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Do computerized clinical decision support systems improve the prescribing of oral anticoagulants? A systematic review

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ABSTRACT

Background: Serious adverse drug reactions have been associated with the underuse or the misuse of oral anticoagulant therapy. We systematically reviewed the impact of computerized clinical decision support systems (CDSS) on the prescribing of oral anticoagulants and we described CDSS features associated with success or failure.

Methods: We searched Medline, Embase, CENTRAL, CINHAL, and PsycINFO for studies that compared CDSS for the initiation or monitoring of oral anticoagulants with routine care. Two reviewers performed study selection, data collection, and risk-of-bias assessment. Disagreements were resolved with a third reviewer. Potentially important CDSS features, identified from previous literature, were evaluated.

Results: Sixteen studies were included in our qualitative synthesis. Most trials were performed in primary care (n = 7) or hospitals (n = 6) and included atrial fibrillation (AF) patients (n = 9). Recommendations mainly focused on anticoagulation underuse (n = 11) and warfarin-drug interactions (n = 5). Most CDSS were integrated in electronic records or prescribing and provided support automatically at the time and location of decision-making. Significant improvements in practitioner performance were found in 9 out of 16 studies, while clinical outcomes were poorly reported. CDSS features seemed slightly more common in studies that demonstrated improvement.

Conclusions: CDSS might positively impact the use of oral anticoagulants in AF patients at high risk of stroke. The scope of CDSS should now evolve to assist prescribers in selecting the most appropriate and tailored medication. Efforts should nevertheless be made to improve the relevance of notifications and to address implementation outcomes.

1. Introduction

Oral anticoagulants are effective drugs for stroke prevention in patients with atrial fibrillation (AF) and for the treatment and secondary prevention of venous thromboembolism (VTE) [1,2]. However, these drugs have frequently been described as a cause of serious adverse drug reactions (ADR) [3–6]. In 2013–2014, vitamin K antagonists (VKA) and direct oral anticoagulants (DOAC) were among the drugs most commonly implicated in emergency department visits in elderly patients [7]. Most importantly, data suggest that a significant proportion of these ADR are the result of medication errors [8,9]. In a prospective study performed in emergency departments, we showed that more than half of the serious ADR related to the use of DOAC or VKA oral anticoagulants were potentially preventable [10]. However, underuse of oral anticoagulants is also a key safety concern in patients with AF [1]. For example, one study reported that 70% of patients with acute ischemic stroke and a known history of AF were not receiving anticoagulation [11]. Concerns about the applicability of evidence to daily practice were reported as one reason for the underuse of anticoagulation in this setting [12].

Computerized clinical decision support systems (CDSS) provide assistance to clinicians in the process of decision-making by comparing individual patient characteristics against computerized knowledge bases [13]. Specifically, CDSS for drug prescribing can assist initiation

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of appropriate therapy, identify drug-drug interactions and determine optimal dosing regimens [14,15]. In previous systematic reviews, CDSS have been shown to reduce medication errors and improve practitioner performance in different areas [15–17]. Nevertheless, the impact of these systems on patient outcomes has been understudied and results are inconsistent, although Varghese et al. recently reported positive effects [18]. Several features have been suggested to explain why some CDSS were successful and others not. For example, systems that provided decision support automatically at the time and location of decision making were more likely to improve clinical practice [19,20].

Many studies have investigated computer-assisted management of anticoagulant therapy. However, these CDSS mostly dealt with INR-based dose adjustments of warfarin [21,22]. Practitioner performance (e.g., proportion of time patients had an INR within the therapeutic range) improved inconsistently across studies, and most trials were underpowered to evaluate clinical outcomes [21]. More recently, evidence has accumulated on the use of CDSS for VTE prophylaxis in hospitalized patients. CDSS implementation was associated with increased use of thromboprophylaxis and reduced VTE occurrence [23,24]. Nevertheless, these results may not be generalizable to patients requiring long-term treatment.

We, therefore, conducted a systematic review of studies that have compared the impact of CDSSs and routine care on oral anticoagulant prescribing. We also performed a descriptive analysis of CDSS features associated with their success or failure.

2. Methods

This systematic review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement [25]. Review protocol was registered with PROSPERO (CRD42018093507).

2.1. Studies eligible for review

We included studies comparing the effect of a CDSS for the prescribing of oral anticoagulants (i.e. DOAC or VKA) to routine care, in actual clinical settings. We defined CDSS as a system matching individual patient characteristics with computerized clinical knowledge bases, and providing patient-specific assessments or recommendations in an electronic format [13]. Decision supports considered were designed to influence prescribers, at the initiation of drug therapy (i.e. support when DOAC or VKA is started, before or after the prescribing choice) or during monitoring (i.e. support when patients are already taking DOAC or VKA) [26]. Recommendations could be delivered directly to the prescriber or through other health care professionals (HCPs).

We excluded CDSS exclusively dedicated to the therapeutic drug monitoring (TDM) and dosing of VKA, CDSS aiming at improving thromboprophylaxis in hospitalized patients and patient-oriented CDSS such as shared-decision making tools. Multifaceted interventions were included if the CDSS effects were reported individually. Similarly, CDSS focusing on various drugs were included if results for oral anticoagulants were available separately. Eligibility criteria were pilot tested on a sample of 50 reports by two reviewers (ALS and BK). Cases of disagreement were discussed with a third reviewer (AS) and eligibility criteria were refined accordingly.

