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Atrial fibrillation patients' adherence to oral anticoagulants:

A systematic review and meta-analysis of observational studies

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ABSTRACT

PURPOSE

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

METHODS

We systematically searched for observational studies measuring adherence, its determinants and impacts in AF patients. 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 AF patients at six-month and one-year were 77 (95% CI: 74-79) and 74 (68-79), respectively. Drug-specific pooled mean adherence score six-month and one-year post index date 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 bleeds and stroke, and incurred higher medical costs compared to patients with poor adherence.

CONCLUSIONS

Our findings show that only up to 70% of AF patients are adherent, suggesting an important therapeutic challenge in this patient population.

Keywords: Atrial fibrillation, anticoagulants, medication adherence, stroke.

Strengths and limitations of this study

- This study synthesized observational data, from prospective and retrospective studies, of over half a million AF patients.
- Drug adherence consists of three phases: initiation, implementation, and discontinuation. This study focused on the implementation phase only.
- The study focused not only on the extent of poor adherence but also its predictors and outcomes (clinical and economical).

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 five-fold, and is responsible for with a third of strokes in people over 60.[2-45] Strokes secondary to AF are far more debilitating and carry three times the risk of death than strokes due to other causes.[6-12]

Oral anticoagulants (OACs), which include vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs), are effective in preventing stroke in AF patients, showing approximately 66% relative risk reduction in clinical trials.[13-17] When used outside the controlled environment of clinical trials, however, the effectiveness of these drugs is impacted by patients' adherence.[18, 19] Interruption of OAC therapy has been associated with substantial risk of stroke and bleeding in AF patients.[20, 21] Our objective was to summarize the evidence from observational studies on the extent, determinants, and impacts of AF patients' adherence to OACs.

METHODS

We conducted a systematic review and meta-analysis following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (Supplementary files 1a and 1b).[22, 23]

Search strategy

On March 2019 we systematically searched PubMed/Medline, Embase, CINAHL and PsycINFO (from inception) using the relevant keywords and MeSH terms (Supplementary 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 utilized a prospective or retrospective observational study design, quantitatively measured secondary adherence (also known as "implementation")[19] and were published in English, French, Spanish, Persian, Finnish, Cantonese or Korean.[24] No limitations were imposed on setting, country, publication date, or quality.

While we were primarily interested in OAC adherence in non-valvular AF (NVAF) patients, we included studies that did not specifically restrict inclusion to this population, with notation in quality assessment. Studies of self-reported adherence were excluded 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 standard deviation (SD) of patients' adherence at six or twelve months. Secondary adherence measure included corresponding

proportions of adherent patients (proportion of patients with mean adherence ≥ the threshold specified by the corresponding authors, usually 80%). Six or twelve months were chosen as these were the most common follow-up times. If a study had variable follow-up time (e.g. 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 analyzed to minimize 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 grouped these under the World Health Organization's (WHO) five dimensions of medication adherence.[25] Finally, we extracted information on the clinical and economic consequences of poor adherence.

Data analysis

Meta-analyses were carried out using Der Simonian & Laird random-effects models to determine the pooled mean adherence and the corresponding pooled proportion of adherent patients [those with mean score >80 (the conventional threshold for "good adherence")] at six-month and one-year of observation.[26, 27] 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, and 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 odds ratio 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,

WA)[30] or RevMan5 (version 5.3, Copenhagen, Denmark) software to illustrate the results and assess publication bias.[31] Clinical and economic impacts of poor adherence were summarized 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 ISPOR Group.[32] We also critically appraised individual study quality using STROBE.[33] Studies received a point for each checklist item they met and a zero 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 categorized as low, moderate or high quality if they scored ≤50%, 51-80%, or >80%, respectively.[34, 35]

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 past a potential conflict of interest with the study sponsor when the sponsor was a for-profit manufacturer or marketer of any of the OACs included in the corresponding study.[36]

Patient and Public involvement

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

Ethical approval

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

RESULTS

Systematic review of the literature led to inclusion of 30 studies[37-66] (Figure 1.0) involving 593,683 participants (NOAC: 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). A majority of the studies had high (59%) or moderate (38%) quality of adherence measurement (Supplementary 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%) at six-month or one-year post index date (Table 2). 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)[60, 63, 66] to 86[57] at six months and 57[60] to 86[43] at one-year post index date, with corresponding reported proportion of adherent patients ranging between 47%[61] to 82%[58] at six months and 41%[60] to 95%[47] at one year. Wide range of adherence results were observed even at the individual OAC level (Table 2).

Pooled mean adherence scores at six-month and one-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 NOACs, although adherence to apixaban and rivaroxaban was slightly higher than dabigatran (Table 3). There was insufficient information on warfarin for inclusion in meta-analysis, therefore, no drug class comparison could be made. Figure 2.0 illustrates the forest plots for patients' mean adherence score at six-month and one-year. The remaining forests plots, including forest plots of mean adherence, adherence to individual OACs, subgroup analyses [by adherence measure (PDC and MPR), study quality and potential for conflict of interest] can be found in supplementary 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 versus MPR), or country (USA versus others) had only minor impacts on pooled adherence results and the detected heterogeneity (Supplementary 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).[37-39, 41-47, 51, 52, 54, 57-60, 62, 64] Odds of being adherent was significantly higher for apixaban compared to dabigatran at both six-month (Odds Ratio (OR):1.24, 95% CI: 1.07-1.45) and one-year post index date (OR:1.76, 95% CI:1.35-2.29). Odds of adherence was significantly higher for rivaroxaban compared to dabigatran at six-months (OR:1.39, 95%CI: 1.15-1.67), but not one-year (OR:1.17, 95%CI: 0.38-3.60). Odds of adherence did not differ between apixaban

and rivaroxaban at six-months (OR:0.80, 95% CI: 0.51-1.24) or one-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.[39, 52, 58] McHorney et al. reported greater mean PDC score for both rivaroxaban and apixaban (0.90 and 0.88, respectively) among prior OAC users compared to naïve users (0.87 and 0.86, respectively).[58] Borne et al. reported a higher mean PDC score for apixaban users with prior warfarin experience compared to naïve users (0.89±0.14 vs naïve: 0.87±0.15, P < 0.01).[39] Confirming these results, Manzoor et al. reported higher mean PDC for experienced users compared to naïve users at six-month (83.3±24.6 vs 72.3±31.3; p< 0.05), nine-month (81.2±26.4 vs 67.3±33.8); p< 0.05) and one-year (79.9±27.6 vs 63.7±35.2; p <0.05).[52]

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 to those prescribed after discharge at three months (84.5% vs 12.3%; P<0.001) and one year (91.6% vs 16.8%; P<0.001).[46]

Determinants of adherence

Significant predictors of higher adherence to OACs included: **Patient factors:** history of hypertension[45, 51], diabetes[39] stroke[39, 54]; **Condition factors:** higher risk of bleeding[45]; **Regimen factors:** once daily dosing[37, 51], concomitant use of statin[45, 54], angiotensin converting enzyme inhibitor or angiotensin II receptor blockers[45, 54]; and **Social/economic factors:** living in rural or deprived areas.[54, 55] Predictors of lower adherence to OAC were: being a naïve OAC user[52, 58], twice daily dosing[37, 51] and impaired cognitive or functional ability.[58] No healthcare system related predictors of adherence were identified.

Conflicting results were reported for female sex[49, 50, 55], age[39, 45, 49-52, 54, 55], risk of stroke[45, 49, 55], presence of multiple comorbidities[45, 52, 53, 58], and higher number of concomitant medications.[52, 53] 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.[37, 39, 40, 44] Alberts et al. reported 50% increased hazard with NOAC non-adherence.[37] Desphande et al. reported non-adherent patients

to be 1.82 times (aHR:1.82, 95% CI: 1.24 to 2.67; p= 0.002) and 2.08 times (aHR:2.08, 95%CI: 1.11 to 3.89; p=0.02) more likely to experience an ischemic stroke compared to adherent patients, over six and 12 months, respectively.[44] 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 to 1.12; p< 0.01)[39] and Casiano et al. reported a significantly higher total number of bleeds (major, minor, other) in non-adherent patients [152 (2.79 per 100 person-years)] compared to adherent patients [97 (2.62 per 100 person-years)].[40]

Two studies measured the economic impacts of adherence. Casciano et al. reported significantly more inpatient and emergency room encounters and longer length of stay for non-adherent patients compare to adherent patients[40] and Desphande et al. reported significantly higher annual adjusted per-patient medical cost (inpatient and outpatient) for non-adherent users compared to adherent ones ($30,485 versus $23,544; p≤0.001).[45]

DISCUSSION

In this systematic review, we synthesized observational data of over half a million AF patients to reveal the extent of adherence to OACs, identify the determinants of adherence among AF patients that could potentially be targeted by interventions to improve it, and assessed the clinical and economic impacts of non-adherence in this patient population.

AF patients' adherence to their OACs has been thoroughly studied in developed countries. Pooled proportion of adherent AF patients at six-month and one-year was 63% and 70%, respectively, which is higher than other chronic cardiovascular medications such as statins (54%) and antihypertensives (59%).[67] However, our finding that up to 37% of AF patients do not adhere to OACs is concerning considering the detrimental consequences of nonadherence to these medications. We were unable to ascertain whether the conveniences of NOACs translates into better adherence compared to 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 NOACs, however, adherence was found to be similar, although dabigatran appeared to have slightly lower adherence than apixaban and rivaroxaban.

Many patient-, condition-, regimen- and social/economic-related factors were identified by the included studies as significant determinants of adherence. 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 patient knowledge gaps, misconceptions, and varying values and preferences, all of which have frequently been reported in AF patients.[35, 68-74] 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 adherence. Our review found evidence of association between lower adherence and strokes, bleeds, death, healthcare utilization and costs. This supports the potential of interventions aimed at increasing OAC adherence in AF patients.

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.[37, 40-42, 52, 66] 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 (e.g. OAC naïve versus experienced); methods for handling and defining medication switches, stockpiling, refill gaps, and hospitalization dates; fixed versus variable observational periods and adherence measure used (PDC versus 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,[19, 75] 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 AF patients' medication taking behaviour.

FUTURE DIRECTIONS

Our understanding of AF patients' comparative adherence between warfarin and NOACs 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 nonadherence to OACs. All of the current studies have treated adherence as a static behavior, calculating and reporting it using a single summary measure. This methodological approach does not provide a complete picture of adherence, which is a dynamic behavior that changes over time.[26, 76] Characterization 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.[77-81]

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. While the association between taking >80% of medications and improved clinical outcomes has been shown in three AF studies, it remains unclear if this is the optimal threshold for AF. Clinically relevant adherence cut-off values have been shown to differ widely (from 58% to 85%) in different diseases, and even among drug classes.[82, 83] As with antiretroviral medications, given the detrimental consequences of OAC nonadherence, the clinically meaningful threshold for "good adherence" to OACs may need to be much higher than 80%.[83]

CONCLUSION

Synthesis of observational data suggests that overall OAC adherence in AF is below the conventional threshold of "adherent" (80%). These findings, combined with evidence that lower adherence is associated with poor clinical outcomes, 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 characterize 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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COMPETING INTERESTS

Authors have no competing interests to declare.

CONTRIBUTIONS

Conceived the study: SS, PL, MDV; Designed the search strategy: SS, MDV, PL; Conducted the literature search: SS; Screened titles and abstracts: SS, RT; Screened full texts: SS, RT; Extracted data: SS, RT; Analyzed the data: SS; Conducted quality assessment; SS, RT; Interpreted the results: SS, PL, MDV; Prepared the manuscript: SS, MDV, PL, RT;

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TABLES:

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	2016	Retrospective	USA	36,868 (55%)	76%>65 years	NVAF	NA	Both	Yes	61%	67%
Beyer-Westendorf	2016	Retrospective	Germany	7,265 (52%)	NA	NVAF	Index OAC	Naïve	Yes	73%	74%
Borne	2017	Retrospective	USA	2,882 (97%)	67.4 (9.5)	NVAF	NA	Naïve to DOACs‡	Yes	73%	78%
Brown	2016	Retrospective	USA	5,223 (40%)	59%≥65 years	NVAF	Both	Naïve	Yes	77%	84%
Casciano	2013	Retrospective	USA	13,289 (47%)	78% ≥75 years	AF	NA	Naïve	Yes	63%	79%
Coleman	2016	Retrospective	USA	21,756 (54%)	66.5 (12.2)	NVAF	NA	Naïve	Yes	55%	50%
Coleman	2017	Retrospective	USA	106,227 (63%)	71.1 (11.0)	NVAF	Index OAC	Naïve	Yes	77%	84%
Crivera	2015	Retrospective	USA	9,948 (53%)	75.5 (8.3)	NVAF	Both	Naïve	Yes	73%	61%
Deshpande PMID: 29694285	2018	Retrospective	USA	2,981 (70%)	64.4 (10.7)	AF	NA	Naïve to DOACs‡	No	77%	83%
Desphande PMID: 29334815	2018	Retrospective	USA	4,856 (52%)	65.0 (10.5)	Both	NA	Naïve	No	81%	83%
Lapen	2014	Retrospective	USA	2,691 (43%)	100%>65 years	AF	NA	Both	No	76%	74%
Forsuland	2016	Retrospective	Sweden	16,096 (52%)	75.45 (SD not reported)	NVAF	Current OAC	Both	No	63%	61%
Gomez-Iumberas	2018	Retrospective	Spain	854 (NA%)	73.2 (11.0)	NVAF	NA	Both	Yes	50%	67%
Gorst-Rasmussen	2015	Retrospective	Denmark	2,960 (54%)	72.1 (10.8)	NVAF	Index OAC	Naïve	Yes	80%	100%
Harper	2018	Retrospective	New Zealand	20,237 (NA%)	83%>60	NVAF	NA	NA	No	47%	53%
Jacobs	2018	Retrospective	Sweden & Netherlands	5,684 (60%)	78%≥65 years	AF	Current OAC	Both	Yes	80%	83%
Manzoor	2017	Retrospective	USA	66,090 (62%)	68.7 (12.1)	AF	Index OAC	Both	Missing	70%	85%
Márquez-Contrera	2016	Prospective	Spain	412 (42%)	75.2 (7.5)	NVAF	NA	Experienced	Yes	63%	83%
Maura	2017	Retrospective	France	22,267 (53%)	74.0 (10.8)	NVAF	Index	Naïve	No	79%	100%
McAlister	2018	Retrospective	Canada	57,669 (56%)	100%>65 years	NVAF	Current OAC	Naïve	No	87%	94%
McCormick	2001	Retrospective	USA	429 (22%)	87 (7.1)	AF	Current OAC	Experienced	No	60%	82%
McHorney	2017	Retrospective	USA	36,675 (67%)	63.1 (SD not reported)	NVAF	Index OAC	Naïve	Yes	87%	89%
McHorney	2018	Retrospective	USA	41,201 (58%)	NA	NVAF	Index OAC	Both	Yes	84%	100%
Mueller	2017	Retrospective	Scotland	5,398 (54%)	74.4 (11.3)	AF	NA	NA	No	70%	53%
Pham	2019	Retrospective	USA	38,947 (60%)	100%>65 years	NVAF	Index OAC & any OAC	Naïve	No	77%	89%
Shore	2014	Retrospective	USA	5,376 (98%)	71.3 (9.7)	NVAF	Index OAC	NA	No	90%	94%
Sørensen	2017	Retrospective	Denmark	46,675 (58%)	79%>65 years	NVAF	Current OAC	Naïve	Yes	67%	79%

Tsai	2013	Retrospective	USA	17,691 (49%)	76.4 (8.7)	NA	Current OAC	Warfarin Naïve and warfarin experienced	No	60%	78%
Yao	2016	Retrospective	USA	64,661 (56%)	75% >65	AF	Index OAC	Naïve	No	77%	84%
Zhou	2015	Retrospective	USA	5,951 (34%)	36.1%>65	AF	Index OAC	Naïve	No	80%	79%

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

Study (year)	Adherence measure (Threshold)	Adherence results 6 months		Adherence results 1 year	
		Mean adherence score ± SD	Proportion adherent	Mean adherence score ± SD	Proportion adherent
Proportion Days Covered (PDC)					
Alberts (2016)	PDC (>80%)	NA	NA	NA	Overall: 0.70 A and D: 0.68 R: 0.73
Borne (2017)	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 (2016)	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 (2013)	PDC (>80%)	NA	NA	NA	W: 0.41
Coleman (2016)	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 (2017)	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 (2015)	PDC (>80%)	NA	NA	**Index NOAC:** 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 NOAC:** A: 0.71 D: 0.68 R: 0.75 **Any OAC:** A: 0.71 D: 0.73 R: 0.77
Deshpande (2018) PMID: 29694285	PDC (≥80%)	NA	R and D: 0.65	NA	R and D: 0.54
Desphande (2018) PMID: 29334815	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 (2016)	PDC (>80%)	NA	NA	NA	A: 0.93 D: 0.92 R: 0.96
Gorst-Rasmussen (2015)	PDC (>80%)	0.84 ± 0.28	NA	NA	D: 0.77
Harper (2018)	PDC (>80%)	NA	NA	NA	D: 0.84
Manzoor (2017)	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 (2017)	PDC>80	NA	NA	NA	**Index OAC:** Overall: 0.71 D: 0.70

					R: 0.72
McHorney (2017)	PDC (>80% & >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 (2018)	PDC (>80% & >90%)	NA	**PDC80:** A:0.78 R: 0.82 **PDC90:** A: 0.60 R: 0.67	NA	NA
Pham (2019)	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 (2014)	PDC (>80%)	NA	D: 0.28	NA	NA
Sørensen (2017)	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 (2013)	PDC (no threshold)	D: warfarin-naïve: 0.67 ± 0.36 warfarin-experienced: 0.71 ± 0.35	NA	NA	NA
Yao (2016)	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 (2016)	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 (2014)	MPR (no threshold)	NA	NA	Median (IQR): 0.77 (0.51- 0.98)	NA
Gomez-lumberas (2018)	MPR (>0.8)	NA	NA	NA	A: 0.62
Jacobs (2018)	MPR (≥0.8)	NA	NA	NA	Sweden: 0.95 Netherlands: 0.93
McHorney (2017)	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 (2015)	MPR (>0.8)	D: 0.73 ± 0.30	D: 0.59	D: 0.65 ± 0.35	D: 0.51
Mueller (2017)	MPR>80‡	NA	NA	NA	DOACs: 0.82 A: 0.88 D: 0.65 R: 0.83

Márquez-Contrera (2016)	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 (2018)	TTR>65% (INR2-3)	NA	W: Percent patients with time in therapeutic range: 4.11%	NA	NA

Footnote:
PDC: proportions days covered; MPR: medication possession ratio; CP: Compliance percentage; TTR: Time in therapeutic range; USA: United States of America; NA: Not available/not applicable; aHR: adjusted Hazard ratio; VKA: Vitamin K antagonist. A: apixaban; D: dabigatran; R: rivaroxaban; W: warfarin.
Drug specific proportion of adherent patients was calculated as the percent 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

Table 3: Pooled adherence results

	Adherence at 6 months post index date		Adherence at 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)
Sub-analysis: 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	One study	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)
Sub-analysis: 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)
Sub-analysis: 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)

***I^2 <80%.**

+ Not pooled. Based on one study

++ Pooled results of only two studies

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	
	Number of unique studies	Odds ratio (95% CI)	Number of unique studies	Odds ratio (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)
Sub-analysis: 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)

***I^2 <80%.**
+ Not pooled. Based on one study

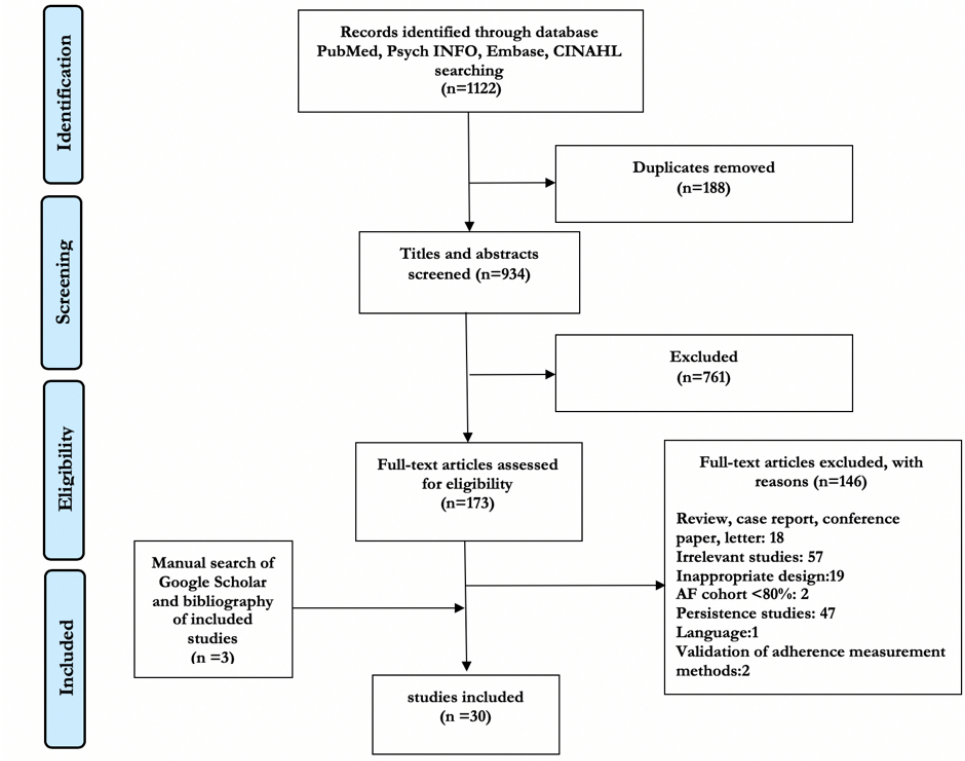


Figure 1.0: PRISMA flow diagram.

