Switching of oral anticoagulants and associated clinical outcomes in patients with non-valvular atrial fibrillation: A narrative review

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Abstract

Approval of direct-acting oral anticoagulants (DOACs) for stroke prevention in atrial fibrillation (AF) was an important milestone, providing widened treatment choices along with the possibility for inter-drug switching after initiation. In addition to improved utilisation of oral anticoagulants (OACs) for stroke prevention, reports of switching among OACs are growing in the literature. Switching may influence clinical outcomes, healthcare costs and patient satisfaction. This review aimed to summarise the current literature on the pattern of OAC switching in patients with AF, including reasons for switching and clinical consequences following switching. A literature search was conducted in PubMed, Scopus, and Embase on June 27, 2020. We included articles published after 2013, following the introduction of apixaban. The review found that switching among OACs was common in clinical practice, significantly varying with the type of OAC. Studies reporting the reason for switching and clinical outcomes were comparatively limited. The decision to switch was often related to safety issues (usually bleeding), poor anticoagulation control and ease of use. Patient characteristics, clinical conditions and co-medications that can increase the risk of bleeding and stroke were found to be associated with switching from vitamin K antagonists, but less for DOAC switching. Findings regarding bleeding outcomes following switching were inconsistent, possibly confounded with the type of OAC, reasons for switching and switching protocol. Despite the limited number of studies included and their relatively short follow-up periods, our review revealed that switching had minimal impact on stroke and other related thrombotic outcomes. Further prospective studies are needed to better understand possible reasons for switching and its influence on clinical outcomes.

1. Introduction

Atrial fibrillation (AF) is associated with significant morbidity and mortality, and increased healthcare costs [1, 2]. AF-associated morbidity and mortality are mainly due to thromboembolic [3] and other cardiovascular complications, such as stroke, myocardial infarction (MI), ischaemic heart disease, heart failure and cardiac arrest [4-7]. Stroke associated with AF is usually more severe and fatal than the stroke of other etiologic origins, but is largely preventable with oral anticoagulation [3]. Oral anticoagulation therapy significantly lowers the risk of stroke in patients with non-valvular AF (NVAF), including a reduction in associated patient morbidity and mortality [8]. The benefits of oral anticoagulants (OACs), both vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs), have been consistently shown in clinical trials [9-14] and real-world studies [15-19].

Previously, VKAs were the only options for oral anticoagulation in AF patients [20]. In the last 12 years, four DOACs (i.e., apixaban, dabigatran, edoxaban, and rivaroxaban) have been approved internationally for thromboprophylaxis in patients with NVAF. Since their approval, the utilisation of DOACs has been increasing with a corresponding decline in warfarin use [21-24]. DOACs have demonstrated comparable efficacy to VKAs with better safety profiles [10-14]. Besides an increased uptake of OAC for stroke prevention, marketing of multiple DOACs created an opportunity to switch among OACs. Unlike initiation of OAC for stroke prevention in NVAF patients, however, guideline recommendations on when to switch an OAC are limited [25], especially switching from or between DOACs, which potentially contributes to practice variation. Switching between OACs may affect, either positively or negatively, clinical outcomes and healthcare costs [26-30].

Literature regarding switching of OACs in people with NVAF is continuously increasing and changing. Some aspects of OAC switching have been reviewed, including clinical outcomes of switching from a VKA to dabigatran or rivaroxaban [28] and the rate of switching between DOACs [31]. Given the dynamic nature of OAC use in clinical practice and the limited scope of previous reviews [28, 31], there is a need to comprehensively review the current literature for a better understanding of OAC switching in real-world settings. This review aimed to comprehensively collate and summarise the most recent literature on the patterns of OAC switching in NVAF patients. We also summarised findings on possible reasons for switching, associated clinical outcomes, and predictors of switching.

2. Methods

2.1. Search strategy

Articles were systematically searched in the major electronic databases (i.e., Medline via PubMed, Embase via Ovid, and Scopus) using key search terms. Search terms employed to locate literature include "Atrial fibrillation" AND ("oral anticoagulant" OR warfarin OR apixaban OR rivaroxaban OR dabigatran) AND switching and other related terms mapped in consultation with a research librarian **(Appendix 1)**. Each database was searched using the most appropriate syntax and Boolean operators for the search function. The searching date was June 27, 2020. The initial search results were restricted using the following filters: publication year after 2010, English language and age ≥ 18 years. The publication year was subsequently modified to 2013, to minimise the possible influence of the difference in the approval year of each DOAC.

2.2. Selection criteria

Non-interventional observational studies reporting the prevalence of OAC switching or clinical outcomes of switching in NVAF patients were included. The inclusion criteria were original studies conducted in the general adult population (≥18 years) and published in English after 2013. Studies were further scrutinised based on the study period to accommodate the introduction of apixaban; the study had to include at least a 12-month data collection period after 2013. Moreover, studies had to report at least one of the following outcomes of interest: the rates of switching among OACs, clinical outcomes of switching or possible reasons for switching. We excluded studies with study periods exclusively before 2013, subgroup populations only (e.g., kidney disease, switching in hospitalised patients, switching after cardioversion or catheter ablation), more than one index OAC, unidentifiable type of OAC and unclear indication.

2.3. Data handling and extraction

Literature search, screening and extraction were done by a single author (ATK). The screening was conducted using Covidence software. Data were extracted from articles that fulfilled eligibility criteria using a tabulated spreadsheet. Data extracted included author name, the country where the study was conducted, journal name, year of publication, study design, data source, study population, study period, sample size, patient characteristics, type of OAC, follow-up duration, and outcomes of interest (switching rate, possible reasons, clinical outcomes, and predictors).

The key outcomes of this review were switching rates of different OACs and associated factors. We sought possible reasons for OAC switching and the effect of switching on clinical outcomes. Clinical outcomes of interest were all-cause mortality, thromboembolic events (systemic embolism, stroke, transient ischaemic attack (TIA), MI), and bleeding events (major bleeding, gastrointestinal (GI) bleeding, clinically significant non-major bleeding). The extracted data are narrated, considering the characteristics of the included studies, study populations, study period, type of OAC, and study outcomes.

3. Results

3.1. Study selection

Searching of the three databases resulted in a total of 1791 articles, and 1173 articles after 618 duplicates were removed. After screening titles and abstracts, 109 articles were left for full-text review. Finally, 70 articles were excluded, leaving 39 studies eligible for inclusion in this review. The details of the selection process are shown in **Fig 1**.

Fig. 1 Flowchart of studies selection process

3.2. Study characteristics

A total of 39 studies met the inclusion criteria of the review. Among those studies, 36 reported the rate of OAC switching [27, 32-66], 13 of which also conducted predictor analysis for switching [32, 34-36, 42, 44, 48, 53, 55, 57, 62, 63, 65]. Five studies assessed clinical outcomes of switching [27, 37, 67-69], while three investigated reasons for switching [46, 47, 66]. The sample size ranged between 233 [66] and 486,215 [55] NVAF patients. Data for approximately 1.8 million participants (708,990 VKA users and 1,090,322 DOAC users), derived from nine prospective [32, 37, 41, 49, 55, 56, 62, 65, 66] and 30 retrospective cohort studies [27, 33-36, 38-40, 42-48, 50-54, 57-61, 63, 64, 67-69] were extracted. The majority of the studies were conducted in the United States (n=10) [27, 34, 35, 38, 45, 46, 53, 59, 62, 69], Nordic countries (n=8) [33, 44, 47, 48, 50-52, 63], and the United Kingdom (n=5) [43, 54, 60, 61, 66], whereas three studies were multinational [32, 37, 56]. Claim databases and medical records were the principal type of data sources in most studies (n=19) [27, 33-36, 38, 40, 42, 45, 51, 53, 57-59, 64, 66-69]. Primary care data, with or without linking to other data sources, were used in five studies, in which, four were conducted in the United Kingdom [43, 54, 60, 61] and one in France [39]. The results of 15 studies were from registries (e.g., disease-based, drug-based, or nationwide registries) [32, 37, 41, 44, 46-50, 52,

55, 56, 62, 63, 65]. Specifically, studies conducted in Nordic countries commonly used data collected by nationwide registries [44, 47, 48, 50, 52, 63].

