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PHARMACOEPIDEMIOLOGY (U HAUG, SECTION EDITOR)

Different Risk Profiles of European Patients Using Direct Oral Anticoagulants or Vitamin K Antagonists: a Rapid Review

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Abstract

Purpose of Review We investigated the risk profiles of patients using direct oral anticoagulants (DOAC) or vitamin K antagonists (VKA) in European cohort studies to estimate the importance of potential (measured or unmeasured) confounding factors in analyses comparing these drugs. We searched MEDLINE and EMBASE (2008–2018) for relevant studies and extracted information on age, sex, comorbidity, Charlson comorbidity index, HAS-BLED score (assessing risk of bleeding) and CHA2DS2-VASc score (assessing risk of stroke).

Recent Findings Overall, 66 studies with 2,808,757 patients were included. Most patients were from France (37%), Denmark (24%) and Germany (23%). In 56 studies (85%), the focus was on patients with atrial fibrillation. Of the 43 studies comparing DOAC with VKA users, 33% reported a higher and 16% a lower age of DOAC compared with VKA users. The mean age varied by about 1 year in most of these studies. Rivaroxaban was used in the widest age range. Patients with DOAC more often had a history of stroke or bleedings, and patients with VKA more often had a history of diabetes, renal failure, cancer, heart failure or other heart diseases. Most studies did not observe differences regarding the HAS-BLED score or the CHA2DS2-VASc score between groups.

Summary Our review suggests that there are relevant differences in the risk profiles of DOAC versus VKA users and between users of individual DOACs. Reported HAS-BLED or CHA2DS2-VASc scores did not reflect these differences. These patterns require careful consideration in the interpretation of observational studies comparing the effectiveness and the risks of these drugs, also when comparing the results of studies conducted in different countries.

Keywords Anticoagulants · Cohort studies · Patient characteristics · Risk profiles

Introduction

In the field of oral anticoagulants, several new substances have been approved over the past decade known as direct oral anticoagulants (DOAC), new oral anticoagulants or non-vitamin K antagonist oral anticoagulants (NOAC). Unlike vitamin K antagonists (VKA), they do not require routine monitoring for potential dose adjustments, as their pharmacokinetic properties are more predictable. The frequency of DOAC prescriptions has constantly increased in Europe [1••]. For instance, for nonvalvular atrial fibrillation (AF), the standardised rate of new DOAC users increased from 0.11 to 8.71 users per 10,000 people (2011–2015) for rivaroxaban and from 0.01 to 8.12 per 10,000 (2012–2015) for apixaban in six European countries (Denmark, France, Germany, Netherlands, Spain and UK) [1••]. In 2015, the rate of new DOAC users treated for AF ranged from nine (Spain) to 28 (Denmark) per 10,000 inhabitants [1••]. Continuing increase is expected due to further extensions of approved indications.

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Following the stepwise approval of different DOAC, the comparison of their effectiveness and safety has been a matter of intense research. This includes observational studies, e.g. based on large healthcare databases where information to adequately control for confounding is often limited. Confounder control, however, is highly relevant as channelling bias and other reasons for selective prescribing could play an important role. Potential differences in the marketing strategies of the competing manufacturers between countries or differences in the health systems may lead to country-specific selection effects. Controlling for measured confounders is often not sufficient to overcome these sources of bias. For example, a recent database study—comparing the risk of bleeding, stroke and death of patients treated with different DOAC or VKA—found a higher mortality rate for rivaroxaban, but the authors argued that this effect may also be due to selective prescription of rivaroxaban for older patients [2•]. To better assess the associated risk, adequate control of potential confounders such as "frailty" would be important, but this is typically challenging due to limited related information in large database studies.

If there are relevant differences in measured confounders between patient groups, it appears plausible that the possibility of unmeasured confounding also requires more attention in the interpretation of results. However, to date, the literature has not been systematically investigated regarding patient profiles of different DOAC users. To fill this gap, we performed a rapid review assessing and comparing the characteristics of patients treated with oral anticoagulants, in particular with DOAC, focusing on cohort studies conducted in Europe.