2.2. Search strategy

We searched Medline (PubMed, 1998 – March 2018), Embase (Ovid, 1998 – March 2018), CENTRAL (Wiley, 1998 – April 2018), CINHAL (EBSCOhost, 1998 – April 2018) and PsycINFO (ProQuest, 1998 – April 2018). We limited our search to full-text reports published in English since 1998, as 2 previous reviews on oral anticoagulation management were published that year [21,22]. Free text terms and subject headings related to the two following search concepts were combined: 1) anticoagulation and 2) CDSS. The Medline search strategy was developed first, and improved after careful consideration of relevant articles. The final version of search strategy, available in Appendix 1, was then applied to the other databases. In order to identify additional potential studies, we handsearched the reference lists of all included studies. We also reviewed: 1) references of previous systematic reviews in the field, 2) citing articles of included studies using Scopus, 3) the trial register clinicaltrials.gov, and 4) Google Scholar.

After duplicate removal, titles and abstracts of identified articles were screened independently by two reviewers (ALS and BK) for compliance with inclusion criteria. Full texts of reports thought to be potentially eligible were then assessed by the two same reviewers. At any stage, disagreements were resolved by consensus and the help of a third reviewer (AS) where necessary. Reviewers were not blinded to journal's name, author's details or outcomes when applying eligibility criteria. A list of excluded full-text reports, with primary reason for exclusion, is available on request.

2.3. Data extraction

Our data collection form was designed based on the Cochrane Handbook for Systematic Reviews of Interventions [27] and the Effective Practice and Organization of Care (EPOC) resources for review authors [28]. We extracted information on study design and setting, inclusion and exclusion criteria, number and characteristics of participants, outcome measures and corresponding results. Regarding the intervention, we recorded details about scope and application of CDSS recommendations (initiation vs. monitoring of oral anticoagulation; support related to indication, choice, dosage or interactions). Potentially important CDSS features, identified from previous literature, were evaluated (Table 1) [19,20,29].

The data collection form was pilot-tested on 3 studies (2 randomized controlled trials (RCT) and 1 interruptive time series analysis (ITS)) by all authors (ALS, BK, BS and AS). Imprecisions were highlighted and the tool was improved accordingly (full version available on request). The final data collection process was performed initially by one reviewer

Table 1
CDSS features that were evaluated in the present systematic review.

General system features
Integration with EMR and/or CPOE
Clinician-system interaction features
Automatic provision as part of physician workflow
No need for additional clinician data entry
Recommendations viewed by the prescriber directly on the computer screen
Request documentation of the reason for not following CDSS recommendations
Provision at time and location of decision making
Recommendations executed by noting agreement
Communication content features
Provision of a recommendation, not just an assessment
Promotion of action rather than inaction
Justification of decision support via provision of reasoning/research evidence
Auxiliary features
Local user involvement in development process
Provision of decision support results to patients as well as providers
Periodic performance feedback
CDSS accompanied by conventional education
Support for CDSS use (e.g. active training, passive instructions, helpdesk)
Monitoring of unintended effects of CDSS
Clear incentives for use

(ALS), and then checked for accuracy by a second reviewer (BK). Disagreements were discussed to reach consensus. We contacted study authors to provide further information where necessary.

2.4. Quality assessment

Methodological quality of RCT was evaluated using the Cochrane Collaboration's tool for assessing risk of bias [30]. Domains of assessment included selection bias (sequence generation and allocation concealment), performance bias (blinding of patients and HCP), detection bias (blinding of assessors), attrition bias (incomplete outcome data) and reporting bias (selective outcome reporting). For non-randomized studies, evaluation was based on the Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) tool [31]. We drew up a table containing the different domains, with examples of low and high risk of bias judgments (Appendix 2). This quality assessment tool was first pilot-tested on three studies by three reviewers (ALS, BK and AS), and improved accordingly. Then, for each included study, two reviewers (ALS and BK) independently assessed the risk of bias. Disagreements were resolved by discussion. All studies were considered for data synthesis, irrespective of their risk of bias.

2.5. Data synthesis and analysis

The following outcomes were searched for: practitioner performance (e.g. appropriateness of oral anticoagulant prescribing), patient outcomes (e.g. adverse events, mortality, or morbidity) and implementation outcomes (e.g. adoption, acceptability, appropriateness or adverse effects of the system). The presence or absence of the previously identified CDSS features was collected for each study. Feature prevalence among studies and median number of CDSS features per study were described separately for trials demonstrating or not improvement in primary outcome measure. As high heterogeneity in interventions and outcome measurements was assumed, no meta-analysis was performed.

3. Results

3.1. Study selection

The search strategy identified 8513 records (Fig. 1). After duplicate removal, titles and abstracts of 7271 records were screened. Among these, 43 full-text articles were reviewed as they were thought to be potentially eligible. Sixteen studies were finally included in our qualitative synthesis. For 10 studies, authors were contacted to provide further information. After sending one reminder, answers were received for 7 studies.

