Patient Preference and Adherence

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REVIEW

Electronic Monitoring of Medication Adherence to Direct Oral Anticoagulants: A Systematic Review

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Abstract: Strict medication adherence, which reflects the process by which patients take their medication as prescribed, is crucial for the use of direct oral anticoagulants (DOACs). Therefore, technological devices may serve as promising tools for assessing adherence. We aimed to systematically review the literature focusing on electronically monitored adherence (EMA) to DOACs. All studies indexed in EMBASE, Cochrane Library, MEDLINE, Scopus, and Web of Science from inception until September 1, 2023, were searched. Original studies targeting the query topics were included, findings were categorized and narratively synthetized. Adherence data, including the quality of data reporting bias, were evaluated using the EMERGE guideline. The review protocol was registered in the PROSPERO database (ID CRD42023441161). Out of the 5911 potential hits, 19 articles, comprising 15 research studies, were identified. These studies enrolled 4163 patients (median 72.1 years; 57.9% males), usually chronically treated with DOACs for atrial fibrillation. EMA was measured in 3451 patients by seven different devices from eight manufacturers; the median population tracked with electronic monitoring was 56 patients over 5 months per study. Observational studies resulted in 88.6% and interventional studies resulted in 92.5% of EMA to DOACs, mostly monitoring regimen and taking adherence. Two studies reported high-quality adherence data, whereas 11 reported low-quality adherence data. The item described in the EMERGE guideline as affecting adherence by measurement method, as appropriate, has rarely been addressed. This review broadens the understanding of the overall high EMA to DOACs reported across various study populations and designs. Furthermore, due to the identified gaps in current literature, it highlights the pressing need for standardized methodologies and improved adherence reporting. This study was supported by the GAUK 328322 and SVV 220665.

Keywords: anticoagulants, atrial fibrillation, bias, electronics, implementation, medication adherence

Introduction

Direct oral anticoagulants (DOACs) are currently considered to have some advantages over vitamin K antagonists, such as more stable therapeutic effects and fewer frequent interactions.[1] However, other characteristics of DOACs (eg, rapid onset or relatively short duration of action) may reflect medication adherence problems in some patients. Still, strict medication adherence (the process by which patients take their medications as prescribed, comprising initiation, implementation, and discontinuation)[2] is crucial in DOACs treatment.[3]

Consequently, precise assessment of adherence to DOACs is required. Although various methods are already available, including self-reported questionnaires, laboratory drug monitoring, and pharmacy refill data, each has some limitations; thus, a universally accepted and scientifically preferred method is still missing. Nevertheless, an increasing trend has been observed in the use of electronic monitoring (EM) devices to assess adherence, and some authors consider EM the most objective method for measuring adherence. This method has been intensively studied and has also shown great potential in enhancing medication adherence.[4–9]

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In light of its increasing utilization,[10] the importance of medication adherence support for DOACs has been extensively discussed even in professional guidelines.[1] According to the required strict dosing regimen of DOACs preventing patients from bleeding and/or thromboembolic events (eg, stroke, pulmonary embolism, etc), EM might serve as an appropriate method because it reflects the timing.[11] A recent meta-analysis revealed suboptimal medication adherence in patients with atrial fibrillation.[12] Non-adherence to DOACs can lead to unsatisfactory anticoagulation effect and worsened health-related outcomes.[12,13] The review excluded questionnaires and EM,[12] which is also reflected in the fragmented literature regarding electronically monitored medication adherence (EMA) data.[12,13]

Considering the low number of studies summarizing the extent of medication adherence measured using EM devices, our primary objective was to perform a systematic review to analyze the reported adherence data measured by EM on diverse populations of outpatients taking DOACs in relation to the implementation phase of adherence (extent to which a patient's actual dosing corresponds to the prescribed dosing regimen);[2] persistence (length of time between initiation and the last dose, which immediately precedes discontinuation);[2] and finally, to determine the quality of reporting adherence data in the included articles.

Methods

Information Sources

A literature search was conducted using the EMBASE, Cochrane Library, MEDLINE, Scopus, and Web of Science databases. Records published before September 1, 2023, were included, except those of EMBASE, a database accessed by our institution before March 23, 2022. This manuscript was written following the PRISMA guideline,[14] and appropriately reflected the EMERGE guideline.[15] The systematic review protocol was registered in the PROSPERO database (ID CRD42023441161; see *1 Registration* in the Supplementary Material 1).

Search Strategy

No language or other restrictions were applied in the database search. The query targeted the following three topics: (1) medication adherence, AND (2) medicines, AND (3) monitoring. The search topics included a combination of MeSH terms and relevant keywords, using descriptor OR: topic (1) comprised "medication adherence", "medication compliance", "patient compliance"; topic (2) comprised "apixaban", "dabigatran", "edoxaban", "rivaroxaban", "DOAC", "NOAC"; topic (3) comprised "patient monitoring", "drug monitoring", "electronic monitoring", "medication adherence monitoring system", "medication event monitoring system", "eHealth", "e-Health", "e Health", "teleHealth", "medical technologies", "medical technology", and "adherence technology". All databases were screened using the same search query (see *2 Search methods* in Supplementary Material 1).

Eligibility Criteria

To be considered eligible, the identified articles had to meet the criteria of being written in English while reporting the measurement of medication adherence to DOACs, regardless of the study design or population characteristics. Only original peer-reviewed articles investigating EMA were included in the analysis. Although monitoring medication adherence was not the primary outcome of the articles searched, adherence measures were required to be provided in the full-text, attachments, or supplements for inclusion. Therefore, literature reviews, protocols, and study registrations were excluded from analysis.

Selection Process

The initial screening phase consisted of database searches, excluding duplicates, and identification of records that matched the eligibility criteria based on the title and abstract by a single investigator (E.M.). Automation tools were not used during this process. To mitigate bias, articles from our previously published literature review[16] and references of records resulting from the initial screening were also checked according to the eligibility criteria.

The second phase of the search was comprised of a full-text review. To avoid selection bias, two investigators (E. M. and S.S.) independently screened the selected full-texts. In case of disagreement, a third investigator (K.M.L.). resolved whether the debated article met the eligibility criteria.

Finally, appropriate data collection and outcome evaluations were performed according to study design and population characteristics.

Data Collection and Analysis

The collected data items were categorized into several groups: general information, pre-enrolment data, medication adherence details, and study results (see *3 Data items* in the Supplementary Material 1). The listed data were drawn from the articles by the first investigator and their accuracy was verified by a second investigator.

