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Systematic Review

Systematic Review of Medicine-Related Problems in Adult Patients with Atrial Fibrillation on Direct Oral Anticoagulants

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ABSTRACT

New oral anticoagulant agents continue to emerge on the market and their safety requires assessment to provide evidence of their suitability for clinical use. Therefore, we searched standard databases to summarize the English language literature on medicine-related problems (MRPs) of direct oral anticoagulants DOACs (dabigtran, rivaroxban, apixban, and edoxban) in the treatment of adults with atrial fibrillation. Electronic databases including Medline, Embase, International Pharmaceutical Abstract (IPA), Scopus, CINAHL, the Web of Science and Cochrane were searched from 2008 through 2016 for original articles. Studies published in English reporting MRPs of DOACs in adult patients with AF were included. Seventeen studies were identified using standardized protocols, and two reviewers serially abstracted data from each article. Most articles were inconclusive on major safety end points including major bleeding. Data on major safety end points were combined with efficacy. Most studies inconsistently reported adverse drug reactions and not adverse events or medication error, and no definitions were consistent across studies. Some harmful drug effects were not assessed in studies and may have been overlooked. Little evidence is provided on MRPs of DOACs in patients with AF and, therefore, further studies are needed to establish the safety of DOACs in real-life clinical practice.

INTRODUCTION

The identification, resolution, and prevention of medicine-related problems (MRPs) has been described as an essential process of pharmaceutical care, where pharmacists and other health care professionals as well as patients work together to achieve improved therapeutic outcomes and quality of life (Basger et al., 2015). According to the Pharmaceutical Care Network Europe, an MRP can be defined as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes". This includes therapeutic failure, patient behaviour, adherence to the medication, and inappropriate drug use. These may set off or comprise risk factors leading to medication errors (MEs) and adverse drug reactions/events (ADRs/ADEs), which could affect patient health outcome. An ME is a preventable event that actually or can potentially lead to inappropriate drug use or injury to the patient when the medication is in the hands of a healthcare professional or patient (the National Coordinating Council for Medication Error Reporting and Prevention [NCC MERP], 2015). ADRs are harmful, unintended, undesired, or excessive responses to a drug, occurring at normal doses in the diagnosis or therapy of a disease or for the restoration or correction of a physiological function,

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whose causality has been known (Hughes and Blegen, 2008). ADEs are injuries resulting from the use of a medicinal product, although the causality of the relationship has not been determined (Strand et al., 1990).

Cardiovascular diseases (CVDs) are the major causes of mortality, contributing to approximately 31% of deaths globally (World Health Organisation WHO, 2015) and in the UK, this figure is estimated to be 25% of deaths (British Heart Foundation BHF, 2015). Of all the CVDs, atrial fibrillation (AF) is the most common, affecting approximately 1.5–2% of the population worldwide (Camm et al., 2012). The presence of AF is associated with a five times higher risk of stroke and three times higher risk of heart failure (Camm et al., 2012). Anticoagulant therapy is a prerequisite to avoiding stroke and systemic embolism in patients with AF. The clinical use of oral anticoagulants began in 1954 after the approval of warfarin, which is a vitamin K antagonist (Plovanich and Mostaghimi, 2015). For more than half a century, warfarin was the only available oral anticoagulant (Bauer, 2013). Although, new categories of anticoagulant drugs were developed and labelled as novel oral anticoagulants, new oral anticoagulants, non-vitamin K antagonist oral anticoagulants (NOACs), and direct oral anticoagulants (DOACs) to be used in clinical practice targeted at overcoming the disadvantage of warfarin. The DOACs have four important pharmacological properties: a rapid onset and offset of action, predictable therapeutic effect, fewer drug-drug interactions, and absence of food interactions (Bauer, 2013; Mekaj et al., 2015). These properties provide them with important advantages over traditional oral vitamin K antagonists such as warfarin (Plovanich and Mostaghimi, 2015). Since 2008, the European Medicine Agency (EMA) and the US Food and Drug Administration (FDA) have approved the clinical use of DOACs such as dabigatran, rivaroxaban, apixaban, and edoxaban in the European Union (EU) and worldwide (Mekaj et al., 2015). In the UK, the National Institute for Health and Care Excellence (NICE) approved dabigatran in 2012, rivaroxaban and apixaban in 2013, and edoxaban in 2015 for the prevention of stroke and systemic embolism in non-valvular AF (NVAF) (National Institute for Health and Care Excellence NICE, 2015). Following the official approval of DOACs, their use has also increased leading to 1,091,000 prescriptions in England by 2014. Moreover, numerous studies from different countries worldwide arrived at the same conclusion that anticoagulants represent a high-risk medication and are a threat to patient safety (Saedder et al., 2014). However, only limited studies examining the MRPs of new oral anticoagulants have been carried out in real world clinical practice (Donaldson and Norbeck, 2013).

Furthermore, anticoagulant-related bleeding is common and often serious (Landefeld and Beyth, 1993; Crowther and Warkentin, 2008). Hence, several meta-analyses of phase III RCTs trials have indicated that the DOACs are as safe and efficient as VKAs in preventing and treating thromboembolic events especially in patients diagnosed with non-valvular AF (Caldeira et al., 2015a; Sardar et al., 2015; Scridon and Constantin, 2015).