Methods

Study Design

A rapid review was conducted considering the recommendations for rapid reviews [3–6]. Additionally, the *Cochrane Handbook of Systematic Reviews* and the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) statement served as guidelines [7–9].

The bibliographic databases MEDLINE via PubMed and EMBASE via Ovid were systematically searched for studies published from January 1, 2008—the year of the first approval of a DOAC within the European Union—until December 31, 2018. The search strategy was developed using the PICO scheme (population, intervention, comparison/study design, outcome) [7]. A search filter for cohort studies was used [10]. The detailed search strategy can be found in the appendix.

Inclusion and Exclusion Criteria

We included articles on studies

(A) Investigating patients with prophylaxis or therapy for thromboembolic diseases (i.e. prophylaxis of venous thromboembolism after hip and knee replacement, prophylaxis of stroke and systemic embolism in patients with atrial fibrillation, therapy and prophylaxis of deep vein thromboses and pulmonary embolism and prophylaxis of thrombotic events after acute coronary syndrome, which were approved indications for at least one DOAC within the European Union before 2018)
(B) Including patients treated with apixaban, dabigatran, edoxaban or rivaroxaban (i.e. studies only including patients treated with VKA were excluded)
(C) Which were cohort studies
(D) Which documented patient characteristics and outcomes with respect to the use, effectiveness and/or safety of the DOAC
(E) Including patients living in the European Union

Furthermore, for reasons of comprehension, only studies published in English, German or French were included (no resources for translation of studies were available). We also excluded studies published as abstract only.

Selection Process

As is customary for rapid reviews, the selection of studies was conducted by one person (KK) [5]. Duplicates were removed, and titles, abstracts and full texts were screened with respect to the inclusion and exclusion criteria [11]. The reasons for exclusion were documented.

The reporting quality of the included studies was described qualitatively with respect to the following domains: study design, research question, presence of a comparative group, potential selection bias or rather the relation of the number of included patients to the whole population, completeness of the searched patient characteristics and disclosure of conflicts of interest and funding.

One person (KK) extracted the characteristics of the studies and the patients. If documented, the HAS-BLED score used to assess the bleeding risk, CHA2DS2-VASc score predicting the risk of stroke and Charlson comorbidity index were considered. We only considered information on baseline characteristics before matching or weighting procedures.

Results

Characteristics of Studies

The search resulted in 2313 hits, 980 in MEDLINE and 1333 in EMBASE (Fig. 1). A total of 66 studies with 2,808,757 patients overall were included [2•, 12•, 13•, 14•, 15•, 16•, 17•, 18•, 19•, 20•, 21•, 22•, 23•, 24•, 25•, 26•, 27•, 28•, 29•,

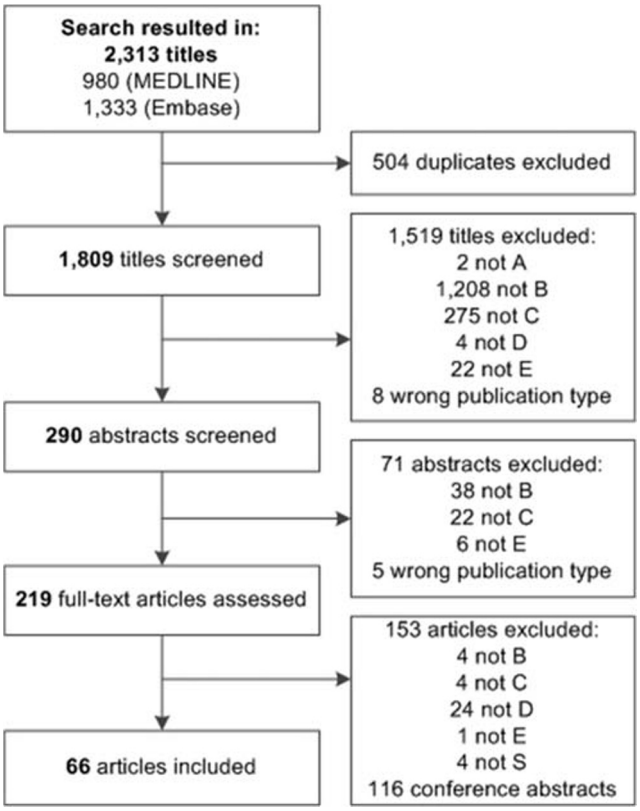

Fig. 1 Inclusion criteria: A = patients with thrombo-embolic diseases (approved for direct oral anticoagulants (DOAC) until 2018); B = therapy with DOAC; C = cohort study; D = patient characteristics; E = European patients; S = language English, German, French