A narrative synthesis of the findings was prepared to summarize the results using descriptive statistics. Tables and schemes were created using Microsoft Office. The numerical values were extracted from the identified articles with respect to the units and statistics used in the studies. Although EM can affect adherence, while data describing both implementation phase of adherence and persistence are usually regarded as non-normally distributed variables, medication adherence was frequently reported as a mean value. Therefore, the EMA values were preferably assessed as means. In cases with missing means, medians were derived by the investigators. The preferred method for presenting EMA was regimen adherence (proportion of days with the correct number of doses taken) followed by schedule adherence (percentage of doses taken within a predefined time) because EM offers the possibility to track the date and time of medication use. Taking adherence (percentage of prescribed doses taken) was used if data for the previous two methods were missing. The summarized EMA values are graphically shown. For this purpose, clinically meaningful thresholds for EMA to DOACs were set at 90%[17–19] and 95%,[17,20] respectively. No further meta-analysis was conducted since high heterogeneity among the identified studies was anticipated.

Whenever unclear or ambiguous data were obtained, a thorough discussion was held within the group of investigators. In certain cases, such as missing relevant information and severe difficulties in pursuing deeper analysis or data clarification, the authors of the identified articles were consulted.

Qualitative Evaluation

EMERGE guideline, designed for reporting of medication adherence research studies as an addition to the existing guidelines for health research reporting utilizing ABC Taxonomy,[2] was used to assess the quality of medication adherence data reporting.[15] Articles were analyzed to determine whether they reflected the four items of the minimum reporting criteria, how accurately they depicted the other 17 items of the EMERGE guideline, and whether they applied ABC Taxonomy.[2] The quality assessment was performed by two reviewers independently (E.M., S.S.), and discrepancies were discussed with a third investigator (K.M.L.). until agreement was reached.

If an article could not be scored according to EMERGE recommendations (eg, items suggested for interventional articles could not be applied to observational articles), such items were considered not applicable. The points were distributed as follows: 2 points (strong evidence) for well-defined items, 1 point (moderate evidence) for not clearly specified items or items listed in a section other than the recommended section of an article, and 0 points (weak evidence) for missing items according to EMERGE.

The final score classified the articles into three levels: high-quality articles with well-described methodology and a low risk of reporting medication adherence bias (81–100% without weak points), moderate-quality articles reflecting good methodology with acceptable limitations in reporting medication adherence bias (51–80% scoring or >80% with only one weak point), and low-quality articles with some reliability but also significant limitations in reporting medication adherence bias (≤50% scoring or with two or more weak points).

Results

Study Selection and Characteristics

During the initial screening phase, a total of 5911 potential hits were identified. These comprised 3104 articles identified by the database search, 2782 references cited in the articles selected for the second review phase, and 25 articles found in

the previously published review (Figure 1).[16] Of those, 109 articles were suitable for full-text analysis. Disagreements were resolved by a third investigator in four instances. These studies were eventually found to be ineligible for final evaluation due to one of the following reasons: missing medication adherence values,[21] not investigating EMA,[22] study protocols,[23] or study registrations.[24] A total of 19 articles[20,25–42] published between 2012 and 2023 were included into the final analysis (Table 1). Eleven articles had interventional study design.[28–37] In four articles[26,29,32,40] EMA was not considered a primary outcome.

The 19 included articles reported data from 15 various research studies conducted in nine countries (mostly from Belgium,[29,31,33–36] Spain,[20,25,26,30,33] and Switzerland[33,38–41]). Four studies were demonstrated in two separate articles, which resulted in repeated adherence data (CUMRIVAFA,[25,26] SMAAP-AF,[27,28] a study by Toscos et al,[34,35] and MAAESTRO[38,39]).

A total of 4163 patients (median 67; IQR 31–412) from hospital or outpatient care settings,[20,27–29,32,39,41,42] visiting pharmacies,[27,28,40,41] or specialized care centers[25,26,30] were enrolled. The shortest study design lasted for one month,[40,42] and the longest 15 months[36] (median 5.0 months; IQR 2.8–11.0). The median dropout rate was 11.0% (IQR 7.5–13.9%). At baseline, the patients were mostly retired (median 72.1 years; IQR 69.2–75.2), males (mean 57.9%; SD±8.9%), and usually taking DOACs chronically.[20,25–32,34–37,40] The most commonly investigated medications were apixaban[20,27–29,31–40] and rivaroxaban,[20,25,26,29,31,32,34–41] both of which were involved in 11 studies. Atrial fibrillation was the most common diagnosis.[20,25–36] Five articles declared no conflicts of interest or funding from pharmaceutical companies that produce DOACs.[37–40,42]

Medication Adherence Data

EMA was measured in 3451 of the entire study population (82.9%) for the total of a seven-year period. The median population tracked with EM was 56 patients (IQR 27–370), followed up for a median of 5.0 months (IQR 2.8–9.0 months) per study. Five studies included patients with various antithrombotic treatments (eg, vitamin K antagonists and antiplatelet medication)[20,32,34–37] however, there were no separate EMA values provided for each treatment group by Toscos et al,[34,35] AF-EduApp.[36]

The overall EMA in the observation groups was 88.6% (Figure 2). Specifically, the EMA of patients in studies with an observational design was 91.4%, whereas that of control groups in interventional studies was 86.3%. The EMA of the

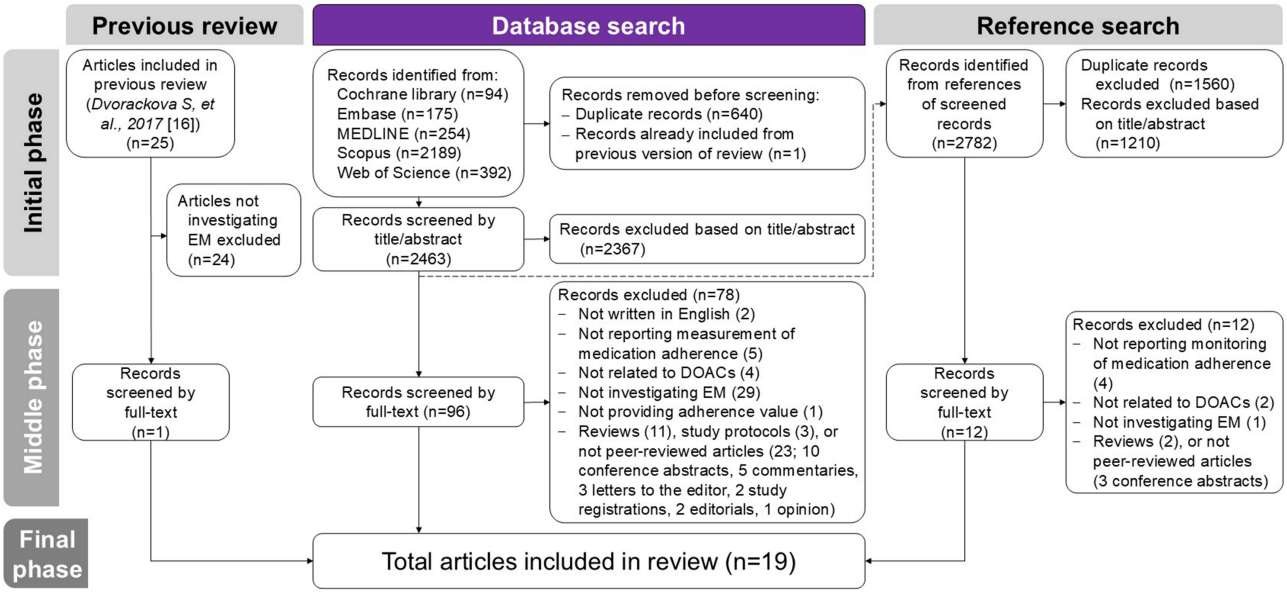

Figure 1 Flow diagram of selection process of included articles. Adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021; 372:n71. Creative Commons.[14]
Abbreviations: DOACs, direct oral anticoagulants; EM, electronic monitoring.