The DOACs have improved the safety of anticoagulation by reducing intracranial haemorrhage, which is a fatal type of bleeding caused by anticoagulants (Caldeira et al., 2015a). The DOACs also reduce the risk of ischemic stroke, major bleeding, myocardial infarction, and mortality (Caldeira et al., 2015b). Although clinical trial data shows a similar ADR profile, there is considerably less knowledge about how this happens in real life setting such as in a secondary care setting or an anticoagulant clinic.

Therefore, a systematic review of published studies on the nature and severity of MRPs in adult patients using DOACs was performed. The aim of this review was to investigate the prevalence, categories, severity, and possible contributing factors of MRPs among adult patients with AF using DOACs reported in the literature.

MATERIALS AND METHODS

Search Strategy

The following electronic databases were searched by HA: Medline, Embase, International Pharmaceutical Abstract (IPA), Scopus, CINAHL, Cochrane Library, and Web of Science from January 2008 to July 2016. To increase the likelihood of identifying additional relevant studies, the reference lists of included studies and relevant review articles were hand searched.

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In searching databases, a combination of free text-words and Medical Subject Heading (MeSH) was used to ensure a comprehensive search of the literature. In addition, synonyms and additional terms were used and truncation symbols such as the asterisk (*) were used. Boolean terms `OR' and `AND' were used to broaden and narrow down the search, respectively.

The search commenced with two main keywords: medicine-related problem and new oral anticoagulant. The search used medicine-related problem as a keyword and a number of terms that described problems related to the use of medication such as drug-related problem. Additional list search terms were generated by going over the literature that was reviewed using medicine-related problem as a keyword (Van Mil et al., 2004; Van den Bemt and Egberts, 2007; Alhomoud et al., 2012; Adusumilli and Adepu, 2014; Al Hamid et al., 2014). Each article suggested a list of search terms for 'medicine-related problem'. The different keywords used to search for relevant articles in this review are presented in Table 1. The search terms and the synonyms were linked using the Boolean operator 'AND' or 'OR' to arrive at the final number of articles titles and abstracts that were reviewed in detail.

Following the conclusion of all database searches, duplicate citations were identified and excluded using a reference management software (Mendeley, Elsevier 2016 Mendeley Ltd) and manual title examination.

Table 1. *Search terms used in this review.*

Search		Keywords - Use of Boolean Search
1.Medicine-related problem	OR	Medication related problem Medicine related morbidity Medication-therapy problems Drug related problem Drug related morbidity Drug induced problem Drug therapy problem Drug management problem Therapy-related problems Treatment related problem Pharmaceutical care issue Drug safety Adverse drug reaction Adverse drug event Medication error Medication adherence Medication compliance Non-compliance
2. Direct oral anticoagulant	OR	Novel oral anticoagulant Non-vitamin K antagonist anticoagulant New oral anticoagulant Dabigatran Rivaroxaban Apixaban Edoxaban NOACs DOACs
3. '1' AND '2'		

Inclusion and Exclusion Criteria

For this review, the inclusion criteria were studies focused on adults ≥ 18 years with AF, those concerning medicine-related problems of DOACs, original studies using quantitative or mixed methodology, and those conducted in a clinical setting. Studies published in English between 2008 and 2016 were included. The researchers excluded studies related to drug abuse and misuse. Conference abstract, reviews, opinions, and editorial papers were also excluded. Case reports were not included in this review because they depended on specific cases.

Data Extraction and Quality Assessment

Data extraction from the retrieved studies was carried out by the first author of this paper (HA) using standardized forms to extract data consisting of the following information: study type, country, settings, population age, duration, sample size, types of MRPs, and reported severe cases. The use of standardized data extraction forms can provide consistency, reduce bias, and improve the validity of the review. The data were reviewed independently by another reviewer (ZA). The screening process was carried out systematically and included the titles, abstracts, and full articles. Once the inclusion/exclusion criteria were applied, a third reviewer (NU) verified the data. For studies that included all anticoagulant drugs, only data for DOACs were included.

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Table 2. *Summary of Studies*