Fifteen studies reported the switching rate of DOACs as a class, with or without individual drug level switching [32, 36, 41, 42, 47, 48, 51-55, 61, 64-66]. Of the studies that assessed the rate of switching, 14 studies were exclusively conducted among DOAC users [33-35, 38, 41, 47, 48, 51, 53, 55, 59, 61, 64, 66], five studies were in VKA users [44, 46, 49, 57, 62] and 13 studies among users of both DOACs and VKAs [32, 36, 39, 42, 43, 45, 50, 52, 54, 58, 60, 63, 65]. The remaining four studies were focused on a single DOAC (i.e. two for dabigatran [37, 56], and one each for rivaroxaban [40] and apixaban [27]). **Table 1** and **Appendix 2** describe the characteristics of the studies included in the review.

Table 1: Characteristics of the studies included in the review

3.3. Patient characteristics

The mean age of patients in the included studies was between 60.8 and 80.0 years [34, 58], specifically, 67.7 to 80.0 years for VKA users [49, 58], 62.0 to 80.0 years for apixaban [34, 58], 61.1 to 77.3 years for dabigatran [34, 58] and 60.8 to 77.4 years for rivaroxaban [34, 35]. The proportion of female patients ranged from 26.2 to 61.8% [34, 38]. The mean CHA_2DS_2-VASc and HAS-BLED scores were between 2.1 to 4.8 [27, 35] and 1.2 to 3.4 [27, 37], respectively. Hypertension was the most common comorbidity reported by the studies (43.5-97.3%) [45, 52]. The majority of studies were conducted exclusively in treatment-naïve patients [27, 32, 34, 35, 37-39, 42-45, 49-60, 62, 63] (**Appendix 3**).

3.4. Patterns of oral anticoagulant switching

3.4.1. Overview of OAC switching

The rate of OAC switching varied depending on the type of OAC, duration of follow-up and to which type of OAC switching was assessed (i.e., for those who initially received a DOAC). For instance, seven studies assessing the rate of switching in DOAC users reported switching to warfarin only [32, 41, 42, 47, 51, 54, 65], which would underestimate the actual rate of switching in clinical practice. One study reported switching of DOACs to another DOAC without assessing switching to a VKA [55]. Six studies reported switching of a VKA to DOACs as a group without specifying to which particular DOAC switching occurred [32, 42, 49, 54, 58, 65]. Also, four studies reported the rate of switching without identifying to which specific OAC switching had occurred [45, 50, 60, 63]. The rate of switching was

reported over a sequential period in three studies [38, 59, 60]. Whilst the cumulative incidence of switching increased with the duration of follow-up, the rate of switching was relatively higher during the first three months of OAC initiation. Of the total switches reported at the end of follow-up (6-19%), 2-12% occurred in the first three months [38, 59, 60] **(Fig 2).**

Fig. 2 Sequential rate of switching at different time-points following initiation

The rates of switching in VKA users ranged from 2.7 to 33.8% [54, 57] within a year of follow-up. With the same duration of follow-up, the rates for DOACs, apixaban, dabigatran and rivaroxaban users were 4.9 to 14.9% [48, 61], 2.8 to 8.6% [61, 63], 8.8 to 21.0% [61, 63], and 4.9 to 15.0% [40, 61], respectively. The rate may increase when the duration of follow-up extended beyond 12 months. The highest switching rate recorded for DOACs was 17.2% within 24 months of therapy initiation [53]. The highest rate for apixaban was 14% [27] during a mean follow-up of 17.6 months, with 27.9% [33] and 21.3% [33] for dabigatran and rivaroxaban at a median follow-up of 367 and 432 days, respectively. Except for patients prescribed apixaban, the highest rates of switching were observed in studies that included patients who started on therapy between 2010 and 2015 [33, 53, 57]. The peak apixaban switching rate occurred between 2013 and 2017 [27].

Switching rates were highest for dabigatran users than the users of any other OAC in all studies included in this review. In contrast, switching rates were lower in apixaban users except in two studies; one compared to rivaroxaban (10.5% apixaban vs. 9.5% rivaroxaban) [38] and the other compared to edoxaban [55]. In comparison, DOAC initiators had a lower switching rate than VKA users, except in two studies (8.6% vs 5.4% and 6% vs 2.7) [32, 39]. Of the six studies that reported switching rates of both rivaroxaban and VKA [39, 43, 45, 50, 52, 63], the rates were lower in rivaroxaban-treated patients, except in one study [43]. Patients who initiated a VKA commonly switched to rivaroxaban (26-58%) [36, 44], dabigatran (10.0-54.2%) [39, 44] and apixaban (17.1-40.0%) [39, 43], whilst patients who initiated DOACs often favoured switching to VKAs [27, 39, 40, 43, 48, 52, 53, 59, 64]. In patients initially treated with apixaban, the recorded switching rates were 43.9-73.1% to warfarin [48, 53], 22.0-46.9% to rivaroxaban [38, 52] and 6.0-19.5% to dabigatran [27, 53]. The rates of switching from dabigatran were 27.7-69.4% to warfarin [33, 48], 6.8-40.9% to apixaban [39, 53] and 16.7-46.9% to rivaroxaban [38, 43]. Finally, among those who switched from rivaroxaban, 31.7-75.0% were switched to warfarin [33, 43], 1.7-44.3% to apixaban [34, 40], and 5.3-29.0% to dabigatran [35, 52] **(Table 2)**.

Table 2: Patterns of OAC switching in NVAF patients

The data source could also influence the reported rates of switching across different OACs. The peak switching rates were commonly reported by studies that used medical records (relatively small sample sizes), while primary care data sets usually reported relatively lower rates of switching. The pattern of OAC switching across data sources is depicted in the figures below **(Fig 3).**

Fig. 3 The rates of OAC switching in different data sources

3.4.2. Summary of OAC switching in clinical practice

Several studies have been conducted to assess the switching patterns of OACs in NVAF patients using real-world clinical data. Fosbol et al., [44] analysed data of 62,065 VKA-treated NVAF patients identified from the Danish nationwide registries. The authors included patients with at least one VKA prescription since 1995 and assessed switching between August 22, 2011 to December 31, 2015. Overall, 29.6% of patients with prior VKA-treatment were switched to a DOAC, where 19.8% switched to apixaban, 54.2% to dabigatran and 26.0% switched to rivaroxaban. The switching pattern showed a relative temporal trend with the market entry of each DOAC in Denmark. Accordingly, until March 2012, all patients were exclusively switched to dabigatran, whereas between March 2012 and December 2013, 33% of patients were switched to rivaroxaban with a parallel decline in switching to dabigatran ($p<0.0001$ for trend). At the end of the study period, 90% of switching was to apixaban and rivaroxaban (equally shared between the two), whereas only 10% was to dabigatran ($p<0.0001$ for trend).