Table 1 Summary of Study Characteristics (n=19)

Author, Year	Study Name and Design	Medication	Enrolled Patients	Population (Country, Age, Gender)	Aim Related to EMA	Other Adherence Method Used
Atrial fibrillation						
Marquez-Contreras E. et al, 2016[25]	CUMRIVAFA observational prospective study	R (Chronic users)	412 (10.2% dropout)	Spain; 75.2 ± 7.5 yrs; 47% men	**Primary**: To assess EMA	—
Marquez-Contreras E. et al, 2017[26]	CUMRIVAFA observational prospective study	R (Chronic users)	412 (10.2% dropout)	Spain; 75.2 ± 7.5 yrs; 47% men	**Primary**: To assess quality of life related to EMA	—
Solla-Ruiz I. et al, 2019[20]	ACO-MEMS observational prospective study	A, D, R, VKA (Chronic users)	304 (15.5% dropout) of which 152 on DOACs	Spain; **DOAC**: 74.3 ± 6.5 yrs, 61.4% men; **VKA**: 71.7 ± 8.3 yrs, 63.2% men	**Primary**: To compare EMA between VKA and DOAC	—
Shiga T. et al, 2021[27]	SMAAP-AF observationa l prospective study	A, E (Chronic users)	301 (11% dropout) of which 175 A and 126 E	Japan; **A**: 76 (66–80) yrs, 61% men; **E**: 75 (69–79) yrs, 61% men	**Primary**: To assess EMA	—
Desteghe L. et al, 2017[29]	Interventional feasibility uncontrolled trial	A, R, (D included but not measured by EM) (All users)	15	Belgium; 69.2 ± 3.7 yrs; 66.7% men	**Primary**: To assess feasibility and usability of the app; **Secondary**: To evaluate the effect of the app on EMA and knowledge level	Pill count; Questionnaire
Desteghe L. et al, 2018[31]	Interventional crossover randomized controlled trial	A, R (All users)	48 of which 24 A and 24 R	Belgium; 71.6 ± 8.6 yrs; 50.0% men (**Intervention group**: NA; **Control group**: NA)	**Primary**: To evaluate the effect of feedback on EMA based on telemonitoring of medication intake	Pill count; Questionnaire
Marquez-Contreras E. et al, 2018[30]	FACILITA interventional randomized controlled trial	D (Chronic users)	726 (13.9% dropout) of which 363 in intervention and 363 in control	Spain; 73.42 ± 8.4 yrs; 49.4% men (**Intervention group**: 73.5 ± 8.3 yrs, 51.4% men; **Control group**: 73.3 ± 8.5 yrs, 49.7% men)	**Primary**: To evaluate the effect of educational intervention and reminder calendar on EMA	Reminder calendar

(*Continued*)

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Table 1 (Continued).

Author, Year	Study Name and Design	Medication	Enrolled Patients	Population (Country, Age, Gender)	Aim Related to EMA	Other Adherence Method Used
Desteghe L. et al, 2019[32]	Interventional randomized controlled trial	A, R (D, APT, VKA included but not measured by EM) (All users)	67 (7.5% dropout) of which 33 in intervention and 34 in control; 46 from 67 on DOACs of which 23 in intervention and 23 in control	Belgium; 72.1 ± 8.6 yrs; 62.7% men (**Intervention group**: 71.5 ± 9.3 yrs, 60.6% men; **Control group**: 72.7 ± 8.1 yrs, 64.7% men)	**Primary**: To evaluate the effect of educational intervention on knowledge level; **Secondary**: To explore its influence on EMA, quality of life and symptom burden	Pill count
Montalescot G. et al, 2020[33]	AEGEAN interventional IV phase randomized controlled trial	A (New users)	1162 (13.7% dropout) of which 579 in intervention and 583 in control	Belgium, France, Germany, Italy, Spain, Switzerland, United Kingdom (**Intervention group**: 73.1 ± 9.1 yrs, 59.6% men; **Control group**: 72.6 ± 8.9 yrs, 60.2% men)	**Primary**: To evaluate the effect of educational intervention on EMA	—
Toscos T. et al, 2020[34]	Interventional randomized controlled trial	A, R, W (Chronic users)	160 (5.0% dropout) of which 80 in intervention and 80 in control; 80 from 160 on DOACs	USA; 71.1 ± 8.5 yrs ; 62.5% men (**Intervention group**: NA; **Control group**: NA)	**Primary**: To assess EMA across two technologies	Pharmacy refill data
Toscos T. et al, 2020[35]	Interventional randomized controlled trial	A, E, R, W (Chronic users)	160 of which 80 in intervention and 80 in control; 80 from 160 on DOACs	USA; 71.1 ± 8.5 yrs ; 62.5% men (**Intervention group**: NA; **Control group**: NA)	**Primary**:T o evaluate the effect of educational intervention on EMA and disease knowledge	Pharmacy refill data
Shiga T. et al, 2022[28]	SMAAP-AF interventional randomized controlled trial	A, E (Chronic users)	268 (11.2% dropout) of which 134 in intervention and 134 in control	Japan (**Intervention group**: 73 ± 9 yrs, 60.0% men; **Control group**: 73 ± 10 yrs, 62.0% men)	**Primary**: To evaluate the effect of educational intervention on EMA	—
Knaepen L. et al, 2023[36]	AF-EduApp interventional randomized controlled trial	A, D, E, R, VKA (Chronic users)	768 of which 677 in intervention and 91 in control; 689 from 768 on DOACs	Belgium; 70.1 ± 7.9 yrs; 69.7% men (**Intervention group**: 70.1 ± 8.0 yrs, 69.7% men; **Control group**: 70.2 ± 7.6 yrs, 69.2% men)	**Primary**: To evaluate the effect of educational interventions on EMA	Pill count