30•, 31•, 32•, 33•, 34•, 35•, 36•, 37•, 38•, 39•, 40•, 41•, 42•, 43•, 44•, 45•, 46•, 47•, 48•, 49•, 50•, 51•, 52•, 53•, 54•, 55•, 56•, 57•, 58•, 59•, 60•, 61•, 62•, 63•, 64•, 65•, 66•, 67•, 68•, 69•, 70•, 71•, 72•, 73•, 74•, 75•, 76•]. A list of excluded full text articles can be found in the appendix.

Forty-seven of the 66 (71%) included studies were published in 2017 or 2018. There were 23 studies (35%) from Denmark [12•, 24•, 25•, 26•, 27•, 36•, 37•, 38•, 39•, 40•, 41•, 42•, 44•, 52•, 53•, 61•, 62•, 63•, 66•, 67•, 68•, 69•, 70•], 12 studies (18%) from Germany [2•, 13•, 14•, 19•, 29•, 30•, 31•, 34•, 43•, 50•, 71•, 76•], 10 studies (15%) from France [15•, 16•, 18•, 20•, 21•, 32•, 47•, 48•, 49•, 60•], four studies (6%) from Italy [57•, 73•, 74•, 75•] and four studies (6%) from Sweden [22•, 23•, 64•, 65•]. For the remaining countries, there were less than four studies each (Table 1). Three studies (5%) included patients from more than one country [17•, 45•, 56•]. Most patients were from France ($n = 1{,}040{,}557$; 37%), Denmark ($n = 667{,}008$; 24%) and Germany ($n = 643{,}665$; 23%).

The included 66 studies investigated the use, effectiveness and/or safety of the drugs. Three studies were reported as post-authorisation effectiveness and safety studies (PAES/PASS) with special methodical requirements of the regulatory authorities [30•, 31•, 55•]. The number of patients per study varied between 103 [33•] and 814,446 [32•]. Different data sources were used; some studies collected primary data, and others used routinely collected data from registries or the healthcare system (data not shown).

The majority of the studies ($n = 56$; 85%) included patients with atrial fibrillation treated with DOAC for stroke and systemic embolism prophylaxis [2•, 12•, 13•, 14•, 15•, 16•, 17•, 19•, 20•, 21•, 22•, 24•, 25•, 26•, 27•, 28•, 29•, 30•, 31•, 32•, 36•, 37•, 39•, 40•, 41•, 42•, 43•, 44•, 45•, 46•, 47•, 48•, 49•, 50•, 51•, 52•, 53•, 54•, 55•, 56•, 57•, 58•, 59•, 60•, 64•, 65•, 67•, 68•, 69•, 70•, 71•, 72•, 73•, 74•, 75•, 76•]. Eleven studies (17%) investigated patients with a DOAC prescription to treat or prevent deep vein thrombosis or pulmonary embolism [18•, 23•, 33•, 34•, 35•, 38•, 61•, 62•, 63•, 66•, 72•]. One study (2%) included patients treated for venous thromboembolism prophylaxis after hip or knee replacement [72•]. There was no study investigating prophylaxis in patients with acute coronary syndrome.

Sixteen studies (24%) assessed direct oral anticoagulants (DOAC) without a comparator [12•, 14•, 17•, 21•, 23•, 24•, 29•, 33•, 34•, 43•, 46•, 49•, 51•, 54•, 55•, 73•], and the others compared different DOAC with one another ($n = 6$; 9%) [13•, 15•, 25•, 63•, 68•, 74•] or DOAC with other anticoagulants ($n = 43$, 65%), mainly with VKA [2•, 16•, 19•, 20•, 22•, 25•,

