al found being female, younger age, having comorbidities like stroke, bleeding and heart failure to be associated with a switch from VKA to DOAC. Fosbol et al found the relationship between CHA2DS2-VASc score and switching to be U-shaped with patients with CHA2DS2-VASc score of 3 having the lowest odds of switching. HAS-BLED scores also had a U-shaped relationship with a score of 3 or above or below 1 associated with a higher likelihood of shifting than HAS-BLED score of 1. Hohnloser et al found being female (HR 1.35, 95% CI 1.25 to 1.47), stroke (HR 7.68, 95% CI 6.09 to 9.69), heart failure
(HR 1.12, 95% CI 1.02 to 1.23), major bleeding (HR 1.73, 95% CI 1.26 to 2.35), gastrointestinal bleeding (HR 2.33, 95% CI 1.68 to 3.24), AF ablation (HR 1.55, 95% CI 1.17 to 2.07), electrical cardioversion (HR 2.05, 95% CI 1.75 to 2.39) to be associated with a switch from VKA to DOAC.18 Dementia and having the index OAC from 2014 to 2016 compared with 2013 were other factors found in the study by Hohnloser et al.18

From studies that reported factors based on unadjusted analysis, factors found to be associated with a switch from VKA to DOAC include age, being female, high socio-economic status, having private insurance and higher income.23 26 59 60 62 63 68 101 131 144 146 OAC switching was also found to vary between practices and among providers.88 While Norby et al identified having more comorbidities as a significant factor for warfarin to rivaroxaban switch, Sholzberg et al identified lower Charlson Comorbidity Index score.68 131 Switching was associated with higher stroke risk factors and/or bleeding.59 62 77 132 Poor INR on apixaban (dabigatran-Ruigómez Garcia-Sempere et al) found history of vascular disease, more primary care and cardiology visits and higher income to be associated with a switch from VKA to DOAC.146

Switch from DOAC

From adjusted analyses, being on either dabigatran or rivaroxaban were associated with switch from DOAC. Being on rivaroxaban (HR 2.08; 95% CI 1.92 to 2.25) or dabigatran (HR 3.74; 95% CI 3.35 to 4.18), compared with apixaban, were significantly associated with a higher risk of switching.107 This was also confirmed in another study by Baker et al (rivaroxaban HR 1.78; 95% CI 1.61 to 1.96; dabigatran HR 3.40; 95% CI 3.03 to 3.82).108 Ruigómez et al also reported a higher likelihood to switch from dabigatran and rivaroxaban, respectively, than those on apixaban (dabigatran-OR 4.28, 95% CI 3.24 to 5.65; rivaroxaban-OR 1.89, 95% CI 1.49 to 2.39).31

Manzoor et al observed the following to be predictors of a switch from a DOAC: older age group (55–64, 65–74 and ≥75 years) compared with <55 age group significantly increased the odds of switching DOAC therapy by 15%–40%; being male decreased the odds of switching therapy (OR 0.82, 95% CI 0.78 to 0.87); using apixaban or rivaroxaban as the index DOAC compared with dabigatran significantly decreased the odds of switching therapy (apixaban: OR 0.25, 95% CI 0.18 to 0.34; rivaroxaban: OR 0.41, 95% CI 0.38 to 0.44).19

Hohnloser et al found being 65–74 years old versus less than 65 years (HR 1.31, 95% CI 1.12 to 1.53), being 75–84 years versus less than 65 years (HR 1.37, 95% CI 1.17 to 1.60), stroke (HR 2.16, 95% CI 1.18 to 3.94), myocardial infarction (HR 7.54, 95% CI 5.38 to 10.56), gastrointestinal bleeding (HR 3.95, 95% CI 2.54 to 6.15) and cardioversion (HR 2.52, 95% CI 2.15 to 2.97) to be associated with a switch from DOAC to VKA.19 The study also found being 75–84 years versus less than 65 years (HR 1.39, 95% CI 1.20 to 1.62), heart failure (HR 1.13, 95% CI 1.01 to 1.27), kidney disease (HR 1.24, 95% CI 1.08 to 1.43), stroke (HR 7.47, 95% CI 5.61 to 9.94), myocardial infarction (HR 3.91, 95% CI 2.56 to 5.98), gastrointestinal bleeding (HR 4.73, 95% CI 3.36 to 6.67), AF ablation (HR 1.56, 95% CI 1.21 to 2.01) and cardioversion (HR 1.50, 95% CI 1.26 to 1.78) to be associated with a switch from DOAC to DOAC.18