No.	Study	Country	Setting	Study Design	Population	Duration	Sample Size	Prevalence Rate of Bleeding ADR (%)	Prevalence Rate of Non-Bleeding ADR (%)	Reported Severe Cases (%)	Main Findings	Other
1.	Larsen et al. (2013)	Denmark	National registry	Retrospective cohort	Patients with AF	10.5 months	13,914	HR Intracranial bleeding 0.24, 95% CI: 0.08-0.56; GIB 0.60, 95% CI: 0.37 to 0.93	NR	NR	No evidence of excessive intracranial and gastrointestinal bleeding events for Dabigatran treated patients compared with Warfarin	
2.	Lee, Han and Miyahara (2013)	US	Pharmacy-managed anticoagulation clinic	Retrospective cohort	Patients on Dabigatran	3 months	68	NR	NR	NR	Adherence of Dabigatran does not significantly differ between patients followed by pharmacy-managed clinic and those followed by usual care.	Adherence Pharmacy-managed 93.1%, usual care 88.3%
3.	Cutler et al. (2014)	US	University of California Davis Medical Centre	Retrospective descriptive	Patients with AF	12 months	159	NR	NR	5 patients hospitalised (5/159=3.14 %)	There is need for improved Dabigatran **adherence** monitoring and follow-up	43.4% non-adherent to Dabigatran therapy
4.	Graham et al. (2014)	US	Medicare Database	Retrospective cohort	Medicare patients with AF	27 months	134,414	2.2%	0.04%	NR	Dabigatran has increased risk of major gastrointestinal bleeding than Warfarin on elderly NVAF patients	
5.	Andreica and Grissinger (2015)	US	Pennsylvania Patient Reporting System	Retrospective	Medication errors	12 months	NA	NR	NR	NR	Extra precaution and risk-reduction strategies are needed to reduce medication errors related to NOACs	831 medication errors
6.	Chang et al. (2015)	US	Database of commercially insured	Retrospective cohort	Commercially insured population	18 months	46,163	HR (Dabigatran 1.2 95% CI 0.96 to 1.53) Rivaroxaban (0.98, 95%, CI 0.36-2.69)	NR	NR	No statistical differences in gastrointestinal bleeding between Dabigatran and Rivaroxaban, and Warfarin but cannot rule out more than 50% and two-fold higher risk of Dabigatran and Rivaroxaban compared to Warfarin.	
7.	Forslund, Wettermark and Hjemdahl (2016)	Sweden	Administrative health data register	Retrospective cohort	Patients with NVAF	32 months	20,636	NR	NR	NR	Persistence for NOACs decreased slightly from 88.2% in year 1 to 82.9% in year 2.	Persistence 88.2% (year 1) and 82.9% (year 2)
8.	Nishtala et al. (2016)	New Zealand	Population-level data	Retrospective cohort	Patients with NVAF	18 months	9,220	HR (0.45 (0.37–0.55) any haemorrhage	NR	NR	Dabigatran has lower risk for any/intra-cerebral haemorrhaging compared to Warfarin	
9.	Donaldson and Norbeck (2008)	US	Pharmacy managed out-patient clinic	Prospective cohort	Out-patients	18 months	221	4.07% (9/221)	2.7% (6/221)	NR	Pharmacists should monitor Patients on Dabigatran for complications to determine compliance.	

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No.	Study	Country	Setting	Study Design	Population	Duration	Sample Size	Prevalence Rate of Bleeding ADR (%)	Prevalence Rate of Non-Bleeding ADR (%)	Reported Severe Cases (%)	Main Findings	Other
10.	Ho et al. (2014)	China	Hospital	Prospective cohort	Patients with AF	16 months	467	16.8% (minor and major bleeding)	45.6% (Dyspepsia, and other side effects)	NR	There is need to determine the high discontinuation rates (21.6%) for Dabigatran for stroke prevention in AF patients in China	
11.	Hu et al. (2015)	Taiwan	Hospital	Prospective cohort	Patients with NVAF on dabigatran	6 months	150	NR	11.3%	NR	Monitoring non-compliance is important to improve compliance of Dabigatran	10.7% non-compliant
12.	Beyer-Westendorf et al. (2015)	Germany	Non-interventional patient registry	Prospective cohort	Stroke prevention in patients with AF	17 months	2,500	2.3% in 100 patient years	NR	25.8%/100 patient years	Dabigatran is effective and relatively safe in unselected patients in daily care.	
13.	Chan et al. (2016)	Taiwan	Taiwan National Insurance Research Database	Prospective study	Patients with AF	8 months	19,853	HR (0.58; $P<0.0001$)	HR (ischemic stroke, 0.62; $P<0.0001$); myocardial infarction, 0.67; $P=0.0803$)	NR	Dabigatran has a reduced risk of all-hospitalised major bleeding events, ischemic stroke and myocardial infarction compared to Warfarin for Asian NVAF patients	
14.	Gorst-Rasmussen et al (2015)	Denmark	Nationwide database	Prospective cohort	Patients with AF	23 months	2,960	NR	NR	NR	Determining the extent and form of Dabigatran non-adherence is important to inform patient education and improve adherence.	76.8% adherence after 1 year
15.	Thorne et al. (2015)	New Zealand	Primary care practice	Prospective cohort	Patients on Dabigatran	10 months	92	10%	17.4%	NR	High rates of Dabigatran discontinuation (30%) associated with gastrointestinal complications.	
16.	Martinez et al. (2016)	UK	Primary care practice database	Prospective cohort	Patients with AF	22.8 months	27,514	1.4%	NR	NR	There is a greater **persistence** for NOACs (79.2%) than warfarin therapy and could lead to fewer cardio-embolic strokes.	
17.	Monteagudo et al. (2015)	UK	Cerebrovascular disease unit	Prospective	Patient treated with Rivaroxaban	15 months	89	6.58%	NR	0.82%	Rivaroxaban is safe and efficacious for the prevention of secondary AF.	

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We used the Critical Appraisal Skills Programme (CASP) to grade the overall strength of the evidence as high, moderate, low, or insufficient. Another assessment was performed after data extraction. An in-depth quality analysis was impractical because of the heterogeneity of the study designs. Quality criteria were applied and considered, including the relevance of the study to the aims of the review, appropriateness of the study design for the research objective, sample size, participant allocation, and outcome assessment.

RESULTS AND DISCUSSION

Results

After the titles had been critically examined to remove obviously irrelevant studies from those obtained through an extensive literature search of relevant electronic databases, we retrieved 3929 primary studies. After excluding all duplications, 3915 studies were selected out of which 15 were identified as being potentially relevant after reviewing the titles, abstracts, and full texts. A hand search of retrieved articles from the electronic database led to the identification of two additional articles. Therefore, the reviewers agreed on a final selection of 17 studies for inclusion. A flow chart of this process is presented in Figure 1.

