BMJ Open

Adherence to oral anticoagulants among patients with atrial fibrillation: a systematic review and meta-analysis of observational studies

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To cite: Salmasi S, Loewen PS, Tandun R, *et al*. Adherence to oral anticoagulants among patients with atrial fibrillation: a systematic review and meta-analysis of observational studies. *BMJ Open* 2020;**10**:e034778. doi:10.1136/bmjopen-2019-034778

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-034778).

Received 05 October 2019
Revised 06 March 2020
Accepted 26 March 2020

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ABSTRACT

Introduction Medications cannot exert their effect if not taken as prescribed by patients. Our objective was to summarise the observational evidence on adherence to oral anticoagulants (OACs) among patients with atrial fibrillation (AF).

Methods In March 2019, we systematically searched PubMed/Medline, Embase, CINAHL and PsycINFO (from inception) for observational studies measuring adherence, its determinants and impacts in patients with AF. Mean adherence measures and corresponding proportions of adherent patients were pooled using random effects models. Factors shown to be independently associated with adherence were extracted as well as the clinical and economic outcomes of adherence.

Results We included 30 studies. Pooled mean adherence scores of over half a million patients with AF 6 months and 1 year after therapy initiation were 77 (95% CI: 74–79) and 74 (68–79) out of 100, respectively. Drug-specific pooled mean adherence score at 6 months and 1 year were as follows: rivaroxaban: 78 (73–84) and 77 (69–86); apixaban: 77 (75–79) and 82 (74–89); dabigatran: 74 (69–79) and 75 (68–82), respectively. There was inadequate information on warfarin for inclusion in meta-analysis. Factors associated with increased adherence included: older age, higher stroke risk, once-daily regimen, history of hypertension, diabetes or stroke, concomitant cardiovascular medications, living in rural areas and being an experienced OAC user. Non-adherent patients were more likely to experience stroke and death, and incurred higher medical costs compared with patients with poor adherence.

Conclusions Our findings show that up to 30% of patients with AF are non-adherent, suggesting an important therapeutic challenge in this patient population.

Strengths and limitations of this study

- ► This is a timely systematic review that synthesises the evidence on extent of poor adherence to oral anticoagulants, its determinants and clinical and economic outcomes, among patients with atrial fibrillation.
- ► We focused on observational studies (retrospective and prospective) to synthesise the evidence on patients' real-world medication taking behaviour.
- ► We considered all oral anticoagulants, including the newer drugs (apixaban, rivaroxaban, dabigatran and edoxaban) and aimed to generate pooled adherence at the individual drug level.
- ► Drug utilisation consists of three interconnected but distinct phases (initiation, implementation and discontinuation) and the focus of this study was confined to the implementation phase.

INTRODUCTION

Atrial fibrillation (AF)—the most common chronic arrhythmia—is an epidemic affecting more than 33 million people worldwide.[1] AF increases stroke risk by up to fivefold and is responsible for a third of strokes in people over 60.[2–5] Strokes secondary to AF are far more debilitating and carry three times the risk of death than strokes due to other causes.[6–8]

Oral anticoagulants (OACs), which include vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs), are the only effective agents thus far in preventing stroke in patient with AF, showing approximately 66% relative risk reduction in clinical trials.[9–13] When used outside the controlled environment of clinical trials, however, the effectiveness of these drugs is impacted by patients' adherence.[14 15] The clinical consequences of non-adherence can potentially be more significant for DOACs, given their short half-lives.[14–18]

Studies have previously attempted to summarise the medication taking behaviour of patients with AF. These reviews, however, focus on discontinuation of therapy (not implementation or execution of dosing), or when looking at implementation, only focus on DOACs, summarise evidence from randomised controlled trials (which do not

reflect the day to day behaviours of patients) and provide a narrative summary of results with no meta-analysis.[19–21] Further, no studies have summarised the evidence on determinants of adherence in this patient population and the association between adherence and outcomes (clinical or economical). The objective of this systematic review and meta-analysis was to summarise the evidence from observational studies on the extent, determinants and impacts of adherence to all OACs among patients with AF.

METHODS

We conducted a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the Meta-analysis Of Observational Studies in Epidemiology guidelines (online supplementary file 1).[22 23]

Search strategy

In March 2019, we systematically searched PubMed/Medline, Embase, CINAHL and PsycINFO (from inception) using the relevant keywords and MeSH terms (online supplementary file 2). The search strategy was designed with the help of a medical librarian and aimed to identify peer-reviewed published manuscripts that reported on extent, determinants and impacts of non-adherence to any OAC. A manual search was also performed on Google Scholar and the bibliography of included studies.

Inclusion criteria and study selection

Studies were included if they used a prospective or retrospective observational study design, and quantitatively measured secondary adherence (also known as the 'implementation' phase), which looks at medication dose omissions, additions or delays and does not involve those who did not initiate their therapy.[15] Studies published in English, French, Spanish, Persian, Finnish, Cantonese or Korean were included.[24] No limitations were imposed on setting, country, publication date or quality.

While we were primarily interested in OAC adherence in patients with non-valvular AF, we included studies that did not specifically restrict inclusion to this population, with notation in quality assessment. Studies of self-reported adherence were excluded (including those using validated scales such as Morisky Medication Adherence Scale©) as they are prone to overestimation of adherence (social desirability bias).[24] Cross-sectional and interventional studies, editorials, conference proceedings and studies that evaluated or validated adherence measurement methods were also excluded.

Two authors independently screened titles and abstracts of the retrieved studies followed by full text review of candidate studies. Disagreements about inclusion were resolved by discussion with a third author.

Data extraction and synthesis

The primary adherence measure extracted was the mean and SD of patients' adherence over 6 months or 12 months post index date (after therapy initiation). The secondary adherence measure was proportions of adherent patients, that is proportion of patients reported in each study to have mean adherence score more than 80 (this could be > or ≥ depending on how the study defined 'adherent'). The 80% adherence is the conventional threshold for 'good adherence'.[25 26] Six or twelve months were chosen as these were the most common follow-up times. If a study had variable follow-up time (eg, from initiation to permanent discontinuation or death), the median follow-up time was used. For studies that reported the proportion of *non*-adherent participants, data were transformed to proportion *adherent* to allow pooling. When both unadjusted and adjusted outcomes were reported, we extracted and analysed the adjusted results. When unmatched and propensity score matched results were reported, we extracted the matched results as they were expected to be more accurate estimates. When a study reported adherence to both index OAC and current OAC (allowing for switching), adherence to index OAC was analysed to minimise heterogeneity since studies defined switching differently. Adherence results with switching allowed were still reported.

We extracted information on the determinants or factors shown in the included studies to be independently associated with adherence in multivariable regression analyses. We classified the identified determinants under the WHO's five dimensions of medication adherence to identify areas in need of more research.[27] Finally, we extracted information on the clinical and economic consequences of poor adherence.

Data analysis

Meta-analyses were carried out using DerSimonian and Laird random-effects models to determine the pooled mean adherence and the corresponding pooled proportion of adherent patients over 6 months and 1 year of observation. If a study reported adherence scores for multiple cohorts, all were included in the meta-analysis (multiple entries per study). In anticipation of heterogeneity, subgroup analysis was performed for each adherence measure, by presence of potential conflict of interest and study quality. Additional meta-analyses were also performed focusing only on studies that reported comparative adherence between different OACs in the same cohort, to calculate the pooled OR of adherence for each comparison.

I^2 statistics was used to quantify heterogeneity between studies.[28] Leave-one-out analysis was also performed for outliers to explore and potentially reduce heterogeneity.[29] Forest plots and funnel plots were constructed using OpenMeta-Analyst (Microsoft Corporation, Redmond, Washington, USA) or RevMan5 (V. 5.3, Copenhagen, Denmark) software to illustrate the results and assess publication bias using funnel plots where relevant, that

is, where studies reported measures of association (eg, OR).[30 31] Clinical and economic impacts of poor adherence were summarised narratively as meta-analysis was not possible.