Table 1 Characteristics of the included studies

	Total	France	Denmark	Germany	Norway	Sweden	Spain	Italy	Great Britain	Europe	Scotland	Switzer-land	Nether-lands	Ireland
Studies n, %	66 (100)	10 (15)	23 (35)	12 (18)	2 (3)	4 (6)	3 (5)	4 (6)	1 (2)	3 (5)	1 (2)	1 (2)	1 (2)	1 (2)
Participants (n, %)	2,808,757 (100)	1,040,557 (37)	667,008 (24)	643,665 (23)	188,695 (7)	181,694 (6)	40,699 (1)	13,703 (<1)	13,221 (<1)	10,808 (<1)	5,398 (<1)	2,062 (<1)	899 (<1)	348 (<1)
Apixaban														
Studies n, %	30 (45)	2 (7)	11 (37)	5 (17)	1 (3)	4 (14)	1 (3)	3 (10)	0	1 (3)	1 (3)	0	0	1 (3)
Participants (n, %)	179,073 (6)	44,377 (25)	56,150 (31)	45,962 (26)	6,506 (4)	2,496 (13)	278 (<1)	2,124 (1)	0	49 (<1)	1,090 (<1)	0	0	41 (<1)
Age (years)*	67–84	75–76	67–84	75–76	75	75	n.r.	78–79	0	n.r.	74	0	0	n.r.
Male (%)	36–60	50–56	36–60	51–52	55	55	n.r.	49–53	0	n.r.	52	0	0	n.r.
Dabigatran														
Studies n, %	45 (68)	8 (18)	18 (40)	7 (16)	1 (2)	4 (9)	1 (2)	3 (7)	0	1 (2)	1 (2)	0	0	1 (2)
Participants (n, %)	456,921 (16)	179,748 (39)	127,927 (28)	118,072 (26)	7,925 (2)	18,345 (4)	1,982 (<1)	1,625 (<1)	0	175 (<1)	1,016 (<1)	0	0	106 (<1)
Age (years)*	66–83	74	66–83	71–78	71	70	n.r.	69–82	0	n.r.	72	0	0	n.r.
Male (%)	43–68	52–68	43–65	51–55	62	61	n.r.	47–42	0	n.r.	61	0	0	n.r.
Rivaroxaban														
Studies n, %	47 (71)	7 (15)	15 (32)	9 (19)	1 (2)	4 (9)	2 (4)	2 (4)	0	3 (7)	1 (2)	1 (2)	1 (2)	1 (2)
Participants (n, %)	493,258 (18)	230,350 (47)	78,929 (16)	143,053 (29)	6,817 (1)	17,945 (4)	1,645 (<1)	796 (<1)	0	8,962 (2)	3,291 (<1)	417 (<1)	899 (<1)	154 (<1)
Age (years)*	56–83	73–74	63–83	61–79	75	74–75	58	79	0	67–72	75	56	69	n.r.
Male (%)	40–67	47–63	40–67	48–59	54	56	56	49	0	50–59	53	56	65	n.r.
Vitamin K antagonists														
Studies n, %	43 (65)	6 (14)	19 (44)	7 (16)	2 (5)	3 (7)	2 (5)	2 (5)	1 (2)	1 (2)	0	0	0	0
Participants (n, %)	1,600,669 (57)	584,987 (37)	394,876 (25)	355,581 (22)	86,368 (5)	122,909 (8)	32,861 (2)	9,158 (<1)	12,307 (<1)	1,622 (<1)	0	0	0	0
Age (years)*	63–79	74–78	63–76	75–79	65–76	74–75	75	72–78	74	69	0	0	0	0
Male (%)	39–76	48–67	39–76	43–54	54–60	55–60	52	52–55	56	55	0	0	0	0

*Age in years, given as range of mean or median from single studies, *n.r.* not reported

26•, 27•, 28•, 30•, 31•, 32•, 36•, 37•, 38•, 39•, 40•, 41•, 42•, 44•, 45•, 47•, 48•, 50•, 52•, 53•, 56•, 57•, 58•, 59•, 60•, 61•, 62•, 64•, 65•, 66•, 67•, 69•, 70•, 71•, 72•, 75•, 76•].