3.2. Study characteristics

Characteristics of the 16 included trials are detailed in Table 2. Most studies were conducted in Europe (44%, n = 7) [32–38] or in North America (44%, n = 7) [39–45], in primary care settings (44%, n = 7) [32,33,37,39,43,45,46] or in hospitals (38%, n = 6) [34,36,38,40–42]. More than half included AF patients (56%, n = 9) [32–34,37,39,40,45–47].

When looking at CDSS that were evaluated, 9 (56%) were exclusively dedicated to the prescribing of oral anticoagulants [32–34,38,39,43,45–47]. CDSS were developed in-house (44%, n = 7) [34–36,39,45–47] or resulted from close collaboration with commercial vendors (56%, n = 9) [32,33,37,38,40–44]. Thirteen (81%) systems were pilot-tested before study initiation [32–35,37,39–44,46,47]. CDSS provided support for the initiation of therapy (88%, n = 14) [32–37,39–42,44–47] or for treatment monitoring (44%, n = 7) [38,39,41–44,46]. Recommendations were mainly related to the indication of oral anticoagulation (69%, n = 11) [32–37,39,40,45–47] and to drug-drug interactions (31%, n = 5) [38,41–44]. Half of CDSS focused specifically on the use of warfarin (n = 8) [35,36,40–44,46]. None individualized assessment regarding the choice between DOAC and VKA or among DOAC was identified. CDSS targeted physicians in all studies, except for one that was unclear [36]. In 5 (31%) studies performed in the US and the UK, nurse practitioners were also CDSS users [33,41–44]. Clinical practice guidelines (50%, n = 8) [32–34,37,39,45–47] and expert opinion (31%, n = 5) [36,38,43,44,46] were common sources of knowledge.

3.3. Study design and methodological quality

Eleven (69%) studies were randomized controlled trials (RCT) [32–34,36,37,39,41,42,44–46]. Randomization was performed at practice level (primary care practices, hospitals or long-stay units, 38%, n = 6) [32,33,36,37,39,44], provider level (19%, n = 3) [41,42,46] or patient level (13%, n = 2) [34,45]. Other non-randomized designs included 2 interrupted time series (ITS) [43,47], 2 historically controlled studies (HCT) [38,40] and 1 controlled before-after study (CBA) [35]. CDSS developers were also evaluators in 11 (69%) trials [32–38,43,44,46,47]. Only one study reported potential financial benefits if the CDSS tested was commercialized [35]. Eight (50%) studies were previously registered in clinical trials databases [32–34,37,39,41,45,46] and, for 4 of these, protocols were published [32,33,37,46].

Methodological quality of included studies is presented in Table 3. Overall 5 (31%) studies were assessed at low risk of bias [32,33,37,40,43], while one or more bias domains were considered at high risk for the 11 (69%) other trials. Performance bias was frequently involved with high risk assessment, especially in RCT. This was partly due to the potential for contamination when physicians allocated to different groups worked together [41,42,44] or when the unit of allocation was the patient [34,45]. Three non-randomized studies were deemed at high risk of detection bias, because methods of outcome assessment differed between groups [35,47] or subjective outcomes were not blindly assessed [38].

3.4. Impact of CDSS on measured outcomes

All trials assessed practitioner performance as a primary outcome measure. Implementation outcomes were further investigated in 11 (69%) studies [32–37,39–41,45,46], and 2 (13%) studies described patient outcomes [32,33].

3.5. Practitioner performance

Overall, significant improvements in practitioner performance were found in 9 (56%) studies [32,34,35,38,41,43,44,46,47]. First, CDSS interventions had a positive effect in 3 of the 8 studies assessing adherence to guidelines or recommendations (2 RCT and 1 ITS) [32,34,47]. Absolute differences between intervention and control groups were nevertheless modest, ranging from 2 to 18% in terms of adequate prescription rates. Second, the prevalence of use of oral anticoagulation was significantly increased in 2 of the 4 studies evaluating this process measure [35,36,45,46]. Third, practitioner performance was improved in 4 of the 5 studies providing support for the management of drug-drug interactions [38,41,43,44]. Results on practitioner performance are detailed in Appendix 3.

3.6. Patient outcomes

In the 2 studies assessing patient outcomes [32,33], CDSS intervention did not influence the incidence of stroke, transient ischemic attack (TIA) or systemic embolism. Karlsson et al. found a lower incidence of significant bleeding in CDSS group (12 vs. 16 events per 1000 patients, p = 0.04) [32]. However, Holt et al. reported