Other indications for DOACs use						
Albert V. et al, 2021[38]	MAAESTRO observational prospective study	Stroke; A, D, E, R (All users)	61 (32.8% dropout)	Switzerland; 77.0 (IQR 69.0–84.0) yrs; 63.4% men	**Primary**: To assess EMA and to propose adherence metrics related to EMA	—
Dietrich F. et al, 2022[39]	MAAESTRO observational prospective study	Stroke; A, D, E, R (All users)	8	Switzerland; 81.5 (IQR 74.8–84.5) yrs; 62.5% men	**Primary**: To assess EMA before and after lockdown during COVID-19	—
Labovitz DL. et al, 2017[37]	Interventional randomized controlled trial	Stroke; A, D, R, W (Chronic users)	28 (3.6% dropout) of which 15 in intervention and 13 in control; 19 on DOACs	USA; 57.0 ± 13.2 yrs; 46% men (**Intervention group**: 58.3 ± 9.8 yrs, 60% men; **Control group**: 55.5 ± 16.6 yrs, 31% men)	**Primary**: To evaluate the effect of artificial intelligence on EMA	Laboratory monitoring; Pill count
Albert V. et al, 2022[40]	INPOLYMA observational prospective qualitative study	Atrial fibrillation, Deep vein thrombosis, Pulmonary embolism; A, D, E, R (Chronic users)	18	Switzerland; 77.5 (IQR 75.0–86.5) yrs; 38.9% men	**Primary**: To explore medication management strategies; **Secondary**: To assess EMA	—
Dotta-Celio J. et al, 2019[41]	RIVA observational prospective study	Deep vein thrombosis; R (New users)	31 (12.9% dropout)	Switzerland; 47.0 ± 13.5 yrs; 67.7% men	**Primary**: To assess EMA	Pill count
Lebel B. et al, 2012[42]	Observational prospective study	Total hip replacement; D (New users)	62 (9.7% dropout)	France; 60 ± 9.8 yrs; 60.7% men	**Primary**: To assess EMA	—

Note: Articles are sorted by the indication for DOACs use, following by study design, and listed chronologically within each group.
Abbreviations: A, apixaban; APT, antiplatelet therapy; D, dabigatran; DOACs, direct oral anticoagulants; E, edoxaban; EM, electronic monitoring; EMA, electronically monitored medication adherence; IQR, interquartile range; R, rivaroxaban; VKA, vitamin K antagonists; W, warfarin; yrs, years (if not specified, described as mean/median and standard deviation).

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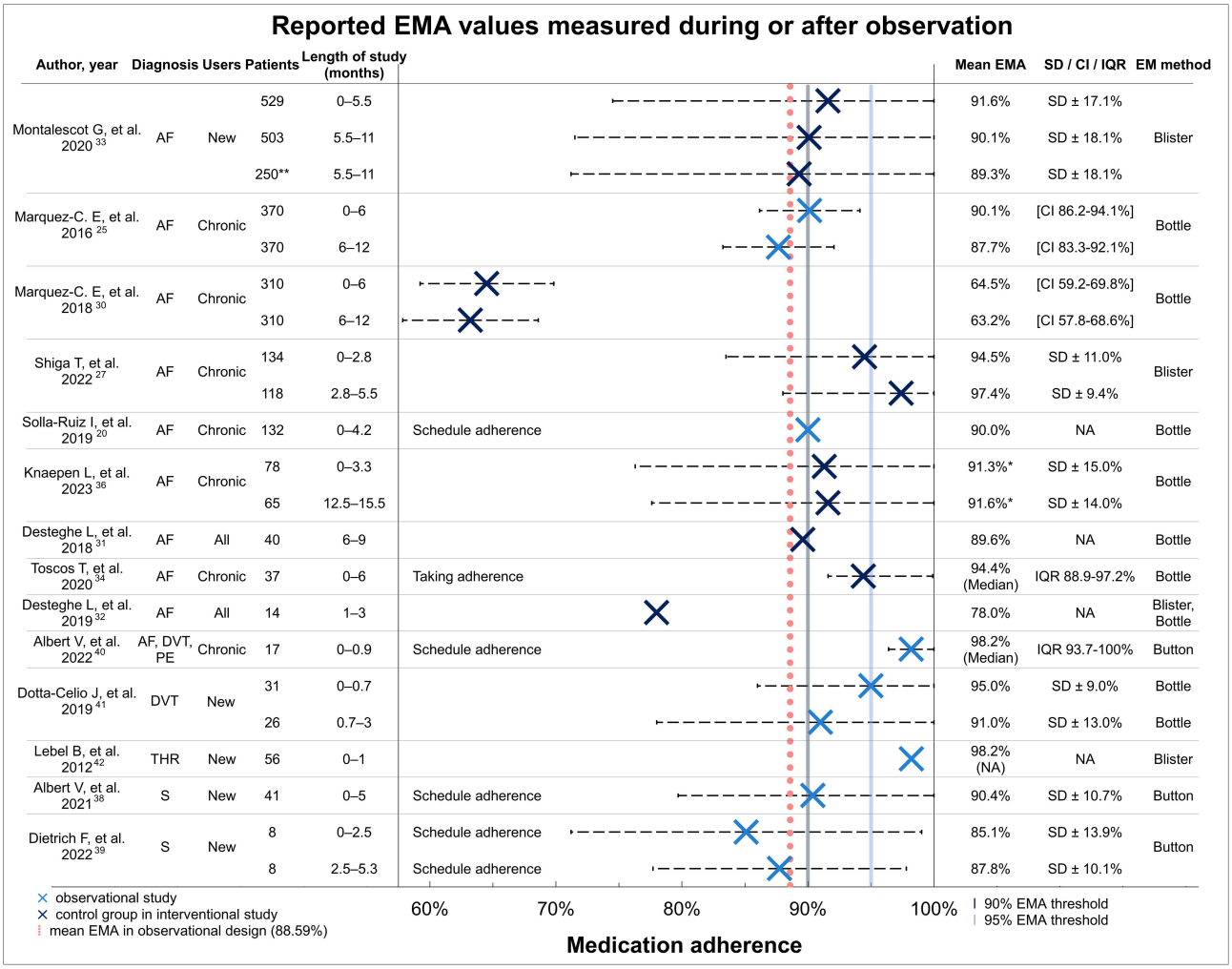

Figure 2 EMA values measured during or after observation.

Notes: * – EMA reported for DOACs and VKA as one value; ** – patients after educational program randomized to standard-of-care. If not specified, EMA was reported as mean regimen adherence.

Abbreviations: AF, atrial fibrillation; Blister, blister pack or sleeve; Bottle, bottle container or cap; Button, button device; CI, confidence interval; DVT, deep vein thrombosis; EM, electronic monitoring; EMA, electronically monitored medication adherence; IQR, interquartile range; NA, not available; PE, pulmonary embolism; S, stroke; SD, standard deviation; THR, total hip replacement.

interventional cohorts was 92.5% (Figure 3). Five studies comprised[31,33–37] direct patient feedback from research personnel or EM device notifications addressing DOACs implementation phase of adherence.