Quality assessment

We critically appraised the quality of adherence measurement in the included studies by adapting a condensed version of the checklist designed by the International Society of Pharmaco-economics and Outcomes Research (ISPOR) Group, designed specifically for medication adherence studies, to establish standards for data sources, operational definitions, measurement of medication adherence and reporting of results, previously used in a systematic reviews of adherence to gout medication.[32] We also critically appraised individual study reporting quality using Strengthening the Reporting of Observational Studies in Epidemiology.[33] Studies received a point for each checklist item they met and a 0 score if not met. A quality score was computed for each study (number of items satisfactorily met/the total number of applicable items) and reported as a percentage. Items deemed not applicable were excluded from the denominator of the study's score. Studies were categorised as low, moderate or high quality if they scored ≤50%, 51%–80% or >80%, respectively (arbitrary thresholds defined by authors).

Following Cochrane's commercial sponsorship policy as a guide, potential conflicts of interest were deemed present if any of the following were met: (1) provision of study funding by the for-profit manufacturer or marketer of any of the OACs included in the corresponding study or (2) disclosure of potential conflict of interest with a for-profit manufacturer or marketer of any of the OACs included in the corresponding study.[34]

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research.

RESULTS

Initial search led to 1122 studies, all of which were in English (figure 1). A total of 30 studies were included in this systematic review[35–64] involving 593 683 participants (DOAC: 437 610, VKA: 156 073). Most studies were published after 2015 (n=22, 73% of total included), conducted in North America (n=19, 63%) and retrospective (n=29, 97%) (table 1). Adherence measurement was assessed to be of high quality in 59% of the included studies and moderate in 38%, according to the ISPOR checklist (online supplementary file 3). The most frequently reported adherence measures were proportion days covered (PDC) (n=21, 70% of the included studies) and medication possession ratio (MPR) (n=9, 20%) over 6 months or 1 year post index date (table 2). The majority of the included studies focused on adherence to DOACs with only four observational studies measuring and reporting adherence to warfarin. There were no data on adherence to edoxaban, betrixaban, phenprocoumon, acenocoumarol or fluindione.

Adherence

The range of reported adherence results was quite wide. Reported mean adherence ranged between 67 (out of 100)[58 61 64] and 86[55] over 6 months and 57[58] and 86[41] over 1 year post index date, with corresponding reported

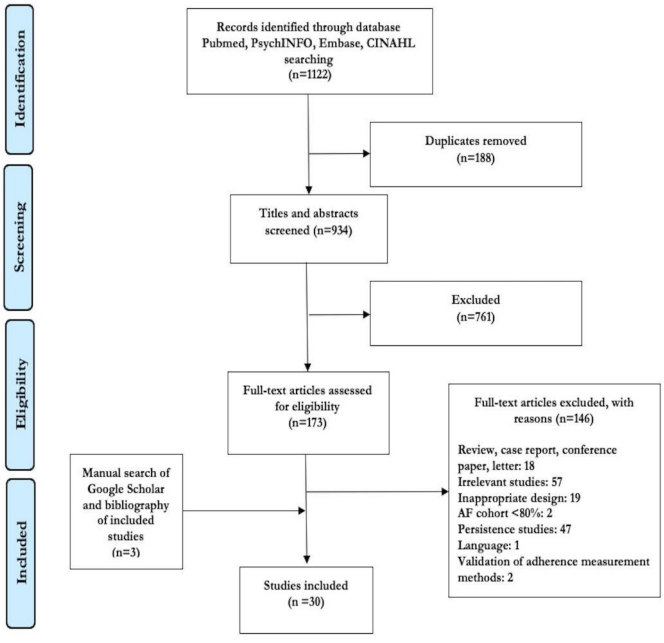

Figure 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram that details the number of studies identified by our search strategy screened and included in the final analysis.

Table 1 Characteristics of the included studies

Author	Year	Design	Country	Total N; (% male)	Age Mean (SD) Unless otherwise stated	Indication for OAC	Adherence reported to index OAC or current OAC	Population OAC naïve vs experienced	Potential conflict of interest	Quality score: STROBE (%)	Quality score: ISPOR (%)
Alberts *et al*[35]	2016	Retrospective	USA	36 868 (55)	76%>65 years	NVAF	NA	Both	Yes	61	67
Beyer-Westendorf *et al*[36]	2016	Retrospective	Germany	7265 (52)	NA	NVAF	Index OAC	Naïve	Yes	73	74
Borne *et al*[37]	2017	Retrospective	USA	2882 (97)	67.4 (9.5)	NVAF	NA	Naïve to DOACs‡	Yes	73	78
Brown *et al*[64]	2016	Retrospective	USA	5223 (40)	59%≥65 years	NVAF	Both	Naïve	Yes	77	84
Casciano *et al*[38]	2013	Retrospective	USA	13 289 (47)	78%≥75 years	AF	NA	Naïve	Yes	63	79
Coleman *et al*[39]	2016	Retrospective	USA	21 756 (54)	66.5 (12.2)	NVAF	NA	Naïve	Yes	55	50
Coleman *et al*[40]	2017	Retrospective	USA	106 227 (63)	71.1 (11.0)	NVAF	Index OAC	Naïve	Yes	77	84
Crivera *et al*[41]	2015	Retrospective	USA	9948 (53)	75.5 (8.3)	NVAF	Both	Naïve	Yes	73	61
Deshpande *et al*[43]	2018	Retrospective	USA	2981 (70)	64.4 (10.7)	AF	NA	Naïve to DOACs‡	No	77	83
Deshpande *et al*[42]	2018	Retrospective	USA	4856 (52)	65.0 (10.5)	AF	NA	Naïve	No	81	83
Eapen *et al*[44]	2014	Retrospective	USA	2691 (43)	100%>65 years	AF	NA	Both	No	76	74
Forsuland *et al*[45]	2016	Retrospective	Sweden	16 096 (52)	75.45 (SD not reported)	NVAF	Current OAC	Both	No	63	61
Gomez-lumberas *et al*[46]	2018	Retrospective	Spain	854 (NA)	73.2 (11.0)	NVAF	NA	Both	Yes	50	67
Gorst-Rasmussen [47]	2015	Retrospective	Denmark	2960 (54)	72.1 (10.8)	NVAF	Index OAC	Naïve	Yes	80	100
Harper *et al*[48]	2018	Retrospective	New Zealand	20 237 (NA)	83%>60	NVAF	NA	NA	No	47	53
Jacobs *et al*[49]	2018	Retrospective	Sweden and Netherlands	5684 (60)	78%≥65 years	AF	Current OAC	Both	Yes	80	83