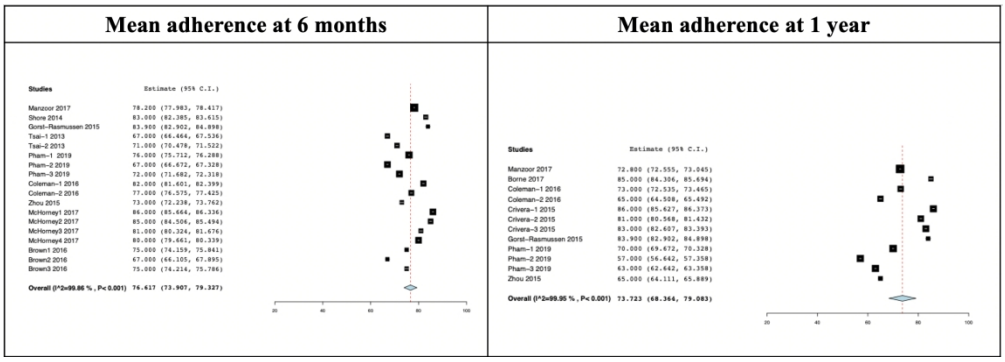


Figure 2.0: Atrial fibrillation patients' mean adherence score at six-months and one-year

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Cover page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Inclusion/Exclusion criteria
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Search strategy
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary File 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Inclusion/Exclusion criteria , Study selection and data extraction
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Study selection and data extraction
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Study selection and data extraction
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Quality assessment, data analysis, supplementary file

PRISMA 2009 Checklist

			3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Data analysis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Data analysis

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Quality assessment, data analysis, supplementary file 3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Data analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results (1st paragraph)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Quality assessment, supplementary file 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 3,4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary file 4.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 3
DISCUSSION			

PRISMA 2009 Checklist

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion, future directions
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies		
Background		
	Problem definition	Introduction
	Hypothesis statement	Introduction
	Description of study outcomes	Introduction
	Type of exposure or intervention used	Introduction
	Type of study design used	Introduction
	Study population	Introduction
Search Strategy		
	Qualification of searchers	Search strategy
	Search strategy including time periods included in the synthesis and keywords	Search strategy
	Effort to include all available studies, including contact with authors	Search strategy
	Databases and registries searched	Search strategy
	Search software used, name and version, including special features used	Google
	Use of hand searching	Search strategy
	List of citations located and those excluded	PRISMA flow chart
	Method of addressing articles published in languages other than English	All included articles were in English
	Method of handling abstracts and unpublished studies	Study selection
	Description of any contact with authors	All relevant information for this systematic review could be find in the published reports. There was no need to contact the respective authors
Methods		
	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Inclusion criteria and study selection
	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Inclusion criteria and study selection
	Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Inclusion criteria and study selection
	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Data analysis. Quality assessment
	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Data analysis. Quality assessment
	Assessment of heterogeneity	Data analysis
	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response	Data analysis

	models, or cumulative meta-analysis) in sufficient detail to be replicated	
	Provision of appropriate tables and graphics	Figure 1
Results		
	Graphic summarizing individual study estimates and overall estimate	Figures 2 and 3
	Table giving descriptive information for each study included	Tables 1 and 2
	Results of sensitivity testing (eg, subgroup analysis)	Table 3
	Indication of statistical uncertainty of findings	Results: adherence
Discussion		
	Quantitative assessment of bias (eg, publication bias)	Supplementary file
	Justification for exclusion (eg, exclusion of non–English-language citations)	Inclusion criteria and study selection. Limitations
	Assessment of quality of included studies	Supplementary file. Results Table 1
Conclusion		
	Consideration of alternative explanations for observed results	Discussion
	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Limitations
	Guidelines for future research	Future directions
	Disclosure of funding sources	Funding

Supplementary file 1: Literature search

Concept	Keywords	MeSH terms (Pubmed)
Medications	Anticoagulant* OR "blood thinner" OR "Vitamin K antagonists"OR "new oral anticoagulants" OR VKA OR NOAC OR DOAC OR Apixaban OR Eliquis OR dabigatran OR "dabigatran etexilate" mesylate OR pradaxa OR edoxaban OR lixiana OR rivaroxaban OR xarelto OR warfarin OR coumadin OR betrixaban OR bevyxxa OR acenocoumarol OR phenprocoumon OR fluindione	Warfarin Anticoagulants Dabigatran Rivaroxaban
Adherence	Adherence OR persistence OR compliance "Medication taking" OR "discontinuation" OR "nonpersistence" OR "nonadherence" OR "noncompliance"	Treatment Adherence and Compliance"[Mesh])
Atrial fibrillation	"atrial fibrillation" OR NVAF OR "non-valvular atrial fibrillation"	atrial fibrillation

Complete search example for Pubmed:
(((((((("atrial fibrillation") OR NVAF) OR "non-valvular atrial fibrillation")) AND (((((((Adherence) OR noncompliance) OR discontinuation) OR nonpersistence) OR nonadherence) OR persistence) OR "Medication taking") OR compliance)) AND ((((((((((((((((((((((((Anticoagulant*) OR "blood thinner") OR "Vitamin K antagonists") OR "new oral anticoagulants") OR VKA) OR NOAC) OR DOAC) OR Apixaban) OR Eliquis) OR dabigatran) OR "dabigatran etexilate") OR "dabigtaran mesylate") OR pradaxa) OR edoxaban) OR lixiana) OR rivaroxaban) OR xarelto) OR warfarin) OR coumadin) OR betrixaban) OR bevyxxa) OR acenocoumarol) OR phenprocoumon) OR fluindione))) AND "Atrial Fibrillation"[Mesh]) AND (("Treatment Adherence and Compliance"[Mesh]) OR ("Warfarin"[Mesh] OR "Anticoagulants"[Mesh] OR "Dabigatran"[Mesh] OR "Rivaroxaban"[Mesh]))):

STROBE	CODE	Alberts 2016	Beyer-Westendorf 2016	Borne 2017	Brown 2016	Casciano 2013	Coleman 2016	Coleman 2017	Civera 2015	Deshpande 2018 PMID: 29694285	Deshpande 2018 PMID: 29334815	Eapen 2014	Forsuland 2016	Gomez-Lumberas 2018	Gorst-Rasmussen 2015	Harper 2018	Jacobs 2018	Manzoor 2017	Marquez 2016	Maura 2017	McAlister 2018	McCormick 2001	McHorney 2017	McHorney 2018	Mueller 2017	Pham 2019	Shore 2014	Sorensen 2017	Tsai 2013	Yao 2016	Zhou 2015
Title and abstract																															
Indicate the study's design with a commonly used term in the title or the abstract	1a	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0
Provide in the abstract an informative and balanced summary of what was done and what was found.	1b	0	1	1	1	1	0	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Background/rationale: Explain the scientific background and rationale for the investigation being reported	2	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1
Objective: State specific objectives, including any prespecified hypothesis.	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Study design: Present key elements of study design early in the paper	4	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Setting: Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	5	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1
Participants: Give the eligibility criteria, and the sources and methods of selection of participants	6a	1	1	1	1	0	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1
For matched studies, give matching criteria and number of exposed and unexposed	6b	1	NA	NA	NA	NA	1	1	NA	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	NA	NA	NA	NA	NA	1	NA
Variables: Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	7	0	1	0	1	0	0	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
Data sources/measurement: For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one grou	8	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Bias: Describe any efforts to address potential sources of bias (e.g. Propensity score)	9	1	0	0	0	0	1	1	0	1	1	0	0	0	0	0	1	1	1	1	0	1	1	1	0	1	1	0	0	0	0
Study size: Explain how the study size was arrived at.	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Quantitative variables/ statistical analysis:																															
Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why. (categorizing)	11	0	1	1	1	1	0	0	0	0	0	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1
Describe all statistical methods, including those used to control for confounding	12a	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1
Describe any methods used to examine subgroups and interactions	12b	1	0	1	1	0	0	1	1	1	1	1	0	0	1	0	1	1	0	1	1	0	1	1	0	0	1	0	1	1	1
Explain how missing data were addressed	12c	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0	0	0	0
Cohort study: If applicable, describe how loss to follow-up was addressed.	12d	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Describe any sensitivity analyses	12e	0	1	1	0	0	0	0	0	0	0	0	1	0	1	0	1	1	0	1	1	0	1	1	0	0	1	1	0	1	1
Participants:																															
Report the numbers of individuals at each stage of the study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed.	13a	0	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	0	0	1	1	0	1	1	1	1	1	1	0	0	1
Give reasons for non-participation at each stage	13b	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Consider use of a flow diagram	13c	0	1	1	1	1	0	1	1	1	1	1	1	0	1	0	0	0	0	1	1	0	1	1	1	1	1	1	0	0	1
Descriptive data:																															
Give characteristics of study participants (e.g. demographic, clinical, social) and	14a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

information on exposures and potential confounders																														
Indicate the number of participants with missing data for each variable of interest.	14b	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0
Summarise follow-up time (eg, average and total amount)	14c	1	1	1	0	1	1	1	1	0	1	1	0		0	0	1	0	1	1	0	0	1	0	1	0	1	0	0	1	0
Outcome data: Report numbers of outcome events or summary measures over time	15	0	1	0	1	0	1	0	0	1	1	1	0	0	0	0	0	1	0	0	1	0	1	1	1	1	1	0	0	1	1
Main results																															
Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	16a	1	0	0	1	0	0	0	1	1	1	1	0	0	1	0	1	0	1	NA	1	1	1	1	0	0	1	1	0	1	1
Report category boundaries when continuous variables were categorized.	16b	1	1	1	1	1	1	1	1	1	1	NA	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	16c	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Other analysis: Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses.	17	1	1	1	1	1	0	1	1	1	1	1	0	1	0	1	1	0	1	1	0	1	1	1	1	1	1	0	1	1	1
Key results: Summarize key results with reference to study objectives.	18	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Limitations: Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	19	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Interpretation: Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Generalizability: Discuss the generalizability (external validity) of the study results	21	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1
Funding: Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1
Sum		19	22	22	23	19	17	24	22	23	25	22	19	15	24	14	24	21	20	23	26	18	26	26	21	23	27	20	18	24	24
Total applicable		31	30	30	30	30	31	31	30	30	31	29	30	30	30	30	30	30	32	29	30	30	30	31	30	30	30	30	30	31	30
Score		0.612903	0.733333	0.73333	0.766667	0.633333	0.548387	0.774193	0.733333	0.766667	0.806451	0.75862	0.633333	0.5	0.8	0.466667	0.8	0.7	0.625	0.793103	0.866667	0.6	0.866667	0.838709	0.7	0.766667	0.9	0.666667	0.6	0.774193	0.8
Percent		61	73	73	77	63	55	77	73	77	81	76	63	50	80	47	80	70	63	79	87	60	87	84	70	77	90	67	60	77	80

Item No	ISPOR	Albert s 2016	Beyer - Westendorf 2016	Borne 2017	Brown 2016	Cascia no 2013	Coleman 2016	Coleman 2017	Civera 2015	Deshpande 2018 PMID: 29694285	Deshpande 2018 PMID: 29334815	Eapen 2014	Forsuland 2016	Gomez-Lumberas 2018	Gorst - Rassussen 2015	Harper 2018	Jacobs 2018	Manzoor 2017	Marquez 2006	Maura 2017	McAlister 2018	McCormick 2001	McHorney 2017	McHorney 2018	Mueller 2017	Pharm 2019	Shore 2014	Sorenson 2017	Tsai 2013	Yao 2016	Zhou 2015
	Title / Abstract																														
1	Title is descriptive and reflective of study purpose	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	1	1	0	1	1	0	0	1	0	0	0	0
2	Abstract is a concise and accurate, reflecting contents of the study	0	1	1	1	1	0	1	0	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Introduction																														
	Clear review of fundamental literature related to topic	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Objectives and Definitions																														
	Objective(s) stated?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Design and Methods																														
	Study design appropriate for objectives	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Data sources adequately described	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1
	Evidence provided for reliability / acuracy of data	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0
	Sampling methods described	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Well describe patient population and Subject inclusion / exclusion criteria stated	1	1	1	1	0	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1
10	Sufficient data to make valid estimate of compliance (i.e. Continuous eligibility for drug during study period verified)	0	1	1	1	1	1	1	0	1	1	1	0	1	1	0	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1
11	Sufficient pre-enrollment period to ensure drug naivety? (If applicable)	NA	1	NA	1	1	NA	1	NA	NA	NA	1	NA	NA	NA	0	NA	1	NA	1	1	NA	1	1	0	1	NA	1	NA	1	1
12	Explanation of how patients who switched drugs within or between therapeutic classes were handled	0	0	0	1	0	0	1	1	0	0	0	1	0	1	0	1	1	0	1	NA	NA	0	1	0	1	1	0	1	1	1
13	Explicit definition of compliance/persistence based on published, accepted definition?	1	1	1	1	1	0	1	0	1	1	1	0	1	1	0	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1
14	Methods for calculating compliance / persistence clearly described (and matches operational definition)	1	1	1	0	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1
15	Was handling of medication gaps described	0	0	0	1	1	0	0	0	1	1	0	0	0	1	1	0	0	1	1	1	0	0	1	0	1	1	0	0	0	0
16	Follow-up period specified	1	1	1	1	1	1	1	0	1	1	1	0	0	1	0	0	1	1	1	1	1	1	1	1	0	1	1	1	1	0
17	Statistics appropriate to design and data	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
18	Test statistics are reported appropriately (i.e. CIs, p-values reported)	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1
19	Appropriate descriptive data on study sample are presented	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
20	Distribution of compliance/persistence variable is presented (i.e. proportion of discontinuers)	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1
	Sum	12	14	14	16	15	9	16	11	15	15	14	11	12	18	10	15	17	15	19	17	14	17	19	10	17	17	15	14	16	15
	Total Applicable	18	19	18	19	19	18	19	18	18	18	19	18	18	18	19	18	20	18	19	18	17	19	19	19	19	18	19	18	19	19
	Score	0.666667	0.736842	0.777778	0.842105	0.789474	0.5	0.842105	0.611111	0.833333	0.833333	0.736842	0.611111	0.666667	1	0.5263	0.833	0.85	0.833333	1	0.944444	0.823529	0.894737	1	0.526315	0.895	0.944	0.789473	0.778	0.842	0.789
	Percent	67	74	78	84	79	50	84	61	83	83	74	61	67	100	53	83	85	83	100	94	82	89	100	53	89	94	79	78	84	79

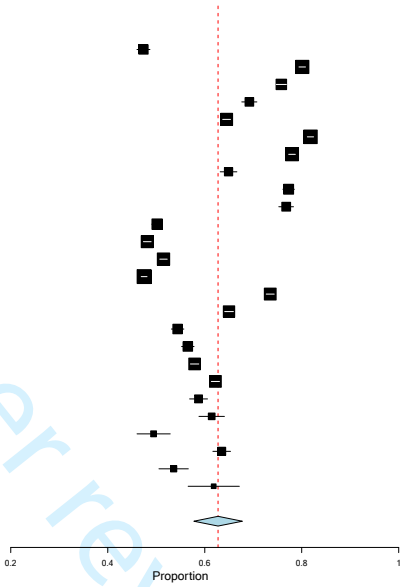
Supplementary 4.0: Forest plots

All OACs

Adherence at 6 months

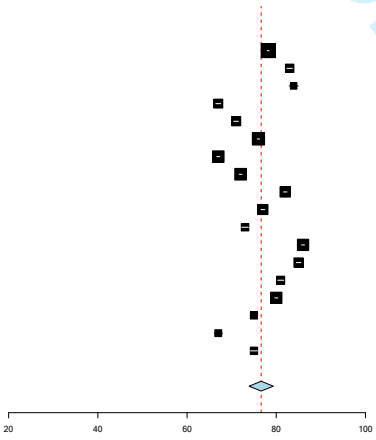
Proportion adherent at 6 months

Studies	Estimate (95% C.I.)	Ev/Trt
Shore 2014	0.474 (0.460, 0.487)	2546/5376
McHorney1 2017	0.801 (0.794, 0.808)	10930/13645
McHorney2 2017	0.758 (0.747, 0.769)	4778/6304
McHorney3 2017	0.692 (0.676, 0.708)	2325/3360
McHorney4 2017	0.645 (0.637, 0.653)	8621/13366
McHorney−1 2018	0.818 (0.812, 0.824)	11362/13890
McHorney−2 2018	0.780 (0.773, 0.787)	10834/13890
Desphande−1 2018	0.649 (0.632, 0.666)	1935/2981
Desphande−2 2018	0.773 (0.761, 0.785)	3753/4856
Gorst−Rasmussen 2015	0.768 (0.753, 0.783)	2273/2960
Pham−1 2019	0.502 (0.491, 0.513)	4054/8078
Pham−2 2019	0.481 (0.473, 0.489)	7156/14864
Pham−3 2019	0.515 (0.507, 0.523)	8241/16005
Yao−1 2016	0.475 (0.469, 0.481)	12574/26471
Coleman−1 2016	0.735 (0.727, 0.743)	7929/10787
Coleman−2 2016	0.650 (0.641, 0.659)	7012/10787
Coleman−3 2017	0.544 (0.531, 0.557)	3135/5762
Coleman−4 2017	0.565 (0.552, 0.578)	3256/5762
Coleman−5 2017	0.579 (0.570, 0.588)	7303/12613
Coleman−6 2017	0.622 (0.614, 0.630)	7845/12613
Zhou 2015	0.587 (0.569, 0.606)	1593/2713
Beyer−Westendorf−1 2016	0.614 (0.588, 0.641)	809/1317
Beyer−Westendorf−2 2016	0.495 (0.460, 0.529)	406/821
Brown1 2016	0.635 (0.617, 0.653)	1711/2695
Brown2 2016	0.536 (0.506, 0.566)	561/1047
Brown3 2016	0.618 (0.566, 0.671)	201/325
Overall (I^2=99.84 % , P< 0.001)	0.627 (0.578, 0.677)	133143/213288



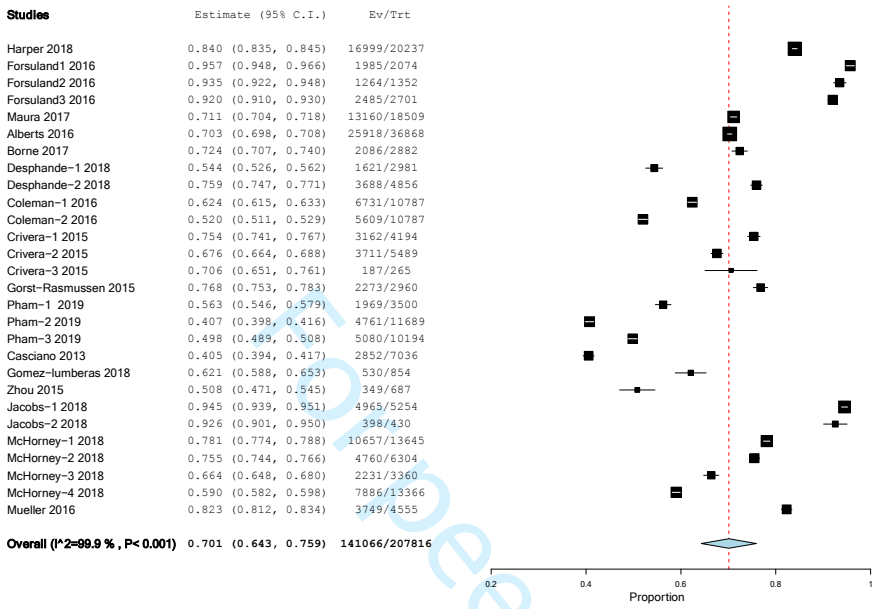
Mean adherence score at 6 months

Studies	Estimate (95% C.I.)
Manzoor 2017	78.200 (77.983, 78.417)
Shore 2014	83.000 (82.385, 83.615)
Gorst−Rasmussen 2015	83.900 (82.902, 84.898)
Tsai−1 2013	67.000 (66.464, 67.536)
Tsai−2 2013	71.000 (70.478, 71.522)
Pham−1 2019	76.000 (75.712, 76.288)
Pham−2 2019	67.000 (66.672, 67.328)
Pham−3 2019	72.000 (71.682, 72.318)
Coleman−1 2016	82.000 (81.601, 82.399)
Coleman−2 2016	77.000 (76.575, 77.425)
Zhou 2015	73.000 (72.238, 73.762)
McHorney1 2017	86.000 (85.664, 86.336)
McHorney2 2017	85.000 (84.506, 85.494)
McHorney3 2017	81.000 (80.324, 81.676)
McHorney4 2017	80.000 (79.661, 80.339)
Brown1 2016	75.000 (74.159, 75.841)
Brown2 2016	67.000 (66.105, 67.895)
Brown3 2016	75.000 (74.214, 75.786)
Overall (I^2=99.86 % , P< 0.001)	76.617 (73.907, 79.327)

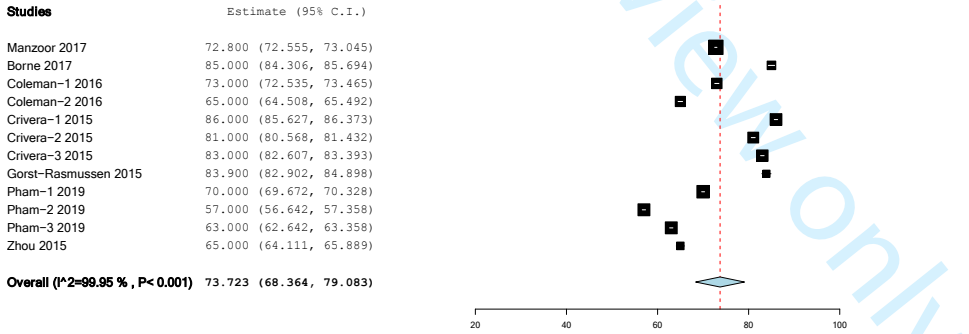


Adherence at 1 year

Proportion adherent at 1 year



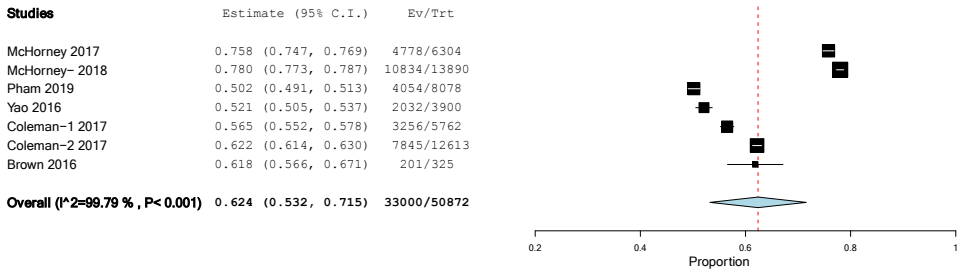
Mean adherence at 1 year



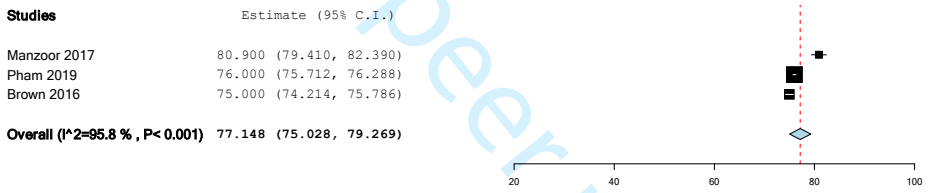
Apixaban

Adherence at 6 months

Proportion adherent at 6 months

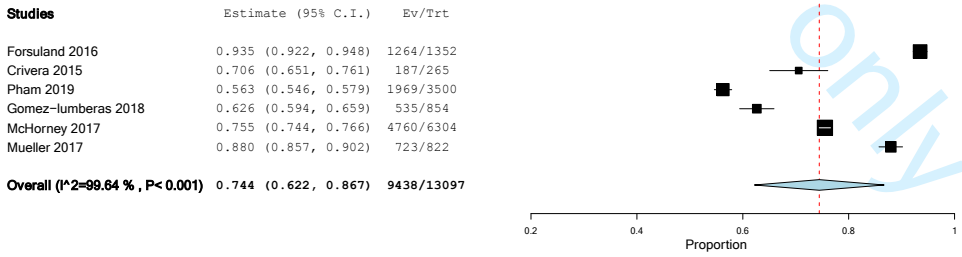


Mean adherence at 6 months

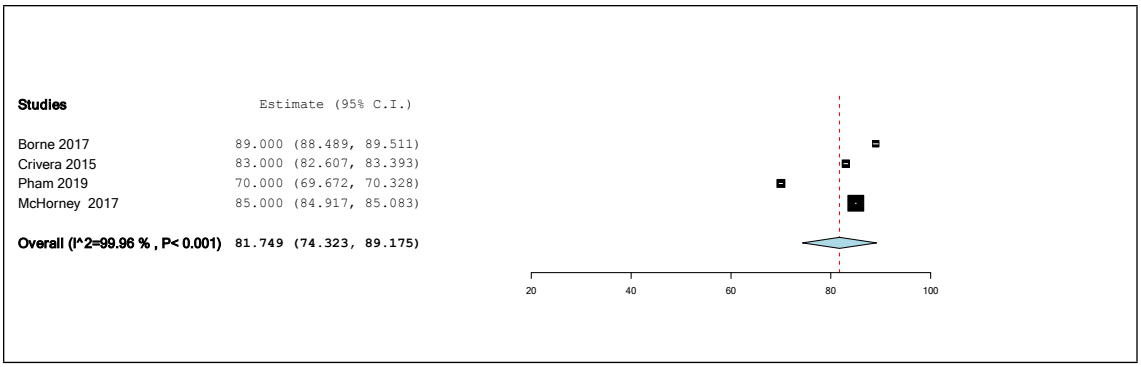


Adherence at 1 year

Proportion adherent at 1 year



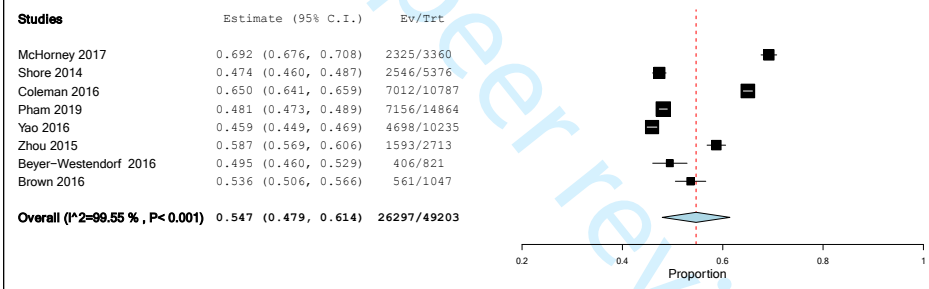
Mean adherence at 1 year



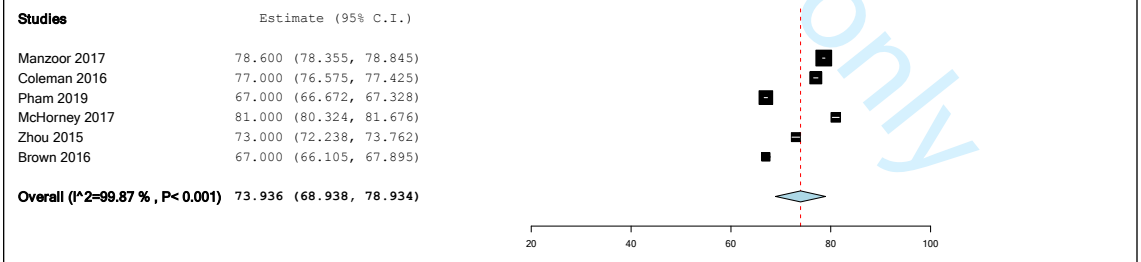
Dabigatran:

Adherence at 6 months

Proportion adherent at 6 months

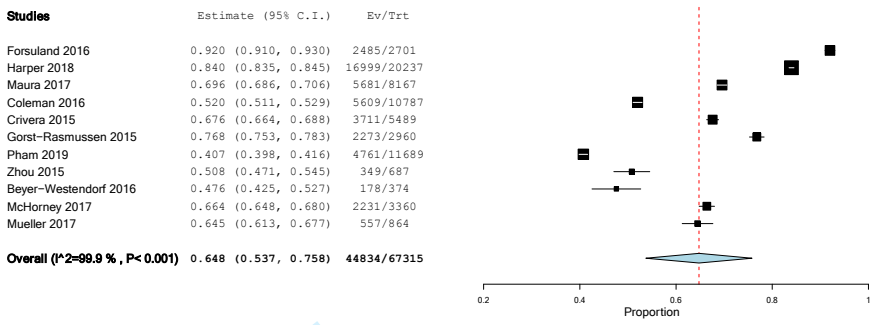


Mean adherence at 6 months

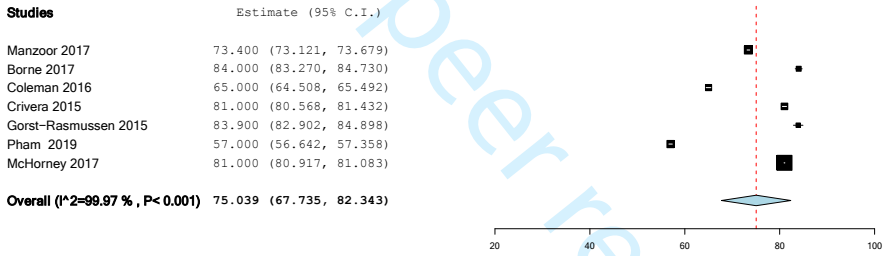


Adherence at 1 year

Proportion adherent at 1 year



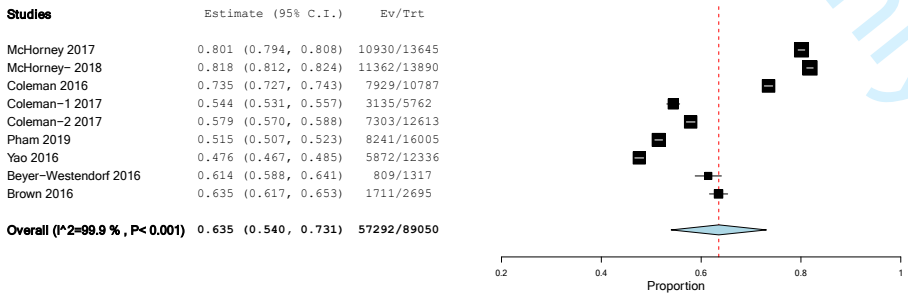
Mean adherence at one year



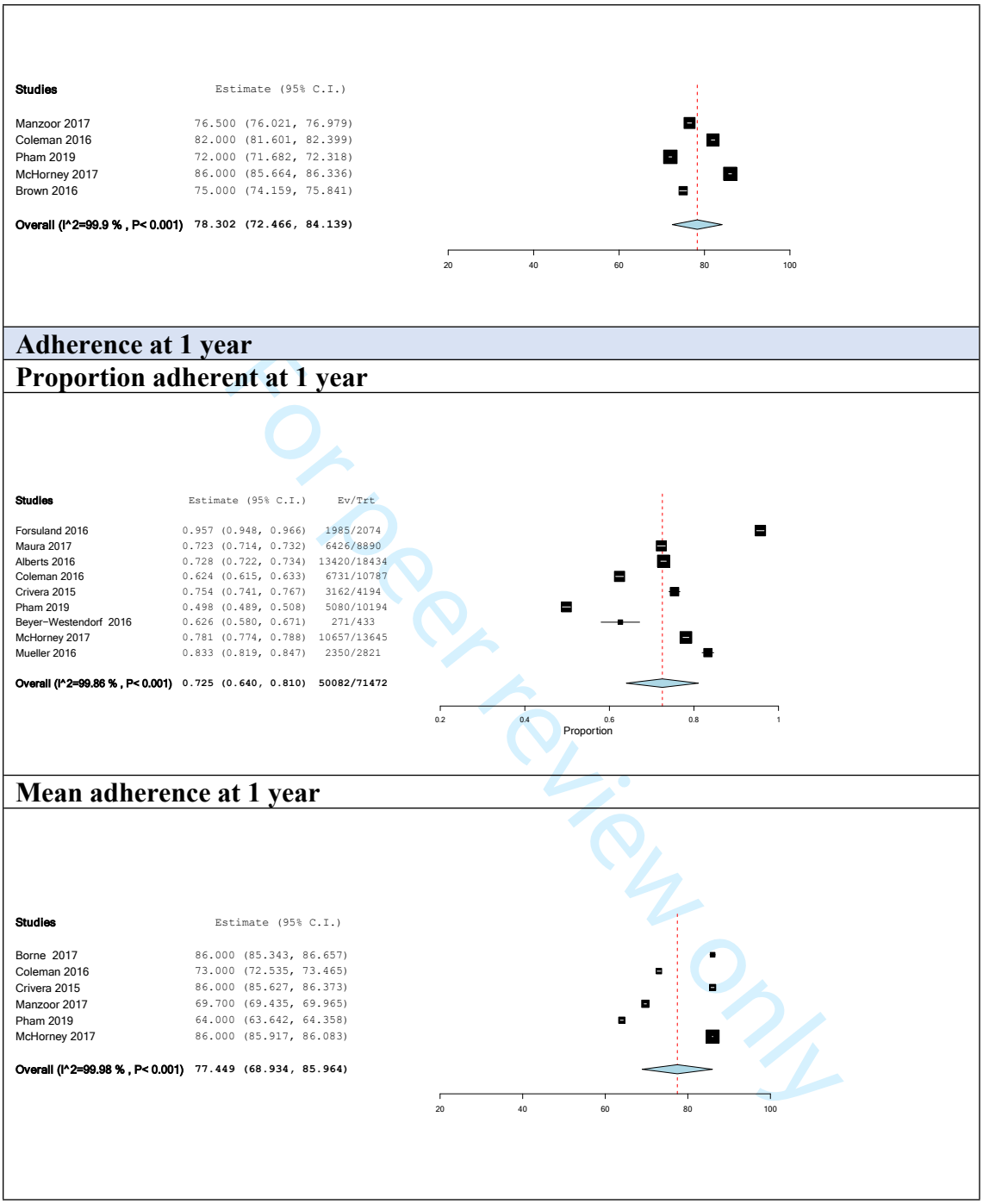
Rivaroxaban:

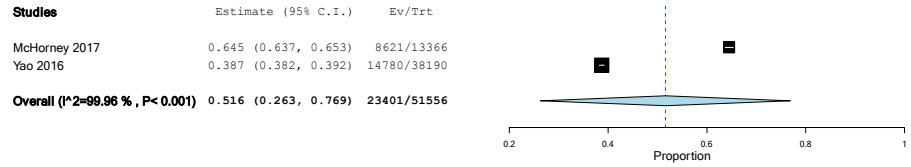
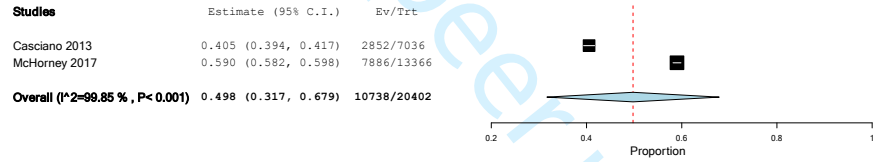
Adherence at 6 months

Proportion adherent at 6 months



Mean adherence at 6 months



Warfarin:
Adherence at 6 months
Proportion adherent at 6 months

Mean adherence at 6 months
NA
Adherence at 1 year
Proportion adherent at 1 year

Mean adherence at 1 year
NA

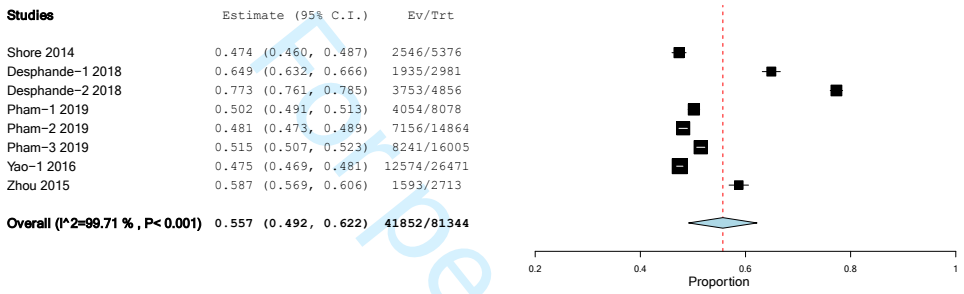
Supplementary 3.1: Sub-group analysis

Supplementary 3.1.1: Sub-group analysis by excluding studies with conflict of interest:

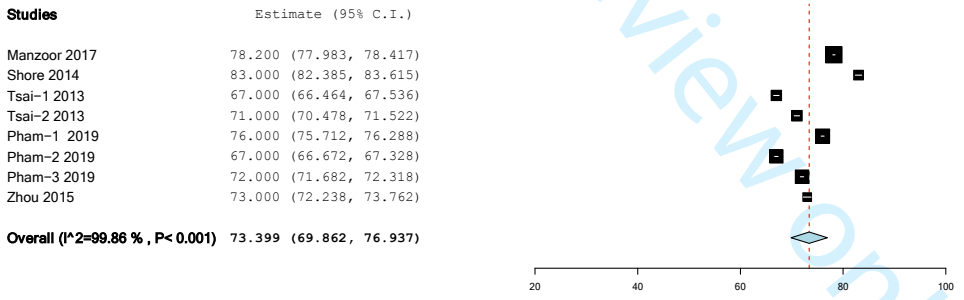
All OACs: Sub-analysis: Excluding studies with conflict of interest

Adherence at 6 months

Proportion adherent at 6 months

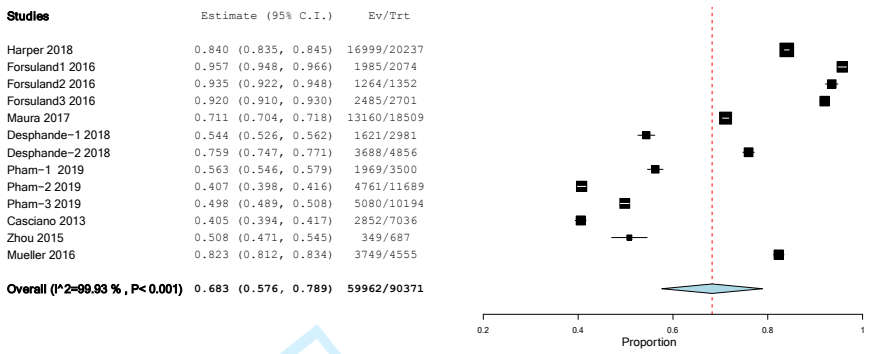


Mean adherence at 6 months

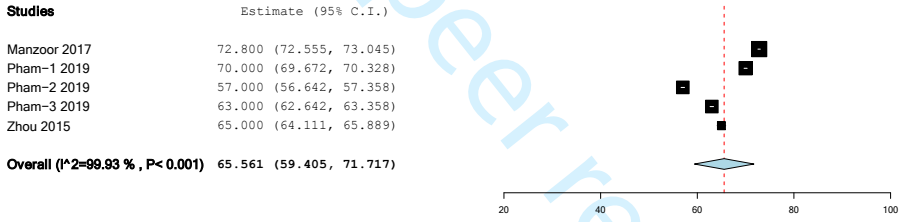


Adherence at 1 year

Proportion adherent at 1 year



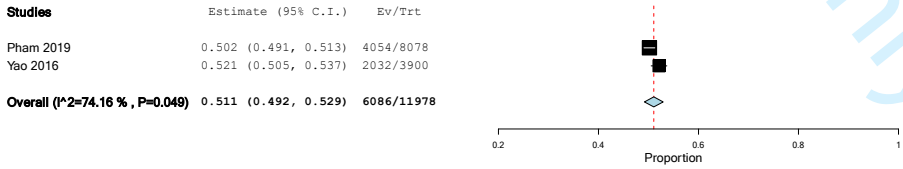
Mean adherence at 1 year



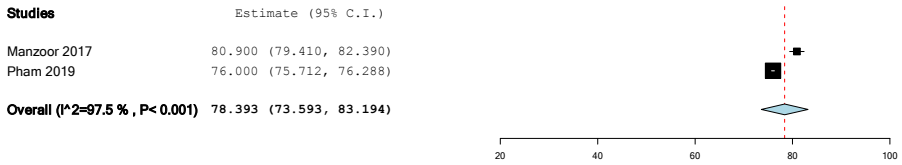
Apixaban: Sub-analysis: Excluding studies with conflict of interest

Adherence at 6 months

Proportion adherent at 6 months

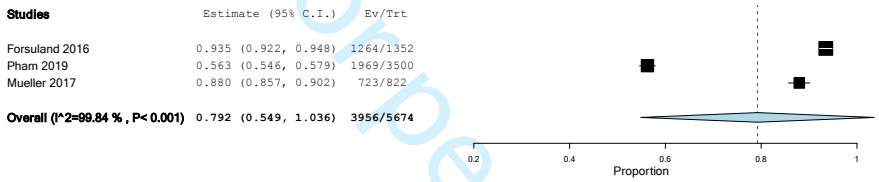


Mean adherence at 1 year



Adherence at 1 year:

Proportion adherent at 1 year



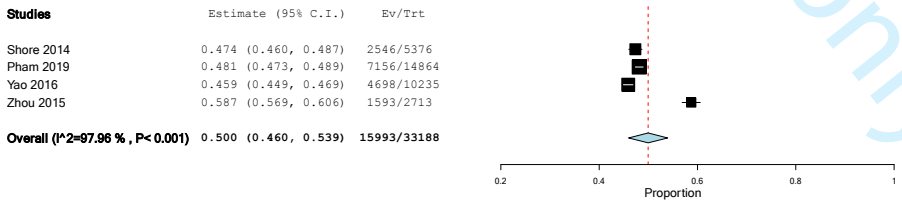
Mean adherence at 1 year

NA (one study)

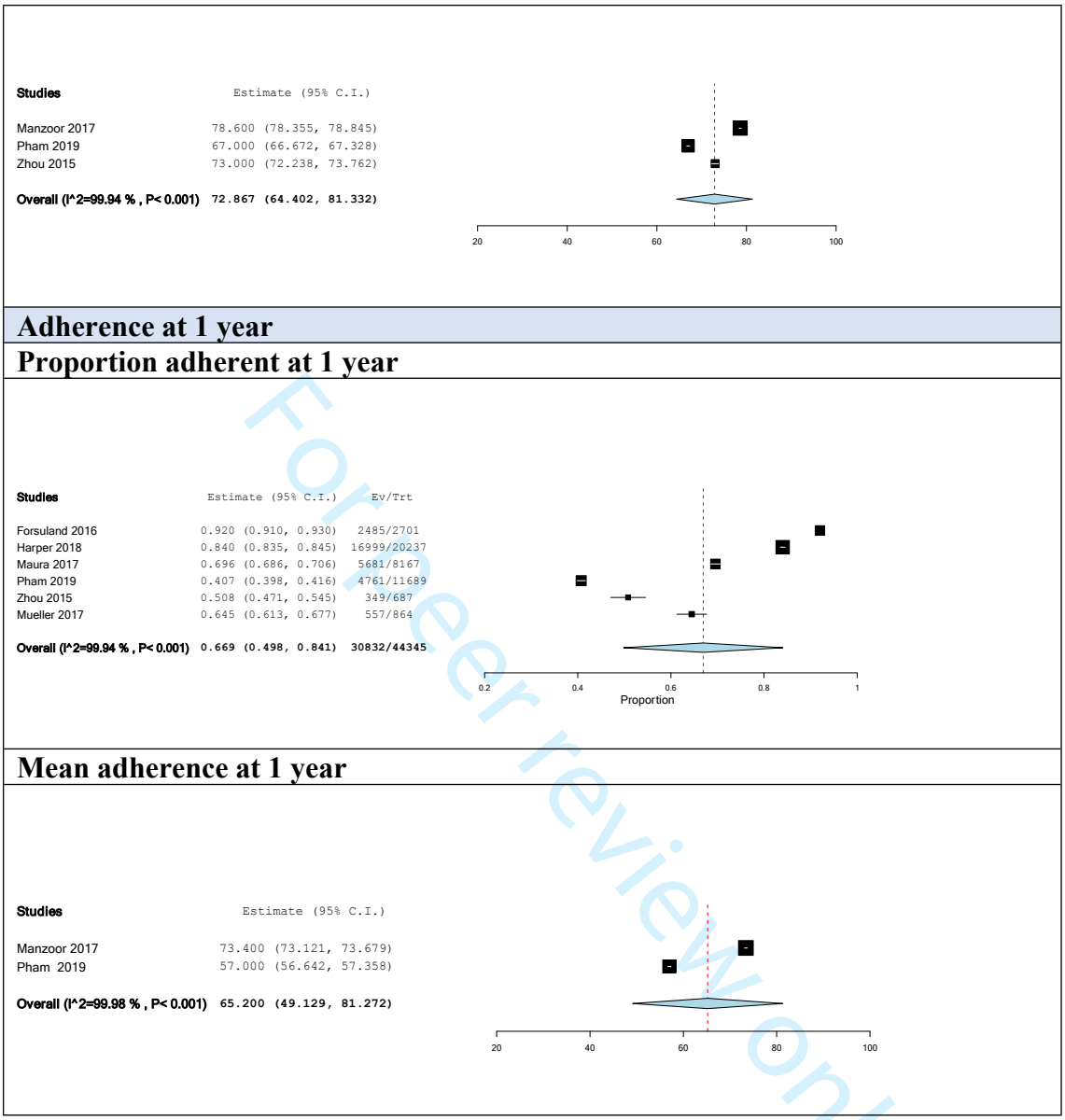
Dabigatran: Sub-analysis: Excluding studies with conflict of interest

Adherence at 6 months

Proportion adherent at 6 months



Mean adherence at 6 months



Adherence at 1 year

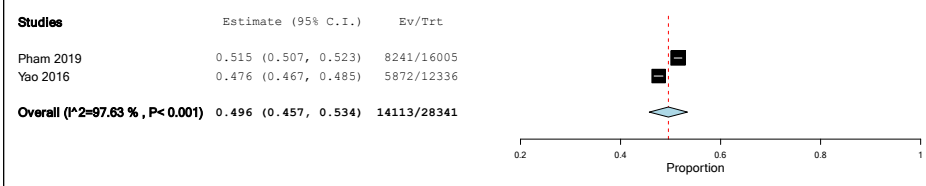
Proportion adherent at 1 year

Mean adherence at 1 year

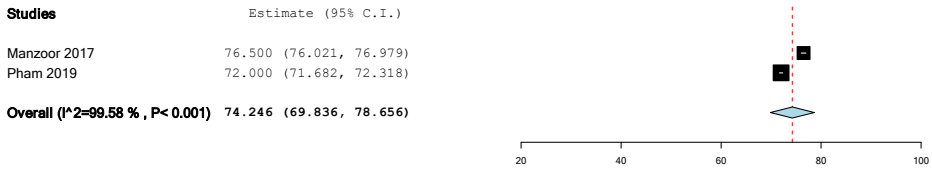
Rivaroxaban: Sub-analysis: Excluding studies with conflict of interest

Adherence at 6 months

Proportion adherent at 6 months

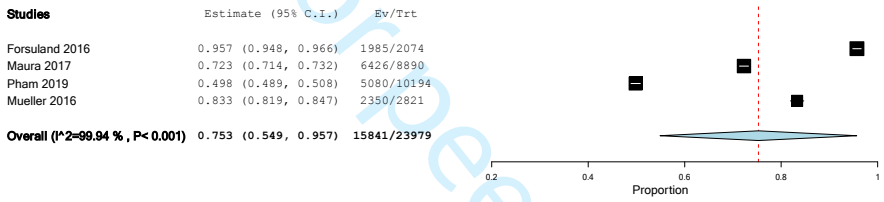


Mean adherence at 6 months

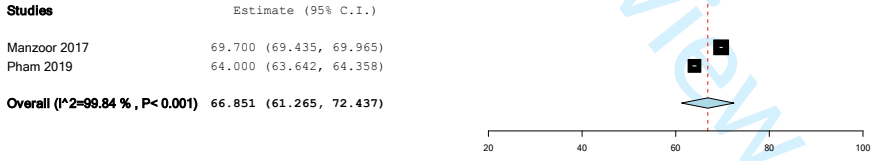


Adherence at 1 year

Proportion adherent at 1 year



Mean adherence at 1 year

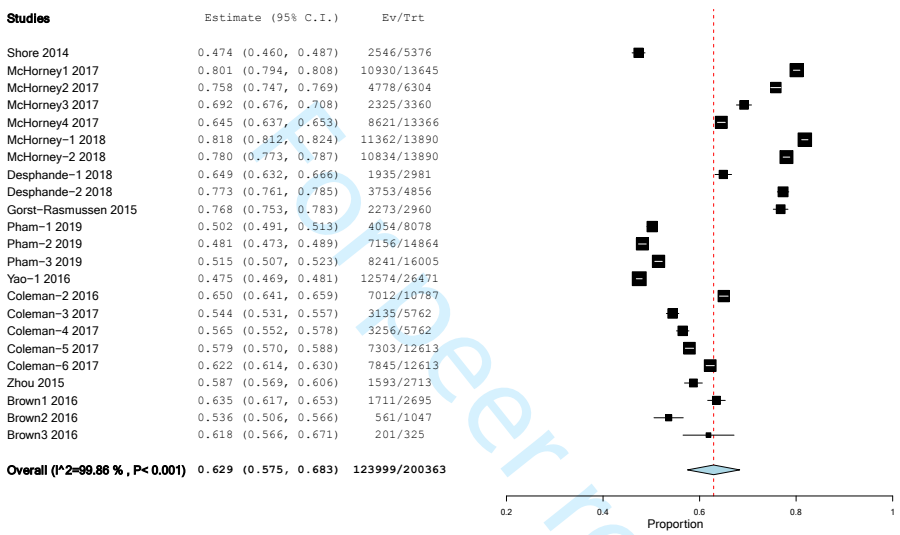


Supplementary 3.1.2: Sub-group analysis by excluding low and medium quality studies.