To avoid duplicate reporting,[25,27,34] the EMA outcomes of CUMRIVAFA,[26] SMAAP-AF,[28] and Toscos et al[35] were excluded from Figures 2 and 3. However, both MAAESTRO articles[38,39] analyzing different subsets of the same population were included (Figure 2).

A threshold of >80% for sufficient EMA was set in CUMRIVAFA,[25,26] FACILITA,[30] and AF-EduApp[36] without any justification. SMAAP-AF[27,28] defined thresholds based on the proportion of days covered as follows: >80% for "usual adherence" related to warfarin and >90% as a "strict adherence" associated with DOACs.

In 12 articles, the most frequently used strategy for reporting EMA was the combination of taking adherence and regimen adherence.[25–33,36,41,42] Schedule adherence has been defined in three distinct ways: 1. Doses administered within ±25% of the median intake time;[38–40] 2. Doses taken no more than a two-hour difference from the prescribed time;[20] 3. Doses taken within prescribed time windows (eg, 7–9 A.M., 9–11 P.M.).[25,26,30] While these articles[25,26,30] reported regimen, schedule, and taking adherence values, Toscos et al[34,35] presented EMA only as taking adherence values, and Labovitz et al[37] did not specify the method of computation of adherence outcomes. On the other hand, both adjusted the

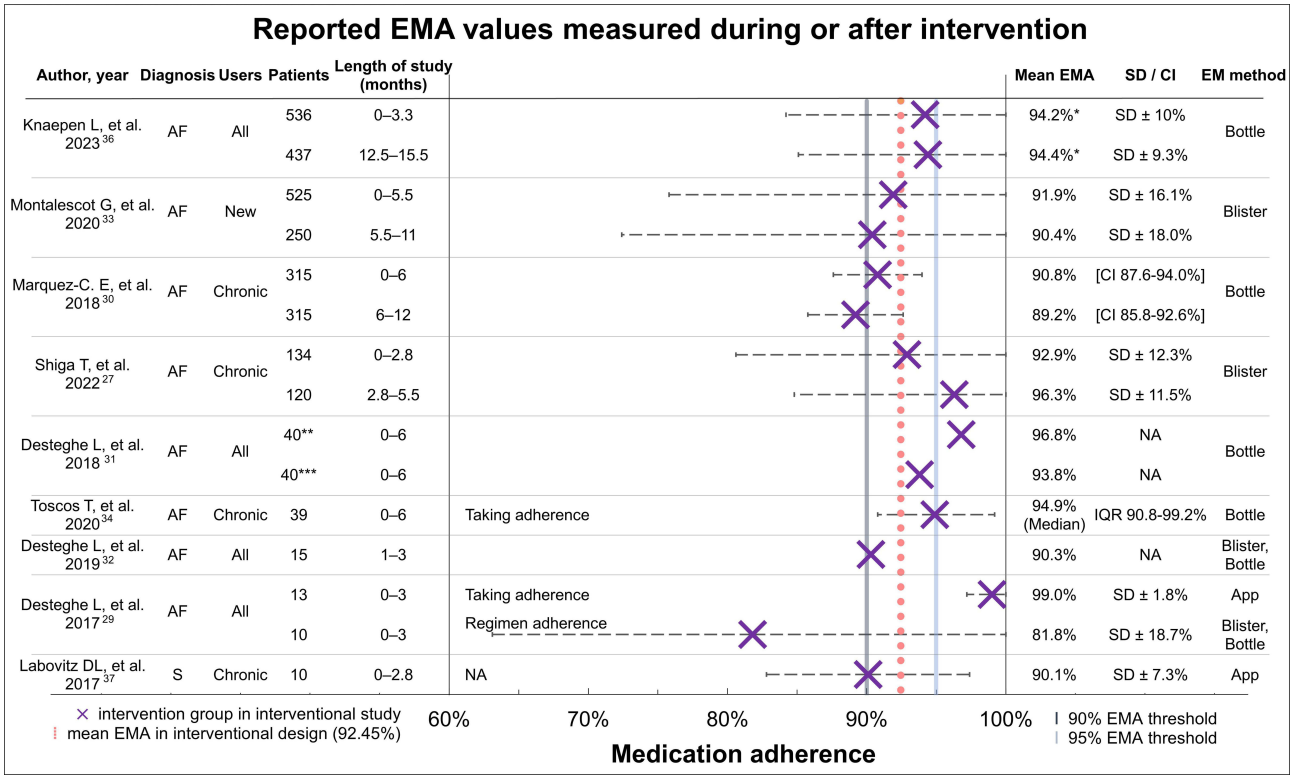

Figure 3 EMA values measured during or after intervention.

Notes: * – EMA reported for DOACs and VKA as one value; ** – intervention 1 (telemonitoring + feedback); *** – intervention 2 (telemonitoring), If not specified, EMA was reported as mean regimen adherence.

Abbreviations: AF, atrial fibrillation; App, mobile application; Blister, blister pack or sleeve; Bottle, bottle container or cap; CI, confidence interval; EM, electronic monitoring; EMA, electronically monitored medication adherence; IQR, interquartile range; NA, not available; S, stroke; SD, standard deviation.

EMA values according to the patients' feedback about missing or not taking medication.[34,35,37] Besides implementation phase of adherence and persistence,[41] other adherence metrics such as overcompliance (taking daily more than 2 capsules of dabigatran[42]) and the number of unprotected days (≥3 or ≥1 consecutively missed doses for twice daily or once daily dosing,[31,32] or excess doses during the prior 24 hours[36]) were also reported.

Eight studies applied a multi-approach examination of medication adherence using pill counts, pharmacy refill data, self-reported questionnaires, laboratory monitoring, and a reminder calendar.[29–32,34–37,41] Despite that, only the FACILITA[30] and AF-EduApp[36] compared the findings and reported the value of overestimation of EMA levels (Table 2). One observational study[41] and four interventional studies[29,31,32,37] collecting pill count data did not present any possible misestimations in reflection with EMA (difference between the two methods). Whenever misestimations of the EMA existed, they ranged from 1.1 to 14.7%.