Continued

Table 1 Continued

Author	Year	Design	Country	Total N; (% male)	Age Mean (SD) Unless otherwise stated	Indication for OAC	Adherence reported to index OAC or current OAC	Population OAC naïve vs experienced	Potential conflict of interest	Quality score: STROBE (%)	Quality score: ISPOR (%)
Manzoor *et al*[50]	2017	Retrospective	USA	66 090 (62)	68.7 (12.1)	AF	Index OAC	Both	Missing	70	85
Márquez-Contrera *et al*[51]	2016	Prospective	Spain	412 (42)	75.2 (7.5)	NVAF	NA	Experienced	Yes	63	83
Maura *et al*[52]	2017	Retrospective	France	22 267 (53)	74.0 (10.8)	NVAF	Index	Naïve	No	79	100
McAlister *et al*[53]	2018	Retrospective	Canada	57 669 (56)	100%>65 years	NVAF	Current OAC	Naïve	No	87	94
McCormick *et al*[54]	2001	Retrospective	USA	429 (22)	87 (7.1)	AF	Current OAC	Experienced	No	60	82
McHorney *et al*[55]	2017	Retrospective	USA	36 675 (67)	63.1 (SD not reported)	NVAF	Index OAC	Naïve	Yes	87	89
McHorney *et al*[56]	2018	Retrospective	USA	41 201 (58)	NA	NVAF	Index OAC	Both	Yes	84	100
Mueller *et al*[57]	2017	Retrospective	Scotland	5398 (54)	74.4 (11.3)	AF	NA	NA	No	70	53
Pham *et al*[58]	2019	Retrospective	USA	38 947 (60)	100%>65 years	NVAF	Index OAC and any OAC	Naïve	No	77	89
Shore *et al*[59]	2014	Retrospective	USA	5376 (98)	71.3 (9.7)	NVAF	Index OAC	NA	No	90	94
Sørensen *et al*[60]	2017	Retrospective	Denmark	46 675 (58)	79%>65 years	NVAF	Current OAC	Naïve	Yes	67	79
Tsai *et al*[61]	2013	Retrospective	USA	17 691 (49)	76.4 (8.7)	NA	Current OAC	Warfarin naïve and warfarin experienced	No	60	78
Yao *et al*[62]	2016	Retrospective	USA	64 661 (56)	75%>65	AF	Index OAC	Naïve	No	77	84
Zhou *et al*[63]	2015	Retrospective	USA	5951 (34)	36.1%>65	AF	Index OAC	Naïve	No	80	79

‡warfarin experienced patients were included.
NA, Not applicable/available
AF, atrial fibrillation (valvular and non-valvular); DOAC, direct oral anticoagulant; ISPOR, International Society of Pharmaco-economics and Outcomes Research; NA, not applicable (no data reported); NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Table 2 Measurement and reporting of adherence to OACs by included studies

Study (year)	Adherence measure (threshold)	Adherence results over 6 months		Adherence results over 1 year	
		Mean adherence score ± SD	Proportion adherent	Mean adherence score ± SD	Proportion adherent
Proportion days covered (PDC)					
Alberts *et al* (2016)[35]	PDC (>80%)	NA	NA	NA	Overall: 0.70 A and D: 0.68 R: 0.73
Borne *et al* (2017)[37]	PDC (>80%)	NA	NA	Overall: 0.85±0.19 A: 0.89±0.14 D: 0.84±0.20 R: 0.86±0.18	Overall: 0.72 A: 0.77 D: 0.71 R: 0.75
Brown *et al* (2016)[64]	PDC (≥80%)	A: 0.75±0.29 D: 0.67±0.33 R: 0.75±0.31	A: 0.62 D: 0.54 R: 0.64	NA	NA
Casciano *et al* (2013)[38]	PDC (>80%)	NA	NA	NA	W: 0.41
Coleman *et al* (2016)[40]	PDC (>80%)	D: 0.77±0.32 R: 0.82±0.30	D: 0.65 R: 0.74	D: 0.65±0.37 R: 0.73±0.35	D: 0.52 R: 0.62
Coleman *et al* (2017)[39]	PDC (≥80%)	NA	A: 0.57 and 0.62 R: 0.54 and 0.58 (Two different databases were used for this study hence two adherence results per drug.)	NA	NA
Crivera *et al* (2015)[41]	PDC (>80%)	NA	NA	**Index DOAC:** A: 0.83±0.20 D: 0.81±0.22 R: 0.86±0.19 **Any OAC:** A: 0.84±0.18; D: 0.85±0.18; R: 0.87±0.17;	**Index DOAC:** A: 0.71 D: 0.68 R: 0.75 **Any OAC:** A: 0.71 D: 0.73 R: 0.77
Deshpande *et al* (2018)[43]	PDC (≥80%)	NA	R and D: 0.65	NA	R and D: 0.54
Deshpande *et al* (2018)[42]	PDC (≥80%)	R and D: 0.86±SD missing	R and D: 0.77	R and D: 0.85±SD missing	R and D: 0.76
Forsuland *et al* (2016)[45]	PDC (>80%)	NA	NA	NA	A: 0.93 D: 0.92 R: 0.96
Gorst-Rasmussen *et al* (2015)[47]	PDC (>80%)	0.84±0.28	NA	NA	D: 0.77
Harper *et al* (2018)[48]	PDC (>80%)	NA	NA	NA	D: 0.84
Manzoor *et al* (2017)[50]	PDC high (≥90%)	Overall: 0.78±28.40 A: 80.90±24.9 D: 78.60±27.70 R: 76.50±30.70	**PDC90** 0.55	Overall: 72.80±32.20 A: No users of A at 12 months D: 73.4±31.6; R: 69.7±34.8	**PDC90** 0.34
Maura *et al* (2017)[52]	PDC>80	NA	NA	NA	**Index OAC:** Overall: 0.71 D: 0.70 R: 0.72

Continued

Table 2 Continued

Study (year)	Adherence measure (threshold)	Adherence results over 6 months		Adherence results over 1 year	
		Mean adherence score ± SD	Proportion adherent	Mean adherence score ± SD	Proportion adherent
McHorney *et al* (2017)[55]	PDC (>80% and >90%)	NA	**PDC 80:** A: 0.76 D: 0.69 R: 0.80 W: 0.65 **PDC90:** A: 0.57 D: 0.51 R: 0.64 W: 0.47	NA	NA
McHorney *et al* (2018)[56]	PDC (>80% and NR2>90%)	NA	**PDC80:** A:0.78 R: 0.82 **PDC90:** A: 0.60 R: 0.67	NA	NA
Pham *et al* (2019)[58]	PDC (>80%)	**Index OAC:** A: 0.76±0.29 D: 0.67±0.33 R: 0.72±0.32	**Index OAC:** A: 0.63 D: 0.53 R: 0.58	**Index OAC:** A: 0.70±0.33 D: 0.57±0.36 R: 0.64±0.36 **Any OAC:** A: 0.73±0.31 D: 0.64±0.34 R: 0.68±0.34	**Index OAC:** A: 0.56. D: 0.41 R: 0.50
Shore *et al* (2014)[59]	PDC (>80%)	NA	D: 0.28	NA	NA
Sørensen *et al*(2017)[60]	PDC (>80%)	NA	**Odds of being adherent** R: reference; A: 0.79 (0.69–0.92) D: 0.72 (0.66–0.80) VKA: 0.76 (0.69–0.83)	NA	NA
Tsai *et al* (2013)[61]	PDC (no threshold)	D: warfarin-naïve: 0.67±0.36 warfarin-experienced: 0.71±0.35	NA	NA	NA
Yao *et al* (2016)[62]	PDC (>80%)	NA	Overall: 47.5% A: 0.52 D: 0.46 R: 0.48 W: 0.39	NA	NA
Medication possession ratio (MPR)					
Beyer-Westendorf *et al* (2016)[36]	MPR (>0.8)	D: 0.67±SD missing R: 0.76±SD missing	D: 0.50 R: 0.61	D: 0.64±SD missing R: 0.75±SD missing	D: 0.48 R: 0.63
Eapen *et al* (2014)[44]	MPR (no threshold)	NA	NA	Median (IQR): 0.77 (0.51–0.98)	NA
Gomez-lumberas *et al* (2018)[46]	MPR (>0.8)	NA	NA	NA	A: 0.62