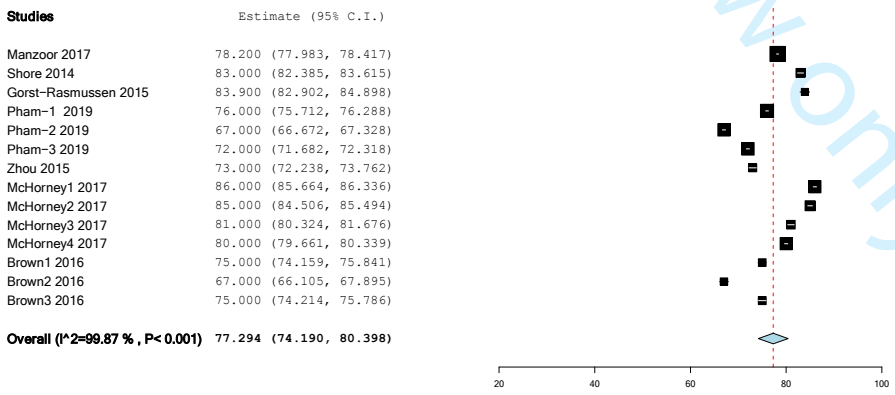
All OAC: Sub-analysis: Excluding low and medium quality studies

Adherence at 6 months

Proportion adherent at 6 months

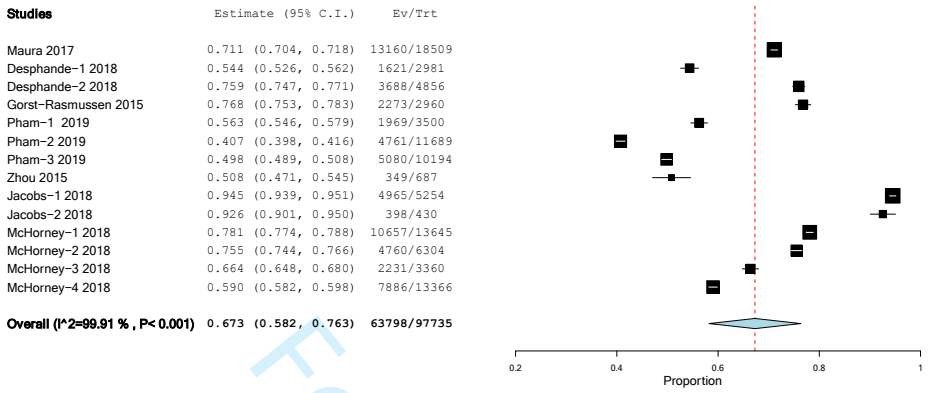


Mean adherence at 6 months

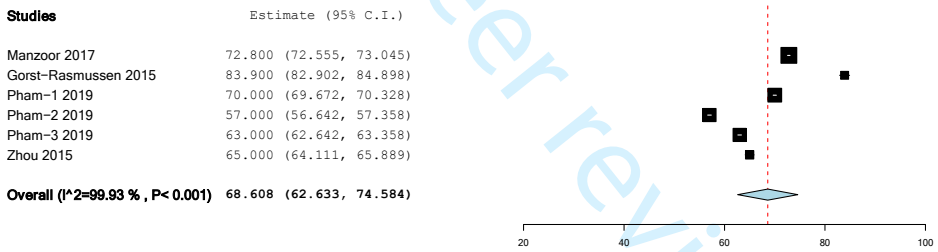


Adherence at 1 year

Proportion adherent at 1 year



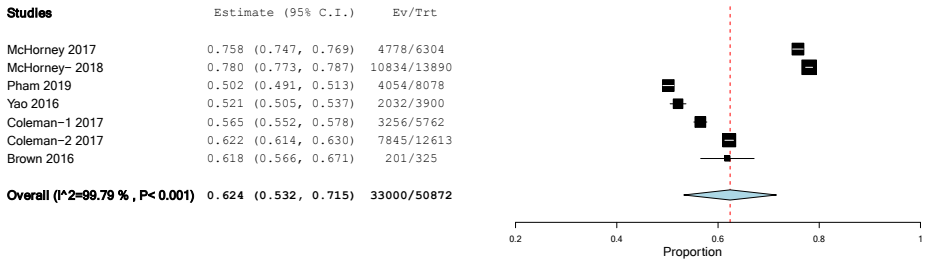
Mean adherence at 1 year



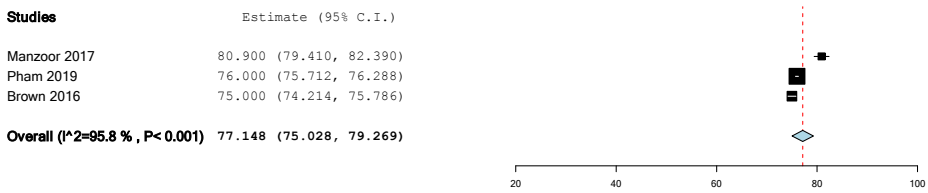
Apixaban: Sub-analysis: Excluding low and medium quality studies

Adherence at 6 months

Proportion adherent at 6 months

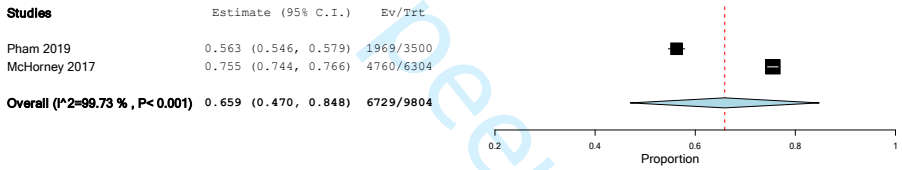


Mean adherence at 6 months



Adherence at 1 year

Proportion adherent at 1 year

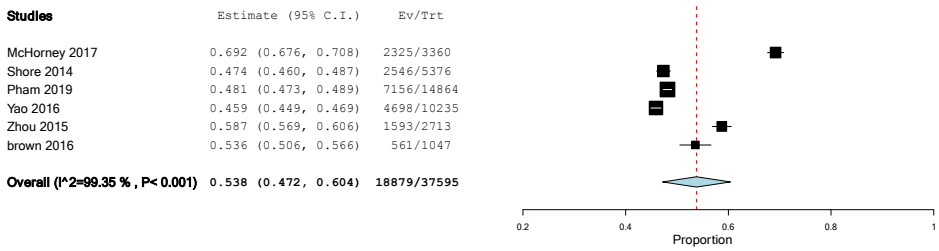


Mean adherence at 1 year

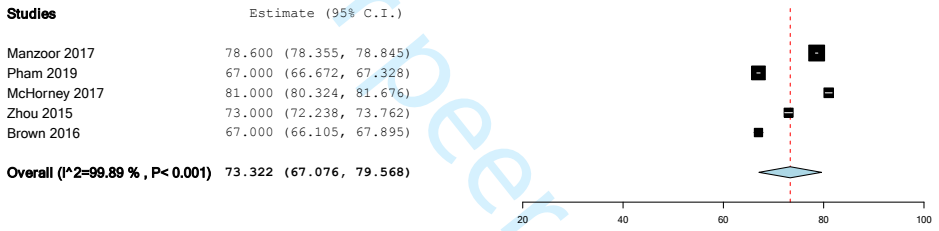
Dabigatran: Sub-analysis: Excluding low and medium quality studies

Adherence at 6 months

Proportion adherent at 6 months

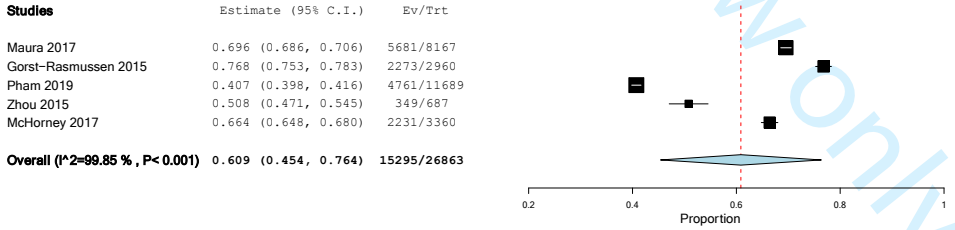


Mean adherence at 1 year

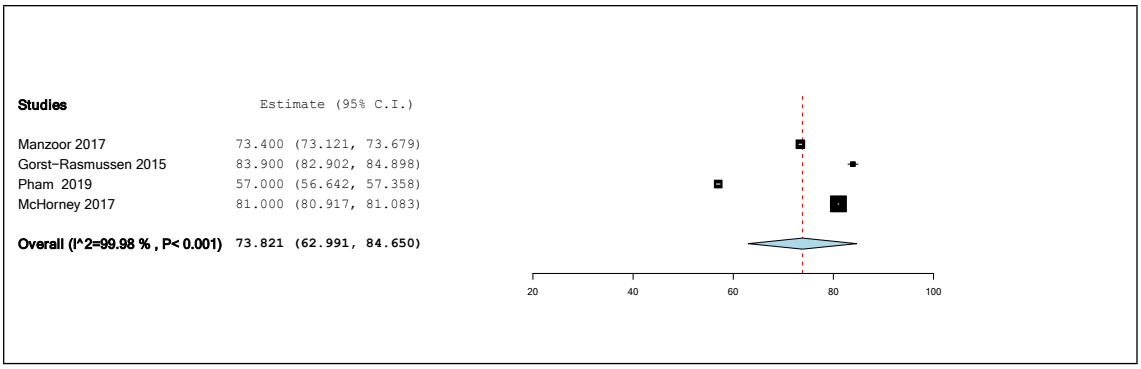


Adherence at 1 year

Proportion adherent at 1 year



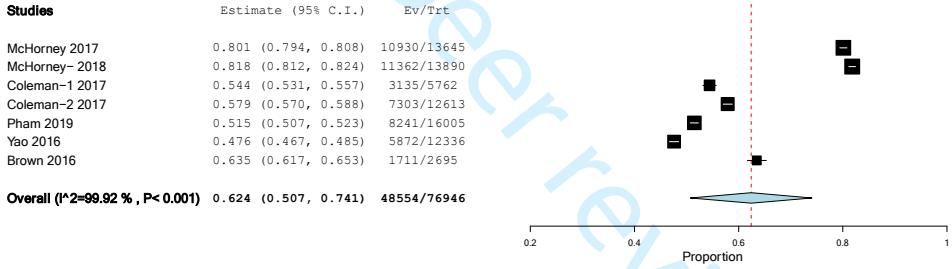
Mean adherence at 1 year



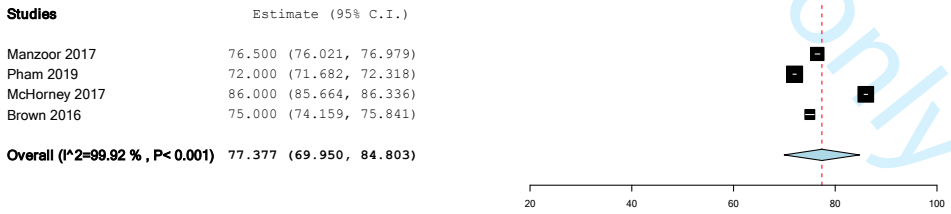
Rivaroxaban: Sub-analysis: Excluding low and medium quality studies

Adherence at 6 months

Proportion adherent at 6 months

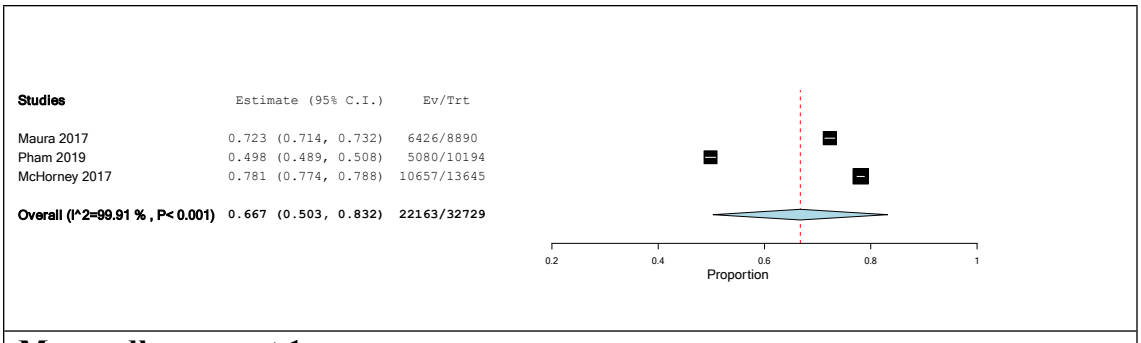


Mean adherence at 1 year

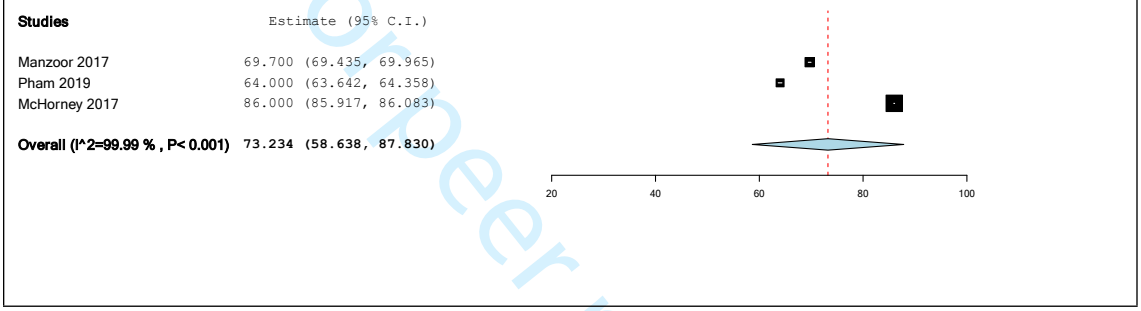


Adherence at 1 year

Proportion adherent at 1 year



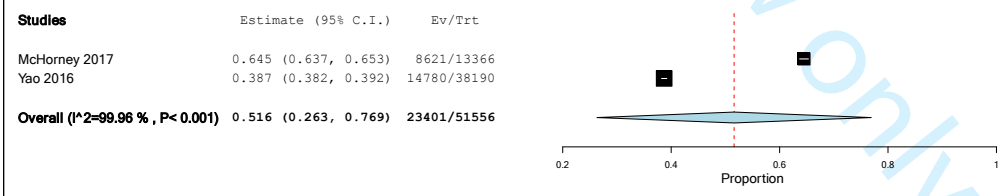
Mean adherence at 1 year



Warfarin: Sub-analysis: Excluding low and medium quality studies

Adherence at 6 months

Proportion adherent at 6 months



Mean adherence at 6 months

NA

Adherence at 1 year

Proportion adherent at 1 year

NA

Mean adherence at 1 year

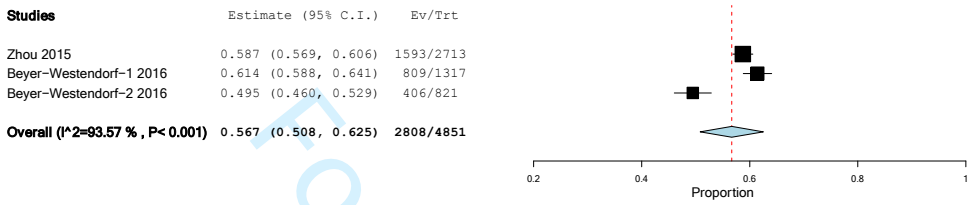
NA

Supplementary 3.1.3: Sub-group analysis by adherence measure

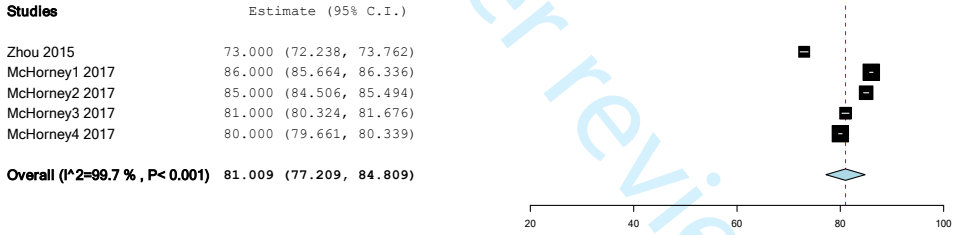
All OACs: Sub-analysis: stratified by adherence measure