Another large retrospective cohort study was conducted in Denmark using nationwide registries to examine the rate of switching in DOAC-prescribed patients [48]. A total of 50,623 patients (30% previously experienced with a VKA) who started any of the three DOACs (i.e., dabigatran (50%), apixaban (25%) and rivaroxaban (25%)) between August 2011 and February 2016 were included in the study. Within one and two years of follow-up, 14.9% and 19.6% of patients were switched to another OAC, respectively. The majority of patients switched to a VKA, 10.1% during the first year and 13.6% in the second year of follow-up. At the individual drug level, 7.8%, 17% and 14.3% of patients initially treated with apixaban, dabigatran and rivaroxaban, respectively, switched to either a VKA or another DOAC within a year of starting therapy. With all agents, the majority of switching was in preference to a VKA; 5.7% from apixaban, 11.8% from dabigatran and 8.5% from

rivaroxaban were switched to a VKA. Switching to a VKA during the first year of DOAC therapy was higher in previously VKA-treated patients (13.7%) than the naïve counterparts (8.5%). However, switching from a DOAC to another DOAC was higher in the naïve patients than VKA-experienced (5.4% vs 3.5%) [48]. A related study was also conducted using the Danish nationwide registries of NVAF patients who newly-initiated on an OAC between August 22, 2011 and Dec 31, 2015 [52]. It included 54,321 patients who filled prescriptions for apixaban (n=7,963), dabigatran (n=15,413), rivaroxaban (6,715) or warfarin (n=24,230) and switching was assessed for the first three years of follow-up. The results showed that 5.0% of apixaban (63% to warfarin, 22% to rivaroxaban and 15% to dabigatran), 19.0% of dabigatran (54% to warfarin, 26% to rivaroxaban and 20% to apixaban), 10.0% of rivaroxaban (45% to warfarin, 29% to dabigatran and 27% to apixaban) and 11.0% of warfarin (52% to dabigatran, 28% to rivaroxaban and 20% to apixaban) treated patients were switched during the mean follow-up periods of 268, 511, 348 and 398 days, respectively [52].

A retrospective study was conducted using claims data of 51,606 patients in Germany who filled OAC prescriptions between January 1, 2013 and March 31, 2016 [36]. The study included patients who were newly-initiated on either a VKA or a DOAC. By the end of a one-year follow-up, 10.7% of patients treated with a VKA were switched to a DOAC, while 10.4% of patients who initiated a DOAC were switched to another OAC. Of the total patients who switched from a VKA, 6.2%, 3.2% and 1.3% were switched to rivaroxaban, apixaban and dabigatran, respectively. Whereas 5.2% of patients who switched from a DOAC changed their treatment to another DOAC, while the remaining 4.9% switching to a VKA. Considering individual DOACs, most of the switching occurred in dabigatran users (5.9% to a VKA and 9.3% to another DOAC) and rivaroxaban users (5.3% to a VKA and 4.5% to another DOAC), while least was contributed by patients who initiated on apixaban (3.6% to a VKA and 2.6% to another DOAC). Dabigatran-treated patients had switched more frequently to another DOAC than to a VKA [36]. Another large retrospective study was conducted in the Netherlands among 77,333 patients who claimed prescriptions of a DOAC between January 1, 2012 and April 1, 2016. During four years of follow-up, 11.0% of patients were switched to another OAC, where 67% were switched to a VKA and 33% were switched to another DOAC [64].

Baker et al., [34, 35] conducted two retrospective cohort studies in the United States, using claims data of patients who newly-treated with DOACs. The first study included data of 41,864 patients aged 18 years and above (15,352 received apixaban, 5,262 dabigatran and

21,250 rivaroxaban) who initiated treatment from January 2013 to September 2016, identified from the Pharmetrics Plus database [34]. About 3.6%, 6.3% and 11.1% of apixaban, rivaroxaban and dabigatran treated patients were switched to another OAC during the mean follow-up of 8.0, 9.0 and 9.1 months, respectively ($p<0.001$ across the groups). Approximately half of the patients who switched from apixaban were changed to warfarin. The rest of the patients were switched to rivaroxaban (38.1%) and dabigatran (12.0%). Dabigatran-treated patients were switched in preference to rivaroxaban (40.8%) followed by apixaban (30.0%) and warfarin (28.8%). Rivaroxaban had a comparable rate of switching to warfarin (43.8%) and apixaban (44.3%) and less to dabigatran (10.8%) [34]. The second study was conducted among 38,250 elderly patients (aged ≥65 years) identified from the Humana research database [35]. The study included 21,376, 14,277 and 2,597 patients who initiated on apixaban, dabigatran and rivaroxaban, respectively, between January 2013 and September 2017. During the mean follow-up of 9.2, 11.3 and 12.3 months, 5.2%, 10.6% and 16.9% of apixaban-, rivaroxaban- and dabigatran-treated patients underwent switching, respectively ($p<0.001$). Of those who switched from apixaban, 61.5% switched to warfarin, 32.3% switched to rivaroxaban and only 6.3% switched to dabigatran. On the other hand, among those patients who switched from dabigatran, 40.4%, 30.4%, and 29.2% were switched to apixaban, rivaroxaban and warfarin, respectively, whereas for those who switched from rivaroxaban, the majority (53.9%) were switched to warfarin, 40.8% switched to apixaban and 5.3% switched to dabigatran. A small number of patients were switched to edoxaban (1.3% from apixaban, 0.3% from dabigatran and 1.2% from rivaroxaban), presumably due to its late approval [35].

The largest study [55] included in this review was conducted in Italy. The study consisted of the national monitoring registries of DOACs prospectively collected by the Italian medicine agency. The primary objective was to assess the prescription pattern of DOACs between June 2013 and December 2017; thus, switching to another DOAC was tangentially assessed only in the portion of study participants and switching to a VKA was not examined. The switching cohort was composed of 486,215 patients who started treatment after January 2015 following approval of apixaban in Italy (dabigatran and rivaroxaban had previously been approved). Among those patients, 15,799 (3.3%) and 16,967 (3.5%) were switched to another DOAC within 24 months of initiation and throughout the entire follow-up period, respectively. Of the total DOAC switching during the first 24 months of therapy, the majority (54%) arose from dabigatran-treated patients (32% switched to apixaban and 22% switched to

rivaroxaban). The contribution of rivaroxaban- and apixaban-treated patients to the total DOAC switch was 30.4% (21.5% switched to apixaban and 8.9% to dabigatran) and 15.7% (9.4% switched to rivaroxaban and 6.4% switched to dabigatran), respectively [55]. Similarly, a study of 13,221 naïve patients (i.e., 914 on a DOAC and 12,307 on a VKA group) in the United Kingdom also assessed inter-class switching rate only. The study retrospectively analysed the general practice data collected by the Clinical Practice Research Datalink between January 2011 and May 2014. Of the patients who initially prescribed a VKA, 2.7% switched to a DOAC, while 6.0% of DOAC-prescribed patients switched to a VKA by one year after initiation of therapy [54]. A related retrospective study conducted in Canada using claims data of 32,431 patients reported gross switching rates between the classes of OACs. The study found that 27% of VKA and 5% of DOAC users were changed their prescriptions to another class of OAC during the three years of follow-up [42]. Komen et al., [51] also reported that 4.3% of patients who were newly-initiated on a DOAC (n=21,028) were switched to a VKA by the median follow-up of two years.

Another large study was conducted in the United States using the MarketScan database of NVAF patients who started on an OAC therapy between October 2010 and September 2015 [45]. The study included 12,578 patients started on apixaban, 24,141 initiated on dabigatran and 26,066 rivaroxaban initiators who were naïve to an OAC. Patients on each DOAC were matched with warfarin in 1:1 using propensity scoring (a total sample of 166,690). The rates of switching were 5.8% for apixaban, 15.0% for dabigatran and 8.9% for rivaroxaban by 12 months of starting therapy. The corresponding rates of warfarin switching were 15.8%, 13.7% and 14.2% in patients matched with apixaban, dabigatran and rivaroxaban, respectively [45]. In a similar study conducted in Norway [50], the rates of warfarin and DOAC switching were reported without assessment of the direction of switching. The study included 45,548 treatment naïve patients from nationwide registries who filled prescriptions from January 1, 2013 through December 31, 2015. The overall switching rate of all OACs was 15.3% by the end of the first-year follow-up. On the other hand, at the individual drug level, 6.1%, 20.3%, 12.4% and 16.1% of patients treated with apixaban, dabigatran, rivaroxaban and warfarin were switched to another OAC within one year of starting the OAC, respectively [50]. Sørensen et al., [63] analysed 46,675 patients' data identified from the Danish registries. The study assessed the rate of switching in patients newly-started on either a VKA or a DOAC between 2011 and 2014. Among patients who were initiated on a VKA, apixaban, dabigatran and rivaroxaban, 16.8%, 8.6%, 21.0% and 13.1% were switched

to another OAC within a year of initiating therapy, respectively [63]. In a study of 33,311 incident OAC users in Quebec province of Canada who filled prescriptions from January 1, 2011 through March 31, 2017, about 12.6% received a prescription of an OAC other than the index OAC in the first year of follow-up. The switching rates were 16.4% in warfarin and 9.6% in DOAC users [58].