Some of the studies did not report baseline characteristics stratified by users of single substances and presented only data for users of the drug class. All studies presented data on age, sex and comorbidity with different levels of detail (Appendix Table 4 and Table 5). Information on the HAS-BLED score was provided in 40 studies (61%), on the CHA2DS2-VASc score in 48 studies (73%) and on the Charlson comorbidity index in nine studies (14%). All studies reported information regarding conflicts of interest; eight studies (12%) reported that there were no conflicts of interest and 42 (64%) declared their funding.

Characteristics of Patients

Anticoagulants

In total, 1,600,669 patients (57%) were treated with VKA, 1,205,908 (43%) with DOAC and 2071 (< 1%) with other anticoagulants (e.g. heparins). Among patients treated with DOAC, 493,258 (41%) used rivaroxaban; 456,921 (38%), dabigatran; and 179,073 (15%), apixaban (Table 1). There was no study describing patients treated with edoxaban.

In the Danish studies, dabigatran was the most often used DOAC (31–78%), except for the prophylaxis of venous thromboembolism where rivaroxaban had the greatest share (80%). In the German studies, the Irish study and the Scottish study, rivaroxaban was the most often prescribed DOAC (59–67%, 44% and 61%, respectively). In France and Spain, dabigatran and rivaroxaban were prescribed with the same frequency. In Italy and Sweden, apixaban, dabigatran and rivaroxaban were used with the same frequency (Appendix Table 4 and Table 5).

Age

Overall, patients treated with DOAC had a higher mean or median age, and their age range was wider compared with patients receiving VKA (mean age 56–84 years vs. 63–79 years). Of the 43 studies comparing DOAC users with VKA users, 15 studies (35%) reported no age differences between the two groups (Appendix Table 4 and Table 5). Fourteen studies (33%) reported a higher age of patients receiving DOAC compared with those treated with VKA [2•, 22•, 26•, 27•, 36•, 44•, 45•, 50•, 52•, 57•, 62•, 69•, 75•, 76•]; the mean age varied by about 1 year in most of these studies. Seven studies (16%) reported that patients using DOAC were younger compared with those receiving VKA [20•, 47•, 58•, 59•, 60•, 65•, 72•], and seven studies (16%) reported age differences related to the received doses of DOAC and VKA [16•, 37•, 39•, 40•, 41•, 67•, 70•].

Eleven studies reported a higher age for patients treated with apixaban and rivaroxaban compared with patients using dabigatran [12•, 22•, 27•, 28•, 36•, 42•, 51•, 64•, 66•, 69•, 73•], and four studies described a higher age for patients with apixaban compared with the other DOAC [30•, 31•, 32•, 52•]. Among DOAC, rivaroxaban was prescribed in the widest age range (mean age 56–83 years vs. 65–84 years). Patients treated with lower doses were older than patients receiving the respective standard dose [13•, 15•, 16•, 24•, 25•, 37•, 39•, 40•, 41•, 67•, 68•, 70•, 74•].

In Italy, patients using apixaban were older than those in the other European countries (78–79 years vs. 74–76 years). In Denmark, the range of mean or median age was wider for patients with apixaban (67–84 years) and dabigatran (66–83 years) compared with patients with rivaroxaban and VKA. This was also the case for dabigatran in Italy (69–82 years) compared with apixaban, rivaroxaban and VKA. Patients treated with rivaroxaban were older in the Danish, Italian and German studies compared with the patients in the studies from the other countries (63–83, 79 and 61–79 years, respectively, vs. 56–75 years). In the Danish and Norwegian studies, VKA were prescribed in a wider mean age range compared with the other European countries (63–76 as well as 65–76 years vs. 74–79 years).

Sex

There were no differences regarding the distribution of sex in 32 studies (48%) (Appendix Table 4 and Table 5). In six studies (10%), a higher proportion of women was observed in patients with reduced doses of dabigatran and rivaroxaban compared those with the standard dose. The studies on DOAC reported a proportion of male patients of 36–68% (Table 1). For apixaban, a proportion of male patients of 49–55% was reported, except for the Danish studies where the proportion varied between 36 and 60%. For dabigatran, 43–68% of male patients were reported, and for rivaroxaban, 40–67%. For VKA, the proportion of male patients was 43–57%, except for Danish studies where the proportion varied between 39 and 76%.