Adherence at 6 months

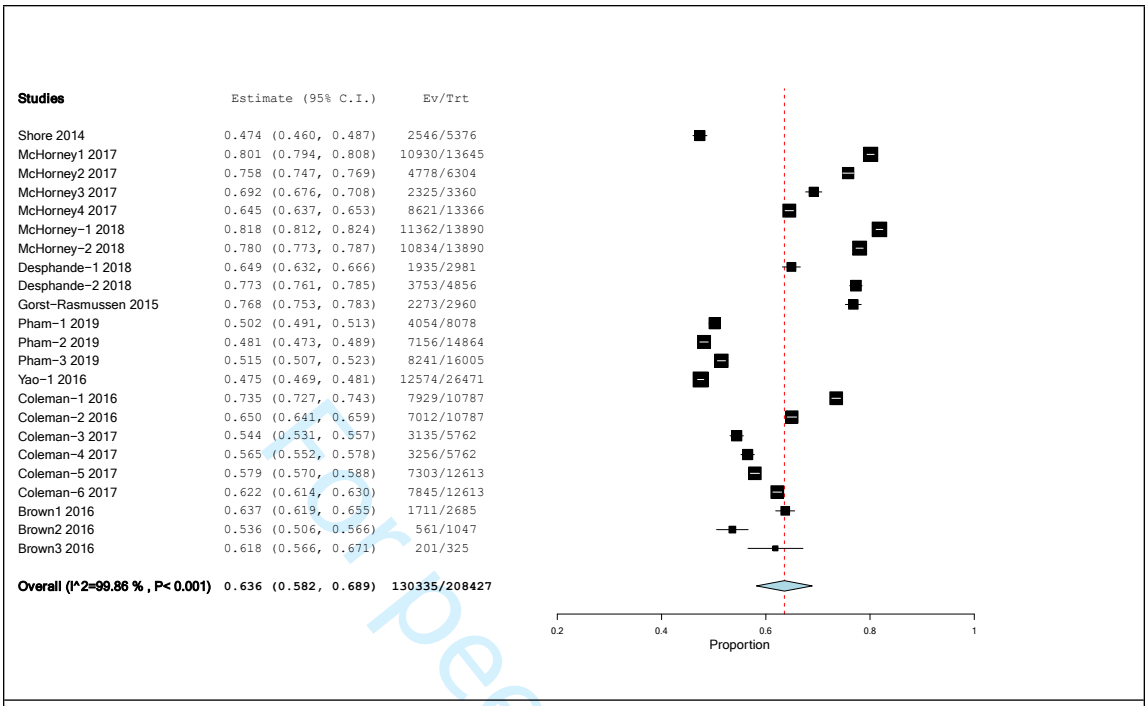
MPR: proportion adherent at 6 months



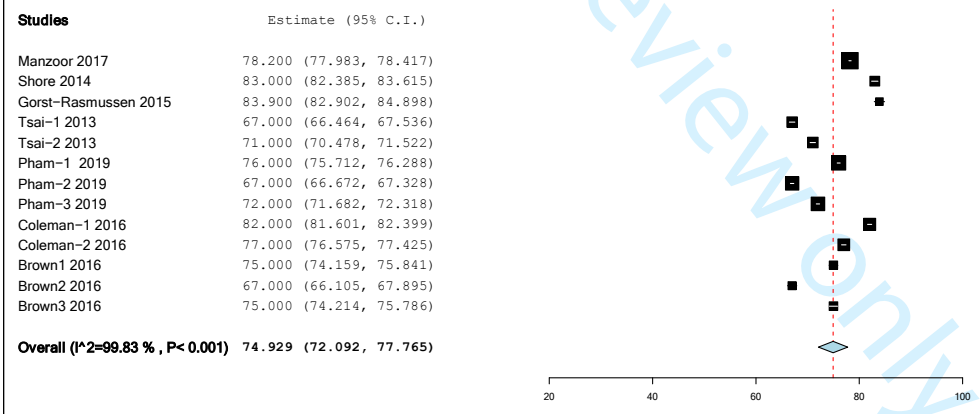
MPR: Mean (SD) adherence at 6 months



PDC: proportion adherent at 6 months

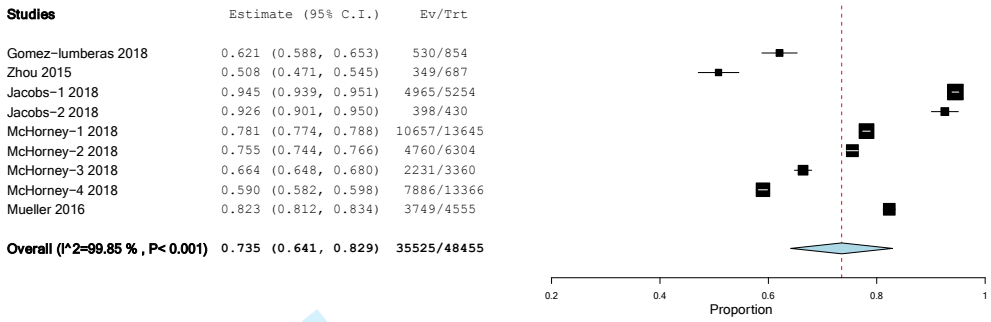


PDC: Mean (SD) adherence at 6 months



Adherence at 1 year

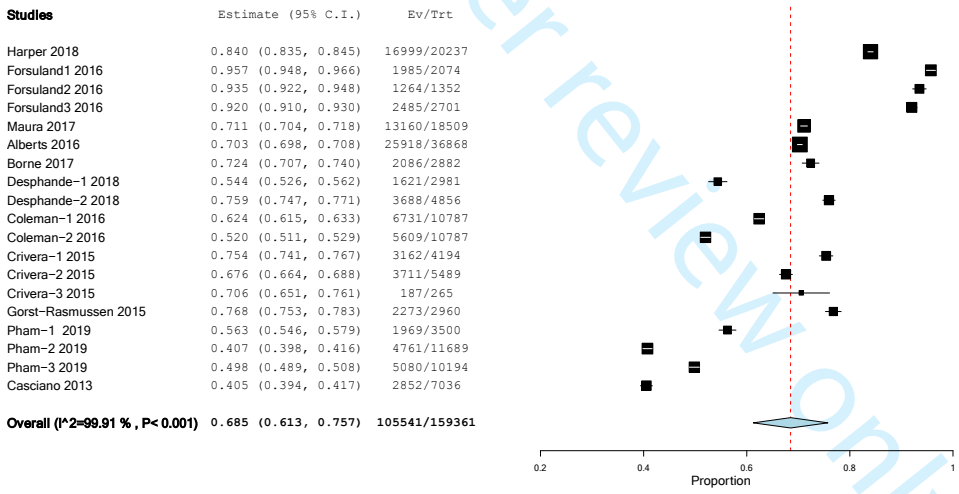
MPR: proportion adherent at 1 year



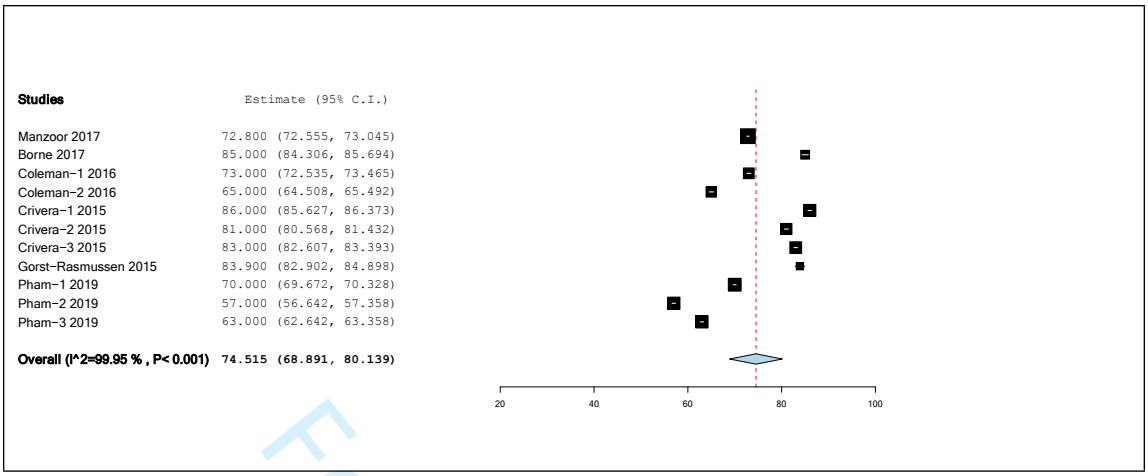
MPR: Mean (SD) adherence at 1 year

NA

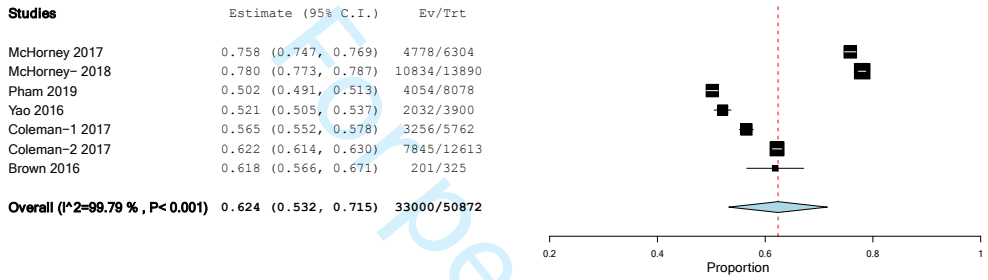
PDC: proportion adherent at 1 year



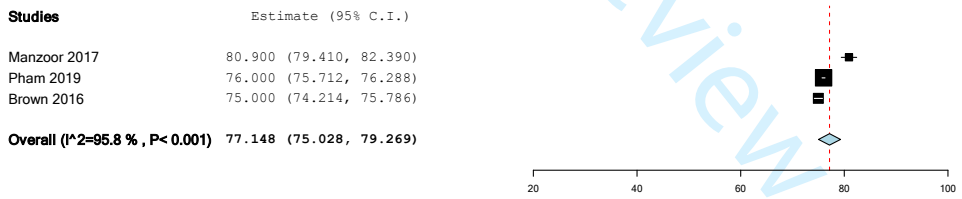
PDC: Mean (SD) adherence at 1 year



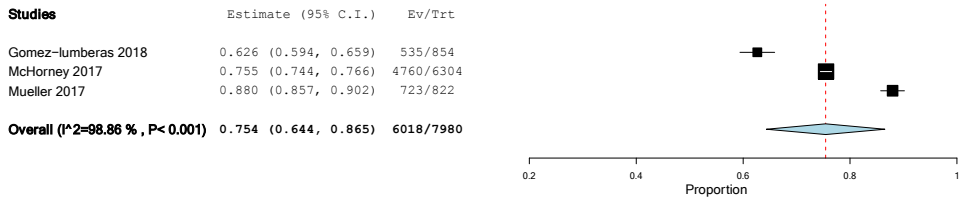
Apixaban: Sub-analysis: stratified by adherence measure
Adherence at 6 months
MPR: proportion adherent at 6 months
NA
MPR: Mean (SD) adherence at 6 months
NA
PDC: proportion adherent at 6 months



PDC: Mean (SD) adherence at 6 months

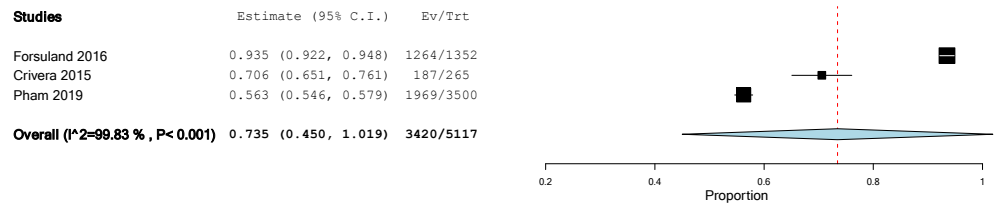


Adherence at 1 year
MPR: proportion adherent at 1 year

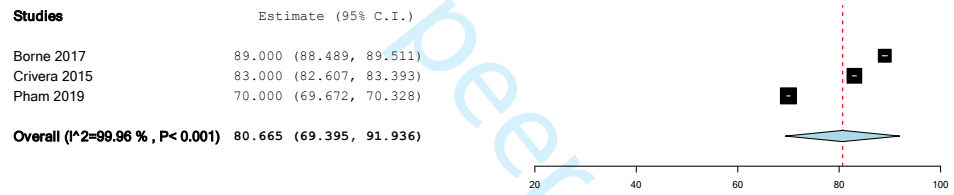


MPR: Mean (SD) adherence at 1 year
NA

PDC: proportion adherent at 1 year



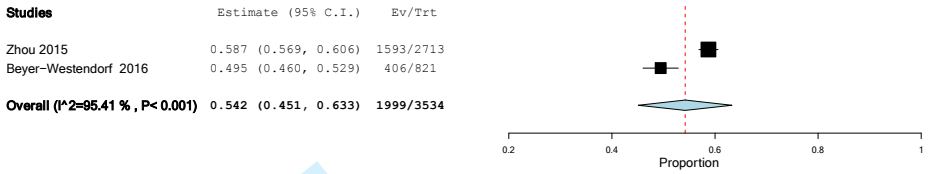
PDC: Mean (SD) adherence at 1 year



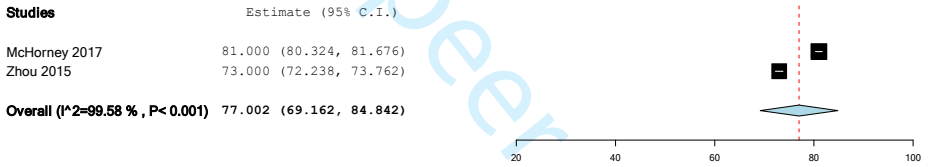
Dabigatran: Sub-analysis: stratified by adherence measure

Adherence at 6 months:

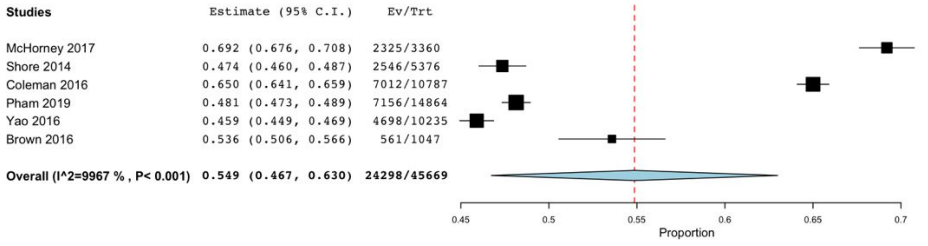
MPR: proportion adherent at 6 months



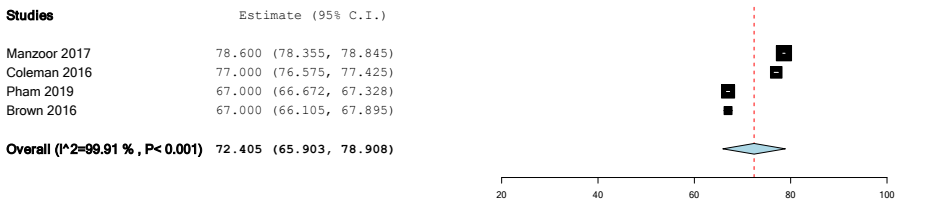
MPR: Mean (SD) adherence at 6 months



PDC: proportion adherent at 6 months

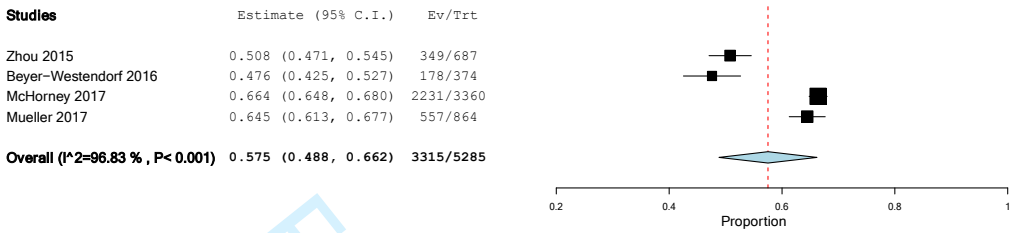


PDC: Mean (SD) adherence at 6 months



Adherence at 1 year

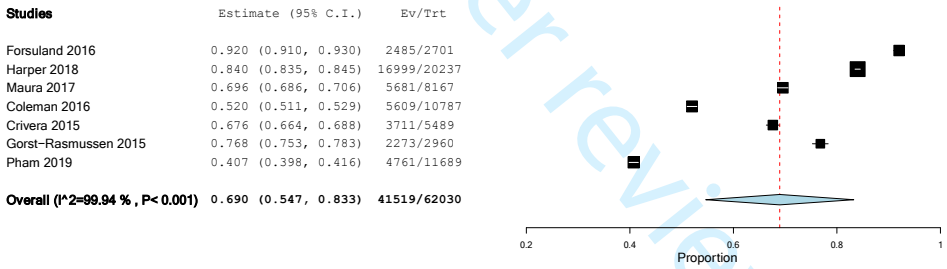
MPR: proportion adherent at 1 year



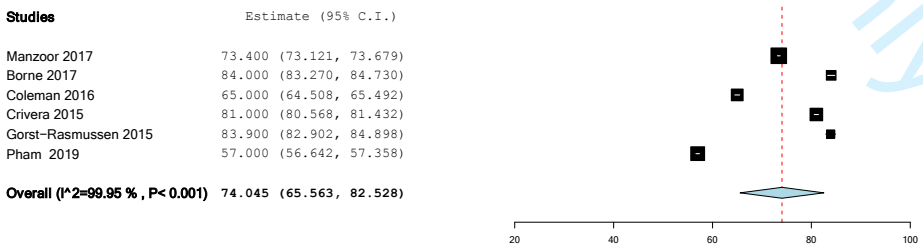
MPR: Mean (SD) adherence at 1 year

NA

PDC: proportion adherent at 1 year



PDC: Mean (SD) adherence at 1 year



Rivaroxaban: Sub-analysis: stratified by adherence measure.

Adherence at 6 months:

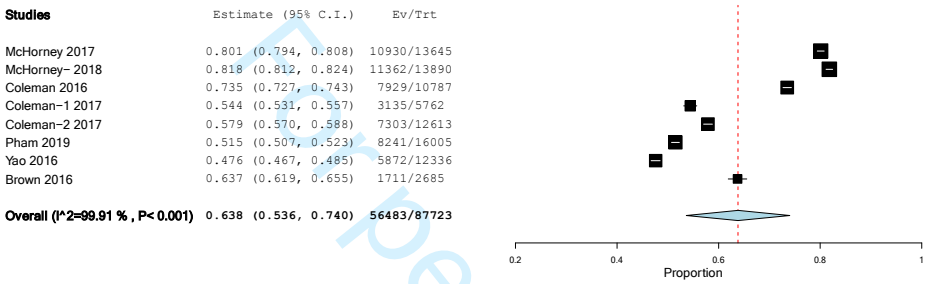
MPR: proportion adherent at 6 months

NA

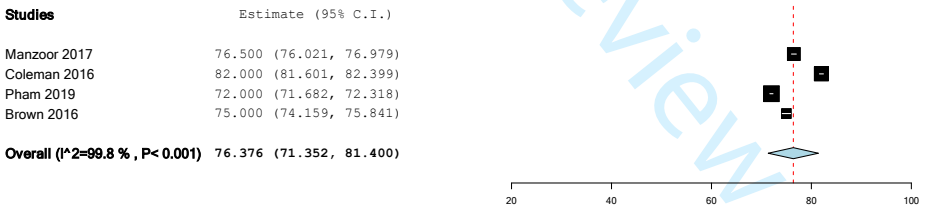
MPR: Mean (SD) adherence at 6 months

NA

PDC: proportion adherent at 6 months

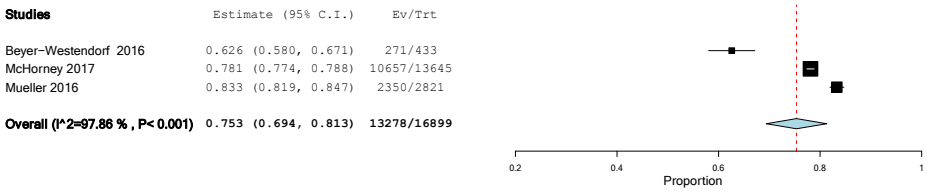


PDC: Mean (SD) adherence at 6 months



Adherence at 1 year:

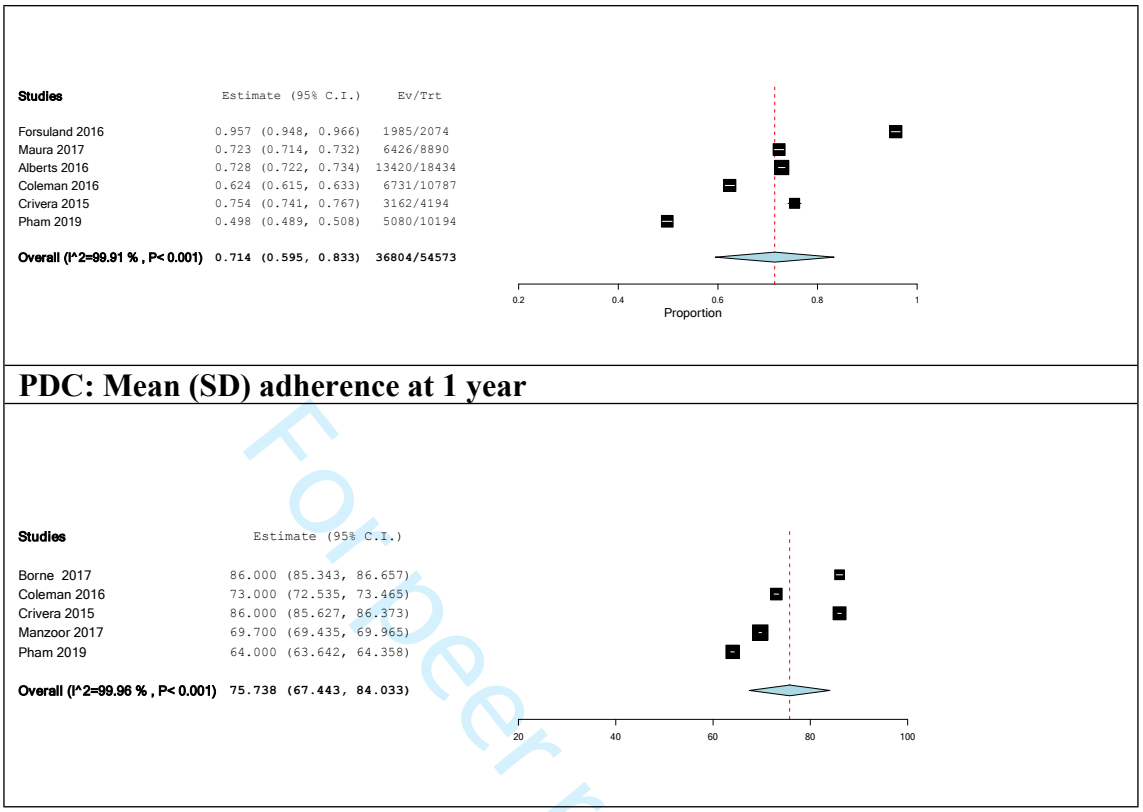
MPR: proportion adherent at 1 year



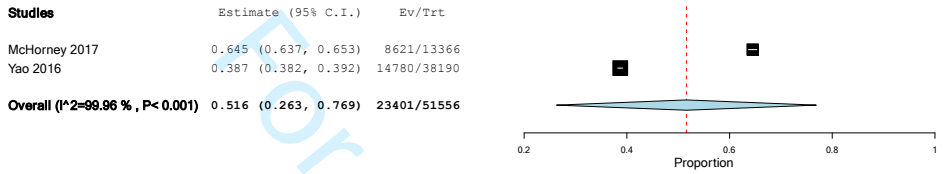
MPR: Mean (SD) adherence at 1 year

NA

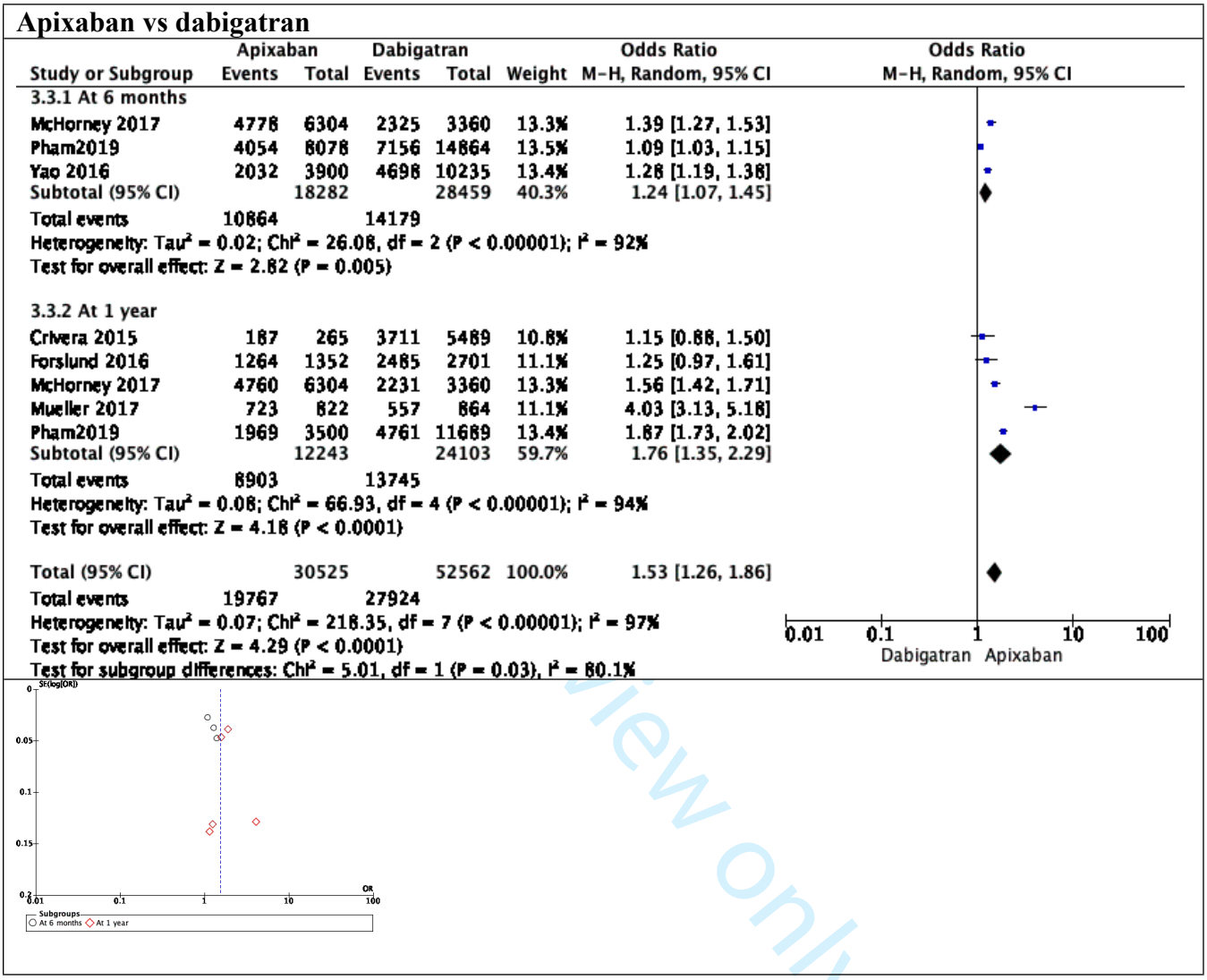
PDC: proportion adherent at 1 year



PDC: Mean (SD) adherence at 1 year

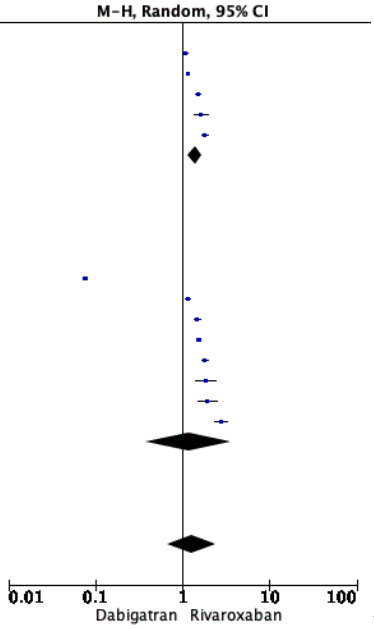
Warfarin: Sub-analysis: stratified by adherence measure
Adherence at 6 months:
MPR: proportion adherent at 6 months
NA
MPR: Mean (SD) adherence at 6 months
NA
PDC: proportion adherent at 6 months

PDC: Mean (SD) adherence at 6 months
NA
Adherence at 1 year
MPR: proportion adherent at 1 year
NA
MPR: Mean (SD) adherence at 1 year
NA
PDC: proportion adherent at 1 year
NA
PDC: Mean (SD) adherence at 1 year
NA

Supplementary 3.2: studies reporting adherence to different medications in the same cohort.