Eight retrospective cohort studies were conducted in four countries (the U.S., Denmark, New Zealand, and Sweden). The study duration ranged between 3 (Lee et al., 2013) and 32 (Forslund et al., 2016) months and the data collection method involved patients or national databases. The nine prospective cohort studies were conducted in seven (countries (the UK, the US, Denmark, New Zealand, China, Taiwan, and Germany). The study duration ranged from 10 (Thorne et al., 2014) to 23 (Gorst-Rasmussen et al., 2015) months and the sample sizes ranged from 150 (Hu et al., 2015) to 27,514 (Martinez et al., 2016) subjects. The data collection method involved electronic medical record reviews (Donaldson and Norbeck, 2013; Lee et al., 2013; Cutler et al., 2014; Ho et al., 2014; Monteagudo et al., 2015; Martinez et al., 2016), electronic national database searches Larsen et al., 2013; Graham et al., 2014; Beyer-Westendorf et al., 2015; Chang et al., 2015; Gorst-Rasmussen et al., 2015; Hu et al., 2015; Chan et al., 2016; Forslund et al., 2016; Nishtala et al. 2016), questionnaires (Thorne et al., 2014; Hu et al., 2015), and a reporting system (Andreica and Grissinger, 2015). The settings of these studies were in hospitals, primary care centres, or both.

Types and Causes of Medicine-Related Problems Identified Across Studies

Two studies compared the hazard ratio (HR) of the DOACs and warfarin and found that DOACs had no significant effect on excessive bleeding with HRs of 0.60 (Larsen et al., 2013) and 0.45 (Nishtala et al., 2016). One study (Graham et al., 2014) examined ADR bleeding-related events associated with dabigatran and found a 2.2% risk of bleeding. The persistence of DOAC therapy decreased from 88.2% in year 1 to 82.9% in year two of dabigatran use (Forslund et al., 2016), and adherence was slightly different between pharmacy-managed anticoagulant care (93.1%) and non-pharmacy care (88.3%) (Lee et al., 2013). Medication errors associated with the oral anticoagulants including warfarin and DOACs were 831 incidents reported in 2014 by the Pennsylvania Patient Safety Advisory. The most common errors were drug omission (32.5%), other errors (prescribing, wrong patient, and inaccurate medication listing) (18.5%), and wrong dose (11.7%) (Andreica and Grissinger, 2015).

DOACs reduce the risk of intracranial bleeding and may decrease the overall risk of major bleeding events in patients with AF. In contrast, there is a possibility of an increased risk of gastrointestinal bleeding associated with the use of DOACs (Miller et. al., 2012). In the prospective studies, the reported ADR-related bleeding events ranged between 2.3% (Beyer-Westendorf et al., 2015) and 16.8% (Ho et al., 2014) of the surveyed population. The rate of non-compliance to dabigatran was 11.3% (Hu et al., 2015) and rates of adherence after one year was 76.8% (Gorst-Rasmussen et al., 2015). In China, dabigatran had a high discontinuation rate of 17.4% associated with gastrointestinal complications (Thorne et al., 2014). However, in the UK, there was a greater persistence (72.9%) for DOAC therapy than there was for warfarin therapy (Martinez et al., 2016). The persistence of DOAC therapy was 83%, and therapy commencement increased to 27% between 2011 and 2014 (Martinez et al., 2016). In Taiwan, non-

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compliance to dabigatran therapy was 10.7%, and little attention was focused on non-compliance (Hu et al., 2015). In New Zealand, there were high rates of dabigatran therapy discontinuation (30% after 8 months), which was attributed to increased gastrointestinal complications (Martinez et al., 2016). Severe cases were those in which hospitalization due to major bleeding resulted in an increased requirement for treatment or caused permanent harm. Only one retrospective study reported severe cases of ADR (3.14%) (Cutler et al., 2014). Among the examined prospective studies, two reported severe cases, with rates of 0.82% (Monteagudo et al., 2015) and 25.8% (Beyer-Westendorf et al., 2015).

