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

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 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 is rapid and chaotic. AF increases the risk of thromboembolic stroke by threefold to fivefold, and oral anticoagulants (OACs) reduce this risk by approximately 66%. 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. Since then, DOAC prescribing in AF has increased, while warfarin use has dropped. Attributes of individual OACs, patient factors and prescriber factors may predispose patients with AF to switching between OACs over time. 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. Compared with warfarin, the risk of major bleeding is significantly lower for dabigatran and apixaban, and lower with apixaban than dabigatran or rivaroxaban. 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. 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. 8 14 16-24 For all of the above reasons, switching between OACs may be common among patients with AF who are prescribed OACs. 6 25-35

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. 36 The other systematic review focused only on DOAC to DOAC switches, examined only the frequency of switching and included only five (mostly older) studies. 37 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. 38

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. 39 40 Reporting in this manuscript follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-extension for Scoping Reviews standards. 41 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. 40 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
Table 1 Outcomes of interest from the scoping review of OAC switching in AF

<table>
<thead>
<tr>
<th>Outcome categories</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Switching characterisation and frequency</td>
<td>Definitions of OAC switch.</td>
</tr>
<tr>
<td></td>
<td>Frequency of OAC switch.</td>
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<tr>
<td></td>
<td>Switch types (the ‘switched-from’ and ‘switched-to’ OAC).</td>
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<tr>
<td></td>
<td>Switch patterns (switching sequences with more than one switch type).</td>
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<tr>
<td></td>
<td>Switchbacks.</td>
</tr>
<tr>
<td></td>
<td>Timing of switch.</td>
</tr>
<tr>
<td>Clinical outcomes in switchers compared with non-switchers</td>
<td>Stroke and systemic embolism.</td>
</tr>
<tr>
<td></td>
<td>Bleeding.</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction.</td>
</tr>
<tr>
<td></td>
<td>Death.</td>
</tr>
<tr>
<td>Adherence and patient-reported outcome measures before and after switching</td>
<td>Adherence.</td>
</tr>
<tr>
<td></td>
<td>Quality of life.</td>
</tr>
<tr>
<td></td>
<td>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>Country of study</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>Study design</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>Year of publication</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>Type of switch described§</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>Studies that included all four DOACs</td>
<td>11 (9.5)</td>
</tr>
<tr>
<td>Multiple switches described</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. 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
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

Figure 2  Switch from vitamin K antagonist (shows the oral anticoagulants patients switched to and their proportions).

<table>
<thead>
<tr>
<th>'Switched to' OAC</th>
<th>Switch proportion range (study period prior to 2015)</th>
<th>Switch proportion range (study period ≥2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>40%–93%</td>
<td>10%–52%</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>7%–78%</td>
<td>24%–58%</td>
</tr>
<tr>
<td>Apixaban</td>
<td>2%–23.7%</td>
<td>19%–46%</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>–</td>
<td>0.2%–1%</td>
</tr>
</tbody>
</table>

Table 3  Range of the proportion of patients switching to each DOAC from VKA

DOAC, direct-acting oral anticoagulant; VKA, vitamin K antagonist.

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 3-year period (2010–2015).67 Sciria et al reported an increase over time (2010–2016) in the switch from VKA to DOAC.88

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 49 75 85 107–111 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 48 49 54 60 62 66 68 71 73–75 77 80 81 83–105 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 23 25 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. Three 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. See online supplemental appendix B, table B3.

A 27% and a 54% increased relative risk of any bleeding and GI haemorrhage was observed (p<0.001) in patients with AF who switched to dabigatran after at least 6 months on warfarin, compared with warfarin users (non-switchers). Holbrook 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 switchers 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).
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.70 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 65 to 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)134,135 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.60,136