Rivaroxaban vs dabigatran

Study or Subgroup	Rivaroxaban Events	Rivaroxaban Total	Dabigatran Events	Dabigatran Total	Weight	Odds Ratio M-H, Random, 95% CI
5.3.1 At 6 months						
Yao 2016	5872	12336	4698	10235	7.7%	1.07 [1.02, 1.13]
Pham2019	8241	16005	7156	14864	7.7%	1.14 [1.09, 1.20]
Coleman 2016	7929	10787	7012	10787	7.7%	1.49 [1.41, 1.58]
Beyer-Westendorf 2016	809	1317	406	821	7.7%	1.63 [1.36, 1.94]
McHorney 2017	10930	13645	2325	3360	7.7%	1.79 [1.65, 1.95]
Subtotal (95% CI)		54090		40067	38.5%	1.39 [1.15, 1.67]
Total events	33781		21597			
Heterogeneity: Tau² = 0.04; Chi² = 162.85, df = 4 (P < 0.00001); I² = 98%						
Test for overall effect: Z = 3.46 (P = 0.0005)						
5.3.2 At 1 year						
Pham2019	5080	101940	4761	11689	7.7%	0.08 [0.07, 0.08]
Maura 2017	6426	8890	5681	8167	7.7%	1.14 [1.07, 1.22]
Crivera 2015	3162	4194	3711	5489	7.7%	1.47 [1.34, 1.61]
Coleman 2016	6731	10787	5609	10787	7.7%	1.53 [1.45, 1.62]
McHorney 2017	10657	13645	2231	3360	7.7%	1.80 [1.66, 1.96]
Beyer-Westendorf 2016	271	433	178	374	7.6%	1.84 [1.39, 2.44]
Forslund 2016	1985	2074	2485	2701	7.6%	1.94 [1.50, 2.50]
Mueller 2017	2350	2821	557	864	7.7%	2.75 [2.32, 3.26]
Subtotal (95% CI)		144784		43431	61.5%	1.17 [0.38, 3.60]
Total events	36662		25213			
Heterogeneity: Tau² = 2.64; Chi² = 10724.75, df = 7 (P < 0.00001); I² = 100%						
Test for overall effect: Z = 0.27 (P = 0.79)						
Total (95% CI)		198874		83498	100.0%	1.25 [0.66, 2.38]
Total events	70443		46810			
Heterogeneity: Tau² = 1.39; Chi² = 12603.04, df = 12 (P < 0.00001); I² = 100%						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%						



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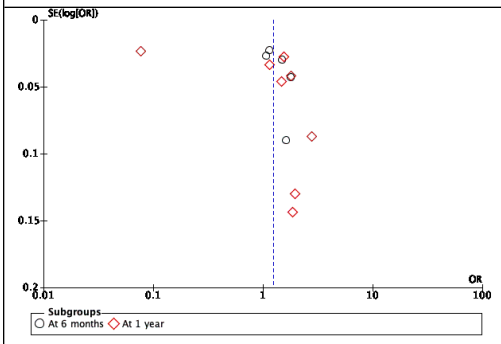

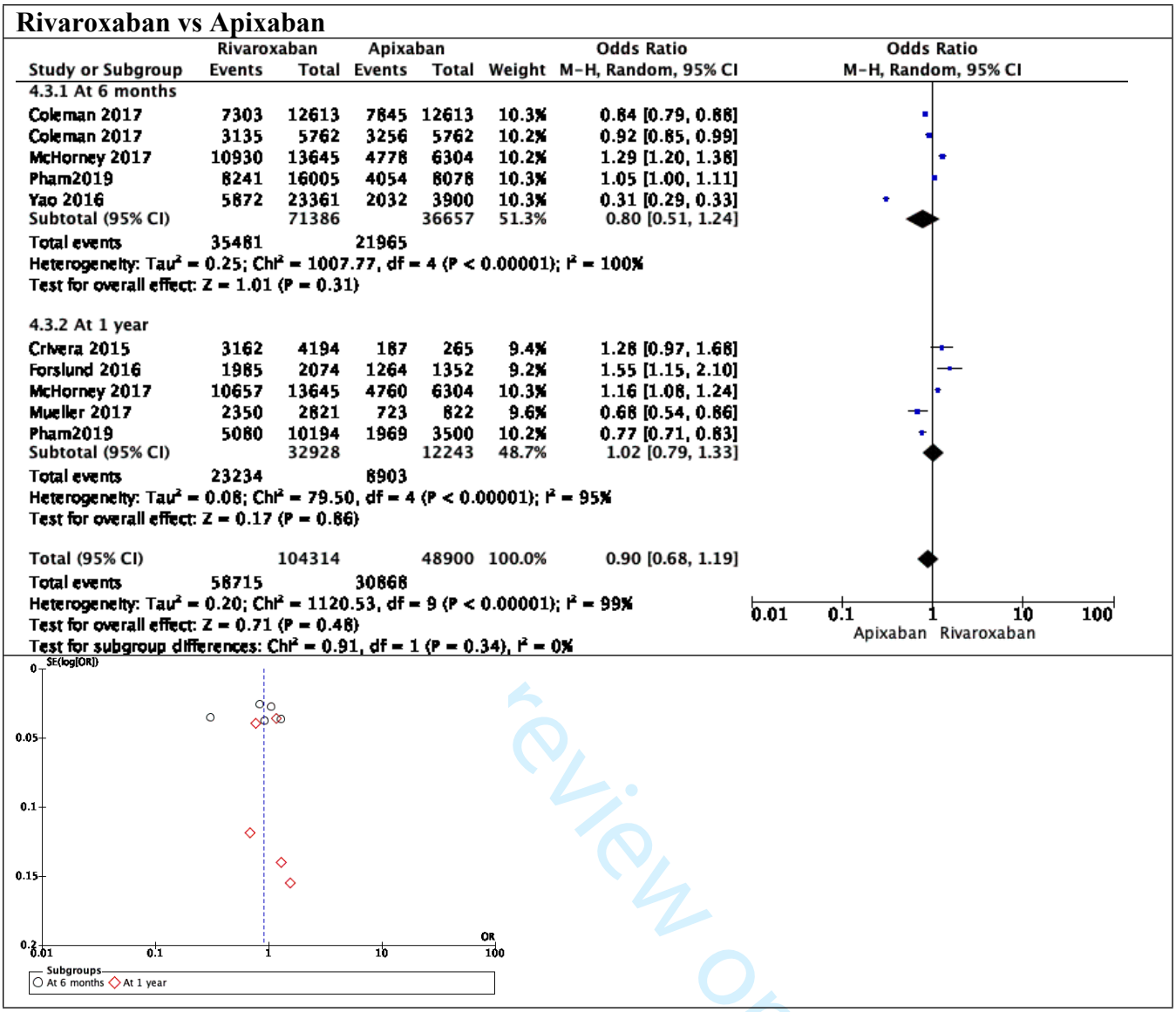

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Adherence to oral anticoagulants among patients with atrial fibrillation:

A systematic review and meta-analysis of observational studies

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ABSTRACT

INTRODCUTION

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

METHODS

We systematically searched 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 six months and one 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 six months and one 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 to 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.

Keywords: Atrial fibrillation, anticoagulants, medication adherence, stroke.

Strengths and limitations of this study

- This is a timely systematic review that synthesizes 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 synthesize 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 five-fold, 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 summarize the medication taking behavior of AF patients. These reviews, however, focus on discontinuation of therapy (not implementation or execution of dosing), or when looking at implementation, only focus on DOACs, summarize evidence from randomized controlled trials (which do not reflect the day to day behaviors of patients), and provide a narrative summary of results with no meta-analysis.[19-21] Further, no studies have summarized 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 summarize 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 (PRISMA) and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (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 (Supplementary 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 utilized 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 non-valvular AF (NVAF) patients, 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 MMAS) 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 standard deviation (SD) of patients' adherence over six- or twelve- months post index date (after therapy initiation). Secondary adherence measure included 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 (e.g. 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 analyzed to minimize 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 World Health Organization's (WHO) 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 Der Simonian & Laird random-effects models to determine the pooled mean adherence and the corresponding pooled proportion of adherent patients over six months and one 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, and 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 odds ratio (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, WA) or RevMan5 (version 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 (e.g. OR).[30,31] Clinical and economic impacts of poor adherence were summarized 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 STROBE.[33] Studies received a point for each checklist item they met and a zero 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 categorized 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.

Ethical approval

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

RESULTS

Initial search led to 1,122 studies, all of which were in English (Figure 1.0). 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 (Supplementary 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 six-month or one-year post index date (Table 2). Majority of the included studies focused on adherence to DOACs with only 4 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] to 86[55] over six months and 57[58] to 86[41] over one-year post index date, with corresponding reported proportion of adherent patients ranging between 47%[59] to 82%[56] over six months and 41%[58] to 95%[45] over one year. Wide range of adherence results were observed even at the individual OAC level (Table 2).

Pooled mean adherence scores over six-month and one-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 were resulted from meta-analysis of 2 studies only (as illustrated in tables 2 and 3). Due to the limited data in warfarin, no drug class comparison could be made. Figure 2.0 illustrates the forest plots for patients' mean adherence score over six months and one 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 supplementary 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 versus MPR), or country (USA versus others) had only minor impacts on pooled adherence results and the detected heterogeneity (Supplementary 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 to dabigatran over both six months (Odds Ratio (OR):1.24, 95% CI: 1.07-1.45) and one-year post index date (OR:1.76, 95% CI: 1.35-2.29). Odds of adherence was significantly

higher for rivaroxaban compared to dabigatran over six months (OR:1.39, 95% CI: 1.15-1.67), but not one year (OR:1.17, 95% CI: 0.38-3.60). Odds of adherence did not differ between apixaban and rivaroxaban over six months (OR:0.80, 95% CI: 0.51-1.24) or one 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 to 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 to 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 to naïve users over six months (83.3±24.6 vs 72.3±31.3; p< 0.05), nine months (81.2±26.4 vs 67.3±33.8); p< 0.05) and one year (79.9±27.6 vs 63.7±35.2; p <0.05).[50]

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 to those prescribed after discharge at three months (84.5% vs 12.3%; P<0.001) and one 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. Summarizing 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], angiotensin converting enzyme 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 ischemic 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 ischemic stroke compared to adherent patients, over six 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 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 compare to adherent patients and Deshpande et al. reported significantly higher annual adjusted per-patient medical cost (inpatient and outpatient) for non-adherent users compared to adherent ones ($30,485 versus $23,544; p≤0.001).[38,43]

DISCUSSION

In this systematic review, we synthesized observational data of over half a million patients with AF to reveal that up to 30% are non-adherent to OACs, and that nonadherent patients are more likely to experience stroke, death and incur higher medical costs compared to 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.

AF patients' adherence to their OACs has been thoroughly studied in developed countries. Pooled proportion of adherent patients at six months and one year was 63% and 70%, respectively, which is higher than 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 nonadherence in this particular clinical context. We were unable to ascertain whether the conveniences of DOACs translates into better adherence compared to 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-, regimen- 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, angiotensin converting enzyme 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 utilization and costs. Our findings

confirm the results of a 2017 systematic review of 79 studies across 14 disease groups which reported that $3,347-19,472 are attributed to nonadherence per patient per year among those with cardiovascular conditions (hypertension, hypercholesterolaemia, and chronic heart failure).[73] As for clinical outcomes, our findings 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 summarize 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, 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 (Supplementary 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 (e.g. OAC naïve versus experienced); methods for handling and defining medication switches, stockpiling, refill gaps, and hospitalization dates; fixed versus variable observational periods and adherence measure used (PDC versus 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 nonadherence to OACs. All of the current studies have treated adherence as a static behavior, calculating and reporting it using a single summary measure. This methodological approach does not provide a complete picture of adherence, which is a dynamic behavior that changes over time.[25,81] Characterization 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 nonadherence, 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 characterize 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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COMPETING INTERESTS

Authors have no competing interests to declare.

CONTRIBUTIONS

Conceived the study: SS, PL, MDV; Designed the search strategy: SS, MDV, PL; 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): MDV, SS; Analyzed the data: SS; Conducted quality assessment; SS, RT; Interpreted the results: SS, PL, JGA, MDV; Prepared the manuscript first draft: SS, MDV, PL, RT; Reviewed the manuscript and provided critical feedback: JGA, MDV, PL; Revised the manuscript: SS, PL, RT, MDV.

DATA AVAILABILITY STATEMENT

No additional data available.

FIGURE LEGENDS

Figure 1.0: PRISMA flow diagram that details the number of studies identified by our search strategy, screened, and included in the final analysis.

Figure 2.0: Forest plots illustrating patients' mean adherence scores over six-month and one-year post index date. See Supplementary 4 for additional forest plots for each OAC and subgroup analyses.

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TABLES

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	2016	Retrospective	USA	36,868 (55%)	76%>65 years	NVAF	NA	Both	Yes	61%	67%
Beyer-Westendorf	2016	Retrospective	Germany	7,265 (52%)	NA	NVAF	Index OAC	Naïve	Yes	73%	74%
Borne	2017	Retrospective	USA	2,882 (97%)	67.4 (9.5)	NVAF	NA	Naïve to DOACs‡	Yes	73%	78%
Brown	2016	Retrospective	USA	5,223 (40%)	59%≥65 years	NVAF	Both	Naïve	Yes	77%	84%
Casciano	2013	Retrospective	USA	13,289 (47%)	78% ≥75 years	AF	NA	Naïve	Yes	63%	79%
Coleman	2016	Retrospective	USA	21,756 (54%)	66.5 (12.2)	NVAF	NA	Naïve	Yes	55%	50%
Coleman	2017	Retrospective	USA	106,227 (63%)	71.1 (11.0)	NVAF	Index OAC	Naïve	Yes	77%	84%
Crivera	2015	Retrospective	USA	9,948 (53%)	75.5 (8.3)	NVAF	Both	Naïve	Yes	73%	61%
Deshpande PMID: 29694285	2018	Retrospective	USA	2,981 (70%)	64.4 (10.7)	AF	NA	Naïve to DOACs‡	No	77%	83%
Deshpande PMID: 29334815	2018	Retrospective	USA	4,856 (52%)	65.0 (10.5)	AF	NA	Naïve	No	81%	83%
Kapen	2014	Retrospective	USA	2,691 (43%)	100%>65 years	AF	NA	Both	No	76%	74%
Forsuland	2016	Retrospective	Sweden	16,096 (52%)	75.45 (SD not reported)	NVAF	Current OAC	Both	No	63%	61%
Gomez-Iumberas	2018	Retrospective	Spain	854 (NA%)	73.2 (11.0)	NVAF	NA	Both	Yes	50%	67%
Gorst-Rasmussen	2015	Retrospective	Denmark	2,960 (54%)	72.1 (10.8)	NVAF	Index OAC	Naïve	Yes	80%	100%
Harper	2018	Retrospective	New Zealand	20,237 (NA%)	83%>60	NVAF	NA	NA	No	47%	53%
Jacobs	2018	Retrospective	Sweden & Netherlands	5,684 (60%)	78%≥65 years	AF	Current OAC	Both	Yes	80%	83%
Manzoor	2017	Retrospective	USA	66,090 (62%)	68.7 (12.1)	AF	Index OAC	Both	Missing	70%	85%
Márquez-Contrera	2016	Prospective	Spain	412 (42%)	75.2 (7.5)	NVAF	NA	Experienced	Yes	63%	83%
Maura	2017	Retrospective	France	22,267 (53%)	74.0 (10.8)	NVAF	Index	Naïve	No	79%	100%
McAlister	2018	Retrospective	Canada	57,669 (56%)	100%>65 years	NVAF	Current OAC	Naïve	No	87%	94%
McCormick	2001	Retrospective	USA	429 (22%)	87 (7.1)	AF	Current OAC	Experienced	No	60%	82%
McHorney	2017	Retrospective	USA	36,675 (67%)	63.1 (SD not reported)	NVAF	Index OAC	Naïve	Yes	87%	89%
McHorney	2018	Retrospective	USA	41,201 (58%)	NA	NVAF	Index OAC	Both	Yes	84%	100%
Mueller	2017	Retrospective	Scotland	5,398 (54%)	74.4 (11.3)	AF	NA	NA	No	70%	53%
Pham	2019	Retrospective	USA	38,947 (60%)	100%>65 years	NVAF	Index OAC & any OAC	Naïve	No	77%	89%
Shore	2014	Retrospective	USA	5,376 (98%)	71.3 (9.7)	NVAF	Index OAC	NA	No	90%	94%
Sørensen	2017	Retrospective	Denmark	46,675 (58%)	79%>65 years	NVAF	Current OAC	Naïve	Yes	67%	79%

Tsai	2013	Retrospective	USA	17,691 (49%)	76.4 (8.7)	NA	Current OAC	Warfarin Naïve and warfarin experienced	No	60%	78%
Yao	2016	Retrospective	USA	64,661 (56%)	75% >65	AF	Index OAC	Naïve	No	77%	84%
Zhou	2015	Retrospective	USA	5,951 (34%)	36.1%>65	AF	Index OAC	Naïve	No	80%	79%

Footnote:

USA: United States of America; NVAF: non-valvular atrial fibrillation; AF: atrial fibrillation (valvular and non-valvular); NA: not applicable (no data reported)

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 (2016)	PDC (>80%)	NA	NA	NA	Overall: 0.70 A and D: 0.68 R: 0.73
Borne (2017)	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 (2016)	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 (2013)	PDC (>80%)	NA	NA	NA	W: 0.41
Coleman (2016)	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 (2017)	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 (2015)	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 (2018) PMID: 29694285	PDC (≥80%)	NA	R and D: 0.65	NA	R and D: 0.54
Deshpande (2018) PMID: 29334815	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 (2016)	PDC (>80%)	NA	NA	NA	A: 0.93 D: 0.92 R: 0.96
Gorst-Rasmussen (2015)	PDC (>80%)	0.84 ± 0.28	NA	NA	D: 0.77
Harper (2018)	PDC (>80%)	NA	NA	NA	D: 0.84
Manzoor (2017)	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 (2017)	PDC>80	NA	NA	NA	**Index OAC:** Overall: 0.71 D: 0.70

					R: 0.72
McHorney (2017)	PDC (>80% & >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 (2018)	PDC (>80% & >90%)	NA	**PDC80:** A:0.78 R: 0.82 **PDC90:** A: 0.60 R: 0.67	NA	NA
Pham (2019)	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 (2014)	PDC (>80%)	NA	D: 0.28	NA	NA
Sørensen (2017)	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 (2013)	PDC (no threshold)	D: warfarin-naïve: 0.67 ± 0.36 warfarin-experienced: 0.71 ± 0.35	NA	NA	NA
Yao (2016)	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 (2016)	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 (2014)	MPR (no threshold)	NA	NA	Median (IQR): 0.77 (0.51- 0.98)	NA
Gomez-lumberas (2018)	MPR (>0.8)	NA	NA	NA	A: 0.62
Jacobs (2018)	MPR (≥0.8)	NA	NA	NA	Sweden: 0.95 Netherlands: 0.93
McHorney (2017)	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 (2015)	MPR (>0.8)	D: 0.73 ± 0.30	D: 0.59	D: 0.65 ± 0.35	D: 0.51
Mueller (2017)	MPR>80‡	NA	NA	NA	DOACs: 0.82 A: 0.88 D: 0.65 R: 0.83

Márquez-Contrera (2016)	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 (2018)	TTR>65% (INR2-3)	NA	W: Percent patients with time in therapeutic range: 4.11%	NA	NA

Footnote:
PDC: proportions days covered; MPR: medication possession ratio; CP: Compliance percentage; TTR: Time in therapeutic range; USA: United States of America; NA: Not available/not applicable; aHR: adjusted Hazard ratio; VKA: Vitamin K antagonist. A: apixaban; D: dabigatran; R: rivaroxaban; W: warfarin.
Drug specific proportion of adherent patients was calculated as the percent 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

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)
Sub-analysis: 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)
Sub-analysis: 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)
Sub-analysis: 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)

[*]I^2 <80%.
[+] Not pooled. Based on one study
[++] Pooled results of only two studies

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	
	Number of unique studies	**Odds ratio (95% CI)**	**Number of unique studies**	**Odds ratio (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)
Sub-analysis: 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)

***I^2 <80%.**
+ Not pooled. Based on one study

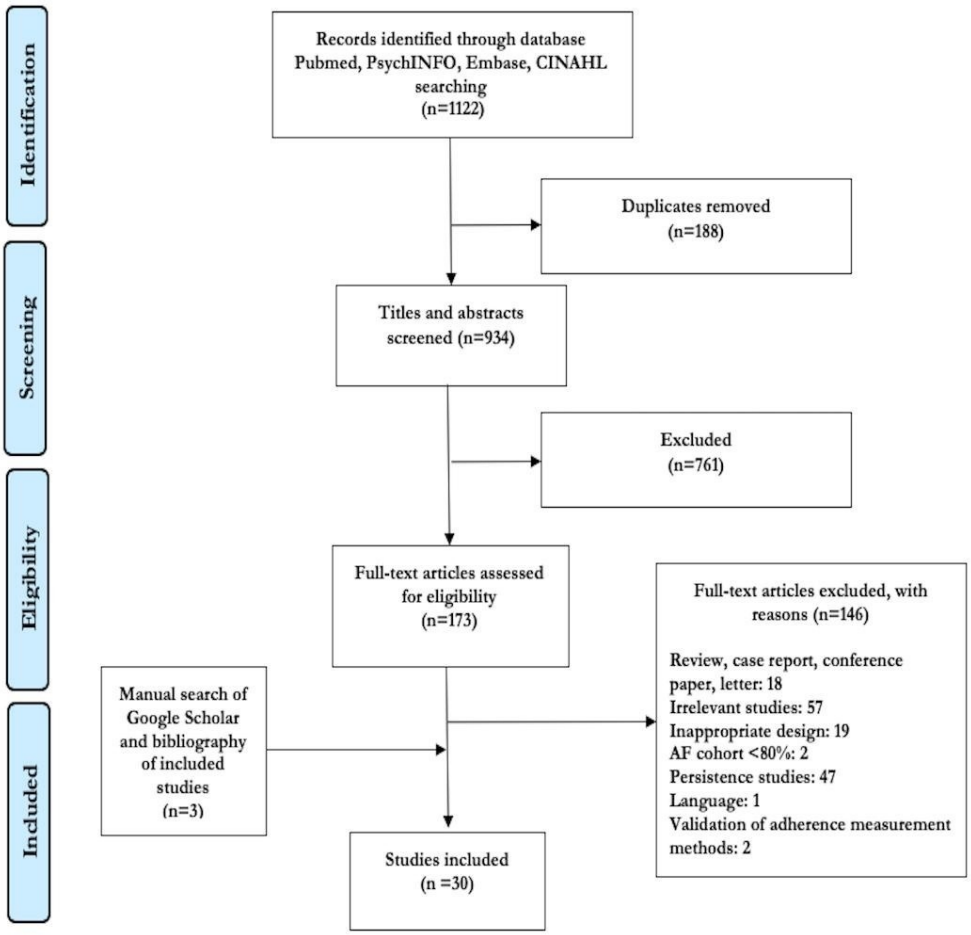


Figure 1.0: PRISMA flow diagram that details the number of studies identified by our search strategy, screened, and included in the final analysis.