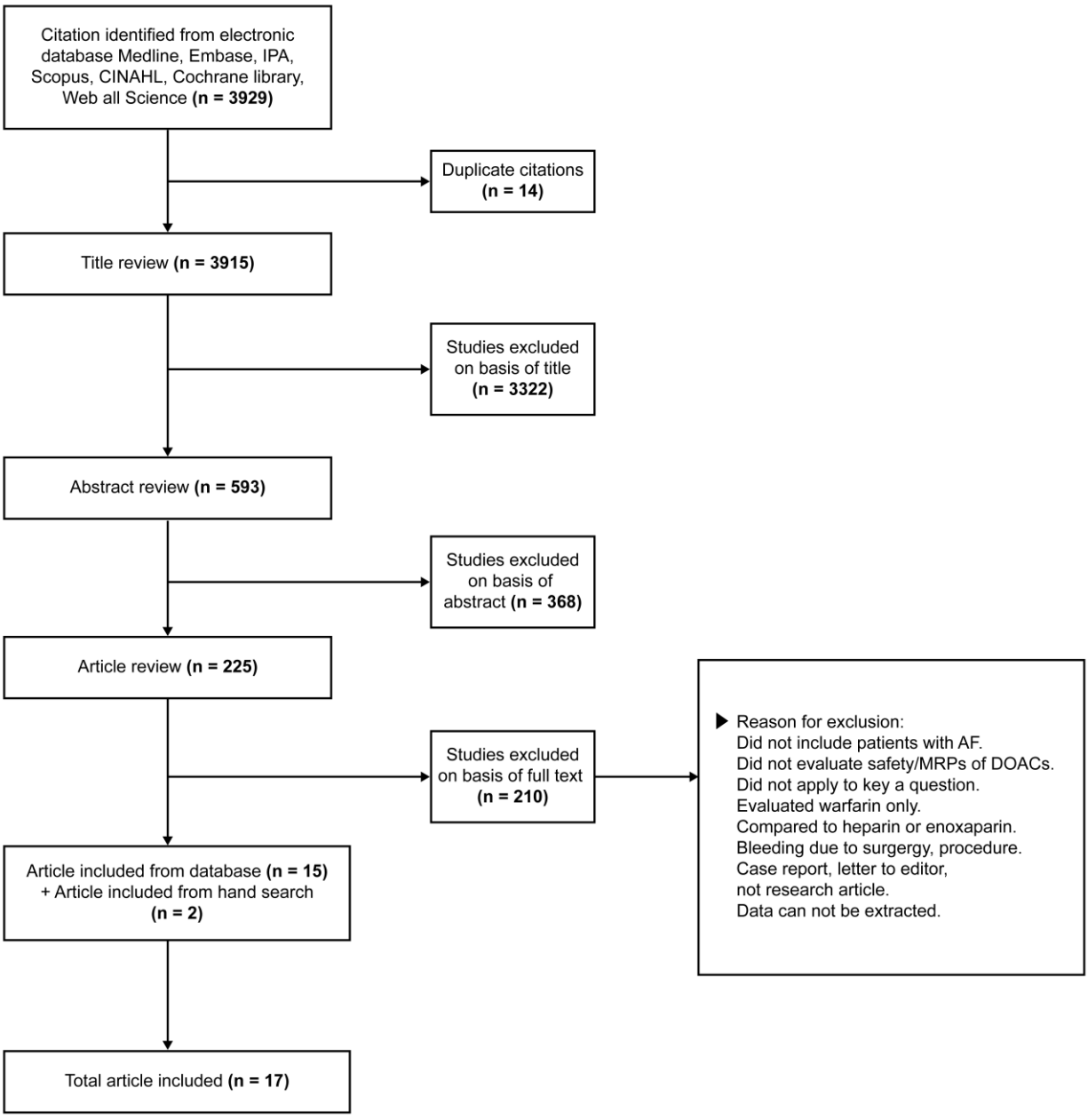

Fig. 1. *Flow chart for identification of selected studies.*

Contributing Factors

The factors that could contribute to the incidences of MRPs include old age, polypharmacy, sex, education, immobilization, depression, and cohabitation (Al Hamid et al., 2013). The meta-analysis of Beijer (2002) showed that the probability of being hospitalized due to ADR-related problems is four times higher for elderly people than for younger people (16.6% vs. 4.1%). In this review only one study reported old age as contributing factors to increased risk of gastrointestinal bleeding (Graham et al., 2014).

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Discussion

Identifying studies that investigated MRPs experienced by patients with AF using DOACs was challenging. In this review, studies focused on the prevalence, categories, and cause and severity of MRPs among adult patients with AF using DOACs were critically reviewed. The findings of this review suggest that no studies defined MRPs involving DOACs, and ADRs and ADEs were used interchangeably. Four of the retrospective studies investigated ADRs (Larsen et al., 2013; Graham et al., 2014; Chang et al., 2015; Nishtala et al., 2016], one investigate medication errors (Andreica and Grissinger, 2015), one investigated persistence (Forslund et al., 2016), and two investigated adherence (Lee et al., 2013; Cutler et al., 2014). Furthermore, six prospective studies investigate ADRs (Donaldson and Norbeck, 2013; Ho et al., 2014; Thorne et al., 2014; Beyer-Westendorf et al., 2015; Monteagudo et al., 2015; Chan et al., 2016), one study investigate persistence (Martinez et al., 2016), and two investigate adherence (Gorst-Rasmussen et al., 2015; Hu et al., 2015). In addition, most of the studies investigated dabigatran, which was the first DOAC available in the market. In the analysis of adherence, all the studies examined patient adherence to dabigatran. The findings of this review for ADR-related bleeding ranged from 2.3 to 16.8%, whereas in the RCTs, the prevalence of ADR-related bleeding with the use of DOACs for preventing stroke and systemic embolism in patients with AF ranged from 1.5% (Holster et al., 2013) to 4.9% (Dentali et al., 2012), which was the percentage of the total population studied. Three meta-analyses compared the safety profile of ADR-related bleeding events between the DOACs and warfarin in patients with AF and found that the DOACs had a better safety profile with an odds ratio (OR) of 0.49 (Lega et al., 2014), 0.33 (Chan et al., 2016) and 0.58 (Caldeira et al., 2015a) for intracranial haemorrhage, gastrointestinal bleeding, and all hospitalised major bleeding events. The efficacy between the DOACs was similar (OR: 0.79, apixaban; 0.77, dabigatran; and 0.86, rivaroxaban), but they differed in risk and safety profile. In patients with renal failure, there was an increase in bleeding events with dabigatran compared to rivaroxaban and apixaban (Lega et al., 2014). The DOACs also showed the same efficacy and safety profiles in the treatment of both male (5.55%) and female (8.4%) patients with AF (Dentali et al., 2015). The DOACs do not cause excessive bleeding in patients > 75 years old compared to the effect of conventional treatments (DOACs 6.5% vs. warfarin 7.1%) (Sardar et al., 2014).