Comorbidity

Ten of the 66 studies did not report on the prevalence of comorbidities stratified by users of different substances, and four studies provided no information on specific comorbidities. Among the 43 studies comparing DOAC with VKA, 32% ($n = 14$) reported more strokes at the baseline in users of DOAC compared with users of VKA [2•, 19•, 25•, 26•, 27•, 30•, 31•, 36•, 40•, 42•, 45•, 52•, 69•, 70•] and in 7% of the studies ($n = 3$) it was the other way around [47•, 61•, 65•]. In 21% of the studies ($n = 9$), the users of DOAC had more prior bleeding compared with VKA users [2•, 25•, 26•, 40•, 52•,

57•, 65•, 67•, 70•], and in one study (2% of the studies (n = 1)), it was the other way around [47•]. VKA users more often showed heart failure in 35% of the studies (n = 15) [16•, 20•, 22•, 35•, 36•, 44•, 47•, 53•, 57•, 58•, 59•, 60•, 65•, 66•, 69•], other cardiovascular diseases in 53% of the studies (n = 23) [2•, 16•, 20•, 22•, 27•, 30•, 31•, 32•, 35•, 37•, 44•, 45•, 57•, 58•, 59•, 60•, 61•, 62•, 65•, 66•, 67•, 69•, 72•], renal failure in 37% of the studies (n = 16) [2•, 18•, 22•, 27•, 30•, 31•, 32•, 47•, 53•, 57•, 58•, 59•, 61•, 62•, 70•, 75•], diabetes mellitus in 35% of the studies (n = 15) [2•, 20•, 22•, 26•, 35•, 37•, 44•, 47•, 58•, 59•, 60•, 65•, 66•, 67•, 70•] and cancer in their history in 7% of the studies (n = 3) [18•, 26•, 35•] (Appendix Table 4 and Table 5).

The HAS-BLED score at the baseline was reported in 40 studies (61%), and the CHA2DS2-VASc score, in 48 studies (73%). These studies reported the mean, the median or the proportion of patients with a score higher than a specific value (Appendix Table 4). Overall, the mean or median HAS-BLED or CHA2DS2-VASc scores were similar between the oral anticoagulants (Table 2). The Charlson comorbidity index (CCI) was reported only in a few studies (n = 9; 14%) and varied widely between 0.5 and 5.0.

Discussion

This rapid review, which included 66 studies from 12 European countries with 2,808,757 patients overall, found marked differences in the characteristics of DOAC vs. VKA users with respect to age and comorbidities. Furthermore, the age structure partly varied between the users of different individual DOAC, which may be associated with further differences in risk factors. Interestingly, the risk scores (HAS-BLED and CHA2DS2-VASc) were typically similar between groups despite the observed differences in age and comorbidity which questions their value for characterizing and comparing user groups—irrespective of their undeniable clinical usefulness.

There are various potential selection mechanisms that could explain why the treatment decision may entail an imbalance in risk profiles (including age) between users of DOAC and users of VKA. In patients who need to see their physician frequently due to severe comorbidities, regular dosage monitoring required for VKA prescriptions may not be perceived as an additional burden, i.e. prescribing of VKA might be preferred in such patients. By contrast, DOAC prescription might be preferred in patients where regular physician visits impose a burden, e.g. in younger, working patients or in older patients with limited mobility who are otherwise healthy. Our finding that a history of either stroke or bleeding was more often reported for DOAC than for VKA users might also suggest a switch due to a prior treatment's lack of effectiveness or safety, respectively. Given that bleeding is the main adverse event of oral anticoagulants, the treatment decisions may also have been affected by the fact that antidotes were only available for VKAs and have only recently become available for DOACs (for dabigatran in 2015 and for apixaban and rivaroxaban in 2018). This is relevant in patients with a high risk of bleeding including frail patients with an increased risk of bleeding due to falls. These aspects may partly explain the differences in risk profiles between DOAC and VKA users observed in our review and which are also supported by recently published findings of the Global Anticoagulant Registry including 24,137 patients from 35 countries with atrial fibrillation who initiated anticoagulation therapy [77•]. At the same time, these aspects illustrate the challenge of adequately balancing the patient groups in observational studies. The severity of comorbidities as well as frailty may play an important role as confounders, i.e. information which is not available or only with varying degrees of validity in many databases. This means that each study comparing DOAC vs. VKA users must be interpreted very carefully, and the comparison of these studies must consider the availability of confounder information as well as the possibility to control for unmeasured confounding in each study.