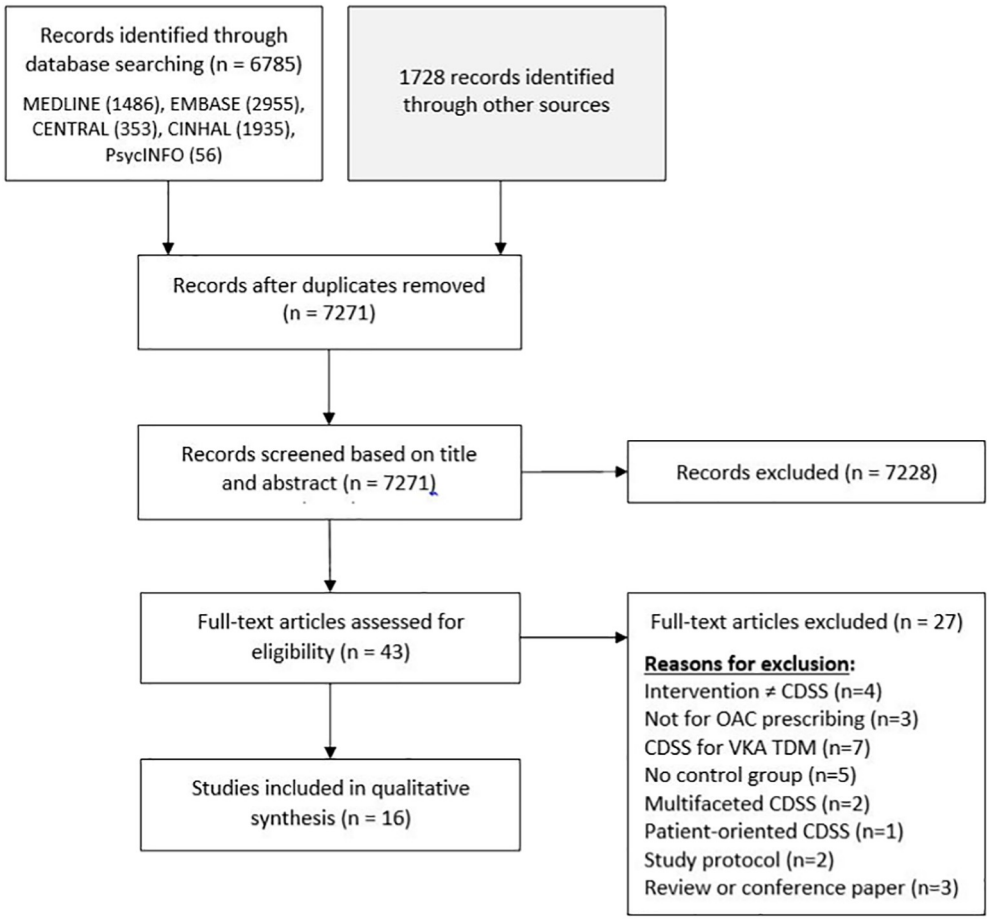

Fig. 1. Study selection (PRISMA flow diagram) [25].

comparable incidences between intervention and control groups (35 vs 50 events per 1000 patients, p = 0.054) [33]. In both studies, clinical outcomes were measured 12 months after study initiation.

3.7. Implementation outcomes

Cook et al. defined alert accuracy as a primary outcome [40]. They found that, among 604 notifications of newly-diagnosed AF received by providers, 44% were confirmed as newly-diagnosed. CDSS utilization was described in 3 studies and ranged between 5 and 30% [34,37,39]. Barriers to the use of CDSS were not reported, although one study team was planning to publish separate data regarding the usefulness, ease of use and acceptance of their CDSS [32]. Reasons for deviating from CDSS recommendations were explored in 6 (38%) studies [32,37,39,40,45,46]. Disagreements with recommendations [39,46], drug management by the specialist [39,46] and patient preferences [32,39,45] were mentioned by providers. Bleeding risk and falls were also reported reasons in primary care [32,45]. Planning of a surgical procedure was another reason for the non-prescribing of warfarin in eligible inpatients [40]. Four cases of delay in prescribing or administration of adequate drugs were monitored in the study of Strom et al., which investigated a hard-stop alert [41]. All adverse events were probably or definitely related to the intervention, leading to the early termination of the study. Implementation outcomes are described in Appendix 4.

3.8. Description of CDSS features

CDSS features are detailed for each study in Table 4. Most CDSS were integrated in electronic medical records (EMR) or computerized provider order systems (CPOE) (69%, n = 11) [32–35,37,38,40–44], and were delivered automatically as part of physician workflow (75%, n = 12) [32–35,37,38,40–45]. Among these, 6 CDSS were flexible (i.e. the user could choose to postpone the decision) [32–34,37,40,45] while 1 was a hard-stop alert (i.e. drug orders were blocked) [41]. Non-integrated CDSS provided support through web-based systems (n = 2) [39,46], smartphone application (n = 1) [47], software (n = 1) [36] or email (n = 1) [45]. Recommendations were viewed directly on the computer screen by the prescriber in all but one study [36], and were provided at the time and location of decision making in all but two studies [39,45]. Fourteen (88%) CDSS gave specific recommendations instead of a simple assessment [32–34,37–47]. Providers were for instance prompted to order acetaminophen when warfarin and NSAID were prescribed simultaneously [42].

Several features were observed in about half of CDSS, such as the provision of reasoning or research evidence (63%, n = 10) [32,34,37–40,43–45,47] or the requirement for response with indication of intention to comply (56%, n = 9) [32–34,37,41–43,45,46]. Among the latter, 4 studies requested justification for not following recommendations [32,33,37,46]. In one third of studies, CDSS users were required to enter or confirm clinical data, before (13%, n = 2) [36,47] or after (19%, n = 3) [33,34,39] provision of first decision support. Recommended drugs could be ordered by a single click in only 4 (25%) studies [32,41–43].