Continued

Table 2 Continued

Study (year)	Adherence measure (threshold)	Adherence results over 6 months		Adherence results over 1 year	
		Mean adherence score ± SD	Proportion adherent	Mean adherence score ± SD	Proportion adherent
Jacobs *et al* (2018)[49]	MPR (≥0.8)	NA	NA	NA	Sweden: 0.95 Netherlands: 0.93
McHorney *et al*(2017)[55]	MPR (>0.8)	NA	NA	A: 0.85±0.2 D: 0.81±0.2 R: 0.86±0.2 W: 0.80±0.2	A: 0.76 D: 0.66 R: 0.78 W: 0.59
Zhou *et al* (2015)[63]	MPR (>0.8)	D: 0.73±0.30	D: 0.59	D: 0.65±0.35	D: 0.51
Mueller *et al* (2017)[57]	MPR >80*	NA	NA	NA	DOACs: 0.82 A: 0.88 D: 0.65 R: 0.83
Márquez-Contrera *et al* (2016)[51]	CP >80%	NA	R: Global compliance: 0.84 Daily compliance: 0.84 % therapeutic cover: 90.04%	NA	R: Global compliance: 0.80 Daily compliance: 0.80 % therapeutic cover: 89.25%
McAlister *et al* (2018)[53]	TTR >65% (INR2–3)	NA	W: Per cent patients with time in therapeutic range: 4.11%	NA	NA

Drug specific proportion of adherent patients was calculated as the per cent of total number of patients taking the respective drug in the study and not the total number of patients in the study.
*Referred to as medication refill adherence in the study (total days' supply/total days in study) x 100.
aHR, adjusted HR; CP, compliance percentage; DOAC, direct oral anticoagulant; MPR, medication possession ratio; NA, not available/not applicable; OAC, oral anticoagulant; PDC, proportions days covered; TTR, time in therapeutic range; VKA, vitamin K antagonist.

proportion of adherent patients ranging between 47%[59] and 82%[56] over 6 months and 41%[58] and 95%[45] over 1 year. A wide range of adherence results were observed even at the individual OAC level (table 2).

Pooled mean adherence scores over 6 month and 1 year post medication initiation were 77 (95% CI: 74–79) and 74 (68–79), with the corresponding pooled proportion of adherent patients as 63% (58%–68%) and 70% (65%–76%), respectively. Adherence was similar between DOACs, although adherence to apixaban and rivaroxaban was slightly higher than dabigatran (table 3). No meta-analysis could be conducted for mean adherence to warfarin since this was not reported by the included studies. Pooled estimates of proportion of adherent patients for warfarin resulted from meta-analysis of two studies only (as illustrated in tables 2 and 3). Due to the limited data in warfarin, no drug class comparison could be made. Figure 2 illustrates the forest plots for patients' mean adherence score over 6 months and 1 year. The remaining forests plots, including forest plots of proportion adherent, adherence to individual OACs, subgroup analyses (by adherence measure (PDC and MPR), study quality and potential for conflict of interest) can be found in online supplementary file 4.

Between-study variance (represented as I^2) was high and not reduced by the leave-one out analysis or subgroup analysis. Exclusion of studies with potential conflicts of interest led to lower adherence scores for all OACs but did not change the rank-order of OACs (adherence to dabigatran remained lower than the others). Excluding studies of low and moderate quality or stratifying the analysis by adherence measure (PDC vs MPR) or country (USA vs others) had only minor impacts on pooled adherence results and the detected heterogeneity (online supplementary file 4).

Studies comparing adherence between different OACs in the same cohort

Nineteen studies reported comparative adherence between different OACs in the same cohort (table 4).[35–37 39–45 49 50 52 55–58 60 62] Odds of being adherent was significantly higher for apixaban compared with dabigatran over both 6 months (OR:1.24, 95% CI: 1.07–1.45) and 1 year post index date (OR:1.76, 95% CI: 1.35–2.29). Odds of adherence was significantly higher for rivaroxaban compared with dabigatran over 6 months (OR:1.39, 95% CI: 1.15–1.67), but not 1 year (OR:1.17, 95% CI: 0.38–3.60). Odds of adherence did not differ

Table 3 Pooled adherence results

	Adherence over 6 months post index date		Adherence over 1 year post index date	
	Mean (95% CI)	Proportion adherent (95% CI)	Mean (95% CI)	Proportion adherent (95% CI)
Apixaban	77.15 (75.03 – 79.27)	0.62 (0.53 – 0.72)	81.75 (74.32 – 89.18)	0.74 (0.62 – 0.87)
Dabigatran	73.94 (68.94 – 78.93)	0.55 (0.48 – 0.61)	75.04 (67.74 – 82.34)	0.65 (0.54 – 0.76)
Rivaroxaban	78.30 (72.47 – 84.14)	0.64 (0.54 – 0.73)	77.45 (68.9 – 85.96)	0.73 (0.64 – 0.81)
Warfarin	No data available	0.52 (0.26 – 0.77)*	No data available	0.50 (0.32 – 0.68)*
All OACs	76.62 (73.91 – 79.33)	0.63 (0.58 – 0.68)	73.72 (68.36 – 79.08)	0.70 (0.65 – 0.76)
Subanalysis: excluding studies with conflict of interest				
Apixaban	78.39 (73.59 – 83.19)*	0.51 (0.49 – 0.53)*	One study	0.79 (0.55 – 1.04)
Dabigatran	72.87 (64.40 – 81.33)	0.50 (0.46 – 0.54)†	65.20 (49.13 – 81.27)*	0.67 (0.50 – 0.84)
Rivaroxaban	74.25 (69.84 – 78.66)*	0.50 (0.46 – 0.53)*	66.85 (61.27 – 72.44)*	0.75 (0.55 – 0.96)
Warfarin	No data available	0.39 (0.38 – 0.39)	No data available	No data available
All OACs	73.40 (69.86 – 76.94)	0.56 (0.49 – 0.62)	65.56 (59.41 – 71.72)	0.68 (0.58 – 0.79)
Subanalysis: excluding studies with low and medium quality (assessed by ISPOR)				
Apixaban	77.15 (75.03 – 79.27)*	0.62 (0.53 – 0.72)*	77.50 (62.80 – 92.20)	0.66 (0.47 – 0.85)
Dabigatran	73.32 (67.08 – 79.57)	0.54 (0.47 – 0.60)	73.83 (62.99 – 84.65)	0.61 (0.45 – 0.76)
Rivaroxaban	77.38 (69.95 – 84.80)	0.62 (0.51 – 0.74)	72.23 (58.64 – 87.83)	0.67 (0.5 – 0.83)
Warfarin	No data available	0.52 (0.26 – 0.77)*	No data available	No data available
All OACs	77.29 (74.19 – 80.40)	0.63 (0.58 – 0.68)	68.61 (62.63 – 74.58)	0.67 (0.58 – 0.76)
Subanalysis: by adherence measure				
		MPR		
Apixaban	No data available	No data available	No data available	0.75 (0.64 – 0.87)
Dabigatran	77.00 (69.16 – 81.84)*	0.54 (0.45 – 0.63)*	No data available	0.58 (0.49 – 0.66)
Rivaroxaban	No data available	No data available	No data available	0.75 (0.69 – 0.81)
Warfarin	No data available	No data available	No data available	0.59†
All OACs	81.01 (77.21 – 84.81)	0.57 (0.51 – 0.63)	No data available	0.74 (0.64 – 0.83)
		PDC		
Apixaban	77.15 (75.03 – 79.27)	0.62 (0.53 – 0.72)	80.67 (69.40 – 91.94)	0.74 (0.45 – 1.02)
Dabigatran	72.41 (65.90 – 78.91)	0.55 (0.47 – 0.63)	74.05 (65.56 – 82.53)	0.67 (0.52 – 0.82)
Rivaroxaban	76.38 (71.35 – 81.40)	0.64 (0.54 – 0.74)	75.74 (67.44 – 84.03)	0.69 (0.57 – 0.82)
Warfarin	No data available	0.52 (0.26 – 0.77)*	No data available	0.41†
All OACs	74.93 (72.09 – 77.77)	0.64 (0.58 – 0.69)	74.5 (68.89 – 80.14)	0.70 (0.62 – 0.77)

*Pooled results of only two studies.
†Not pooled. Based on one study.
‡
ISPOR, International Society of Pharmaco-economics and Outcomes Research; MPR, medication possession ratio; OAC, oral anticoagulant; PDC, proportions days covered.

between apixaban and rivaroxaban over 6 months (OR:0.80, 95% CI: 0.51–1.24) or 1 year (OR:1.02, 95% CI: 0.79–1.33).