One of the earliest studies was conducted by Manzoor et al., [53] that analysed claims data of 34,022 patients newly-started on a DOAC. Patients were identified from the MarketScan database, who filled prescriptions for apixaban (n=626), dabigatran (n=23,521) or rivaroxaban (n=9,875) until the end of 2013. During two years of follow-up, the index DOAC was switched in 17.2% of participants, and 50.3% were switched to warfarin. Among individual DOAC type, 6.5%, 20.8% and 9.2% of the index apixaban, dabigatran and rivaroxaban users were switched to another OAC, respectively. In all cases, the majority of patients switched to warfarin (66.5% from rivaroxaban, 47.3% from dabigatran and 43.9% from apixaban). The respective rates of switching to rivaroxaban were 45.9% from dabigatran and 36.6% from apixaban. Only a small fraction switched from rivaroxaban to dabigatran (17.6%) and apixaban (15.9%) [53]. Similarly, Ruigómez et al., [61] reported the switching pattern of 11,481 DOAC users in the United Kingdom conducted using the primary care data from the Health Improvement Network. The patients were newly-started on their index OAC from January 1, 2012, through 2016 and followed for one year. The corresponding rates of switching from the index apixaban, dabigatran and rivaroxaban users were 2.8%, 8.8% and 4.9%, respectively. The majority of patients were switched to another DOAC (64.2% from apixaban, 57.1% from dabigatran and 58.6% from rivaroxaban) [61].

Switching patterns have also been assessed in well-designed prospective registry studies. In a large prospective cohort study of 383,008 warfarin users in the National Cardiovascular Disease Registry's (NCDR) Practice Innovation and Clinical Excellence (PINNACLE) registry, who started on treatment from 2008 through 2015 and were followed from 2010 to 2016, 16.3% of patients were switched to a DOAC during the entire follow-up period (median follow-up of 375 days). The majority of patients were switched to dabigatran (37.6%) and rivaroxaban (37.0%), while 24.4% were switched to apixaban and 1.0% to edoxaban [62]. In addition, the KORean Atrial Fibrillation Investigation II (KORAF II) registry prospectively enrolled 866 patients who newly-started warfarin between April 2013 and March 2014. Within a year of follow-up, 6.6% of warfarin users were switched to a DOAC [49]. The EURObservational Research Programme on Atrial Fibrillation (EORP-AF)

pilot general registry enrolled 3,804 patients from hospitals and office-based clinics in nine European countries. The study reported the rate of switching between classes of OACs within three years of follow-up. Accordingly, 5.4% of patients were switched from a VKA to a DOAC and 8.6% of patients were switched from a DOAC to a VKA [32]. Similarly, in a small prospective registry of 1,024 patients in Switzerland, who were enrolled between 2010 to 2015, 2.9% and 9.7% of patients treated with a DOAC and a VKA, respectively, were switched to another class of OAC during the entire study period [65]. Two studies [37, 56] reported dabigatran switching from the Global Registry on Long-Term Oral Anti-Thrombotic Treatment in Patients with Atrial Fibrillation Phase II (GLORIA-AF II) registry. In each study, 2,9232 [56] and 4,859 [37] newly-diagnosed patients were consecutively enrolled from outpatient settings from 44 countries between 2011 and 2014. During two years of follow-up, 13.3% (54.9% to another DOAC and 45.1% to a VKA) [56] and 12.7% (57.9% to another DOAC and 42.1% to a VKA) [37] of patients were switched from their dabigatran therapy.

3.5. Factors associated with OAC switching and reasons for switching

3.5.1. Predictors of OAC switching

Thirteen studies were identified that investigated factors affecting OAC switching [32, 34-36, 42, 44, 48, 53, 55, 57, 62, 63, 65]. Of these, six studies reported a comparative rate of switching among OACs by controlling covariates [34, 35, 48, 53, 55, 63].

Baker et al., [34, 35] conducted two retrospective cohort studies that assessed the rate of switching among DOAC users in the United States. The first study was conducted in adults aged 18 and above years (N=41,864) to compare switching among DOACs [34], who were newly-initiated on apixaban, rivaroxaban or dabigatran. The study found that patients who were taking dabigatran had a greater than a three-fold increased chance of switching than those taking apixaban (HR: 3.4; 95% CI 3.0-3.8, $p<0.001$). Similarly, patients who were treated with rivaroxaban had a nearly two-fold increased hazard of switching than apixaban users (HR 1.8; 95% CI 1.6-2.0, $p<0.001$) [34]. The second study was conducted among 38,250 naïve elderly NVAF patients (age ≥65 years). The findings were consistent with the previous study, showed that dabigatran and rivaroxaban treated patients had an increased risk of switching (HR 3.7; 95% CI 3.4-4.2, $p<0.001$ and 2.1; 95% CI 1.9-2.3, $p<0.001$, respectively) [35]. These findings were further corroborated with the nationwide Italian registries of DOACs that enrolled 486,215 patients from 2015 through 2017 [55]. According to this study, patients treated with dabigatran had almost a five times higher likelihood of

switching (OR 4.7; 95% CI 4.1-5.5), while rivaroxaban was associated with an approximately two-fold increased chance of switching (OR 1.8; 95% CI 1.5-2.1) compared to apixaban. In comparison to edoxaban, apixaban was associated with 1.5 times increased likelihood of switching (OR 1.5; 95% CI 1.1-2.1) [55]. Another two retrospective cohorts, one conducted in Denmark [48] and the other in the United States [53], reported that patients taking apixaban were 50% (OR 0.50; 95% CI 0.44-0.56) [48] and 75% (OR 0.25; 95% CI 0.18-0.34, p<0.0001) [53] less likely to be switched to another OAC compared to dabigatran.

Three studies were identified that compared the rate of switching between dabigatran and rivaroxaban [48, 53, 63]. Manzoor et al., [53] found that rivaroxaban was associated with a 59% lower chance of switching than dabigatran (OR 0.41; 95% CI 0.38-0.44, p<0.0001). In a related study conducted in Denmark, patients who received rivaroxaban were 28% less likely to switch than dabigatran (OR 0.72; 95% CI 0.65-0.79) [48]. In another study, dabigatran was associated with a 1.3 times greater likelihood of switching compared to rivaroxaban [63]. Studies comparing switching between a VKA and DOACs were limited. A study by Sørensen et al., [63] did not show a statistically significant difference in switching between rivaroxaban and a VKA (HR 0.96; 95% CI 0.88-1.05, p=0.38). In general, apixaban users had a lower probability of switching to another OAC compared to dabigatran and rivaroxaban. Compared to rivaroxaban users, dabigatran users had an increased likelihood of switching.