Among auxiliary features, the involvement of local users in the development process was inconsistently reported (56%, n = 9) [32,33,35,38–40,43,44,47]. In 8 (50%) studies [32–35,37,43,46,47], CDSS implementation was accompanied by support in the form of active training (n = 7) [32,33,35,37,43,46,47], passive instructions (n = 4) [32,34,37,46] or helpdesk (n = 1) [37]. Feedback on the

Table 2
characteristics and main results of included studies.

Study	Design	Setting and patients	No. of patient/HCP/centre	CDSS description	Control	1ary outcome	CDSS effect
Arts, 2017 [37]	RCT	1ary care practices The Netherlands AF patients	781/39/18[a]	Tx recommendations in AF patients (OAC or AP)	No CDSS	P: proportion of patients treated according to the guideline	NS
Ashburner, 2018 [45]	RCT	1ary care practices USA OAC-naïve AF patients	2336[a]/175/18	Alert for OAC-naïve AF patients at high risk of stroke	No CDSS	P: proportion of patients receiving OAC	NS
Bajorek, 2016 [46]	RCT	1ary care practices Australia AF patients	393/48[a]/−	Tx recommendations in AF patients (warfarin, ASA or none)	No CDSS	P: proportion of patients receiving OAC	↑
Cook, 2015 [40]	HCT	Hospital USA New AF inpatients	494/−/1	Alert for OAC-naïve new AF patients	No CDSS	P: proportion of eligible patients who were prescribed warfarin I: accuracy of notifications	NS 44%
Eckman, 2016 [39]	RCT	1ary care practices USA AF patients	1493/70/15[a]	Tx recommendations in AF patients (OAC, ASA or none)	No CDSS	P: discordance between CDSS recommendation and actual Tx	NS
Feldstein, 2006 [43]	ITS	1ary care clinics USA VKA-treated patients	9910/−/15	Alert for co-prescribing of warfarin and 5 interacting drugs	No CDSS	P: interacting prescription rate	↓
Holt, 2017 [33]	RCT	1ary care practices UK AF patients	5339/−/46[a]	Alert for eligible OAC-naïve AF patients	No CDSS	P: proportion of eligible patients who were prescribed OAC	NS
Judge, 2006 [44]	RCT	Academic long-stay units USA All residents	445/−/7[a]	Alert for co-prescribing of warfarin and interacting drugs + INR > 3	No CDSS	P: proportion of alerts followed by an appropriate action	↑
Karlsson, 2018 [32]	RCT	1ary care clinics Sweden AF patients	14,800/−/42[a]	Alert for eligible OAC-naïve AF patients	No CDSS	P: proportion of eligible patients who were prescribed OAC	↑
Kruger, 2011 [35]	CBA	Nursing homes Norway All residents	388/504/2	Alert for OAC-naïve AF patients	No CDSS	P: use of warfarin	↑
Sheibani, 2017 [47]	ITS	Offices of cardiologists Iran New AF patients	373/10/10	Mobile application to assess stroke and bleeding risks in AF patients	No CDSS	P: proportion of patients treated according to the guideline	↑
Silbernagel, 2016 [34]	RCT	Academic hospital Switzerland OAC-naïve AF inpatients	889[a]/−/1	Alert for OAC-naïve AF patients	No CDSS	P: rate of adequate OAC prescription at discharge	↑
Strom, 2010 (A) [42]	RCT	Academic hospitals USA All inpatients	−/1963[a]/2	Alert for co-prescribing of warfarin and NSAID	Passive alert	P: not reordering the alert-triggering drug after firing	NS
Strom, 2010 (B) [41]	RCT	Academic hospitals USA All inpatients	96/1971[a]/2	Hard-stop alert for co-prescribing of warfarin and TMP-SMX	No CDSS	P: not reordering the alert-triggering drug after firing	↑
Velez, 2014 [38]	HCT	Academic hospital Spain VKA-treated inpatients	−/−/1	Alert for co-prescribing of OAC and interacting drugs	No CDSS	P: medication errors caused by drug interactions	↓
Weir, 2003 [36]	RCT	Hospitals UK Stroke or TIA patients	637/−/16[a]	Ischemic and bleeding risks associated with Tx (warfarin, ASA, DPY, ASA + DPY, warfarin + ASA or none)	No CDSS	P: risk reduction in ischemic and bleeding events achieved by Tx	NS

1ary: primary, AF: atrial fibrillation, AP: antiplatelet therapy, ASA: aspirin, CBA: controlled before-after study, DPY: dipyridamole, HCP: health care professional, HCT: historically controlled trial, I: implementation outcome, ITS: interrupted time series, NS: not significant, NSAID: non-steroidal anti-inflammatory drugs, OAC: oral anticoagulant, P: practitioner performance, RCT: randomized controlled trial, TIA: transient ischemic attack, TMP-SMX: co-trimoxazole, Tx: treatment, VKA: vitamin K antagonist.
[a] Unit of allocation.

compliance with CDSS recommendations was observed in only 1 (6%) study [39]. Finally, 3 (19%) studies were closely monitored for safety outcomes or inappropriate drug use triggered by the CDSS [32,33,41].