Studies reporting adherence among several cohorts with different characteristics

Three studies compared adherence between new versus experienced users.[37 50 56] McHorney *et al* reported greater mean PDC score for both rivaroxaban and apixaban (0.90 and 0.88, respectively) among prior OAC users compared with naïve users (0.87 and 0.86, respectively).[56] Borne *et al* reported a higher mean PDC score for apixaban users with prior warfarin experience compared with naïve users (0.89±0.14 vs naïve: 0.87±0.15, p<0.01).[37] Confirming these results, Manzoor *et al* reported higher mean PDC for experienced users compared with naïve users over 6 months (83.3±24.6 vs 72.3±31.3; p<0.05), 9 months (81.2±26.4 vs 67.3±33.8); p<0.05) and 1 year (79.9±27.6 vs 63.7±35.2; p<0.05).[50]

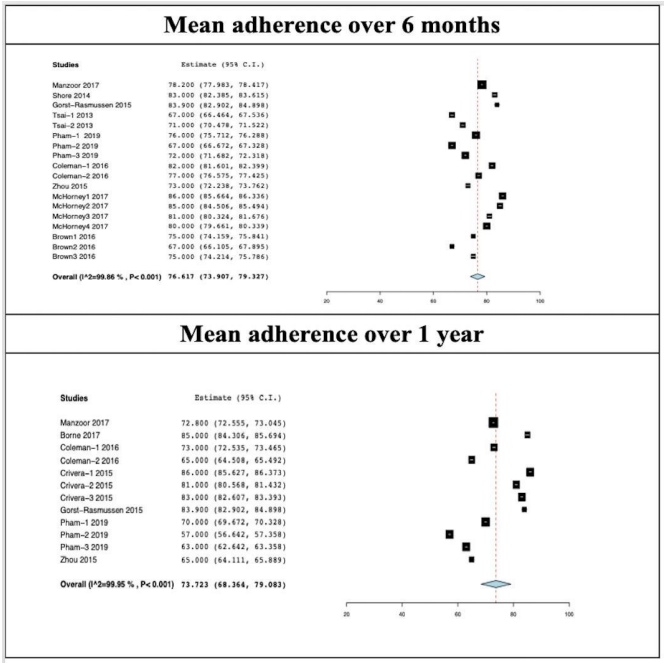

Figure 2 Forest plots illustrating patients' mean adherence scores over 6 months and 1 year post index date. See online supplementary file 4 for additional forest plots for each oral anticoagulant and subgroup analyses.

One study, Eapen *et al*, compared adherence among those prescribed OAC at discharge versus after discharge and reported that patients prescribed warfarin at discharge had significantly higher prescription fill rates compared with those prescribed after discharge at 3 months (84.5% vs 12.3%; p<0.001) and 1 year (91.6% vs 16.8%; p<0.001).[44]

Determinants of adherence

Many factors were identified by the included studies as significant determinants of adherence. Summarising these under WHO's classification, the factors identified in the included studies to be significantly and positively associated with adherence were: *Patient factors*: history of hypertension,[43 49] diabetes,[37] stroke[37 52]; *Regimen factors*: once daily dosing,[35 49] concomitant use of statin,[43 52] ACE inhibitor or angiotensin II receptor blockers,[43 52] higher risk of bleeding[43]; and *Social/economic factors*: living in rural or deprived areas.[52 53] Factors found to be significantly and negatively associated with adherence to OAC were: being a naïve OAC user,[50 56] twice daily dosing[35 49] and impaired cognitive or functional ability.[56] No *healthcare system* and *condition factors* related predictors of adherence were identified.

Conflicting results were reported for female sex,[47 48 53] age,[37 43 47–50 52 53] risk of stroke,[43 47 53] presence of multiple comorbidities[43 50 51 56] and higher number of concomitant medications.[50 51] These factors were found to be predictors of high and low OAC adherence in different studies.

Impacts of adherence

Four studies assessed the clinical impact of adherence.[35 37 42 59] Alberts *et al* reported 50% increased hazard of ischaemic stroke with DOAC non-adherence (aHR:1.50, 95% CI:1.30–1.73).[35] Deshpande *et al* reported non-adherent patients to be 1.82 times (aHR:1.82, 95% CI: 1.24–2.67; p=0.002) and 2.08 times (aHR:2.08, 95% CI: 1.11–3.89; p=0.02) more likely to experience an ischaemic stroke compared with adherent patients, over 6 and 12 months, respectively.[42] Similarly, Borne *et al* reported a higher risk of death or stroke per 0.1 drop in the PDC among dabigatran users (HR:1.07, 95% CI: 1.03–1.12; p<0.01).[37] Shore *et al* reported a 13% increase in risk of combined all-cause mortality and stroke with

Table 4 Pooled adherence results from studies reporting adherence to more than one drug in the same cohort

	Adherence at 6 months post index date		Adherence at 1 year post index date	
	Unique studies (n)	OR (95% CI)	Unique studies (n)	OR (95% CI)
Apixaban vs dabigatran	3	1.24 (1.07 – 1.45)	5	1.76 (1.35 – 2.29)
Rivaroxaban vs dabigatran	5	1.39 (1.15 – 1.67)	8	1.17 (0.38 – 3.60)
Rivaroxaban vs apixaban	4	0.80 (0.51 – 1.24)	5	1.02 (0.79 – 1.33)
Subanalysis: by adherence metric				
MPR				
Apixaban vs dabigatran	NA	NA	2	2.49 (0.98 – 6.30)
Rivaroxaban vs dabigatran	1	1.63 (1.36 – 1.94)	3	2.10 (1.56 – 2.81)
Rivaroxaban vs apixaban	NA	NA	2	0.90 (0.54 – 1.17)
PDC				
Apixaban vs dabigatran	3	1.24 (1.07 – 1.45)	3	1.41 (0.99 – 2.01)
Rivaroxaban vs dabigatran	4	1.34 (1.09 – 1.65)	5	0.82 (0.18 – 3.69)
Rivaroxaban vs apixaban	4	0.80 (0.51 – 1.24)	3	1.13 (0.71 – 1.82)

MPR, medication possession ratio; PDC, proportions days covered.

lower adherence (aHR:1.13, 95% CI: 1.07–1.19 per 10% decrease in PDC) but found no association between adherence and non-fatal bleeding events (aHR:1.04 per 10% increase in PDC, 95% CI: 0.94–1.14) or myocardial infarction (aHR:0.97 per 10% increase in PDC, 95% CI: 0.78–1.21).[59]

Two studies measured the economic impacts of adherence.[38 43] Casciano *et al* reported significantly more inpatient and emergency room encounters and longer length of stay for non-adherent patients compared to adherent patients and Deshpande *et al* reported significantly higher annual adjusted per-patient medical cost (inpatient and outpatient) for non-adherent users compared with adherent ones (US$30 485 vs $23 544; p≤0.001).[38 43]

DISCUSSION

In this systematic review, we synthesised observational data of over half a million patients with AF to reveal that up to 30% are non-adherent to OACs, and that non-adherent patients are more likely to experience stroke, death and incur higher medical costs compared with adherent patients. We also found that older age, higher stroke risk, once-daily regimen, history of hypertension, diabetes or stroke, concomitant cardiovascular medications, living in rural areas and being an experienced OAC user could be associated with better adherence.