In addition to comparing OACs, studies have attempted to assess the association of baseline characteristics of patients with the rate of switching. These factors could be generally categorised as patient-related, disease-related, or medication-related factors. Notably, despite some inconsistencies, factors (i.e., demographic, clinical and medication-related) that can increase the risk of bleeding and stroke were associated with a higher likelihood of switching from a VKA, but commonly had a negative association with switching from DOACs [36, 44, 48]. Renal impairment was found to increase the probability of switching from DOACs, but it was negatively associated with switching from a VKA [36, 42, 48]. In addition, thrombotic events (i.e., stroke (HR 2.16; 95% CI 1.18-3.94), MI (HR 7.54; 95% CI 5.38-10.56)), GI bleeding (HR 3.95; 95% CI 2.54-6.15) and cardioversion (HR 2.52; 95% CI 2.15-2.97) after initiation of a DOAC were the strongest predictors of switching to a VKA [36]. Similarly, events that occurred after a VKA initiation, such as stroke (HR 7.68; 95% CI 6.09-9.69), major bleeding (HR 1.73; 95% CI 1.26-2.35), GI bleeding (HR 2.33; 95% CI 1.68-3.24), catheter ablation (HR 1.35; 1.17-2.07) and cardioversion (HR 2.05; 95% CI 1.75-2.39), were strong predictors of switching to a DOAC [36]. The year of OAC initiation was also found to

be correlated with switching. Patients who started on a DOAC between 2014 and 2016 had a lower likelihood of switching to a VKA, compared to those who initiated in 2013. In contrast, patients who initiated a VKA from 2014 to 2016 had an increased rate of switching to a DOAC, compared to those who initiated in 2013 [36] **(Table 3).**

Table 3: Predictors of OAC switching extracted from include studies

3.5.2. Reasons for OAC switching

Changing a prescription of an OAC to another is under the discretion of a prescriber; thus, there may be several clinical or patient behavioural factors that motivate providers to switch an OAC. These factors may be related to the OAC itself (e.g., poor anticoagulation control, adverse effects, bleeding) or patient-related issues (e.g., ease of use, non-adherence). Only a few studies were identified reporting reasons triggering switching. Hellfritzsch et al., [47] conducted a retrospective study in Denmark using nationwide registries data with a total of 50,623 patients, aimed to investigate clinical conditions leading to switching. The results showed that about 41% and 45% of switching from a VKA to a DOAC and a DOAC to a VKA were preceded by hospitalisation, respectively. Clinical events that potentially contributed to switching were identified in 18.3% of a VKA to a DOAC switching and 23.0% of a DOAC to a VKA switching. The clinical events identified include thrombotic complications (7.0% vs. 5.7%), bleeding complications (4.3% vs. 2.8%), anaemia (2.2% vs. 1.9%), new contraindications (0.8% vs. 2.5%), and procedures to restore sinus rhythm (3.3% vs. 11.7%). Clinical events were more commonly identified in patients who switched from a VKA to a DOAC than those who switched a DOAC to a VKA, except for new contraindications and procedures. Ischaemic stroke/TIA was the most common thrombotic event reported in both scenarios (5.0% vs. 2.7%). Kidney diseases (1.8%) and cardioversion (11.4%) were the prevalent clinical conditions known to precede switching from a DOAC to a VKA [47].

In a study that investigated switching from warfarin, most of the reasons attributed were related to the intrinsic nature of the drug [46]. This was clearly shown in the retrospective cohort of 3,873 patients initially treated with warfarin. Of those, 400 patients were switched to a DOAC with reasons identified, including ease of use (37.5%) and clinical reasons (16.5%). The ease-of-use concerns included unstable international normalised ratio (13.5%), inconvenience with frequent monitoring (9.8%), poor adherence (4.3%), dietary restrictions (4.0%), and side effects (3.0%). The clinical reasons reported were bleeding (3.8%), better

efficacy (3.3%), drug interactions (3.0%) and the occurrence of thrombotic complications (1.5%). Nevertheless, the reasons for switching were unknown in the majority (58.8%) of cases [46]. In a small cohort study of 233 patients who were prescribed a DOAC, bleeding (36.4%) and GI discomfort (26.3%) were the prominent reasons for switching to another DOAC [66].

3.6. Clinical outcomes of OAC switching

As the majority of studies included in the review were retrospectively designed, data were limited regarding the subsequent influence of switching on effectiveness and patient safety. Dhamane et al., [27] retrospectively evaluated major bleeding and stroke-associated hospitalisation following switching from apixaban in 7,858 elderly patients (≥65 years), identified from the Humana database (1,110 switched and 6,748 continued on apixaban) from January 2013 to September 2017. The mean follow-up period was 7.6 and 17.6 months for continuers on apixaban and switchers, respectively. Patients were switched to warfarin (62%), rivaroxaban (32%) and dabigatran (6%). A higher proportion of switchers experienced major bleeding (8.2% vs. 2.2%, $p<0.001$) or stroke/systemic embolism (SE) (3.2% vs. 1.4%, $p<0.001$) than those who continued on apixaban. Adjusted to covariates, switching was significantly associated with an increased risk of major bleeding (HR 2.00; 95% CI 1.52-2.64, $p<0.001$), while stroke/SE was not significantly different (HR 1.36; 95% CI 0.89-2.06, $p=0.154$) [27]. Consistent findings were reported in a prospective study of dabigatran-treated patients who switched to either a VKA or another DOAC in the GLORIA-AF II registry [37]. According to this multinational study that enrolled 4,859 initially naïve patients treated with dabigatran, the risk of stroke was similar between switched patients and those who continued on dabigatran (HR 1.02; 95% CI 0.43-1.76). In addition, the difference in major bleeding was not significant, but more than a 3-fold increased likelihood of death was observed in switchers [37].

A large retrospective cohort study (n=55,749) was conducted to assess the clinical outcomes of switching from warfarin to rivaroxaban in patients identified from the MarketScan databases [69]. Patients who switched to rivaroxaban (n=11,845) were matched with warfarin-only users (n=43,904) using propensity scoring. The findings showed that switchers had an increased risk of GI bleeding than warfarin continuers (HR 1.55; 95% CI 1.32-1.83, $p<0.0001$). The risk of GI bleeding was higher during the first 90 days of switching compared to beyond 90 days of switching (HR 2.33; 95% CI 1.71-3.11 vs. 1.33; 1.10-1.62). However,

no significant difference in the rates of ischaemic stroke (HR 1.06; 95% CI 0.83-1.36, p=0.62), intracranial haemorrhage (ICH) (HR 1.04; 95% CI 0.66-1.65, p=0.86), and MI (HR 1.08; 95% CI 0.84-1.40, p=0.55) were reported [69]. In another study [68], the clinical outcomes of switching from warfarin to dabigatran were investigated in a 1:1 matched Taiwanese patients (total n=4,792). The study identified patients from the national health insurance database of patients who received treatment between 2012 and 2015. Switching from warfarin to dabigatran resulted in a reduced rate of GI bleeding (HR 0.69; 95% CI 0.51-0.92) and ICH (HR 0.53; 0.31-0.91). It was also associated with a 43% reduction in all-cause mortality (HR 0.57; 95% CI 0.47-0.69). Regardless, the difference in the rate of ischaemic stroke was not significant (HR 1.19; 95% CI 0.94-1.50) [68]. The effectiveness and safety of switching from a VKA to a DOAC were also investigated in Italian patients [67]. It included 1,594 patients (i.e., 239 in the switched cohort) with a CHA_2DS_2-VASc score ≥2 and who were taking a VKA at least for 6 months before switching, and with at least 6 months of post-switching follow-up. It was shown that the switched patients had a 50% lower risk of cardiovascular events (HR 0.5; 95% CI 0.3-0.9, p=0.026) and bleeding (HR 0.5; 95% CI 0.3-1.0, p=0.042) [67].