The prevalence of CDSS features among studies is presented in Table 4. Although the number of trials included in the descriptive analysis was small, a trend towards higher prevalence of CDSS features in studies demonstrating improvement in primary outcome seemed to emerge. Particularly, support for CDSS use was more frequently provided in this subgroup. The median number of CDSS features per study was 8 in trials showing no significant effect (range 2–10) and 9 in trials showing statistically significant effect (range 6–14). Two studies specifically assessed the contribution of a single characteristic to the impact of CDSS. As previously mentioned, Strom et al. found that the requirement for indication of intention did not improve practitioner performance [42]. In the study of Feldstein et al., academic detailing addressing barriers to the use of alerts did not influence interacting prescription rates [43].

4. Discussion

In this systematic review, CDSS for the prescribing of oral anticoagulant therapy improved practitioner performance in 9 of 16

Table 3
assessment of risk of bias for the 16 included studies.

Study	Design	Sequence generation	Allocation concealment	Bias due to confounding	Selection bias	Performance bias	Misclassification bias	Attrition bias	Detection bias	Reporting bias	Other risk of bias
Arts, 2017 [37]	RCT	Low	Low			Low		Low	Low	Low	
Ashburner, 2018 [45]	RCT	Low	Low			High		Low	Low	Low	
Bajorek, 2016 [46]	RCT	Low	Low			Low		Low	Low	High	High
Eckman, 2016 [39]	RCT	Unclear	Unclear			Low		Low	Low	Low	High
Holt, 2017 [33]	RCT	Low	Low			Low		Low	Low	Low	
Judge, 2006 [44]	RCT	Unclear	Unclear			High		Low	Low	Low	
Karlsson, 2018 [32]	RCT	Low	Low			Low		Low	Low	Low	
Silbernagel, 2016 [34]	RCT	Low	Low			High		Low	Low	Low	
Strom, 2010 (A) [42]	RCT	Unclear	Unclear			High		Low	Low	Low	
Strom, 2010 (B) [41]	RCT	Low	Low			High		Low	Low	Low	
Weir, 2003 [36]	RCT	Low	Low			High		Low	Low	Low	
Cook, 2015 [40]	HCT			Low	Low	Low	Low	Low	Low	Low	
Feldstein, 2006 [43]	ITS			Low	Low	Low	Low	Low	Low	Low	
Kruger, 2011 [35]	CBA			High	High	Low	Low	Low	High	Low	
Sheibani, 2017 [47	ITS			Low	High	High	Low	Low	High	Low	
Velez, 2014 [38]	HCT			Low	Low	Low	Low	Low	High	Low	

CBA: controlled before-after study, HCT: historically controlled trial, ITS: interrupted time series, RCT: randomized controlled trial, Low: low risk of bias, High: high risk of bias. Grey zone = not applicable.

Table 4
CDSS features evaluated.

	Non-significant CDSS effect (N=7)								Significant CDSS effect (N=9)									
	Arts, 2017[37]	Ashburner, 2018[45]	Cook, 2015[40]	Eckman, 2016[39]	Holt, 2017[33]	Strom, 2010[42] (A)	Weir, 2003[36]	**Prevalence, n (%)**	Bajorek, 2016[46]	Feldstein, 2006[43]	Judge, 2006[44]	Karlsson, 2018[32]	Kruger, 2011[35]	Sheibani, 2017[47]	Silbernagel, 2016[34]	Strom, 2010[41] (B)	Velez, 2014[38]	**Prevalence, n (%)**
GENERAL SYSTEM FEATURES																		
Integration with EMR and/or CPOE	+	−	+	−	+	+	−	**4 (57)**	−	+	+	+	+	−	+	+	+	**7 (78)**
CLINICIAN-SYSTEM INTERACTION FEATURES																		
Automatic provision as part of physician workflow	+	+	+	−	+	+	−	**5 (71)**	−	+	+	+	+	−	+	+	+	**7 (78)**
No need for additional clinician data entry	+	+	+	−	−	+	−	**4 (57)**	?	+	+	+	+	−	−	+	+	**6 (67)**
Rec. viewed directly on the computer screen	+	+	+	+	+	+	−	**6 (86)**	+	+	+	+	+	+	+	+	+	**9 (100)**
Justification for not following CDSS rec.	+[a]	−	−	−	+	−	−	**2 (29)**	+	−	−	+	−	−	−	−	−	**2 (22)**
Provision at time and location of decision making	+	−	+	−	+	+	+	**5 (71)**	+	+	+	+	+	+	+	+	+	**9 (100)**
Recommendations executed by noting agreement	−	−	−	−	−	+	−	**1 (14)**	−	+	−	+	?	−	−	+	−	**3 (33)**
COMMUNICATION CONTENT FEATURES																		
Recommendation, not just an assessment	+	+	+	+	+	+	−	**6 (86)**	+	+	+	+	−	+	+	+	+	**8(89)**
Action rather than inaction	+	+	+	+	+	+	+	**7 (100)**	+	+	+	+	+	+	+	+	+	**9 (100)**
Provision of reasoning or research evidence	+	+	+	+	−	−	−	**4 (57)**	?	+	+	+	−	+	+	−	+	**6 (67)**
AUXILIARY FEATURES																		
Local user involvement in development process	?	?	+	+	+	−	−	**3 (43)**	−	+	+	+	+	+	−	−	+	**6 (67)**
Provision of decision support results to patients	−	−	−	−	−	−	−	**0 (0)**	−	−	−	−	−	−	−	−	−	**0 (0)**
Periodic performance feedback	−	−	−	+	−	−	−	**1 (14)**	−	−	−	−	−	−	−	−	−	**0 (0)**
CDSS accompanied by conventional education	−	−	−	+	−	−	−	**1 (14)**	−	−	?	+	+	−	−	−	−	**2 (22)**
Support for CDSS use	+	−	−	−	+	−	−	**2 (29)**	+[b]	+	−	+	+	+	+	−	−	**6 (67)**
Monitoring of unintended effects of CDSS	−	−	−	−	+	−	−	**1 (14)**	−	−	−	+	−	−	−	+	−	**2 (22)**
Clear incentives for use	−	−	−	−	−	−	−	**0 (0)**	−	−	−	−	−	−	−	−	−	**0 (0)**
TOTAL NUMBER OF FEATURES PER STUDY	**10**	**6**	**9**	**7**	**10**	**8**	**2**		**6**	**11**	**9**	**14**	**9**	**7**	**8**	**9**	**9**	
MEDIAN NUMBER OF FEATURES (RANGE)	**8 (2-10)**								**9 (6-14)**									