90x90mm (300 x 300 DPI)

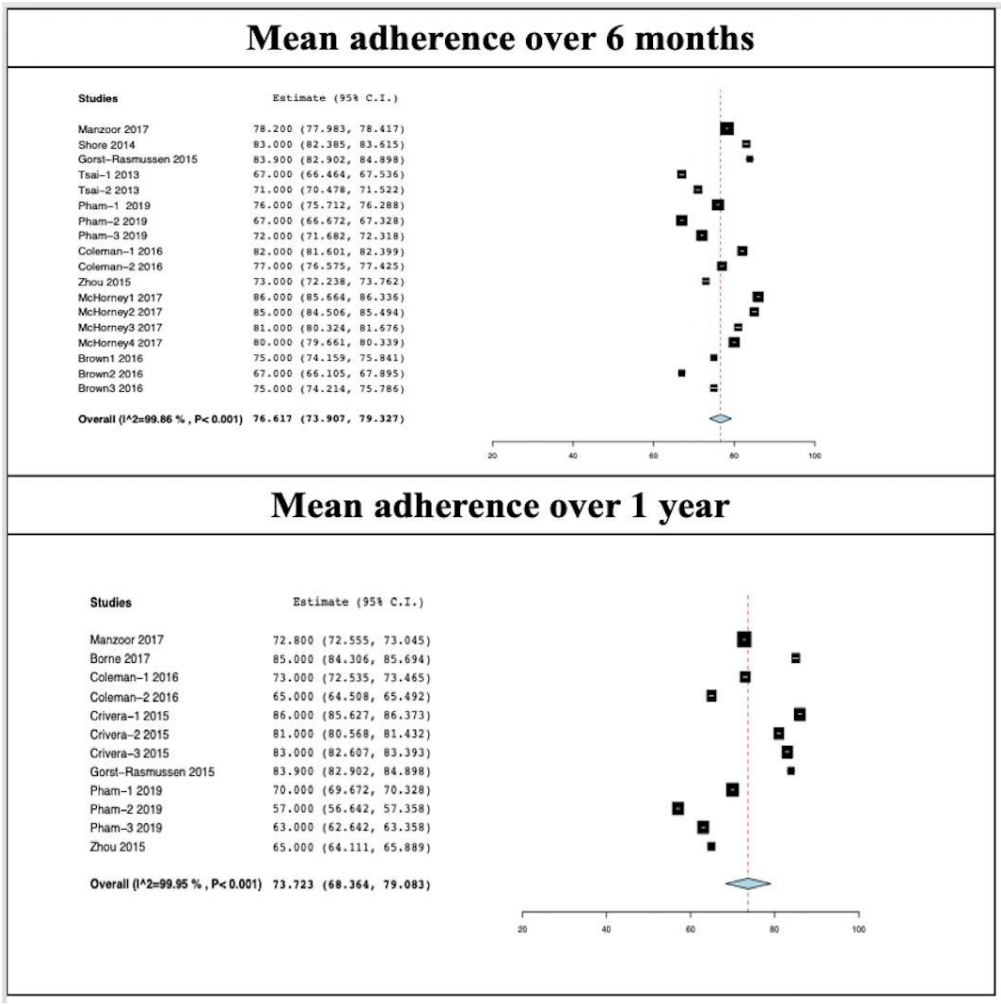


Figure 2.0: Forest plots illustrating patients' mean adherence scores over six-month and one-year post index date. See Supplementary 4 for additional forest plots for each OAC and subgroup analyses.

90x90mm (300 x 300 DPI)

PRISMA 2009 Checklist (Supplementary 1a)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Cover page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Inclusion criteria and study selection 5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Search strategy 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary File 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Inclusion criteria and study selection, Data extraction and synthesis 5, 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Inclusion criteria and study selection, Data extraction and synthesis 5, 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Inclusion criteria and study selection, Data extraction and synthesis 5, 6

PRISMA 2009 Checklist (Supplementary 1a)

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Supplementary File 3, Quality assessment, Data analysis 6, 7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Data analysis 6, 7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Data analysis 6, 7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Supplementary File 3, Quality assessment, Data analysis 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Data analysis 6, 7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results 9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1 31, 32
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary File 3, Quality assessment 7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2 33, 34
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 3,4 37, 37
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary File 4.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 3 36
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion 12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Limitations 14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion, Future directions

PRISMA 2009 Checklist (Supplementary 1a)

			12, 13, 14, 15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding 16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

MOOSE Guidelines (Supplementary 1b)

MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies	
Background	
Problem definition	Introduction 4
Hypothesis statement	NA- The study is mostly descriptive
Description of study outcomes	Introduction, Data extraction and synthesis 4, 6
Type of exposure or intervention used	Introduction, Inclusion criteria and study selection 4, 5
Type of study design used	Inclusion criteria and study selection 5
Study population	Inclusion criteria and study selection 5
Search Strategy	
Qualification of searchers	Search strategy 5
Search strategy including time periods included in the synthesis and keywords	Supplementary File 2, Search strategy 5
Effort to include all available studies, including contact with authors	Inclusion criteria and study selection 5, Authors were not contacted
Databases and registries searched	Search strategy 5
Search software used, name and version, including special features used	NA
Use of hand searching	Search strategy 5
List of citations located and those excluded	Figure 1.0: PRISMA flow chart
Method of addressing articles published in languages other than English	Inclusion criteria and study selection 5
Method of handling abstracts and unpublished studies	Inclusion criteria and study selection 5
Description of any contact with authors	All relevant information for this systematic review could be found in the published reports. There was no need to contact the respective authors
Methods	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Introduction, Supplementary File 3 4

MOOSE Guidelines (Supplementary 1b)

Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Introduction, Inclusion criteria and study selection, Data extraction and synthesis, Data analysis 4, 5, 6, 7
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Inclusion criteria and study selection, Data extraction and synthesis, Data analysis 5, 6, 7
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	NA
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Data analysis. Quality assessment 6, 7
Assessment of heterogeneity	Data analysis 7
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Data analysis 6, 7
Provision of appropriate tables and graphics	Figure 1
Results	
Graphic summarizing individual study estimates and overall estimate	Figures 2 and 3
Table giving descriptive information for each study included	Tables 1 and 2
Results of sensitivity testing (eg, subgroup analysis)	Table 3
Indication of statistical uncertainty of findings	Results 10
Discussion	
Quantitative assessment of bias (eg, publication bias)	Supplementary File 3
Justification for exclusion (eg, exclusion of non–English-language citations)	Inclusion criteria and study selection. Limitations 5, 14
Assessment of quality of included studies	Supplementary File 3, Results, Table 1 9, 31, 32
Conclusion	
Consideration of alternative explanations for observed results	Discussion 12, 13, 14
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Limitations 14
Guidelines for future research	Future directions 15
Disclosure of funding sources	Funding 16

Supplementary file 1: Literature search

Concept	Keywords	MeSH terms (Pubmed)
Medications	Anticoagulant* OR "blood thinner" OR "Vitamin K antagonists"OR "new oral anticoagulants" OR VKA OR NOAC OR DOAC OR Apixaban OR Eliquis OR dabigatran OR "dabigatran etexilate" mesylate OR pradaxa OR edoxaban OR lixiana OR rivaroxaban OR xarelto OR warfarin OR coumadin OR betrixaban OR bevyxxa OR acenocoumarol OR phenprocoumon OR fluindione	Warfarin Anticoagulants Dabigatran Rivaroxaban
Adherence	Adherence OR persistence OR compliance "Medication taking" OR "discontinuation" OR "nonpersistence" OR "nonadherence" OR "noncompliance"	Treatment Adherence and Compliance"[Mesh])
Atrial fibrillation	"atrial fibrillation" OR NVAF OR "non-valvular atrial fibrillation"	atrial fibrillation

Complete search example for Pubmed:
(((((((("atrial fibrillation") OR NVAF) OR "non-valvular atrial fibrillation")) AND (((((((Adherence) OR noncompliance) OR discontinuation) OR nonpersistence) OR nonadherence) OR persistence) OR "Medication taking") OR compliance)) AND ((((((((((((((((((((((((Anticoagulant*) OR "blood thinner") OR "Vitamin K antagonists") OR "new oral anticoagulants") OR VKA) OR NOAC) OR DOAC) OR Apixaban) OR Eliquis) OR dabigatran) OR "dabigatran etexilate") OR "dabigtaran mesylate") OR pradaxa) OR edoxaban) OR lixiana) OR rivaroxaban) OR xarelto) OR warfarin) OR coumadin) OR betrixaban) OR bevyxxa) OR acenocoumarol) OR phenprocoumon) OR fluindione))) AND "Atrial Fibrillation"[Mesh]) AND (("Treatment Adherence and Compliance"[Mesh]) OR ("Warfarin"[Mesh] OR "Anticoagulants"[Mesh] OR "Dabigatran"[Mesh] OR "Rivaroxaban"[Mesh]))):

STROBE	CODE	Alberts 2016	Beyer - Westendorf 2016	Borne 2017	Brown 2016	Casciano 2013	Coleman 2016	Coleman 2017	Civera 2015	Deshpande 2018 PMID: 29694285	Deshpande 2018 PMID: 29334815	Eapen 2014	Forsuland 2016	Gomez-Lumberas 2018	Gorst - Rasmussen 2015	Harper 2018	Jacobs 2018	Manzoor 2017	Marquez 2016	Maura 2017	McAlister 2018	McCormick 2001	McHorney 2017	McHorney 2018	Mueller 2017	Pham 2019	Shore 2014	Sorensen 2017	Tsai 2013	Yao 2016	Zhou 2015
Title and abstract																															
Indicate the study's design with a commonly used term in the title or the abstract	1a	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0
Provide in the abstract an informative and balanced summary of what was done and what was found.	1b	0	1	1	1	1	0	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Background/rationale: Explain the scientific background and rationale for the investigation being reported	2	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1
Objective: State specific objectives, including any prespecified hypothesis.	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Study design: Present key elements of study design early in the paper	4	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Setting: Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	5	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1
Participants: Give the eligibility criteria, and the sources and methods of selection of participants	6a	1	1	1	1	0	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1
For matched studies, give matching criteria and number of exposed and unexposed	6b	1	NA	NA	NA	NA	1	1	NA	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	NA	NA	NA	NA	NA	1	NA
Variables: Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	7	0	1	0	1	0	0	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
Data sources/measurement: For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one grou	8	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Bias: Describe any efforts to address potential sources of bias (e.g. Propensity scores)	9	1	0	0	0	0	1	1	0	1	1	0	0	0	0	0	1	1	1	1	0	1	1	1	0	1	1	0	0	0	0
Study size: Explain how the study size was arrived at.	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Quantitative variables/ statistical analysis:																															
Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why. (categorizing)	11	0	1	1	1	1	0	0	0	0	0	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1
Describe all statistical methods, including those used to control for confounding	12a	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1
Describe any methods used to examine subgroups and interactions	12b	1	0	1	1	0	0	1	1	1	1	1	0	0	1	0	1	1	0	1	1	0	1	1	0	0	1	0	1	1	1
Explain how missing data were addressed	12c	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0	0	0	0
Cohort study: If applicable, describe how loss to follow-up was addressed.	12d	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Describe any sensitivity analyses	12e	0	1	1	0	0	0	0	0	0	0	0	1	0	1	0	1	1	0	1	1	0	1	1	0	0	1	1	0	1	1
Participants:																															
Report the numbers of individuals at each stage of the study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed.	13a	0	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	0	0	1	1	0	1	1	1	1	1	1	0	0	1
Give reasons for non-participation at each stage	13b	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Consider use of a flow diagram	13c	0	1	1	1	1	0	1	1	1	1	1	1	0	1	0	0	0	0	1	1	0	1	1	1	1	1	1	0	0	1
Descriptive data:																															
Give characteristics of study participants (e.g. demographic, clinical, social) and	14a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

information on exposures and potential confounders																														
Indicate the number of participants with missing data for each variable of interest.	**14b**	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0
Summarise follow-up time (eg, average and total amount)	**14c**	1	1	1	0	1	1	1	1	0	1	1	0		0	0	1	0	1	1	0	0	1	0	1	0	1	0	0	1	0
Outcome data: Report numbers of outcome events or summary measures over time	**15**	0	1	0	1	0	1	0	0	1	1	1	0	0	0	0	0	1	0	0	1	0	1	1	1	1	1	0	0	1	1
Main results																															
Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**16a**	1	0	0	1	0	0	0	1	1	1	1	0	0	1	0	1	0	1	NA	1	1	1	1	0	0	1	1	0	1	1
Report category boundaries when continuous variables were categorized.	**16b**	1	1	1	1	1	1	1	1	1	1	NA	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**16c**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Other analysis: Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses.	**17**	1	1	1	1	1	0	1	1	1	1	1	0	1	0	1	1	0	1	1	0	1	1	1	1	1	0	1	1	1	1
Key results: Summarize key results with reference to study objectives.	**18**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Limitations: Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	**19**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Interpretation: Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**20**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Generalizability: Discuss the generalizability (external validity) of the study results	**21**	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1
Funding: Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**22**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1		1	1	1	1
Sum		19	22	22	23	19	17	24	22	23	25	22	19	15	24	14	24	21	20	23	26	18	26	26	21	23	27	20	18	24	24
Total applicable		31	30	30	30	30	31	31	30	30	31	29	30	30	30	30	30	30	32	29	30	30	30	31	30	30	30	30	30	31	30
Score		0.612903	0.733333	0.73333	0.766667	0.633333	0.548387	0.774193	0.733333	0.766667	0.806451	0.75862	0.633333	0.5	0.8	0.466667	0.8	0.7	0.625	0.793103	0.866667	0.6	0.866667	0.838709	0.7	0.766667	0.9	0.666667	0.6	0.774193	0.8
Percent		61	73	73	77	63	55	77	73	77	81	76	63	50	80	47	80	70	63	79	87	60	87	84	70	77	90	67	60	77	80

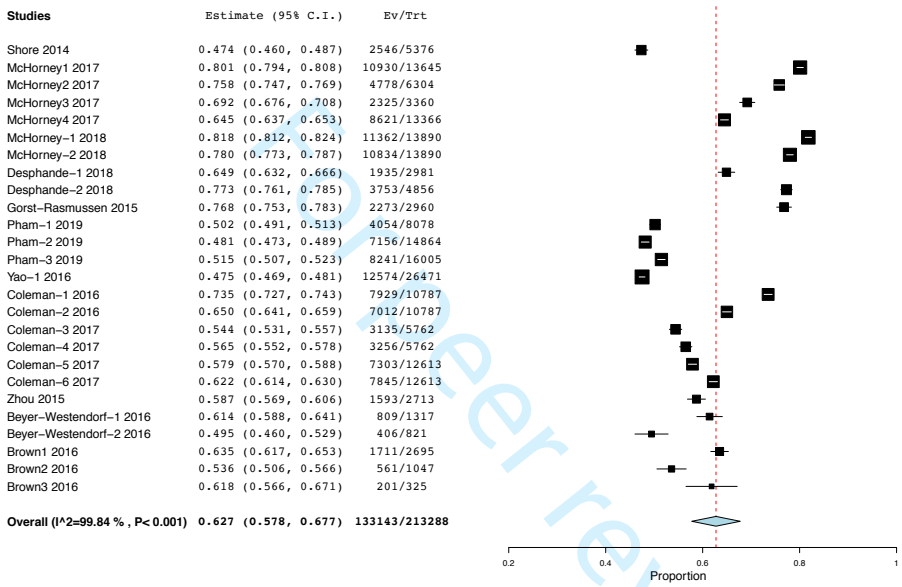
Item No	ISPOR	Alberts 2016	Beyer-Westendorf 2016	Borne 2017	Brown 2016	Cascia no 2013	Coleman 2016	Coleman 2017	Civera 2015	Deshpande 2018 PMID: 29694285	Deshpande 2018 PMID: 29334815	Eapen 2014	Forsuland 2016	Gomez-Lumberas 2018	Gorst-Rassussen 2015	Harper 2018	Jacobs 2018	Manzoor 2017	Marquez 2006	Maura 2017	McAlister 2018	McCormick 2001	McHorney 2017	McHorney 2018	Mueller 2017	Pharm 2019	Shore 2014	Sorenson 2017	Tsai 2013	Yao 2016	Zhou 2015
	Title / Abstract																														
1	Title is descriptive and reflective of study purpose	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	1	1	0	1	1	0	0	1	0	0	0	0
2	Abstract is a concise and accurate, reflecting contents of the study	0	1	1	1	1	0	1	0	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Introduction																														
	Clear review of fundamental literature related to topic	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Objectives and Definitions																														
	Objective(s) stated?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Design and Methods																														
	Study design appropriate for objectives	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Data sources adequately described	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1
	Evidence provided for reliability / accuracy of data	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0
	Sampling methods described	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Well describe patient population and Subject inclusion / exclusion criteria stated	1	1	1	1	0	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1
	Sufficient data to make valid estimate of compliance (i.e. Continuous eligibility for drug during study period verified)	0	1	1	1	1	1	1	0	1	1	1	0	1	1	0	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1
	Sufficient pre-enrollment period to ensure drug naivety? (If applicable)	NA	1	NA	1	1	NA	1	NA	NA	NA	1	NA	NA	NA	0	NA	1	NA	1	1	NA	1	1	0	1	NA	1	NA	1	1
	Explanation of how patients who switched drugs within or between therapeutic classes were handled	0	0	0	1	0	0	1	1	0	0	0	1	0	1	0	1	1	0	1	NA	NA	0	1	0	1	1	0	1	1	1
	Explicit definition of compliance/persistence based on published, accepted definition?	1	1	1	1	1	0	1	0	1	1	1	0	1	1	0	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1
	Methods for calculating compliance / persistence clearly described (and matches operational definition)	1	1	1	0	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1
	Was handling of medication gaps described	0	0	0	1	1	0	0	0	1	1	0	0	0	1	1	0	0	1	1	1	0	0	1	0	1	1	0	0	0	0
	Follow-up period specified	1	1	1	1	1	1	1	0	1	1	1	0	0	1	0	0	1	1	1	1	1	1	1	1	0	1	1	1	1	0
	Statistics appropriate to design and data	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Test statistics are reported appropriately (i.e. CIs, p-values reported)	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1
	Appropriate descriptive data on study sample are presented	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Distribution of compliance/persistence variable is presented (i.e. proportion of discontinuers)	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1
	Sum	12	14	14	16	15	9	16	11	15	15	14	11	12	18	10	15	17	15	19	17	14	17	19	10	17	17	15	14	16	15
	Total Applicable	18	19	18	19	19	18	19	18	18	18	19	18	18	18	19	18	20	18	19	18	17	19	19	19	19	18	19	18	19	19
	Score	0.666667	0.736842	0.777778	0.842105	0.789473	0.5	0.842105	0.611111	0.833333	0.833333	0.736842	0.611111	0.666667	1	0.5263	0.833	0.85	0.833333	1	0.944444	0.823529	0.894736	1	0.526315	0.895	0.944	0.789473	0.778	0.842	0.789
	Percent	67	74	78	84	79	50	84	61	83	83	74	61	67	100	53	83	85	83	100	94	82	89	100	53	89	94	79	78	84	79