Adherence to OACs among patients with AF has been thoroughly studied in developed countries. In our study, pooled proportion of adherent patients at 6 months and 1 year were 63% and 70%, respectively, which are higher than those found for other chronic cardiovascular medications such as statins (54%) and antihypertensives (59%).[65] However, our finding that up to 37% of patients with AF do not adhere to OACs is concerning considering the detrimental consequences of non-adherence in this particular clinical context. We were unable to ascertain whether the conveniences of DOACs translates into better adherence compared with warfarin due to lack of adherence data on warfarin, a likely result of warfarin dose variations complicating MPR and PDC ascertainment from administrative data. Between DOACs, however, adherence was found to be similar, although dabigatran appeared to have slightly lower adherence than apixaban and rivaroxaban.

Many patient-related-related, regimen-related and social/economic-related factors were identified by the included studies as significant determinants of adherence. It should be noted that each of these factors were reported to have a significant impact on adherence by one or two studies. The limited number of prospective observational studies on the topic restricted our ability to identify important psychosocial determinants as administrative data fall short in recording patients' knowledge gaps, misconceptions and varying values and preferences, all of which have frequently been reported in patients with AF.[66–71] Further, questions remain about the role of sex, age, risk of stroke, presence of multiple comorbidities and number of concomitant medications on adherence. One explanation for the inconsistencies we observed could be differences in how these factors were defined in our included studies. A 2019 systematic review of 34 systematic reviews on determinants of adherence to cardiovascular medications (beta blockers, calcium channel blockers, ACE inhibitors, angiotensin II receptor blockers and diuretics) also reported inconsistent results for the role of gender in adherence.[72] These authors also found that the effects of concomitant medications and comorbidities seem to be drug-specific and condition-specific, which could explain some of the inter-study variability with this factor.[72] A multivariate patient-level meta-regression analysis could provide more clarity to these issues with OACs in patients with AF. Nevertheless, our findings indicate potential opportunities for interventions such as education and counselling for younger or newly diagnosed patients (naïve users) and adherence support for those on twice daily dosed OACs.

Lastly, we looked at outcomes of poor adherence. Our review found evidence of association between lower adherence and strokes, mortality, healthcare utilisation and costs. Our findings confirm the results of a 2017 systematic review of 79 studies across 14 disease groups which reported that $3347–$19 472 are attributed to non-adherence per patient per year among those with cardiovascular conditions (hypertension, hypercholesterolaemia and chronic heart failure).[73] Our findings in relation to clinical outcomes are in line with results of meta-analyses of a large body of research showing that poor adherence across a range of conditions was associated with a 26% increased risk of poor treatment outcomes.[74] The adherence–outcome relationship is, however, very complex, and dependant on many factors, including the nature of the disease.[74] This is why it was important to summarise the strength of this relationship specifically in AF. Our findings, while based on only four studies, reveal the relationship between lower adherence and poor clinical outcomes in patients with AF, and support the potential of interventions aimed at increasing adherence in patients with AF.[73–79]

Limitations

This review was primarily limited by gaps in the available evidence. Given our interest in observational data, our evidence was narrowed to developed countries where the technology and infrastructure for systematic collection of such data is available. The high number of studies from a few developed countries introduced the possibility of duplicate patients in the analysis since many of the included studies used the same database with overlapping periods.[35 38–40 50 64] Furthermore, there may be potential for publication bias or under-representation from studies from developing countries. As described in the Methods section, we attempted to assess publication bias using funnel plots but were limited with few studies reporting measures of association. Nonetheless, for these

meta-analyses, findings do not suggest presence of publication bias (online supplementary file 3).

Another limitation of our analysis was the high heterogeneity (I^2 >80%) among the studies. Possible sources of heterogeneity include differences in patient inclusion criteria (eg, OAC naïve vs experienced); methods for handling and defining medication switches, stockpiling, refill gaps and hospitalisation dates; fixed versus variable observational periods and adherence measure used (PDC vs MPR). Subgroup analyses did not affect the amount of statistical heterogeneity detected. Nonetheless, in addition to the summary measures derived from meta-analysis, we were able to detect the range of adherence measures from the included studies. Finally, drug utilisation consists of initiation, implementation and discontinuation,[15 80] and the focus of this study was confined to the implementation phase. Systematic reviews of OAC initiation and discontinuation are needed to provide a complete picture of medication taking behaviour in patients with AF.

FUTURE DIRECTIONS

Our understanding of the comparative adherence between warfarin and DOACs among patients with AF is currently impeded by lack of observational data on warfarin. Sophisticated statistical models are needed to calculate days' supply of warfarin, despite its varying dose, to allow measurement of MPR or PDC for this drug using administrative data. Furthermore, we lack information on patterns of non-adherence to OACs. All of the current studies have treated adherence as a static behaviour, calculating and reporting it using a single summary measure. This methodological approach does not provide a complete picture of adherence, which is a dynamic behaviour that changes over time.[25 81] Characterisation of adherence patterns over time is vital in understanding the problem of poor adherence and targeting the right patients at the right time with the right interventions.[82–86]

There is a need for more research investigating the clinical and economic consequences of poor adherence as the current evidence is limited to findings of four studies. Moreover, a clinically meaningful OAC adherence threshold has yet to be determined in AF.[35 37 42 59] While the association between taking more than 80% of medications and improved clinical outcomes has been shown in four AF studies, it remains unclear if this is the optimal threshold for AF.[35 37 42 59] Clinically relevant adherence cut-off values have been shown to differ widely (from 58% to 85%) in different diseases, and even among drug classes.[14 87] As with antiretroviral medications, given the detrimental consequences of OAC non-adherence, the clinically meaningful threshold for 'good adherence' to OACs may need to be much higher than 80%.[87]

CONCLUSION

Synthesis of observational data suggests that overall OAC adherence in patients with AF is below the conventional threshold of 'adherent' (80%). These findings, combined with evidence that lower adherence is associated with poor clinical outcomes and higher costs, suggest an important therapeutic challenge in this patient population. Our study also highlights the need for more consistent measures of adherence, and more research to characterise patterns of OAC non-adherence, identifying determinants of poor OAC adherence and investigate the clinical and economic consequences of OAC non-adherence.

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Contributors Conceived the study: SS, PSL, MADV; Designed the search strategy: SS, MADV, PSL; Conducted the literature search: SS; Screened titles and abstracts: SS, RT; Screened full texts: SS, RT; Extracted data: SS, RT; Made methodological decisions (data synthesis and analysis): MADV, SS; Analysed the data: SS; Conducted quality assessment; SS, RT; Interpreted the results: SS, PSL, JA, MADV; Prepared the manuscript first draft: SS, MDV, PSL, RT; Reviewed the manuscript and provided critical feedback: JA, MADV, PSL; Revised the manuscript: SS, PSL, RT, MADV.

Funding PSL's research is partially supported by the UBC David H MacDonald Professorship in Clinical Pharmacy. MADV holds a Canada Research Chair in Medication Adherence, Utilisation and Outcomes and is a Michael Smith Foundation for Health Research Scholar.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Ethical approval for this study was not required per our institution's policies.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. No data are available.

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REFERENCES

1 Morillo CA, Banerjee A, Perel P, *et al*. Atrial fibrillation: the current epidemic. *J Geriatr Cardiol* 2017;14:195–203.
2 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke* 1991;22:983–8.
3 Hart RG, Pearce LA, McBride R, *et al*. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. The stroke prevention in atrial fibrillation (SPAF) Investigators. *Stroke* 1999;30:1223–9.
4 World Health Organization. The top 10 causes of death 2018. Available: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death [Accessed 2 May 2019].
5 Wolf PA, Dawber TR, Thomas HE, *et al*. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology* 1978;28:973–7.
6 Marini C, De Santis F, Sacco S, *et al*. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke* 2005;36:1115–9.
7 McGrath ER, Kapral MK, Fang J, *et al*. Association of atrial fibrillation with mortality and disability after ischemic stroke. *Neurology* 2013;81:825–32.