Three meta-analyses studied non-ADR-related bleeding events of DOACs. The DOACs do not show an increased risk of causing drug-induced liver injury (0.22% of the study population), and they had a lower risk of substantial intraocular bleeding (0.04%) than warfarin did; however, they showed a similar risk of renal failure to that of warfarin (OR, 0.96)(Caldeira et al. 2014, Caldeira et al. 2015a, Caldeira et al. 2015b). In this review, the prevalence of non-ADR-related bleeding events ranged from 45.6%-2.7%. Only one meta-analysis investigated discontinuation of DOACs therapy and found the rate (6.08%) was similar to that of conventional drugs used in the treatment of thromboembolism and the prevention of stroke in patients with AF (Chatterjee et al., 2014).

Summary of Study Strengths and Limitations

To the best of our knowledge, this study is the first systematic review of MRPs in adult patients with AF using DOACs. Two independent reviewers investigated the data retrieved from previous studies to avoid bias. Moreover, the inclusion and exclusion criteria used met the research aim. Some of the study limitations are that the included studies in this review varied in sample sizes that were in the range of 68-20,636 subjects, and they had different settings and data collection methods. The results are also limited by the length of follow-up, which was from 3-27 months. There were countries other than the US, Europe, UK, and Asia, which showed differences in medicine used. An additional limitation the use of different terms to described the MRPs such as ADR, ADE, medication errors, and adherence. However, this review clearly shows that articles on MRPs experienced by patients with AF using DOACs are limited. Therefore, more studies examining medicine-related problems in patients with AF using DOACs and the contributing factors in clinical settings are needed to ensure patient outcomes are effectively improved and risk to patients are reduced.

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CONCLUSIONS

There have been no systematic investigations of MRPs in adult patients with AF using DOACs in clinical practice. This review indicates that DOACs have a favourable risk/safety profile for treatment of patients with AF, given the reduced risk of ADR-related major and minor bleeding events; however, there was a variation in the measured risk among the studies. In addition, 12 of the 17 studies only investigated dabigatran. Non-bleeding ADRs were reported in five studies with limited specification. The discontinuation rates for the dabigatran therapy showed mixed findings. Although they were similar to those for warfarin, the discontinuation rates for dabigatran were higher in China and New Zealand than in other countries because of gastrointestinal complications. Persistence rates for dabigatran therapy remained high (> 80%) but slightly decreased between the first and the second year (88.2–82.9%). Medication errors associated with oral anticoagulants including DOACs were relatively frequent. More attention should be focused to adherence, persistence, monitoring, and follow-up for all DOAC therapy to reduce the rate of ADR-related bleeding events. Encouraging continuous ADR reporting is important to improve patient safety.

One recommendation for future work is to compare oral anticoagulants in the clinical practice setting on the basis of specific outcome measures. In addition, head-to-head comparisons of different types of DOACs are needed. In this manner, clinical practice will be informed with quality information regarding the safety of DOACs. Future combination of qualitative and quantitative studies with such research questions will enable the formulation of clinically relevant policies and guidelines. Therefore, further studies are needed to further examine the medicine-related problems of DOACs in patients with AF.

REFERENCES

Adusumilli, P.K., Adepu, R., 2014. Drug-related problems-an over view of various classification systems. Asian Journal of Pharmaceutical and Clin Res, 7, 7-10.

Al Hamid, A., Ghaleb, M., Aljadhey, H., Aslanpour, Z., 2014. A systematic review of hospitalization resulting from medicine-related problems in adult patients. Br J Clin Pharmacol, 78, 202-217.

Alhomoud, F., Dhillon, S., Aslanpour, Z., Smith, F., 2013. Medicine use and medicine-related problems experienced by ethnic minority patients in the United Kingdom: a review. Int J Pharm Pract, 21, 277-287.

Andreica, I., Grissinger, M., 2015. Oral anticoagulants: A review of common errors and risk reduction strategies. Pennsylvania Patient Safety Advisory, 12, 54-61.

Basger, B. J., Moles, R. J., Chen, T. F., 2015. Development of an Aggregated System for Classifying Causes of Drug-Related Problems. Ann Pharmacother, 49, 405-418.

Bauer, K. A., 2013. Pros and cons of new oral anticoagulants. ASH Education Program Book, 2013, 1, 464-470.

Beijer HJ, de Blaey CJ: Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. Pharm World Sci. 2002, 24 (2): 46-54. 10.1023/A:1015570104121.

Beyer-Westendorf, J., Ebertz, F., Foerster, K., Gelbricht, V., Michalski, F., Köhler, C., Werth, S., Endig, H., Pannach, S., Tittl, L., Sahin, K., Daschkow, K., Weiss, N., 2015. Effectiveness and safety of dabigatran therapy in daily-care patients with atrial fibrillation. Thromb Haemost, 113, 1247-1257.