For different reasons, the HAS-BLED score and the CHA2DS2-VASc score used for patients with atrial fibrillation appear suboptimal to detect relevant differences in the risk profiles between users of different oral anticoagulants. The HAS-BLED score only considers an age above 65 years and does not take into account, for example, diabetes mellitus or heart failure although these comorbidities are also associated with an increased risk of

Table 2 Summary of risk scores of included studies

Anticoagulants	HAS-BLED Score	CHA2DS2-VASc Score	CCI Score
Apixaban	1.5–2.9	2.8–4.3	3.4
Dabigatran	1.5–3.2	2.1–4.6	2.9–5.0
Rivaroxaban	1.5–3.0	2.8–4.5	0.5–3.0
Vitamin K antagonists	1.5–3.1	2.2–4.8	0.6–5.0

bleeding [78•]. Furthermore, the HAS-BLED score typically has been reported in a dichotomous way (< 3 or ≥ 3). The CHA2DS2-VASc score includes information on heart failure, hypertension, diabetes mellitus, prior stroke or transient ischemic attack, prior vascular diseases and sex and age (< 65 years, 65–74 years, > 74 years) [79••, 80••]. A CHA2DS2-VASc score of 2 and higher classifies a high risk of stroke. This is likely for the majority of patients using oral anticoagulants, i.e. there is limited differentiation if the score is not reported quantitatively. We did not observe differences in the scores between DOAC and VKA in the studies, but we did see differences with respect to age which might be due to the rough classification of age in these scores. However, it could also be that one group has a higher age but lower prevalence of comorbidities, while the opposite is true for the other group, resulting in a similar score in both groups. These aspects point to the importance of reporting the prevalence of relevant comorbidities for different patient groups in studies, in addition to scores which ideally should be reported quantitatively rather than dichotomously.

When comparing the studies conducted in different countries, we observed some differences in the distribution of age. For example, patients treated with rivaroxaban tended to be older in studies conducted in Denmark, Italy and Germany compared with the studies from the other European countries. We also observed marked differences between countries regarding the share of individual DOAC in all DOAC prescriptions which might be due to differences in marketing strategies, costs or reimbursement. This should also be kept in mind when comparing results between different countries. If, for example, there was a "standard" DOAC A in one country prescribed to the majority of patients, alternative DOAC may only be prescribed to patients with special characteristics in that country. The situation could be entirely different in another country. The selection mechanisms could thus differ between countries and entail inter-country differences in the distribution of risk profiles among users of oral anticoagulants. This is even more relevant given that the databases available in the various countries differ regarding the availability of information on relevant confounders. A recently published study reporting the share of DOAC vs. VKA in various countries also supports a strong variation in prescribing behaviour across countries [77•].

To the best of our knowledge, this is the most comprehensive overview of studies reporting on the risk profiles among users of oral anticoagulants in Europe to date. We used a methodology similar to a systematic review. We searched the two most important electronic databases in the field (MEDLINE and EMBASE) but cannot rule out that relevant articles were missed. It is possible that relevant articles were not found because of the restriction of search terms within the title or because of the language restriction. The screening and extraction processes were conducted by one person, following the method of rapid reviews. The information provided in this review is partly limited due to differences in the methods of the included studies; incompleteness of data, i.e. not all of the studies reported baseline characteristics stratified by single substances; and differences in the level of details in included data. Additionally, another limitation is that studies may have used different approaches to assess differences between groups. We hope that this review stimulates a more comprehensive reporting in future studies that will facilitate the comparison of risk profiles.

In conclusion, our review found relevant differences in the risk profiles of DOAC vs. VKA users and also between users of individual DOAC. Furthermore, our review suggests that the user characteristics may partly differ between countries. This requires careful consideration in the interpretation of observational studies comparing the effectiveness and risks of these drugs.

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- • Of importance
- •• Of major importance

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