4. Discussion

Several studies and reviews have been conducted on the comparative effectiveness and safety of DOACs with a VKA or among DOACs. Evidence from randomised controlled trials (RCTs) and real-world data consistently show a better efficacy and safety profile of DOACs over a VKA [15, 20, 70]. Despite limited data on head-to-head comparison of individual DOACs from RCTs, comparative data from clinical practice are emerging and showing better effectiveness and safety of apixaban [15, 71, 72]. However, the issue of switching from one OAC to another and its clinical consequences are not well-reviewed. This is the first comprehensive review of the incidence of OAC switching rate, reasons, clinical consequences, and associated factors in NVAF patients using data derived from real-world settings.

Adjusted to covariates, the probability of switching was in the descending order of dabigatran, rivaroxaban and apixaban. The same trend was reported in a review that estimated the rate of DOAC-to-DOAC switching [31]. Although data comparing the adjusted switching rate of a VKA with a DOAC were limited, gross findings showed a higher rate of VKA switching in several studies [42, 52, 58, 65]. However, VKA users had a lower rate of

switching compared to dabigatran users [50, 52, 63]. Apixaban users had the lowest rate of switching in comparison to other OACs, except edoxaban [55] and one study with rivaroxaban [38]. Data regarding edoxaban were limited, however, as it was recently introduced into clinical practice. Dabigatran had a higher rate of switching compared to other OACs, and it was the least preferred agent to switch to from another OAC. An increased rate of switching from dabigatran and the least preference to switch to it may be related to its poor safety profile. Dabigatran was associated with increased GI bleeding and other non-bleeding GI discomfort [11, 72, 73], leading to intolerance by patients. In addition to the safety, prescribers may decide to switch an OAC and select the second OAC based on efficacy profile [71]. This would potentially contribute to an increasing trend in switching to apixaban in preference of other DOACs and its lowest rate of switching, partially due to its marginal efficacy and safety advantages [71, 74].

The direction of switching was influenced by patients' enrolment date and the difference in market entry of DOACs. As dabigatran was the first DOAC approved for stroke prevention in NVAF, studies that included patients who filled prescriptions during the early period (e.g., before 2013) primarily switched to dabigatran [44]. The approval of rivaroxaban and apixaban changed the preference in patients initiated with warfarin and more patients were switched from dabigatran to another OAC. The trending of switching towards apixaban is now growing with an accumulation of knowledge about its effectiveness and safety [71, 74, 75], although a significant proportion of patients initially treated with rivaroxaban or dabigatran were still switching to warfarin. Patients initially treated with a VKA were most commonly switched to rivaroxaban.

The review identified several factors that influenced OAC switching. Notably, renal impairment was positively associated with switching from a DOAC to a VKA [48], but was a negative predictor of switching to DOACs [42, 44]. This is related to the intrinsic pharmacokinetic nature of DOACs, in that they are predominantly excreted renally [76, 77]. Moreover, events that occurred after the initiation of an OAC (e.g., stroke, bleeding, MI) were significantly associated with switching [36]. The occurrence of thrombotic events is a potential measure of poor anticoagulation control, while major or GI bleeding are safety concerns that prompt switching to minimise such adversities [78, 79]. Other factors reported to significantly associated with switching were APT [36, 44, 62] and NSAIDs use [44]. Concomitant use of antiplatelets and NSAIDs may be associated with an increased risk of

bleeding, especially in patients taking warfarin, which partly contributes to shifting to a DOAC. Moreover, patients who initiated treatment in the earlier year (i.e., 2013) showed a higher likelihood of switching from DOACs than patients started in 2014 and onwards, whilst the reverse was true for VKA users. This might be related to limited experience with DOACs in the earlier period. Advances in knowledge regarding the relative benefit-risk profiles of OACs [15], and a change in guidelines recommendations (i.e., DOACs as preferred agent) [8, 78, 80] may also have contributed to this variation.

Some studies tried to identify reasons for OAC switching in NVAF patients. A large retrospective study revealed that approximately two-fifth of switching events were preceded with hospitalisation and immediate specific clinical causes attributed for switching were identifiable in one-fifth of cases [47]. The decision to switch an OAC may arise from clinical reasons, including the occurrence of thrombotic events despite anticoagulation, bleeding complications, adverse effects, or drug interactions [46, 47, 66]. The occurrence of new contraindication, such as deterioration of renal function was also identified as a reason for switching, especially from a DOAC to a VKA [47]. In some cases, patient preference to switch was also reported, particularly a VKA to DOACs because of their convenience (e.g., no need for laboratory monitoring, fewer drug interactions and no diet restrictions) [46, 81].

The potential influence of OAC switching on clinical outcomes, either from an effectiveness or safety point-of-view, is one of the compelling reasons to be concerned. This review identified a handful of studies that reported clinical outcomes following switching [27, 37, 67-69]. Those studies found that switching from apixaban and dabigatran to any alternative OAC was not associated with a significant increase in the risk of ischaemic stroke [27, 37]. However, there was a higher risk of major bleeding following switching from apixaban [27], while this did not differ in those switched from dabigatran [37]. The findings may, however, be confounded with variation in switching procedure, reasons for switching and the type of an index OAC as well as the choice of the second agent [82]. Dabigatran has been generally associated with a higher risk of bleeding than apixaban and other OACs; therefore, switching from dabigatran to an agent with a lower risk of bleeding would not be expected to show a significantly increased risk of bleeding [15]. Switching from warfarin to rivaroxaban was associated with a significant increase in GI bleeding, while the risk of thrombotic events was similar [69]. These findings are in line with a previous review [28] and with clinical trial data [14]. It was also shown that, in the subgroup analysis of the clinical trial, the risk of bleeding

and efficacy outcomes of rivaroxaban were similar, regardless of the previous VKA-exposure [83]. In contrast, switching from warfarin to dabigatran resulted in a significant reduction in GI bleeding and ICH [68]. Despite the discrepancy in GI bleeding, the previous review [28], and the RE-LY trial [11] showed consistent results in ICH. Our review also showed that switching from warfarin to either dabigatran or rivaroxaban was not associated with an increased rate of ischaemic stroke, as shown in two matched cohorts [68, 69]. Overall, the evidence available to date consistently showed minimal impact of switching an OAC on stroke and other thrombotic events, while bleeding outcomes were variable depending on the index OAC and direction of switching.

4.1. Future research

We only included a small number of studies, with a limited sample size, investigating clinical outcomes and reasons for switching. More studies are needed to fully understand the impact of switching on clinical outcomes and causes for switching.

4.2. Limitations

Interpretation of the review findings should be with the consideration of the following limitations. Firstly, as it is a narrative review, the quality and risk of bias of the included studies were not assessed. Secondly, in some studies, switching from DOACs was assessed either to a VKA only, or to another DOAC, which might not represent the true incidence of switching. Finally, there may be data not captured from studies potentially published in a non-English language. Furthermore, there was limited data regarding reasons for switching and clinical outcomes; thus, extrapolation should be done with caution.

5. Conclusions

The widening of therapeutic options for stroke prevention is an important change in the last decade and creates the possibility to switch among OACs. Parallel with the recent increase in the initiation of OAC for thromboprophylaxis in people with NVAF, the rate of switching from one OAC to another is increasing over time. We found that dabigatran was more prone to switching than other agents and was the least preferred agent to switch to from another OAC. Apixaban had a relatively lower rate of switching, and switching from other agents towards it is increasing compared to its late introduction. Several factors (i.e., demographics, clinical and medication-related) were identified to affect OAC switching in people with NVAF. Our review has shown that OAC switching was not associated with the risk of

thrombotic events, while its influence on bleeding outcomes was inconsistent. Further prospective studies should be conducted for a complete understanding of explicit reasons for switching and clinical outcomes following switching. Moreover, economic consequences, patient satisfaction, and preference for switching OACs need to be considered.