British Heart Foundation BHF, 2015. BHF Headline Statistics. [Online] Available at: https://www.bhf.org.uk/[Accessed 4 June 2015].

Caldeira, D., Barra, M., Santos, A. T., de Abreu, D., Pinto, F.J., Ferreira, J.J., Costa, J., 2014. Risk of drug-induced liver injury with the new oral anticoagulants: systematic review and meta-analysis. Heart, heartjnl-2013.

Caldeira, D., Canastro, M., Barra, M., Ferreira, A., Costa, J., Pinto, F.J., Ferreira, J.J., 2015a. Risk of substantial intraocular bleeding with novel oral anticoagulants: systematic review and meta-analysis. JAMA Ophthalmol, 133, 834-839.

Caldeira, D., Gonçalves, N., Pinto, F. J., Costa, J., Ferreira, J.J., 2015b. Risk of renal failure with the non-vitamin K antagonist oral anticoagulants: systematic review and meta-analysis. Pharmacoepidemiol Drug Saf, 24, 757-764.

Camm, A. J., Lip, G. Y., De Caterina, Savelieva, I., Atar, D., Hohnloser, S.H., Hindricks, G., Kirchhof, P.; ESC Committee for Practice Guidelines (CPG), 2012. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. Eur Heart J, ehs253.

Chan, Y. H., Yen, K. C., See, L. C., Chang, S.H., Wu, L.S., Lee, H.F., Tu, H.T., Yeh, Y.H., Kuo, C.T., 2016. Cardiovascular, bleeding, and mortality risks of dabigatran in Asians with nonvalvular atrial fibrillation. Stroke, 47, 441-449.

Chang, H. Y., Zhou, M., Tang, W., Alexander, G.C., Singh, S., 2015. Risk of gastrointestinal bleeding associated with oral anticoagulants: population based retrospective cohort study. BMJ, 350, h1585.

Chatterjee, S., Sardar, P., Giri, J. S., Ghosh, J., Mukherjee, D., 2014. Treatment discontinuations with new oral agents for long-term anticoagulation: insights from a meta-analysis of 18 randomized trials including 101,801 patients. In Mayo Clinic Proceedings 89, 896-907. Elsevier.

Crowther, M. A., Warkentin, T. E. 2008. Bleeding risk and the management of bleeding complications in patients

https://doi.org/10.5920/bjpharm.2017.07

undergoing anticoagulant therapy: focus on new anticoagulant agents. Blood, 111, 4871-4879.

Cutler, T. W., Chuang, A., Huynh, T. D., Witt, R.G., Branch, J., Pon, T., White R., 2014. A retrospective descriptive analysis of patient adherence to dabigatran at a large academic medical center. J Manag Care Spec Pharm, 20, 1028-1034.

Dentali, F., Riva, N., Crowther, Turpie, A.G., Lip, G.Y., Ageno, W., 2012. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. Circulation, 126, 2381-2391.

Dentali, F., Sironi, A. P., Gianni, M., Orlandini, F., Guasti, L., Grandi, A.M., Franchini, M., Ageno, W., Squizzato, A., 2015. Gender difference in efficacy and safety of nonvitamin K antagonist oral anticoagulants in patients with nonvalvular atrial fibrillation or venous thromboembolism: a systematic review and a meta-analysis of the literature. In Seminars in Thromb Hemost, 41, 7, 774-787).

Donaldson, M., Norbeck, A. O. 2013. Adverse events in patients initiated on dabigatran etexilate therapy in a pharmacist-managed anticoagulation clinic. Pharm Pract, 11, 90-95

Forslund, T., Wettermark, B., Hjemdahl, P. 2016. Comparison of treatment persistence with different oral anticoagulants in patients with atrial fibrillation. Eur J Clin Pharmacol, 72, 329-338.

Gorst-Rasmussen, A., Skjøth, F., Larsen, T. B., Rasmussen, L.H., Lip, G.Y., Lane, D.A., 2015. Dabigatran adherence in atrial fibrillation patients during the first year after diagnosis: a nationwide cohort study. J Thromb Haemost, 13, 495-504.

Graham, D. J., Reichman, M. E., Wernecke, M., Zhang, R., Southworth, M.R., Levenson, M., Sheu, T.C., Mott, K., Goulding, M.R., Houstoun, M., MaCurdy, T.E., Worrall, C., Kelman, J.A., 2014. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for non-valvular atrial fibrillation. Circulation, 131, 57-164.

Ho, M. H., Ho, C. W., Cheung, E., Chan, P.H., Hai, J.J., Chan, K.H., Chan, E.W., Leung, G.K., Tse, H.F., Siu, C.W., 2014. Continuation of dabigatran therapy in "real-world" practice in Hong Kong. PloS one, 9, e101245.

Holster, I. L., Valkhoff, V. E., Kuipers, E. J., Tjwa, ETTL, 2013. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. Gastroenterology, 145, 105-112.

Hu, Y. F., Liao, J. N., Chern, C. M., Weng, C.H., Lin, Y.J., Chang, S.L., Wu, C.H., Sung, S.H., Wang, K.L., Lu, T.M., Chao, T.F., Lo, L.W., Chung, F.P., Hsu, L.C., Chen, S.A., 2015. Identification and management of noncompliance in atrial fibrillation patients receiving dabigatran: the role of a drug monitor. Pac Clin Electrophysiol, 38, 465-471.