EMR: electronic medical record, CPOE: computerized provider order entry, rec: recommendation, −: absence of feature, +: presence of feature, ?: unclear.
*Significant improvement in 1ary outcome (practitioner performance).
[a]4 of 13 intervention practices justified reasons for deviating from recommendations (but pooled analysis).
[b]7 of 15 clinics received academic detailing (no improved effect).

included studies. CDSS were mainly designed to tackle the issues of anticoagulation underuse and drug-drug interactions. Most systems provided specific recommendations automatically, at the time and location of decision making. However, the small number and the heterogeneity of studies, the limited impact and the risk of bias preclude general conclusions regarding the impact of CDSS on oral anticoagulant prescribing. Moreover, the effect on clinical outcomes remains unclear.

Consistently with previous more general reviews (including CDSS for diagnosis, for prevention, or for the prescription of any drug), our results show positive impact on practitioner performance in over half of the studies (56%). In 2005, Garg and colleagues demonstrated that CDSS improved practitioner performance in 64% of 97 controlled trials [15]. Similarly, a systematic review investigating CDSS for drug prescribing revealed improvement in process of care outcomes in 63% of 59 studies [14]. Although an important quality of care outcome [48], adherence to guidelines may not translate into patient benefit. In this review, only 2 studies explored the impact of CDSS on clinical outcomes [32,33], with no statistically significant influence on the rate of thromboembolic events. However, these studies showed no or minimal changes in guidelines adherence and were not powered for the detection of clinical events.

A difficulty encountered when conducting this systematic review was the heterogeneity of outcomes, limiting the comparability of studies [49]. Future work should focus on developing core outcome sets (COS) for interventions to improve anticoagulant prescribing [50,51]. The appropriateness of oral anticoagulant therapy appears a relevant process-related outcome and should be measured using comprehensive instruments such as the Medication Appropriateness Index [52,53]. To assess CDSS effect on clinical outcomes like ADR or drug-related hospital admissions, studies with a larger sample size and a longer follow-up period are needed. Cluster RCT, recommended to avoid contamination bias, are nevertheless unlikely to be performed on that scale given the considerable time and resources they would require [15].

This systematic review highlighted a shift over time from CDSS for the management of warfarin-drug interactions (4 studies in 2006–2010 [41–44]) to notifications regarding the indication of anticoagulation (9 studies in 2015–2018 [32–34,37,39,40,45–47]). Although oral anticoagulants are strongly recommended in AF patients at high risk of stroke, their underuse remains substantial and represents a key safety issue [1,11,54]. It is therefore not surprising that CDSS moved in that direction. However, none CDSS provided recommendations regarding the choice between VKA and DOAC or among DOAC. In a previous analysis, we have shown that prescribing issues were frequently involved in serious ADRs related to the use of oral anticoagulants [10]. It included inadequate drug choice or DOAC dose, or pharmacodynamics interactions. Therefore, CDSS for selecting the most appropriate oral anticoagulant, tailored to patient characteristics, should be developed. It is also definitely worth integrating alerts in CPOE systems to notify prescribers of DOAC doses not adapted to renal function, or to manage DOAC-drug interactions. Data on CDSS focusing on DOAC are still sparse, possibly given the more recent advent of these drugs on the market. The Canadian IMPACT-AF randomized trial is currently investigating a CDSS that provides individualized medication and dosage recommendations, with VKA and DOAC as therapeutic options [55,56]. In the same way, an Australian decision support tool integrating DOAC (CARATv2.0) has been pilot-tested to assist the selection of antithrombotic therapy [57].