8 Fang MC, Go AS, Chang Y, *et al*. Long-Term survival after ischemic stroke in patients with atrial fibrillation. *Neurology* 2014;82:1033–7.
9 Connolly SJ, Ezekowitz MD, Yusuf S, *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–51.
10 Giugliano RP, Ruff CT, Braunwald E, *et al*. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093–104.
11 Hart RG, Pearce LA, Aguilar MI. Meta-Analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857–67.
12 Patel MR, Mahaffey KW, Garg J, *et al*. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883–91.
13 Kirchhof P, Benussi S, Kotecha D, *et al*. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur J Cardiothorac Surg* 2016;50:e1–88.
14 Karve S, Cleves MA, Helm M, *et al*. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. *Curr Med Res Opin* 2009;25:2303–10.
15 De Geest S, Zullig LL, Dunbar-Jacob J, *et al*. ESPACOMP medication adherence reporting guideline (emerge). *Ann Intern Med* 2018;169:30–5.
16 Aronis KN, Hylek EM. Evidence gaps in the era of non-vitamin K oral anticoagulants. *J Am Heart Assoc* 2018;7:e007338.
17 Chin PK, Doogue MP. Long-Term prescribing of new oral anticoagulants. *Aust Prescr* 2016;39:200–4.
18 Mekaj YH, Mekaj AY, Duci SB, *et al*. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. *Ther Clin Risk Manag* 2015;11:967–77.
19 Obamiro KO, Chalmers L, Bereznicki LRE. A summary of the literature evaluating adherence and persistence with oral anticoagulants in atrial fibrillation. *Am J Cardiovasc Drugs* 2016;16:349–63.
20 Chatterjee S, Sardar P, Giri JS, *et al*. Treatment discontinuations with new oral agents for long-term anticoagulation: insights from a meta-analysis of 18 randomized trials including 101,801 patients. *Mayo Clin Proc* 2014;89:896–907.
21 Shehab A, Bhagavathula AS, Abebe TB, *et al*. Patient adherence to novel oral anticoagulants (NOACs) for the treatment of atrial fibrillation and occurrence of associated bleeding events: a systematic review and meta-analysis. *Curr Vasc Pharmacol* 2019;17:341–9.
22 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100.
23 Stroup DF, Berlin JA, Morton SC, *et al*. Meta-Analysis of observational studies in epidemiology: a proposal for reporting. meta-analysis of observational studies in epidemiology (moose) group. *JAMA* 2000;283:2008–12.
24 Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353:487–97.
25 Andrade SE, Kahler KH, Frech F, *et al*. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf* 2006;15:565–74.
26 Baumgartner PC, Haynes RB, Hersberger KE, *et al*. A systematic review of medication adherence thresholds dependent of clinical outcomes. *Front Pharmacol* 2018;9:1290.
27 World Health Organisation. *Adherence to long-term therapies: evidence to action. towards the solution: five interacting dimensions affect adherence*. Switzerland, 2003.
28 Higgins JPT, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
29 Willis BH, Riley RD. Measuring the statistical validity of summary meta-analysis and meta-regression results for use in clinical practice. *Stat Med* 2017;36:3283–301.
30 Wallace BC, Dahabreh IJ, Trikalinos TA, *et al*. Closing the Gap between Methodologists and End-Users: *R* as a Computational Back-End. *J Stat Softw* 2012;49:15.
31 Peters JL, Sutton AJ, Jones DR, *et al*. Comparison of two methods to detect publication bias in meta-analysis. *JAMA* 2006;295:676–80.
32 Peterson AM, Nau DP, Cramer JA, *et al*. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health* 2007;10:3–12.
33 von Elm E, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg* 2014;12:1495–9.
34 Cochrane community. Editorial and publishing policy resource conflicts of interest and Cochrane reviews, 2014. Available: https://community.cochrane.org/editorial-and-publishing-policy-resource/ethical-considerations/conflicts-interest-and-cochrane-reviews [Accessed 10 July 2019].
35 Alberts MJ, Peacock WF, Fields LE, *et al*. Association between once- and twice-daily direct oral anticoagulant adherence in nonvalvular atrial fibrillation patients and rates of ischemic stroke. *Int J Cardiol* 2016;215:11–13.
36 Beyer-Westendorf J, Ehlken B, Evers T. Real-World persistence and adherence to oral anticoagulation for stroke risk reduction in patients with atrial fibrillation. *Europace* 2016;18:1150–7.
37 Borne RT, O'Donnell C, Turakhia MP, *et al*. Adherence and outcomes to direct oral anticoagulants among patients with atrial fibrillation: findings from the Veterans health administration. *BMC Cardiovasc Disord* 2017;17:236.
38 Casciano JP, Dotiwala ZJ, Martin BC, *et al*. The costs of warfarin underuse and nonadherence in patients with atrial fibrillation: a commercial insurer perspective. *J Manag Care Pharm* 2013;19:302–16.
39 Coleman C, Yuan Z, Schein J, *et al*. Importance of balancing follow-up time and impact of oral-anticoagulant users' selection when evaluating medication adherence in atrial fibrillation patients treated with rivaroxaban and apixaban. *Curr Med Res Opin* 2017;33:1033–43.
40 Coleman CI, Tangirala M, Evers T. Medication adherence to rivaroxaban and dabigatran for stroke prevention in patients with non-valvular atrial fibrillation in the United States. *Int J Cardiol* 2016;212:171–3.
41 Crivera C, Nelson WW, Bookhart B, *et al*. Pharmacy quality alliance measure: adherence to non-warfarin oral anticoagulant medications. *Curr Med Res Opin* 2015;31:1889–95.
42 Deshpande CG, Kogut S, Laforge R, *et al*. Impact of medication adherence on risk of ischemic stroke, major bleeding and deep vein thrombosis in atrial fibrillation patients using novel oral anticoagulants. *Curr Med Res Opin* 2018;34:1285–92.
43 Deshpande CG, Kogut S, Willey C. Real-World health care costs based on medication adherence and risk of stroke and bleeding in patients treated with novel anticoagulant therapy. *J Manag Care Spec Pharm* 2018;24:430–9.
44 Eapen ZJ, Mi X, Qualls LG, *et al*. Adherence and persistence in the use of warfarin after hospital discharge among patients with heart failure and atrial fibrillation. *J Card Fail* 2014;20:23–30.
45 Forslund T, Wettermark B, Hjemdahl P. Comparison of treatment persistence with different oral anticoagulants in patients with atrial fibrillation. *Eur J Clin Pharmacol* 2016;72:329–38.
46 Gomez-Lumbreras A, Cortes J, Giner-Soriano M, *et al*. Characteristics of apixaban-treated patients, evaluation of the dose prescribed, and the persistence of treatment: a cohort study in Catalonia. *J Cardiovasc Pharmacol Ther* 2018;23:494–501.
47 Gorst-Rasmussen A, Skjøth F, Larsen TB, *et al*. Dabigatran adherence in atrial fibrillation patients during the first year after diagnosis: a nationwide cohort study. *J Thromb Haemost* 2015;13:495–504.
48 Harper P, Pollock D, Stephens M. Dabigatran persistence and adherence in New Zealand: a nationwide retrospective observational study. *BMJ Open* 2018;8:e020212.
49 Jacobs MS, Schouten JF, de Boer PT, *et al*. Secondary adherence to non-vitamin-K antagonist oral anticoagulants in patients with atrial fibrillation in Sweden and the Netherlands. *Curr Med Res Opin* 2018;34:1839–47.
50 Manzoor BS, Lee TA, Sharp LK, *et al*. Real-World adherence and persistence with direct oral anticoagulants in adults with atrial fibrillation. *Pharmacotherapy* 2017;37:1221–30.
51 Márquez-Contreras E, Martell-Carlos N, Gil-Guillén V, *et al*. Therapeutic compliance with rivaroxaban in preventing stroke in patients with non-valvular atrial fibrillation: CUMRIVAFA study. *Curr Med Res Opin* 2016;32:2013–20.
52 Maura G, Pariente A, Alla F, *et al*. Adherence with direct oral anticoagulants in nonvalvular atrial fibrillation new users and associated factors: a French nationwide cohort study. *Pharmacoepidemiol Drug Saf* 2017;26:1367–77.
53 McAlister FA, Wiebe N, Hemmelgarn BR. Time in therapeutic range and stability over time for warfarin users in clinical practice: a retrospective cohort study using linked routinely collected health data in Alberta, Canada. *BMJ Open* 2018;8:e016980.
54 McCormick D, Gurwitz JH, Goldberg RJ, *et al*. Prevalence and quality of warfarin use for patients with atrial fibrillation in the long-term care setting. *Arch Intern Med* 2001;161:2458–63.
55 McHorney CA, Ashton V, Laliberté F, *et al*. Adherence to rivaroxaban compared with other oral anticoagulant agents among patients with nonvalvular atrial fibrillation. *J Manag Care Spec Pharm* 2017;23:980–8.