Hughes, R. G., Blegen, M. A. 2008. Medication administration safety. In: Hughes RG (Ed) Patient Safety and Quality: An Evidence-Based Handbook for Nurses. Rockville (MD): Agency for Healthcare Research and Quality (US), 397-457.

Landefeld, C. S., Beyth, R. J. 1993. Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. Am J Med, 95, 315-328.

Larsen, T. B., Rasmussen, L. H., Skjøth, F., Due, K.M., Callréus, T., Rosenzweig, M., Lip, G.Y., 2013. Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation: a prospective nationwide cohort study. J Am Coll Cardiol, 61, 2264-2273.

Lee, P. Y., Han, S. Y., Miyahara, R. K. 2013. Adherence and outcomes of patients treated with dabigatran: Pharmacist-managed anticoagulation clinic versus usual care. Am J Health-Sys Pharm, 70.

Lega, J. C., Bertoletti, L., Gremillet, C., Chapelle, C., Mismetti, P., Cucherat, M., Vital-Durand, D., Laporte, S., 2014. Consistency of safety and efficacy of new oral anticoagulants across subgroups of patients with atrial fibrillation. PloS one, 9, e91398.

Martinez, C., Katholing, A., Wallenhorst, C., Freedman, S.B., 2016. Therapy persistence in newly diagnosed nonvalvular atrial fibrillation treated with warfarin or NOAC. Thromb Haemost, 115, 31-39.

Mekaj, Y. H., Mekaj, A. Y., Duci, S. B., Miftari, E.I., 2015. New oral anticoagulants: Their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. Ther Clin Risk Manag, 11, 967-977.

Miller, C. S., Grandi, S. M., Shimony, A., Filion, K. B., & Eisenberg, M. J. (2012). Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. The American journal of cardiology, 110(3), 453-460.

Monteagudo, M., Fernández-Díaz, E., García-García, J., Ayo-Martín, O., Hernández-Fernández, F., Segura, T., 2015. Efficacy, safety and tolerability of rivaroxaban for the secondary prevention of stroke in patients with atrial fibrillation in clinical practice. Future Neurology, 10, 529-536.

National Institute for Health and Care Excellence, 2015. Implementation of NICE TAs 249, 256 and 275 Dabigatran, Rivaroxaban and Apixaban for the prevention of stroke and systemic embolism in atrial fibrillation. Retrieved from http://www.neneccg.nhs.uk/resources/uploads/files/implementation-of-nice-tas-249-256-and-275-dabigatran-rivaroxaban-and-apixaban-april-2013-final.pdf

Nishtala, P. S., Gnjidic, D., Jamieson, H. A., Hanger, H.C., Kaluarachchi, C., Hilmer, S.N., 2016. 'Real-world' haemorrhagic rates for warfarin and dabigatran using population-level data in New Zealand. Int J Cardiol, 203, 746-752.

Pharmaceutical Care Network Europe Foundation, 2006. Classification for Drug related problems: The PCNE Classification V 5.01 (revised 01-05-06 vm). Retrieved from http://www.pcne.org/upload/files/16_PCNE_classification_V5.01.pdf

Plovanich, M., Mostaghimi, A., 2015. Novel oral anticoagulants: What dermatologists need to know? J Am Acad Dermatol, 72, 535-540.

https://doi.org/10.5920/bjpharm.2017.07

Saedder, E. A., Brock, B., Nielsen, L. P., Bonnerup, D.K., Lisby, M., 2014. Identifying high-risk medication: a systematic literature review. Eur J Clin Pharmacol, 70, 637-645.

Sardar, P., Chatterjee, S., Chaudhari, S., Lip, G.Y., 2014. New oral anticoagulants in elderly adults: evidence from a meta-Analysis of randomized trials. J Am Geriatr Soc, 62, 857-864.

Sardar, P., Chatterjee, S., Lavie, C.J., Giri, J.S., Ghosh, J., Mukherjee, D., Lip, G.Y. 2015. Risk of major bleeding in different indications for new oral anticoagulants: Insights from a meta-analysis of approved dosages from 50 randomized trials. Int J Cardiol, 179, 279-287.

Scridon, A., Constantin, S. R., (2015). Laboratory monitoring-a turning point in the use of new oral anticoagulants. Thera Drug Monit, 38, 12-21.

Strand, L, Morley P, Cipolle R, et al. 1990. Drug-related problems: Their structure and function. DICP, 24, 1093–1097.

The National Coordinating Council for Medication Error Reporting and Prevention, 2015. About medication errors? Retrieved from http://www.nccmerp.org/about-medication-errors.

Thorne, K., Jayathissa, S., Dee, S., Briggs, N., Taylor J., Reid, S., De Silva, K., Dean, J., 2014. Adherence and outcomes of patients prescribed dabigatran (Pradaxa) in routine clinical practice. Int Med J, 44, 261-265.

Van den Bemt, P. M. L. A., Egberts, A. C. G. 2007. Drug-related problems.

Van Mil, J. F., Westerlund, L. T., Hersberger, K. E., Schaefer, M.A., 2004. Drug-related problem classification systems. Ann Pharmacother, 38, 859-867.

World Health Organisation, 2015. Cardiovascular Diseases (CVD's). [Online] Available at: http://www.who.int/mediacentre/factsheets/fs317/en/[Accessed 4 June 2015].