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Table 1: Characteristics of the studies included in the review

Study	**Sample size**	**Study design; data source**	**Country**	**Study period**	**Type of OAC**
1. Al-Khalili et al.[33]	766	Retrospective cohort; Medical records	Sweden	Dec 2011-May 2014	DOACs
2. Baker et al. [34]	41,864	Retrospective cohort; Claims data	United States	Jan 1, 2013-Sep 30 2016	DOACs
3. Baker et al. [35]	38,250	Retrospective cohort; Claims data	United States	Jan 1, 2012-Dec 31, 2017	DOACs
4. Bellin et al. [67]	1,594	Retrospective cohort; Claims data	Italy	Jan 2012- Dec 2016	VKA
5. Boriani et al.[32]	3,804	Prospective cohort; AF registry	Multiple	Feb 2012-Mar 2014	DOACs, VKA
6. Brown et al. [38]	15,341	Retrospective cohort; Claims	United States	Jan 1, 2013-Sept 30, 2014	DOACs

		data			
7. Collings et al.[39]	3,256	Retrospective cohort; Primary care data	France	Jan 1, 2014 - Jan 31, 2016	VKA, DOACs
8. Dallongeville et al.[40]	1,278	Retrospective cohort; Claims data	France	Aug 1, 2012- Dec 31, 2014	Rivaroxaban
9. De Veer et al.[41]	799	Prospective cohort; DOAC registry	Netherlands	2013- Jun 2017	DOACs
10. Dhamane et al.[27]	7,858	Retrospective cohort; Claims data	United States	Jan 1, 2013- Sept 30, 2017	Apixaban
11. Douros et al.[42]	32,431	Retrospective cohort; Claims data	Canada	Jan 2011- Dec 21, 2014	VKA, DOACs
12. Durham et al.[43]	3,166	Retrospective cohort; Primary care data	United Kingdom	2013-2014	Warfarin, DOACs
13. Fosbol et al. [44]	62,065	Retrospective cohort; Nationwide registries	Denmark	Aug 22, 2011- Dec 31, 2015	VKA
14. Gopalakrishnan et al. [45]	125,920	Retrospective cohort; Claims data	United States	Oct 2010- Sep 2015	Warfarin, DOACs
15. Hale et al. [46]	3,873	Retrospective cohort; AF registry	United States	Jan 2010-Jun 2015	Warfarin
16. Hellfritzsch et al.[47, 48]	50,623	Retrospective cohort; Nationwide registries	Denmark	Aug 2011-Feb 2016	VKA, DOACs
17. Hohnloser e	51,606	Retrospective	German	Jan 1, 2013-	VKA,

t al.[36]		cohort; Claims data	y	Mar 31, 2016	DOACs
18. Kim et al. [49]	866	Prospective cohort, AF registry	Korea	Apr 2013-Mar 2014	Warfarin
19. Kjerpeseth et al.[50]	48,548	Retrospective cohort; Nationwide registries	Norway	Jan 1, 2013-Dec 31, 2015	Warfarin, DOACs
20. Komen et al.[51]	21,028	Retrospective cohort; Claims data	Sweden	Jul 2011-Oct 2018	DOACs
21. Lamberts et al.[52]	54,321	Retrospective cohort; Nationwide registries	Denmar k	Aug 22, 2011-Dec 31, 2015	Warfarin, DOACs
22. Lee et al. [66]	233	Prospective cohort; Medical records	United Kingdo m	Jan 2013-Aug 2014	DOACs
23. Lin et al. [68]	4,792	Retrospective cohort; Claims data	Taiwan	2012-2015	Warfarin, dabigatran
24. Manzoor et al.[53]	34,022	Retrospective cohort; Claims data	United States	Jan 1, 2009-Dec 31, 2013	DOACs
25. Martinez et al.[54]	13,221	Retrospective cohort; Primary care data	United Kingdo m	Jan 2011-May, 2015	VKA, DOACs
26. Norby et al. [69]	55,749	Retrospective cohort; Claims data	United States	Jan 1, 2010-Dec 31, 2014	Warfarin, rivaroxaban
27. Olimpieri et al.[55]	486,215	Prospective cohort; DOACs	Italy	Jan 1, 2015-Dec 31, 2017	DOACs

		registry			
28. Paquette et al.[37]	4,859	Prospective cohort; AF registry	Multiple	2011-2014	Dabigatran
29. Paquette et al.[56]	2,932	Prospective cohort; AF registry	Multiple	2011-2014	Dabigatran
30. Park et al. [57]	7,111	Retrospective cohort; Claims data	Korea	Jan 1, 2015-Dec 31, 2015	Warfarin
31. Perreault et al.[58]	33,311	Retrospective cohort; Claims data	Canada	Jan 1, 2011-Mar 31, 2017	Warfarin, DOACs
32. Pham et al. [59]	38,947	Retrospective cohort; Claims data	United States	Oct 19, 2010-Oct 1, 2015	DOACs
33. Ramagopalan et al.[60]	5,390	Retrospective cohort; Primary care data	United Kingdom	Dec 1, 2012-Jul 1, 2017	Apixaban, warfarin
34. Ruigómez et al.[61]	11,481	Retrospective cohort; Primary care data	United Kingdom	Jan 1, 2012-Dec 31, 2016	DOACs
35. Sciria et al. [62]	383,008	Prospective cohort; Cardiovascular Registry	United States	Oct 1, 2010-May 1,2016	Warfarin
36. Sørensen et al.[63]	46,675	Retrospective cohort; Nationwide registries	Denmark	2011-2014	VKA, DOACs
37. Zielinski et al.[64]	87,412	Retrospective cohort; Claims data	Netherlands	Jan 1, 2012-Apr 1, 2016	VKA, DOACs
38. Zimny et al.	1,024	Prospective	Switzerl	2010- Aug	VKA,

[65]		cohort; AF registry	and	2015	dabigatran, rivaroxaban

AF: atrial fibrillation; DOAC: direct-acting oral anticoagulant; OAC: oral anticoagulant; VKA: vitamin K antagonist

Table 2: Patterns of OAC switching in NVAF patients

Author	Index OAC	Follow-up (months)	Rate of switching (%)	Agent switched to (%)				
				WAR	API	DAB	RIV	DOAC
1. Al-Khalili et al. [33]	API	11.4[a]	6.8	47.0	NA	NA	NA	53.0
	DAB	12.1[a]	27.9	27.7	NA	NA	NA	72.3
	RIV	14.2[a]	21.3	31.7	NA	NA	NA	68.3
4. Baker et al. [34]	API	8.0[b]	3.6	48.7	-	12.0	38.1	NA
	DAB	9.0[b]	11.1	28.8	30.0	-	40.8	NA
	RIV	9.1[b]	6.3	43.8	44.3	10.8	-	NA
7. Baker et al.[35]	API	9.2[b]	5.2	61.5	-	6.3	32.3	NA
	DAB	11.3[b]	16.9	29.2	40.4	-	30.4	NA
	RIV	12.3[b]	10.6	53.9	40.8	5.3	-	NA
10. Boriani et al. [32]	VKA	36	5.4	-	NA	NA	NA	100
	DOAC	36	8.6	100	NA	NA	NA	NA