Four types of EM produced by eight different manufacturers were used (Table 3). Most frequently, they were smart pill bottles,[20,25,26,29–32,34,35,41] followed by blister packs,[27–29,32,33,42] button devices,[38–40] and mobile applications.[29,37] Desteghe et al utilized mobile application[29] as well as two different devices for monitoring of specific DOACs medication.[29,32] Conversely, one of the CUMRIVAFA articles did not specify the type of EM method used.[26] The articles reported EM to be effective and an easy-to-use method[31,34] for longitudinal, real-life measurement of exact intake time,[20,25,27–34,37,38,41,42] with the possibility to describe the dynamics of adherence (ie, morning vs evening doses, beginning vs end of the monitoring),[40,41] and to correct irregularities reported by patients.[31,36] Some of the pointed-out limitations comprised the necessity of patient cooperation and acceptance of the device,[27,28,34,40,41] deviation from routine medication intake (eg, extra steps),[34] possible inaccuracy and unreliability (eg, using device is not equal to taking DOACs at the same time if at all, Hawthorne effect, device misuse),[20,25,26,29,30,32–34,36,38,41] and device imperfections (eg, reported technical issues, high cost, limited battery).[25,29,30,34,36,38]

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Table 2 Misestimation of EMA Compared With Other Measuring Methods

Author, year	Misestimation	EMA	Other method	Length of study (months)	Details
Pill count					
Desteghe L. et al, 2017[29]	12.7%	81.8%	94.5%	0–3	—
Labovitz DL. et al, 2017[37]	6.3%	90.1%	96.4%	0–3	Intervention group
	NA	NA	90.9%	0–3	Control group
Desteghe L. et al, 2018[31]	2.3%	96.8%	99.1%	0–6	Group with telemonitoring + feedback
	3.9%	93.8%	97.7%	0–6	Group with telemonitoring only
	7.1%	89.6%	96.7%	6–9	Observational group
Dotta-Celio J. et al, 2019[41]	8%	95%	103%	0–0.7	Group with twice daily regimen
	3%	91%	94%	0.7–3	Group with once daily regimen
Desteghe L. et al, 2019[32]	14.7%	78.0%	92.7%	1–3	Control group
	7.9%	90.3%	98.2%	1–3	Intervention group
Knaepen L. et al, 2023[36]	6%*	98.3%	92.3%	0–3	Standard care group
Pharmacy refill data					
Toscos T. et al, 2020,[34] Toscos T. et al, 2020[35]	2.2%	90.0% adjusted taking adherence	92.2%	0–6	Adherent patients, one value for intervention and control group

Note: Marquez-Contreras E. et al, 2018[30] reported misestimation 1.12%* without further explanation.
Abbreviations: EMA, electronically monitored medication adherence (if not specified, reported as mean regimen adherence); NA, not available; * – values explicitly reported in full-texts.

Table 3 Summary of Electronic Monitoring Devices

Device Name	Recording	Notifications	Details About Monitoring
Smart pill bottle			
MEMS[20,25,29–32,36,41]	Opening of a bottle recorded by bottle cap	• with or without display showing number of openings over 24 h • telemonitoring feedback in case of intake irregularities via phone	• validated method • not suitable for dabigatran (no protection from moisture) • individual bottle refill • used as a regular pillbox • instructions not to open bottle for any other reason than medication intake during monitoring • necessity to place bottle with cap on a wireless reader after each medication intake • blinded outcomes to patients and investigators during the study • corrections of irregularities between intake and recording if needed • pill count assessment at the end of monitoring period • high cost
AdhereTech[34,35]	Opening of a bottle recorded by drug container	• reminder (light, sound) funcionality disabled • alerts send automatically to research team and intervention group	• not suitable for dabigatran (no protection from moisture) • bingo chips for patients to use in weekly pill organizers • instructions not to open bottle for any other reason than medication intake during monitoring • adherence self-tracking account in MyChart • pill count assessment at the end of monitoring period

(*Continued*)

Table 3 (Continued).

Device Name	Recording	Notifications	Details About Monitoring
Blister pack			
Helping Hand[29,32,33]	Removal and reinsertion of blister from blister sleeve	• with or without display showing medication intake	• not suitable for dabigatran (does not fit in the inserting device)
Your Manager[27,28]	Perforation of blister with a card-type press-through-pack	NA	NA
ARB Pharma[42]	Device glued to the blister	NA	NA
Button			
Time4Med[38–40]	Pressing the button	• beeping sound confirming recording of intake	• patients had to replace device every month, obtained via delivery • feedback for patients via dot chart at the end of the study • no adherence values over 100% (even in case of overuse or accidental dupplication)
Mobile device			
AiCure[37]	Visual confirmation by AI, and daily intake self-reported in the app	• dosing instructions • clinic staff recieved alerts in case of missed, late doses and incorrect usage	NA
Health Buddies app[29]	Daily intake self-reported in the app	• info about the need to refill	• developed to target atrial fibrillation patients initiating DOACs with educational aspect • game-like experience • communication with health care professionals if needed • effects on adherence and knowledge improvemenent were limited

Abbreviations: AI, artificial intelligence; DOACs, direct oral anticoagulants; MEMS, medication event monitoring system; NA, not available in any article.

Qualitative Evaluation

Of the 19 articles, 11[20,27,28,33–36,38–41] were published only after the EMERGE guideline were disseminated[15] (Table 4). Two articles with an observational study design[38,41] reflected the EMERGE in reporting their study outcomes, resulting in an overall high-quality evaluation of medication adherence data. Of the 11 studies rated as low-quality papers, one observational[40] and two interventional[34,37] articles were evaluated as low-quality papers because they implemented less than 50% of the recommended 17 items. Articles in which medication adherence was not the primary outcome[26,29,32,40] generally had a poorer quality of adherence data reporting.

The observational articles were more precise at reporting adherence outcomes than the interventional ones (two high-quality, four moderate-quality, and three low-quality articles vs zero, two, and eight, respectively). The most common missing item was 6a (addressing the problem of affecting medication adherence by measurement methods as appropriate).[15] Also, items 5a (describing setting and its relevant factors to medication adherence) and 5b (statement whether medication adherence was an eligibility criterion)[15] were underreported. In most cases, the authors omitted specifying or justifying the exact phases of medication adherence (1a) and neglected to account for the generalizability of their study outcomes with reference to medication adherence (10c).[15]

Regarding interventional studies, the description of routine care related to the management of medication adherence (5c) and the depiction of the implementation strategy (7b)[15] were mostly lacking. With a few exceptions, statistics (8a), non-participation and/or dropout association with non-adherence (9a), discussion of strengths and limits referring to medication adherence (10a), and study findings in the context of existing evidence on medication adherence (10b)[15] were appropriately described.

Among the 18 articles[20,25–41] published after the establishment of the ABC Taxonomy,[2] only five[31,33,38,39,41] implemented the recommended terminology. Furthermore, three articles[25,26,42] used the term "compliance" for reporting adherence values and one article[30] utilized the terms "compliance" and "adherence" interchangeably.