Hellfritzsch et al reported being less than 55 years (OR 1.56, 95% CI 1.33 to 1.82), stroke risk score of 0 compared with score ≥2 (OR 1.70, 95% CI 1.41 to 2.06), dabigatran use (apixaban as reference OR 2.00, 95% CI 1.79 to 2.27; rivaroxaban as reference OR 1.39, 95% CI 1.27 to 1.54), previous VKA use (OR 1.77, 95% CI 1.64 to 1.91), ischaemic heart disease (OR 1.25, 95% CI 1.14 to 1.37) and chronic renal failure (OR 1.58, 95% CI 1.28 to 1.96) as factors associated with a switch from DOAC to VKA.25

From unadjusted analysis, one in five switches from DOAC to VKA was preceded by ischaemic stroke/TIA, gastrointestinal bleeding or a cardioversion procedure.132 Hernandez et al reported that patients with AF on dabigatran were more likely to switch to warfarin after a bleeding event than warfarin users switching to dabigatran (17% vs 2%, p<0.001).130 Older age, being female and having a Charlson Comorbidity Index of 5 and above were other factors associated with a switch from DOAC.23 35 Higher copayment in commercially insured patients was significantly associated with switching to a different OAC within 1 year of DOAC initiation.115

Overall, the factors associated with increased likelihood of OAC switch were mostly risk factors for stroke and bleeding, presence of high comorbidity and poor clinical outcomes.

DISCUSSION

This study included 116 studies that described OAC switching in patients with AF and provides the most comprehensive review of the evidence so far. Switching between OACs is common in real-world practice. The definition of what constitutes an OAC switch is not standardised in the literature. Switching from VKA to dabigatran was prevalent; however, for patients starting on VKA, switching to apixaban is becoming more common over time, reflecting the changing performance of various DOACs on the market over time. Patients on DOACs were switched more commonly to warfarin than other DOACs. Switch patterns and switchbacks were sparsely studied but switching back to VKA was the most common type of switchback. Post-switch adherence and satisfaction data were largely on VKA to DOAC switches with no significant improvement in adherence compared with non-switchers. Satisfaction with therapy was observed to increase in VKA to DOAC switches compared with non-switchers. The data on clinical outcomes post-switch were also more on VKA to DOAC switch, sparsely on switches from DOACs, and inconsistent in the effect sizes. Our study was able to study OAC switching in AF far more
broadly and in more detail than previous reviews. Its unique features included the inclusion of more, and more recent studies, switchbacks, patterns of switching, patient-report outcomes measures and data on switching from DOACs.

The large variation in definitions of switching we observed likely contributes to misclassification and possibly bias in study design, interpretation and cross-study synthesis, particularly those involving clinical and patient-reported outcomes. Some studies in this review classified switching as either discontinuation or non-persistence, although the initiation, implementation, discontinuation and persistence facets in the International Society for Medication Adherence taxonomy do not mention medication switches. Also, the European Society for Patient Adherence, Compliance and Persistence (ESPACOMP) Medication Adherence Reporting Guidelines which was based on the taxonomy does not mention switching. There is a need to increase consistency in the terminology and definition of medication switching. Based on this review, we propose the following definition of a switch: ‘A change from one medication to a different medication with the same indication within a gap of ≤30 days between prescriptions’, and suggest ESPACOMP add medication switches to its adherence framework.

Among VKA users, switching to DOACs followed the sequence of market introduction, with dabigatran, rivaroxaban, and presently, apixaban being the most switched to DOAC. This may be due to increasing awareness of apixaban’s optimal efficacy/safety profile compared with other DOACs. This pattern may not have been followed with edoxaban, although data on its uptake is sparse. None of the switching studies included in this review accounted for OAC dose. A switch from warfarin to dabigatran 110 mg and a switch from warfarin to dabigatran 150 mg have different efficacy and safety attributes. A more detailed characterisation of dose selection in OAC switches is needed.

A patient’s OAC may need to be switched more than once to arrive at a suitable stroke prevention therapy. Although most studies censored after the first switch, switchbacks to a previously taken OAC were somewhat common (5%–21%) in studies that evaluated multiple switches, which may reflect a variety of tolerability, preference, economic or access issues with the switched-to OAC. Switching back to warfarin was found to be the most frequent, which may be due to the lower out-of-pocket cost for warfarin than the DOACs. There may be untoward adherence and efficacy consequences of these experiences, and this area deserves further study to determine the reasons, predictors and consequences of these unsuccessful switches.