12. Brown et al.[38]	API	9	10.5	45.6	-	7.5	46.9	NA
	DAB	9	18.8	40.1	13.1	-	46.9	NA
	RIV	9	9.5	65.1	23.1	11.9	-	NA
15. Collings et al. [39]	VKA	11.9[a]	6.4	-	40.0	10.0	50.0	NA
	API	8.8[a]	4.9	60.7	NA	NA	35.7	NA
	DAB	14.5[a]	6.7	31.8	40.9	NA	27.3	NA
	RIV	11.9[a]	5.9	62.5	30.4	NA	-	NA
19. Dallongeville et al.[40]	RIV	12	15.0	70.8	1.7	27.5	-	NA
20. De Veer et al. [41]	DOAC	20.4[b]	4.1	100	NA	NA	NA	NA
21. Dhamane et al. [27]	API	17.6[b]	14.0	62.0	-	6.0	32.0	NA
22. Douros et al.[42]	VKA	36	27.0	-	NA	NA	NA	100
	DOAC	36	5.0	100	NA	NA	NA	NA
24. Durham et al. [43]	WAR	23.2[b]	6.5	-	17.1	33.1	49.7	NA
	API	23.2[b]	6.2	46.7	-	13.3	40.0	NA
	DAB	23.2[b]	17.5	50.0	33.3	-	16.7	NA
	RIV	23.2[b]	7.3	75.0	NA	25.0	-	NA
28. Fosbol et al.[44]	VKA		29.6		19.8	54.2	26.0	NA
29. Gopalakrishnan et al.[45]	WAR	12	14.2	NA	NA	NA	NA	NA
	API	12	5.8	NA	NA	NA	NA	NA
	DAB	12	15.0	55.4	9.3		35.3	NA
	RIV	12	8.9	NA	NA	NA	NA	NA
33. Hale et al.[46]	VKA		10.3	-	18.8	47.8	32.5	NA
34. Hellfritzsch et al.[48]	DOAC	24	19.6	69.4	NA	NA	NA	30.6
	DOAC	12	14.9	67.8	NA	NA	NA	32.2
	API	12	5.7	73.1	NA	NA	NA	26.9
	DAB	12	17	69.4	NA	NA	NA	30.6
	RIV	12	14.3	59.4	NA	NA	NA	40.6
39. Hellfritzsch et al.[47]	DOAC	12	10.3	100	NA	NA	NA	NA
40. Hohnloser et al.	VKA	12	10.7	-	29.	12.1	57.	NA

[36]					9		9	
	DOAC	12	10.4	48.5	NA	NA	NA	51.5
42. Kim et al.[49]	WAR	12	6.6	NA	NA	NA	NA	100
43. Kjerpeseth et al. [50]	WAR	12	16.1	NA	NA	NA	NA	NA
	API	12	6.1	NA	NA	NA	NA	NA
	DAB	12	20.3	NA	NA	NA	NA	NA
	RIV	12	12.4	NA	NA	NA	NA	NA
47. Komen et al.[51]	DOAC	24[b]	4.3	100	NA	NA	NA	NA
48. Lamberts et al. [52]	WAR	36	11.0	-	20.0	52.0	28.0	NA
	API	36	5.0	63.0	-	15.0	22.0	NA
	DAB	36	19.0	54.0	26.0	-	20	NA
	RIV	36	10.0	45.0	27.0	29.0	-	NA
	DOAC	36	9.4	100	NA	NA	NA	NA
53. Lee et al.[66]	DOAC	11[a]	9.0	9.5	NA	NA	NA	90.5
54. Manzoor et al. [53]	DOAC	24	17.2	50.3	NA	NA	NA	49.7
	API	24	6.5	43.9	-	19.5	36.6	NA
	DAB	24	20.8	43.3	6.8	-	45.9	NA
	RIV	24	9.2	66.5	15.9	17.6	-	NA
58. Martinez et al. [54]	VKA	12	2.7	-	NA	NA	NA	100
	DOAC	12	6.0	100	NA	NA	NA	NA
60. Olimpieri et al. [55]	DOAC	24	3.3	NA	54	15	31	100
61. Paquette et al. [37]	DAB	24	12.7	42.1	NA	NA	NA	57.9
62. Paquette et al. [56]	DAB	24	13.3	45.1	NA	NA	NA	54.9
63. Park et al.[57]	WAR	12	33.8	-	23.9	35.5	40.6	NA
64. Perreault et al. [58]	WAR	12	16.4	NA	NA	NA	NA	100
	DOAC	12	9.6	NA	NA	NA	NA	NA
66. Pham et al. [59]	API	12	7.5	46.0	-	7.2	46.8	NA
	DAB	12	14.7	54.2	7.2	-	38.6	NA
	RIV	12	9.4	56.8	31.	11.4	-	NA

					8			
69. Ramagopalan et al.[60]	WAR	12	11.6	NA	NA	NA	NA	NA
	API	12	6.4	NA	NA	NA	NA	NA
71. Ruigómez et al. [61]	API	12	2.8	47.0	NA	NA	NA	53.0
	DAB	12	8.8	35.8	NA	NA	NA	64.2
	RIV	12	4.9	42.9	NA	NA	NA	57.1
	DOAC	12	4.9	41.4	NA	NA	NA	58.6
75. Sciria et al.[62]	WAR	12.3[a]	16.3	-	24.4	37.6	37.0	NA
76. Sørensen et al. [63]	VKA	12	16.8	NA	NA	NA	NA	NA
	API	12	8.6	NA	NA	NA	NA	NA
	DAB	12	21.0	NA	NA	NA	NA	NA
	RIV	12	13.1	NA	NA	NA	NA	NA
80. Zielinski et al. [64]	DOAC	48	11.0	67.0	NA	NA	NA	33.0
81. Zimny et al.[65]	VKA	NA	9.7	NA	NA	NA	NA	100
	DOAC	NA	2.9	100	NA	NA	NA	NA

[a] median follow-up, [b] mean follow-up, NA: not available

API: Apixaban; DAB" Dabigatran; DOAC: Direct-acting oral anticoagulant; OAC: oral anticoagulant; RIV: Rivaroxaban; VKA: Vitamin K antagonist

Table 3: Predictors of OAC switching extracted from include studies

Category of factors	**VKA to DOAC**	**DOAC to VKA/DOAC**
Patient-related factors	**Higher likelihood of switching** • Older age [42] • Private insurance [62] **Lower chance of switching** • Male gender [36, 44, 57, 62] • Older age [44, 65]	**Higher likelihood of switching** • Older age [36, 53] **Lower chance of switching** • Older age [32, 48] • Male gender [36, 53]
Disease-related factors	**Higher likelihood of switching** • Index years (2014 to 2016) [36] • Congestive heart failure [42, 44] • Liver disease [42] • History of GI bleeding [44] • Prior stroke/TIA [44, 57] • Higher CHA_2DS_2-VASc score	**Higher likelihood of switching** • Lower CHA_2DS_2-VASc score [48] • Congestive heart failure [32, 36] • Chronic kidney disease [36, 48]

	[44] • Higher HAS-BLED score [44] **Lower chance of switching** • Baseline characteristics ✓ Hypertension [36, 44] ✓ Congestive heart failure [62] ✓ Coronary heart disease [32, 44] ✓ Diabetes mellitus [44, 62] ✓ Myocardial infarction (MI) [42] ✓ Venous thromboembolism [42] ✓ Vascular disease [42] ✓ Chronic kidney disease [42, 44] ✓ Alcohol abuse [44] • Higher CHA_2DS_2-VASc score [62]	• Hypertension [48] • Coronary heart disease [48] • Higher Charlson's comorbidity index [35] **Lower chance of switching** • Index years (2014 to 2016) [36] • Baseline characteristics ✓ Prior stroke/TIA [36, 48] ✓ Diabetes mellitus [48] ✓ Peripheral artery disease [48] ✓ Dementia [36] ✓ Prior GI bleeding [36] ✓ Alcohol abuse [48]
Medication-related factors	**Higher likelihood of switching** • Antiplatelet therapy (APT) [36, 44, 62] • Non-steroid anti-inflammatory drugs (NSAIDs) use [44] • Antiarrhythmic drug use [62]	• Type of OAC [34, 35, 48, 53, 55, 63] • Previous VKA use [48]
Other factors	• Rhythm restoration intervention (e.g., cardioversion) [36]	• Rhythm restoration intervention (e.g., cardioversion) [56]

Lists of Figures

Fig. 3 The rates of OAC switching in different data sources

Appendices

Appendix 1: Search terms used in the literature search

Appendix 2: Study characteristics included in the review

Appendix 3: Patients' characteristics included in the review