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, 55.6, 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. 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-naive 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 OAC (4.7% vs 0.8%). Persistence and rate of discontinuation were similar in switches from VKA to DOAC and patients newly initiating DOAC. There was a decrease in 6 and 12 months post-discharge adherence in patients switching from warfarin to DOAC versus other OAC switch types compared with discharge adherence (6 months, 4.6% vs 7.9%; 12 months, 15% vs 16.2%). Discontinuations were highest at 6 months of rivaroxaban use for patients switched from VKA to rivaroxaban, 10% (95% CI 7.3% to 12.7%); after 12 months 7.7% (95% CI 6.0% to 9.2%) discontinued. In the study by Zielinski et al, 13% of switchers were non-persistent with their OAC before the end of the 1 year of follow-up. Toorop et al reported that patients who had a low TTR pre-switching from VKA to DOAC had a worse persistence pattern to DOAC than patients with a high pre-switch TTR. Overall, the evidence shows that switching does not result in meaningful improvement in OAC adherence.

**Reasons for OAC switching**

Unstable INR (60%), patient’s decision (24%) and physician reasons other than unstable INR (15%) were the major reasons for switching from VKA to rivaroxaban in the Study of Atrial Fibrillation Reduction (SAFARI). Other studies also reported unstable INR as a common reason for switching from VKA to DOAC along with ineffective prior therapy, bleeding during VKA treatment, difficulty in patient compliance and frequent falls. Ikeda et al identified better effectiveness and safety of DOACs as the primary reason for physicians advising patients to switch from VKA. Patient preference and convenience of DOACs were also identified as a major reason for the switch from VKA to DOAC. General practitioner or specialist recommendations were the top reasons for VKA to DOAC switch in the study by Bernatis et al. In a survey of physicians managing ischaemic stroke in patients with AF, 83% said they routinely switched patients to a DOAC for those who experience ischaemic stroke on VKA while only 38% did so for patients experiencing ischaemic stroke while on DOAC. The major reason for not switching while on DOAC was the paucity of randomised trial on switching.

Reasons for switching from DOACs included bleeding complications, stroke/TIA/systemic embolism, physician’s decision, efficacy, safety concerns, potential side effects, blood test results, GI symptoms, decreasing renal function and cost. Patient choice followed by renal impairment were the top reasons for switching from DOAC in the study by Middeldorp et al.

Overall, reasons for OAC switching encompass patient, prescriber and drug factors as well as the need to improve clinical outcomes and patient experience.

**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 CHADS2-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 CHADS2-VASc score and switching to be U-shaped with patients with CHADS2-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 switching 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{59, 62, 77, 132} Poor INR on apixaban (dabigatran-from dabigatran and rivaroxaban, respectively, than those on warfarin) were significantly associated with a higher risk of switching.\textsuperscript{51} 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).\textsuperscript{108} Ruigómez et al also reported a higher likelihood to switch from dabigatran and rivaroxaban compared with apixaban, respectively, than those switching to VKA (HR 1.58, 95% CI 1.26 to 1.95; apixaban OR 0.25, 95% CI 0.18 to 0.34; rivaroxaban: OR 0.41, 95% CI 0.38 to 0.44).\textsuperscript{19} Hohnloser et al found being 65–74 years old 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.\textsuperscript{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.\textsuperscript{25}

From unadjusted analysis, one in five switches from DOAC to VKA was preceded by ischaemic stroke/TIA, gastrointestinal bleeding or a cardioversion procedure.\textsuperscript{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).\textsuperscript{130} Older age, being female and having a Charlson Comorbidity Index of 5 and above were other factors associated with a switch from DOAC.\textsuperscript{23, 53} Higher copayment in commercially insured patients was significantly associated with switching to a different OAC within 1 year of DOAC initiation.\textsuperscript{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.\textsuperscript{36–38} 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\textsuperscript{46–57} although the initiation, implementation, discontinuation and persistence facets in the International Society for Medication Adherence taxonomy do not mention medication switches.\textsuperscript{153} 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.\textsuperscript{154} 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.\textsuperscript{155} 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 switches from VKA to DOAC (including risk of GI bleeding), and in switches 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.\textsuperscript{36} While the review on switches from DOAC by Romoli et al reported insufficient data to ascertain the clinical outcomes associated with switching.\textsuperscript{37} 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.\textsuperscript{156} 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.\textsuperscript{38} 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.\textsuperscript{157} 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.\textsuperscript{158} 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 (e.g., 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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