The risk of ischaemic stroke/TIA/systemic embolism in switchers from VKA to DOAC (including risk of GI bleeding), and in switchers from DOAC, compared with non-switchers were conflicting. However, the risk of any bleeding, major bleeding, ICH or MI was not significantly increased in VKA to DOAC switches compared with non-switchers. In a previous review, the risk of stroke/TIA/thromboembolism and MI was higher in VKA to DOAC switches than in those who remained on VKA, the risk of GI bleeding was higher while the risk of ICH was lower. While the review on switches from DOAC by Romoli et al reported insufficient data to ascertain the clinical outcomes associated with switching. Simulation studies have shown that exposure history, time to switch and time since initiation of the comparator are potential threats to validity in studies of patient outcomes associated with medication switching. There is a need for more studies on clinical outcomes of switching that address these methodological challenges. Such studies should also capture reasons for switching whenever possible.

Most of the studies that associated variables to switching did not adjust for confounders. Like our scoping review, a previous review also reported history of stroke and bleeding as being factors associated with OAC switching. Our results suggest adding high risk of stroke or bleeding based on existing risk scores, as well as heart failure and being female to this list for VKA to DOAC switches. Factors found to be consistently associated with a switch from DOAC to other OACs in our review included being on dabigatran or rivaroxaban, older age, myocardial infarction, heart failure and kidney disease. Some of the studies on factors associated with OAC switch did not specify the type of OAC switch. There is a need to differentiate the factors associated with a switch from DOAC to those associated with DOAC to VKA and DOAC to DOAC switches.

Switching from VKA to DOAC was associated with a consistent and significant improvement in patient-reported satisfaction with OAC therapy. Analogous evidence for switches from DOAC were not found in our review. Convenience of therapy, poor anticoagulation profile, bleeding, patient’s decision and poor adherence were reported reasons for switching from VKA to DOAC. The reasons for switching from DOAC were primarily based on safety and effectiveness, decreasing renal function and cost. However, in the ARISTOTLE trial, patients with AF with severe renal dysfunction (creatinine clearance of 25–30 mL/min) on apixaban had less bleeding, lower rates of major bleeding and similar stroke/systemic embolism (SSE) rates compared with those on warfarin. Our review found no data on switching from DOACs due to extreme body weight changes. Low body weights (<60 kg) are recommended to use low dose apixaban or edoxaban, while high body weights (>120 kg) may use rivaroxaban and apixaban with caution.

Considering the extent of OAC switching revealed in this review, we believe several responses are warranted. First, for future research on the topic standardised definitions of switching are needed. Varying definitions will continue to lead to uncertainty in interpreting epidemiologic and outcome studies involving switching. Second, our results highlight knowledge gaps warranting research, especially into the effects of OAC switching on subsequent patient adherence and on peri-switching and
post-switching clinical outcomes (eg, stroke, bleeding, hospitalisations). Third, our result point to the high likelihood that patients who switch OACs are in need of OAC education and adherence support. Finally, reimbursement criteria may drive switching, and our findings point to the need for evaluation of how, ultimately, switching as a result of such policies affects patient outcomes. This review illuminates the complexity of OAC switching in AF and provides information that can help policymakers and clinicians make informed decisions regarding OAC switching.

**Limitations**

This study should be interpreted in light of its limitations, many of which are related to heterogeneity and timing of existing studies, as described above. These may affect the interpretation of the results. Switch outcomes did not adjust for reasons for switching which may bias the results. The results on clinical outcomes associated with OAC switching may be biased in either direction due to a lack of adjustment for pre-switch factors. There was inconsistent data and sparse reporting of some outcomes.

**CONCLUSION**

While OAC switching is common in patients with AF there are still many aspects of OAC switching that have received little study, especially in switches from DOACs. The review showed switching from VKA to DOACs followed the sequence of market introduction of the DOACs while switching from DOAC were mostly to VKA. The review also showed patients often switched back to an OAC they have previously been on. Switching from VKA to DOAC did not confer improvement in adherence, however there was consistent improvement in treatment satisfaction. Clinical outcomes post-switch need to be adjusted for pre-switch characteristics, to better understand the direction of effect. Establishing reporting guidelines on medication switching definition will ensure consistency.

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