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Table 4 Quality Assessment of Includes Studies Using EMERGE Guideline

Design		Observational									Interventional									
Author, year		Lebel B. et al, 2012[42]	Marquez-C. E. et al, 2016[25] CUMRIVAFA	Marquez-C. E. et al, 2017[26] CUMRIVAFA	Dotta-Celio J. et al, 2019[41] RIVA	Solla-Ruiz I. et al, 2019[20] ACO-MEMS	Albert V. et al, 2021[38] MAAESTRO	Shiga T. et al, 2021[27] SMAAP-AF	Albert V. et al, 2022[40] INPOLYMA	Dietrich F. et al, 2022[39] MAAESTRO	Desteghe L. et al, 2017[29]	Labovitz DL. et al, 2017[37]	Desteghe L. et al, 2018[31]	Marquez-C. E. et al, 2018[30] FACILITA	Desteghe L. et al, 2019[32]	Montalescot G. et al, 2020[33] AEGEAN	Toscos T. et al, 2020[34]	Toscos T. et al, 2020[35]	Shiga T. et al, 2022[28] SMAAP-AF	Knaepen L. et al, 2023[36] AF-EduApp
ABC Taxonomy		X	No	No	Yes	No	Yes	No	No	Yes	No	No	Yes	No	No	Yes	No	No	No	No
EMERGE		X	X	X	Yes	No	Yes	No	No	No	X	X	X	X	X	No	No	No	No	No
Minimum reporting criteria	1a																			
	1b																			
	1c																			
	1d																			
4-items scoring		63%	75%	75%	100%	88%	100%	63%	75%	75%	63%	50%	75%	88%	63%	100%	75%	75%	88%	88%
Quality assessment		M	M	M	H	H	H	M	M	M	M	L	M	H	M	H	M	M	H	H
Abstract	2a																			
Introduction	3a																			
	3b																			
Aim	4a																			
Methods	5a																			
	5b																			
	5c																			
	6a																			
	7a																			
	7b																			
	8a																			
	8b																			
Results	9a																			
	9b																			

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Discussion	10a																		
	10b																		
	10c																		
17-items scoring		58%	77%	68%	96%	77%	81%	69%	45%	77%	67%	38%	69%	78%	50%	72%	47%	50%	66%	75%
Quality assessment		L	M	M	H	M	H	L	L	M	L	L	L	M	L	M	L	L	L	L

Notes: green – 2 points for well included item; H – high (>80%, 0 weaks); orange – 1 point for item included but not described in detail or listed in different section of the article; M – moderate (51–80%, 1 weak); red – 0 points for not including the item at all; L – low (≤50%, 2 or more weaks); grey – not applicable (criterions: study design [observational/interventional] and electronically monitored adherence as primary aim of the article [yes/no]); X – study published before release of ABC Taxonomy or the EMERGE guideline. The colors have been chosen to have enough contrast even for readers with color deficiency or color blindness, as well as in black and white mode.

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Discussion

To the best of our knowledge, this is the first systematic review focused on EMA to DOACs. All eligible literature, according to the inclusion and exclusion criteria, revealed 15 research studies published in 19 articles. The identified studies showed that EM of DOACs treatment was mostly conducted using smart pill bottles to track medication adherence in chronic outpatients with atrial fibrillation.

EM is generally considered to be an objective tool for adherence assessment and is free from subjective influence. This has been confirmed by the increasing number of articles published in the last decade. However, adherence rates can be affected by measurement methods.[15,29,34,43,44] Each technology has specific features;[4] therefore, different approaches to employing EM have made it difficult to compare the outcomes among studies. Some of the identified studies used multiple measuring devices to adjust for different medication requirements.[29,32] Among DOACs, dabigatran is the most storage-demanding medication and must be protected against humidity. Therefore, several studies have not assessed EMA to this drug, despite including patients taking dabigatran in the study population.[29,32] Another study analyzed a proxy medication used concomitantly with dabigatran to measure EMA;[36] however, two others neglected this obligation and inserted patients' medications into the drug container.[20,30]

Similarly to our review, smart pill bottles are the most frequently used devices for various chronic diseases, such as hypertension,[45] diabetes mellitus,[46] or dyslipidaemia.[47] In such studies, EMA was usually analyzed in populations ranging from 100 to 200 patients for 3, 6, or 24 months. Although the length of follow-up was comparable to that of DOACs, surprisingly, the population size of patients on DOACs resulted in a median of <60 patients. Moreover, it is not common to include chronic and new users simultaneously, and yet this has been observed in four DOACs studies.[29,31,32,36] Since a shorter period following diagnosis was found to be a statistically higher risk factor for non-adherence to DOACs,[34] it could have possibly influenced the outcomes. Other factors, including the number of concomitant medications,[25,26,30,38] multiple diseases,[25,26] and male sex[35,48–50] were significantly associated with non-adherence to DOACs. These findings are consistent with our current knowledge of adherence to cardiovascular medications.[48–56]

The EMA to apixaban and rivaroxaban was analyzed most frequently, whereby once and twice daily regimens were analyzed simultaneously.[20,27–29,31,32,34–40] It was shown that patients on once-daily regimen had better adherence than patients using DOACs twice-daily;[38,41] beyond that, adherence was higher in the morning than in the evening.[38] Nonadherence to DOACs with once-daily regimen is generally less forgiving in terms of thrombotic complications than a twice-daily dosing.[13] Nevertheless, no statistical difference in EMA between once-daily and twice-daily regimens has been confirmed in any study.[20,38]

Only the SMAAP-AF study examined the level of medication adherence among all individual DOACs molecules, showing that edoxaban users met the strict adherence threshold of >90% more frequently than apixaban users did.[27] Nevertheless, it is not easy to confirm this result because five other studies enrolling edoxaban users[34–36,38–40] did not report the number of patients using each specific DOACs or the adherence levels for each medication separately. Three studies independently investigating EMA to apixaban,[33] dabigatran,[41] and rivaroxaban[25] during the observation phases showed the lowest adherence to dabigatran.[41] Adherence levels for apixaban[33] exceeded those for rivaroxaban.[25] Similarly to pharmacy refill data, dabigatran users usually have the lowest adherence levels, and apixaban users have the highest adherence levels, with a decline over time and variation across countries.[12,51,57–61] Overall, there is a lack of reports on EMA data separately for individual DOACs in studies that analyze multiple DOACs molecules. Moreover, two studies[34–36] that analyzed various antithrombotic treatments concomitantly disregarded different treatment groups and presented EMA values for the studied medications simultaneously. In our opinion, presenting adherence outcomes together for once- and twice-daily regimens within the same treatment group remains questionable. However, combining adherence outcomes across different treatment groups is even more disputable because of the distinct pharmacokinetic and pharmacodynamic profiles of various types of drugs and varied psychological factors that influence patients.