As CDSS interventions improved process outcomes inconsistently, we may ask which characteristics are essential to ensure success. Several meta-regression analyses were carried out for that purpose. They were nevertheless constrained by the limited number of good quality studies and the lack of consistent and systematic report of CDSS characteristics [58]. Kawamoto and Lobach identified 4 independent predictors of improved clinical practice: automatic provision as part of physician workflow, recommendations viewed by the prescriber directly on the computer screen, provision of a recommendation (not just an assessment), and provision at time and location of decision making [19,59]. These characteristics were highly prevalent for the CDSS we investigated (75 to 94%), similarly to previous reports [19,20]. Two thirds of our included studies combined all 4 features, but proportions were identical whether or not a significant effect of CDSS intervention was proved. This suggests that other content or implementation characteristics play a pivotal role in CDSS effectiveness. Six other successful features were identified in 2012, such as the lack of additional data entry or the involvement of local users [59]. On the contrary, having to click many times to access information could negatively influence CDSS effects in a context of click burden and physician burnout [60]. In 11 studies, decision support was integrated with electronic records or prescribing. CPOE + CDSS systems have been increasingly implemented as a patient safety strategy and were reported to reduce prescribing errors [61]. However, in two previous systematic reviews, integrated CDSS were less likely to be effective compared to stand-alone systems [14,62]. Reasons advanced for this apparent paradox include the phenomenon of alert fatigue, which can easily arise in integrated systems when many alerts are added. This is illustrated in 2 included studies [37,40], showing no significant effect of CDSS not restricted to the prescribing of oral anticoagulants.

One striking finding was the low usage of CDSS – between 5 and 30% for the 3 studies reporting this outcome [34,37,39]. Arts and colleague have recently carried out a mixed method evaluation to gain a better understanding of this issue [63]. They found that 60% of physicians stopped using their primary care CDSS during the study period. Shortage of time was a main barrier, especially as notifications were often not related to the patient's reason for consultation. In such cases, planning a follow-up visit dedicated to the management of oral anticoagulation could be suggested and reminded by the CDSS. This is especially important for DOAC patients for whom clinical follow-up seems overlooked due to the lack of regular therapeutic monitoring [64]. Besides a high intensity of alerts, irrelevant recommendations are also significant discouraging factors [65,66]. Future work is needed to determine the clinical relevance of drug-drug interactions (DDI) with DOAC (e.g. statins, bisoprolol) [67,68]. In recent years the concept of context-aware DDI alerts has emerged, integrating patient-specific data for risk assessment [69,70]. Applied to oral anticoagulants, this would, for instance, restrict notifications for pharmacodynamics interactions to patients with other risk factors for bleeding [71].

There is growing acceptance that an effective CDSS implementation is as important as a relevant and accurate content [72]. The GUIDES checklist, headed by the Norwegian Institute of Public Health, has recently been developed to help professionals implement CDSS successfully [73]. According to this tool, key factors affecting CDSS integration include a clear communication and training sessions, an assessment of barriers and facilitating factors, and feedback and monitoring to detect CDSS malfunctions. In this review, we observed a trend towards a higher prevalence of support for CDSS use in successful studies. This hypothesis remains nevertheless to be confirmed, given the small number of trials. Only 3 studies mentioned monitoring procedures for unintended consequences. The alarming frequency of CDSS malfunctions and the risk of e-iatrogenesis have been clearly highlighted in previous reports, but often remain undetected [74–76]. Finally, targeting the right user is essential when designing effective CDSS interventions [77]. In our review, CDSS for the prescribing of oral anticoagulants were equally assessed in primary care and hospital settings. Interestingly, Eckman and colleagues considered targeting cardiologists or clinical pharmacists in addition to primary care physicians, as the latter indicated they were not taking decisions about anticoagulation [39]. On the contrary, Weir and colleagues hypothesized that their CDSS may have greater utility in primary care as physicians have less experience of anticoagulation [36].

This systematic review has several limitations. First we limited our search strategy to full-text papers published in English. We cannot exclude publications in other languages, even though 93% of Medline

records were in English. Publication bias may also have influenced results. However, we searched the trial register clinicaltrials.gov and contacted authors of registered studies without subsequent publication. Second, in order to limit variability in interventions and outcome measurements, we focused on CDSS designed to influence the prescriber only. The incorporation of patient preferences into antithrombotic therapy decisions is increasingly emphasized [78,79]. As an example, the “Excellence in anticoagulation care” guidance from the National Health Service (NHS) recommends that all decisions should be made in partnership with patients [80]. In 2017, O'Neill and colleagues systematically reviewed patient decision aids for stroke prevention in AF [81]. Most interventions were educational booklets that were viewed outside the clinical visit.

5. Conclusion

This systematic review suggests that CDSS might positively impact the use of oral anticoagulants in AF patients at high risk of stroke. The scope of CDSS should now evolve to assist prescribers in the choice of the most appropriate medication, tailored to patient characteristics. Systems included several potentially successful features. However, efforts should be made to improve the relevance and accuracy of notifications, and address implementation outcomes. Future research is needed to evaluate the impact of CDSS tackling the misuse of DOAC on prescribing appropriateness.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.12.023.

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