56 McHorney CA, Crivera C, Laliberté F, *et al*. Adherence to rivaroxaban versus apixaban among patients with non-valvular atrial fibrillation: analysis of overall population and subgroups of prior oral anticoagulant users. *PLoS One* 2018;13:e0194099.
57 Mueller T, Alvarez-Madrazo S, Robertson C, *et al*. Use of direct oral anticoagulants in patients with atrial fibrillation in Scotland: applying a coherent framework to drug utilisation studies. *Pharmacoepidemiol Drug Saf* 2017;26:1378–86.
58 Pham PN, Brown JD. Real-world adherence for direct oral anticoagulants in a newly diagnosed atrial fibrillation cohort: does the dosing interval matter? *BMC Cardiovasc Disord* 2019;19:64.
59 Shore S, Carey EP, Turakhia MP, *et al*. Adherence to dabigatran therapy and longitudinal patient outcomes: insights from the Veterans health administration. *Am Heart J* 2014;167:810–7.
60 Sørensen R, Jamie Nielsen B, Langtved Pallisgaard J, *et al*. Adherence with oral anticoagulation in non-valvular atrial fibrillation: a comparison of vitamin K antagonists and non-vitamin K antagonists. *Eur Heart J Cardiovasc Pharmacother* 2017;3:151–6.
61 Tsai K, Erickson SC, Yang J, *et al*. Adherence, persistence, and switching patterns of dabigatran etexilate. *Am J Manag Care* 2013;19:e325–32.
62 Yao X, Abraham NS, Alexander GC, *et al*. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. *J Am Heart Assoc* 2016;5.
63 Zhou M, Chang H-Y, Segal JB, *et al*. Adherence to a novel oral anticoagulant among patients with atrial fibrillation. *J Manag Care Spec Pharm* 2015;21:1054–62.
64 Brown JD, Shewale AR, Talbert JC. Adherence to rivaroxaban, dabigatran, and apixaban for stroke prevention in incident, treatment-naïve nonvalvular atrial fibrillation. *J Manag Care Spec Pharm* 2016;22:1319–29.
65 Chowdhury R, Khan H, Heydon E, *et al*. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J* 2013;34:2940–8.
66 Salmasi S, De Vera MA, Barry A, *et al*. Assessment of condition and medication knowledge gaps among atrial fibrillation patients: a systematic review and meta-analysis. *Ann Pharmacother* 2019;53:1060028019835845:773–85. 0(0).
67 Salmasi S, Kwan L, MacGillivray J, *et al*. Assessment of atrial fibrillation patients' education needs from patient and clinician perspectives: a qualitative descriptive study. *Thromb Res* 2019;173:109–16.
68 Lee VWY, Tam CS, Yan BP, *et al*. Barriers to warfarin use for stroke prevention in patients with atrial fibrillation in Hong Kong. *Clin Cardiol* 2013;36:166–71.
69 McCabe PJ, Barnason SA, Houfek J. Illness beliefs in patients with recurrent symptomatic atrial fibrillation. *Pacing Clin Electrophysiol* 2011;34:810–20.
70 McCabe PJ, Rhudy LM, DeVon HA. Patients' experiences from symptom onset to initial treatment for atrial fibrillation. *J Clin Nurs* 2015;24:786–96.
71 Loewen PS, Ji AT, Kapanen A, *et al*. Patient values and preferences for antithrombotic therapy in atrial fibrillation. A narrative systematic review. *Thromb Haemost* 2017;117:1007-1022.
72 Leslie KH, McCowan C, Pell JP. Adherence to cardiovascular medication: a review of systematic reviews. *J Public Health* 2019;41:e84–94.
73 Cutler RL, Fernandez-Llimos F, Frommer M, *et al*. Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ Open* 2018;8:e016982.
74 DiMatteo MR, Giordani PJ, Lepper HS, *et al*. Patient adherence and medical treatment outcomes: a meta-analysis. *Med Care* 2002;40:794–811.
75 Bramley TJ, Gerbino PP, Nightengale BS, *et al*. Relationship of blood pressure control to adherence with antihypertensive monotherapy in 13 managed care organizations. *J Manag Care Pharm* 2006;12:239–45.
76 Ho PM, Rumsfeld JS, Masoudi FA, *et al*. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Arch Intern Med* 2006;166:1836–41.
77 Kennedy-Martin T, Boye KS, Peng X. Cost of medication adherence and persistence in type 2 diabetes mellitus: a literature review. *Patient Prefer Adherence* 2017;11:1103–17.
78 Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA* 2007;297:177–86.
79 Tangkiatkumjai M, Walker D-M, Praditpornsilpa K, *et al*. Association between medication adherence and clinical outcomes in patients with chronic kidney disease: a prospective cohort study. *Clin Exp Nephrol* 2017;21:504–12.
80 Vrijens B, De Geest S, Hughes DA, *et al*. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol* 2012;73:691–705.
81 Gellad WF, Thorpe CT, Steiner JF, *et al*. The myths of medication adherence. *Pharmacoepidemiol Drug Saf* 2017;26:1437–41.
82 Franklin JM, Krumme AA, Tong AY, *et al*. Association between trajectories of statin adherence and subsequent cardiovascular events. *Pharmacoepidemiol Drug Saf* 2015;24:1105–13.
83 Franklin JM, Shrank WH, Pakes J, *et al*. Group-Based trajectory models: a new approach to classifying and predicting long-term medication adherence. *Med Care* 2013;51:789–96.
84 Lo-Ciganic W-H, Donohue JM, Jones BL, *et al*. Trajectories of diabetes medication adherence and hospitalization risk: a retrospective cohort study in a large state Medicaid program. *J Gen Intern Med* 2016;31:1052–60.
85 Lo-Ciganic W-H, Gellad WF, Gordon AJ, *et al*. Association between trajectories of buprenorphine treatment and emergency department and in-patient utilization. *Addiction* 2016;111:892–902.
86 Modi AC, Rausch JR, Glauser TA. Patterns of nonadherence to antiepileptic drug therapy in children with newly diagnosed epilepsy. *JAMA* 2011;305:1669–76.
87 Viswanathan S, Justice AC, Alexander GC, *et al*. Adherence and HIV RNA suppression in the current era of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2015;69:493–8.