The literature is also inconsistent with the thresholds used to assess adherence. A more evidence-based approach is recommended than applying an 80% threshold for each medication.[38,43] The clinically relevant adherence threshold should reflect pharmacokinetics as well as dosing regimens to divide patients into adherent and non-adherent groups.[43]

Currently, there is no uniform threshold for DOACs, although the above-mentioned threshold has been applied in several studies.[25–28,30,36] Incoherent findings were likewise found across studies analysing pharmacy refill data of DOACs, whenever the adherence thresholds for once-daily rivaroxaban were proposed as 78%,[62] 80% for twice-daily apixaban,[62] or 90%[17–19] and 95%[17,20] for all DOACs. Apparently, higher thresholds may serve better in DOACs according to the required strict adherence, as well as better fit the higher adherence outcomes identified in this review (88.6% in observation and 92.6% in intervention studies).

Additionally, the style of reporting medication adherence differed among the identified studies. EM technology usually ensures that regimen or schedule adherence data are available to the investigator, which is one of the positive attributes of EM compared with pill counts or self-reported data. Even so, two studies presented taking adherence,[34,35] ie, the least accurate and informative way to present EMA, while another did not specify the measuring method at all.[37] The majority of studies reported on regimen adherence[25–33,36,41,42] allowing the authors to focus on adherence at greater depths.[31,32,36,42] The scheduled adherence reflects a stricter approach for the analysis of medication-taking behaviour, thus enabling researchers to verify the accuracy and reliability of DOACs.[20,25,26,30,38–40] The Research Methods Framework for assessing medication adherence using EM devices has proposed the reporting of regimen adherence data.[63] Other approaches, published soon enough to be considered in identified articles, recommended multiple methods for measuring medication adherence or aggregating data in pre-specified time windows (ie, weeks, months).[44,64] None of these frameworks was applied to the included articles.

A framework for understanding the sources of bias in medication adherence research has been recently published.[65] To our best knowledge, there is not any available tool published for assessing the risk of bias related to adherence data. The literature shows that authors do not use the EMERGE guideline[15] properly.[66–68] Hence, we decided to assess the quality of adherence data reported in anticoagulation-related literature using such a guideline. This method was previously briefly described in a protocol for another systematic review;[69] it was used as a bivariate evaluation tool in oncologic patients,[70] as well as in senior patients with chronic morbidity, focusing only on the minimum reporting criteria and on the implementation of a framework.[68] Our literature review showed that the medication adherence reporting quality did not improve with regard to anticoagulation. Only two articles[38,41] referred to the EMERGE guideline, and the overall reporting quality was very low. Despite the long-standing demand for guidance in reporting medication adherence study outcomes,[71] it has still rarely been used by the authors. Nonetheless, some essential elements should not be neglected, such as the minimum reporting criteria in the EMERGE guideline.[15] Yet, with a few exceptions,[33,38,41] the authors did not explicitly specify the phase of medication adherence,[15] which could be inferred from the study methodology. Implementation of ABC Taxonomy[2] in five articles,[31,33,38,39,41] as well as adaptation of the term "compliance" in four articles[25,26,30,42] demonstrated that researchers are still not familiar or confident with the application of adherence terminology. Adherence is frequently defined operatively and/or indirectly, with authors simultaneously focusing on multiple phases without reliability to validate the classification.[67]

Some equally important elements to be reported include the acknowledgement that adherence monitoring results can be influenced by the Hawthorne effect. Addressing this problem appropriately[15] was still the most frequently omitted item in seven articles.[27,29,35,37,39,40,42] Additionally, adherence depends on multiple influencing factors, such as patient (routine, comorbidity, polypharmacotherapy), setting (clinic, hospital), and healthcare system (medication cost, health-care availability), which are specific to each environment. Therefore, to achieve reproducible research, scientists are recommended to describe the complete setting with all relevant factors pertaining to medication adherence as well as routine care related to the management of medication adherence.[15] However, these elements were ignored or explained very briefly in the majority of articles.

Strengths and Limits

The strength of this systematic review stems from the thorough search of all essential databases and a review of the relevant literature. This is the first review focusing on EMA to DOACs, as well as combining findings in an unprecedented way, presenting approximate adherence levels in observational and interventional study designs. The three investigators worked together to ensure unbiased methodology, data withdrawal, and quality evaluation. Equally important is reaching out to the authors of articles multiple times, when incomplete or ambiguous data arise to provide

more reliable information about EMA to DOACs. Moreover, a detailed evaluation of the quality of medication adherence reporting was conducted based on the EMERGE guideline, despite the current lack of any other tool to assess the risk of bias in medication adherence-focused literature.

This review has several limitations. For example, a shorter search window was applied in the EMBASE database compared to other databases because of limited institutional access. To avoid missing important records, a total of five databases were screened. Screening of the related references in the records was also performed, resulting in no new related articles, which confirmed a thorough search from the beginning. Furthermore, targeting all published articles focusing on EMA to DOACs without excluding specific design or population aspects resulted in anticipated diversity across the articles. Data extraction and summarizing of all evidence did not allow researchers to perform quantitative analyses. Adherence measurements were applied differently across the included studies; some of them did not report adherence to individual DOACs but to all drugs indiscriminately. Notably, the EMERGE guideline was published to provide recommendations to authors reporting adherence to study findings and has not been primarily intended for use as a qualitative assessment tool. To get closer to the real risk of evaluation bias, precise instructions reflecting a detailed three-rank evaluation for objective reproducible analysis were prepared and are described in the methodology. Nevertheless, medication adherence reporting quality was the only aspect of the retrieved articles that could be analyzed.

Conclusion

This systematic review showed that electronic monitoring has been utilized more frequently in assessing medication adherence to direct oral anticoagulants over the last decade, particularly in the use of smart pill bottles in populations with chronic conditions. The summary outcomes suggested that medication adherence exceeded 90% across both observational and interventional study designs, irrespective of sample size. Our review may serve as a basis for further research, and the results can be considered a first step towards establishing evidence-based adherence thresholds for direct oral anticoagulants. However, the heterogeneity of the included studies and very low adherence to reporting quality require further exploration. It is necessary to clarify the use of electronic monitoring and to establish a reliable methodology for its application in adherence to direct oral anticoagulants, along with its adoption in daily clinical practice, while the EMERGE guideline remains a useful approach to assess and improve adherence reporting quality in future studies.

Abbreviations

DOACs, direct oral anticoagulants; EM, electronic monitoring; EMA, electronically monitored medication adherence.

Data Sharing Statement

The data extracted from the included studies (ie, analysis data and well-defined point distribution according to the EMERGE recommendations) not listed either in the manuscript or in the supplementary material 1, as well as other materials used in the review, can be provided based on a well-founded request to the research team via the corresponding author.

Ethics Approval

This study was conducted in accordance with The Declaration of Helsinki from 1964. As all sources used in this study were publicly available, there was no need for approval from the ethics committee.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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