Supplementary 4.0: Forest plots

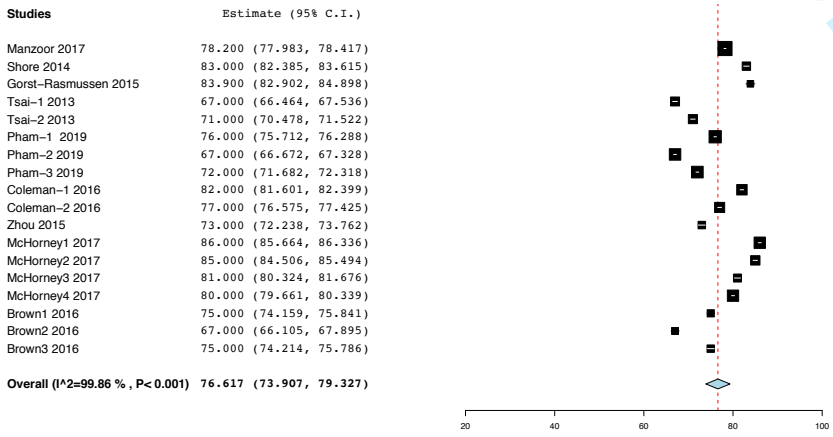
All OACs

Adherence at 6 months

Proportion adherent at 6 months

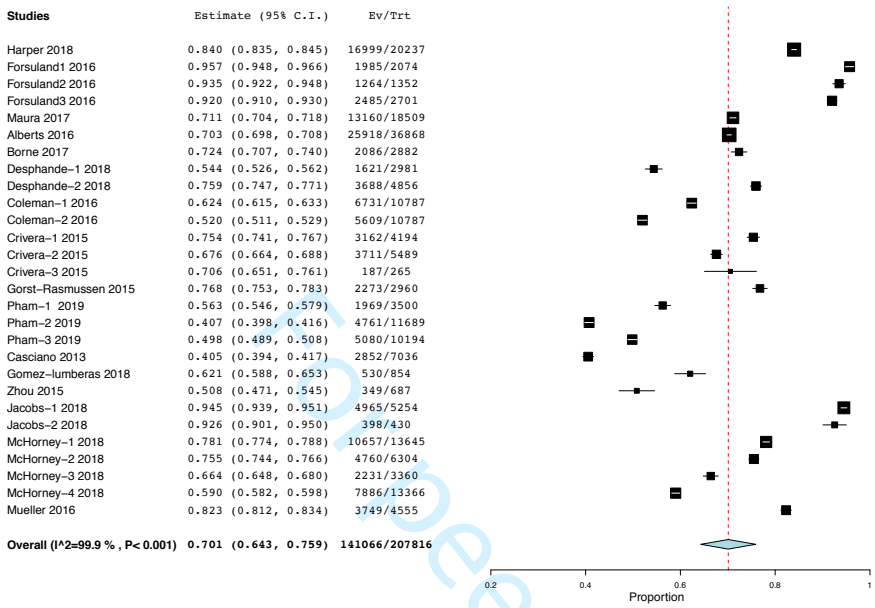


Mean adherence score at 6 months

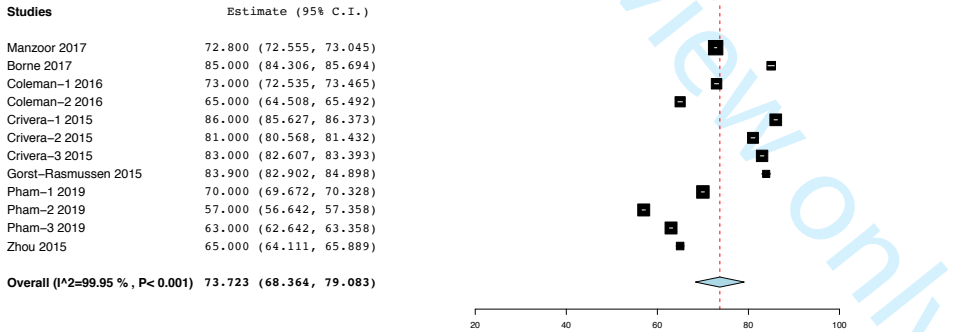


Adherence at 1 year

Proportion adherent at 1 year



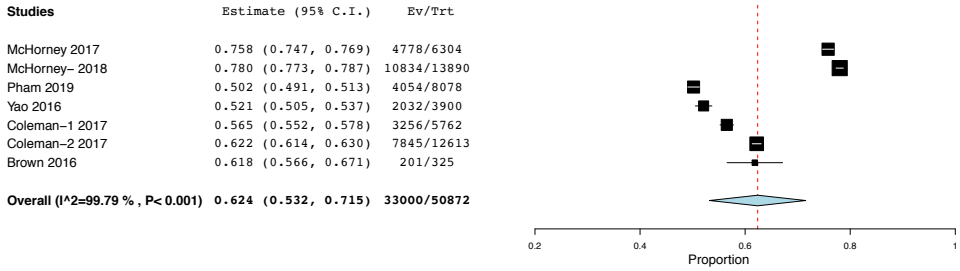
Mean adherence at 1 year



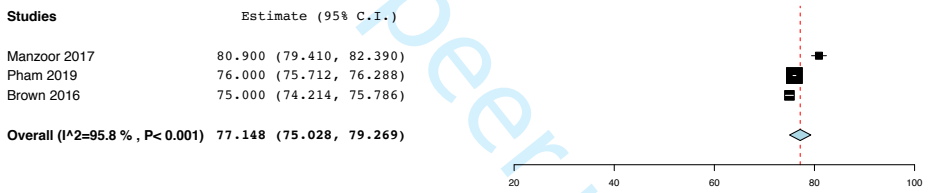
Apixaban

Adherence at 6 months

Proportion adherent at 6 months

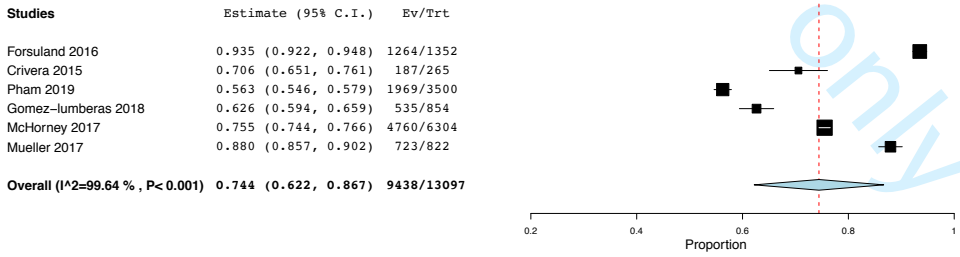


Mean adherence at 6 months

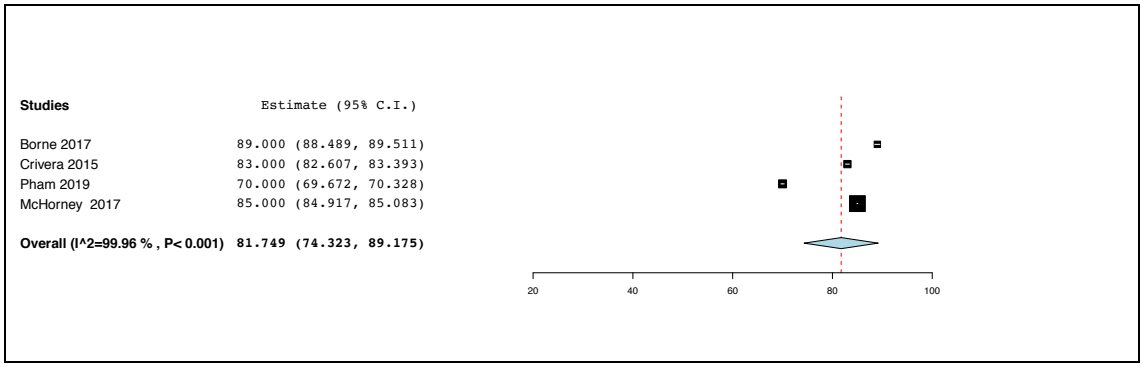


Adherence at 1 year

Proportion adherent at 1 year



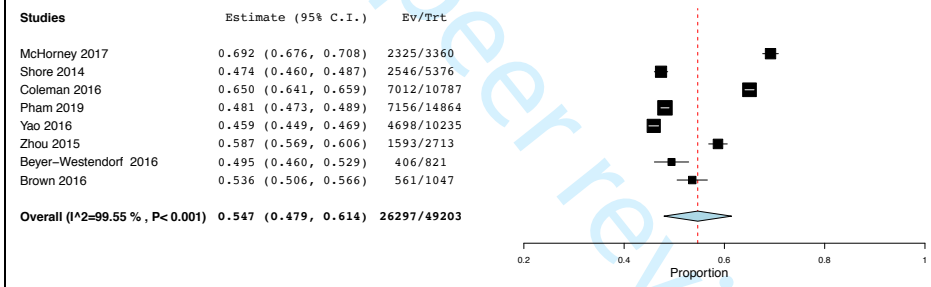
Mean adherence at 1 year



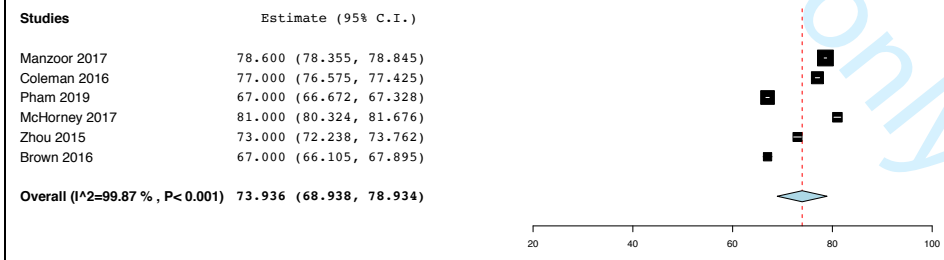
Dabigatran:

Adherence at 6 months

Proportion adherent at 6 months

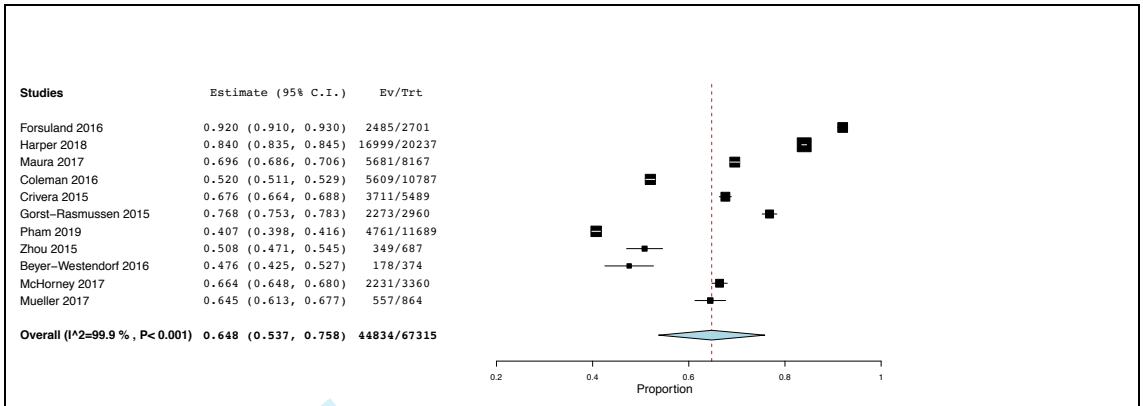


Mean adherence at 6 months

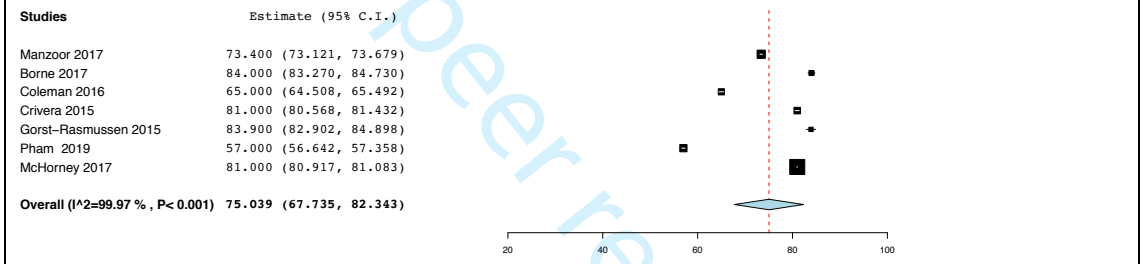


Adherence at 1 year

Proportion adherent at 1 year



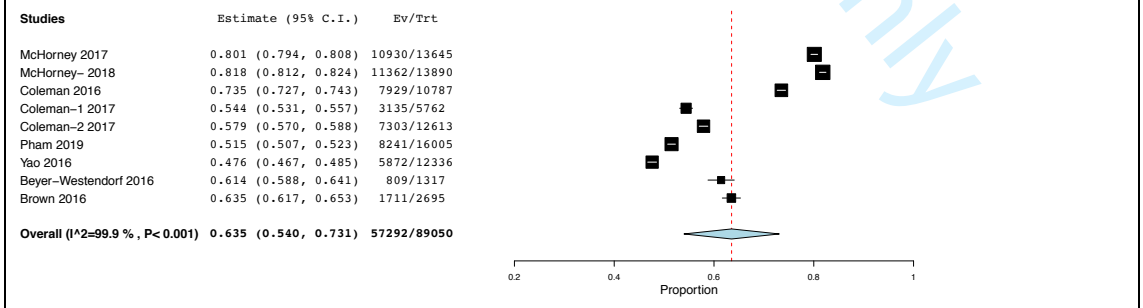
Mean adherence at one year



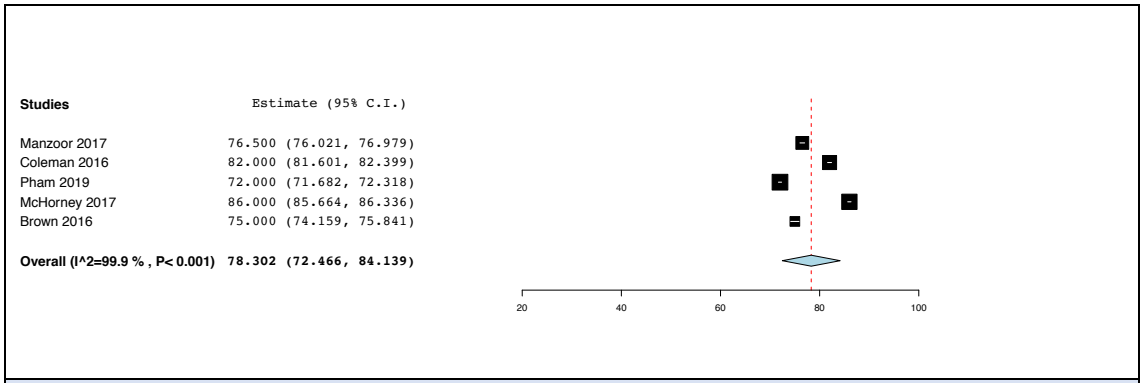
Rivaroxaban:

Adherence at 6 months

Proportion adherent at 6 months

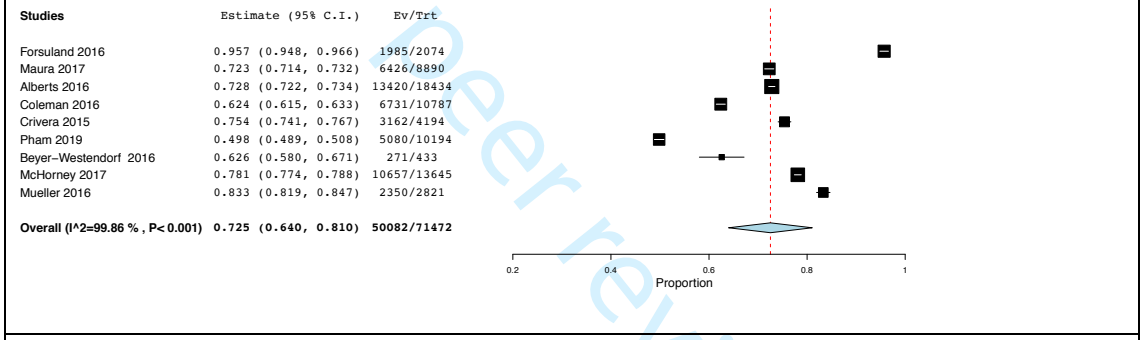


Mean adherence at 6 months

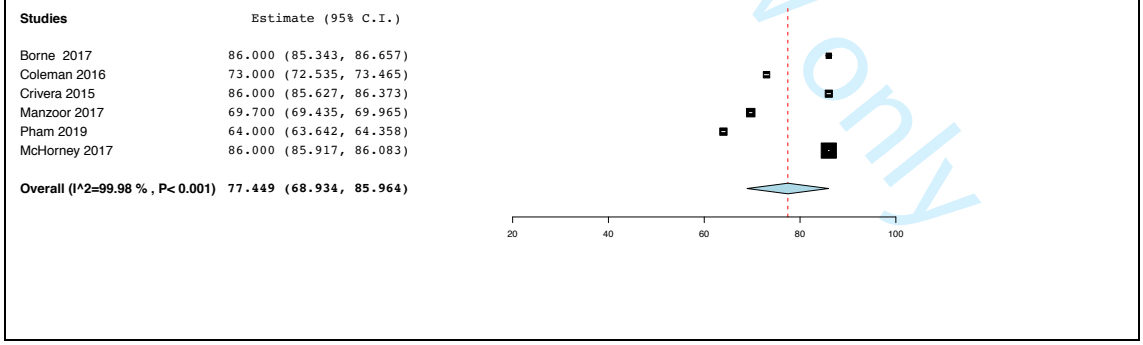


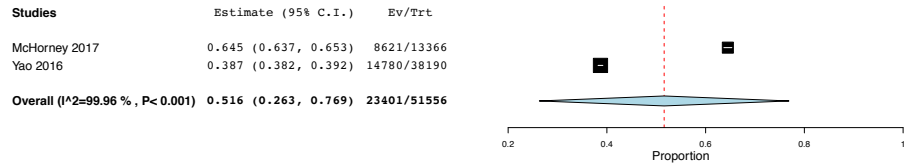
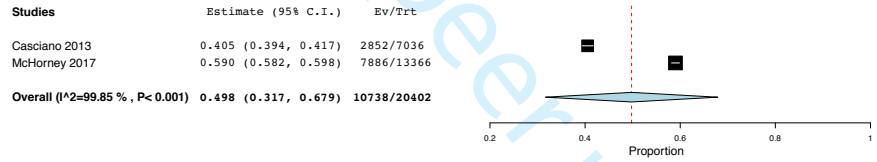
Adherence at 1 year

Proportion adherent at 1 year



Mean adherence at 1 year



Warfarin:
Adherence at 6 months
Proportion adherent at 6 months

Mean adherence at 6 months
NA
Adherence at 1 year
Proportion adherent at 1 year

Mean adherence at 1 year
NA

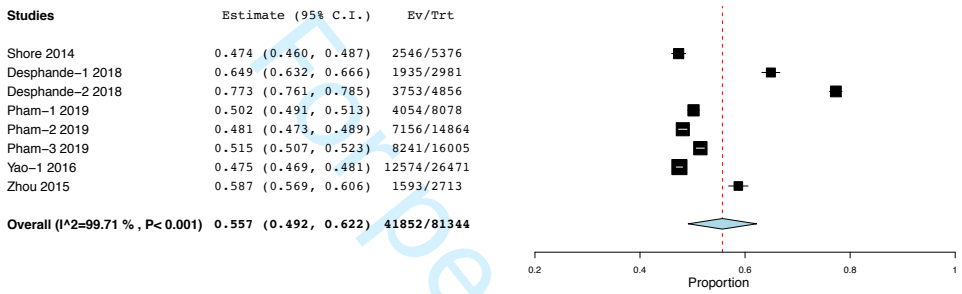
Supplementary 4.1: Sub-group analysis

Supplementary 4.1.1: Sub-group analysis by excluding studies with conflict of interest:

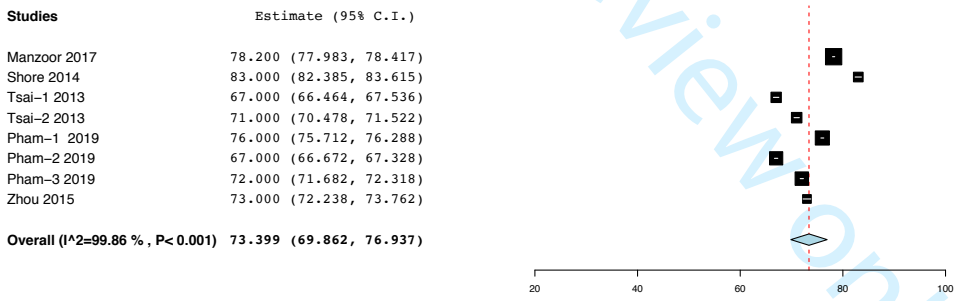
All OACs: Sub-analysis: Excluding studies with conflict of interest

Adherence at 6 months

Proportion adherent at 6 months

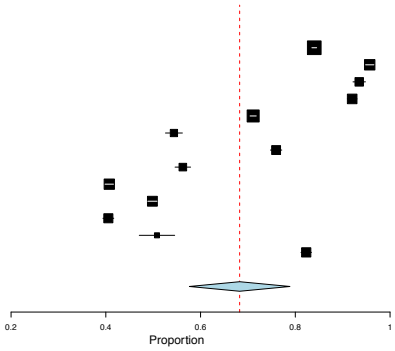


Mean adherence at 6 months

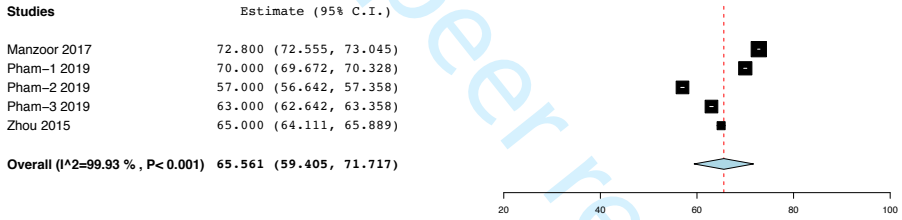


Adherence at 1 year

Proportion adherent at 1 year



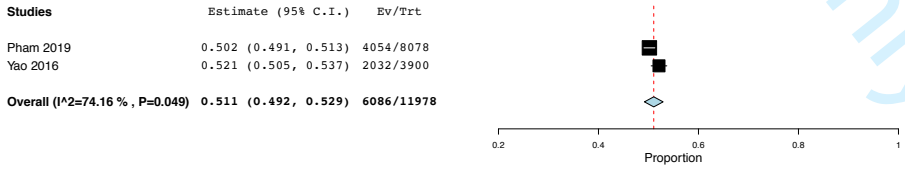
Mean adherence at 1 year



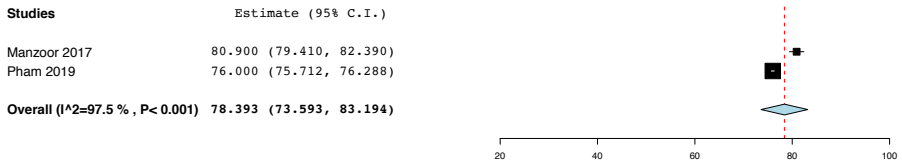
Apixaban: Sub-analysis: Excluding studies with conflict of interest

Adherence at 6 months

Proportion adherent at 6 months

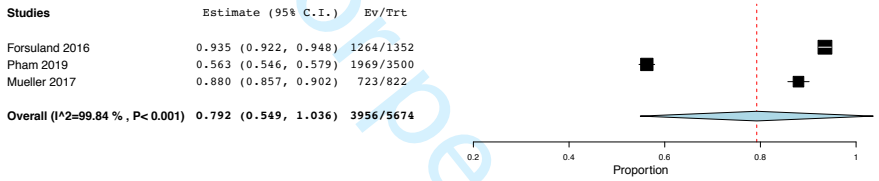


Mean adherence at 1 year



Adherence at 1 year:

Proportion adherent at 1 year



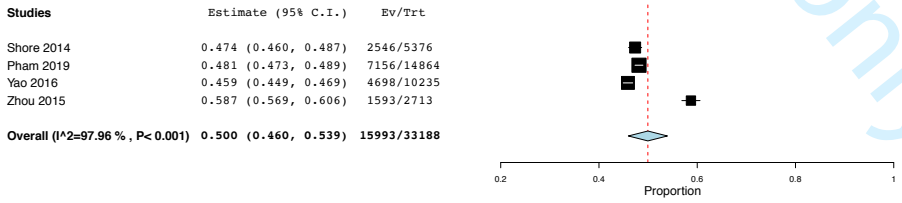
Mean adherence at 1 year

NA (one study)

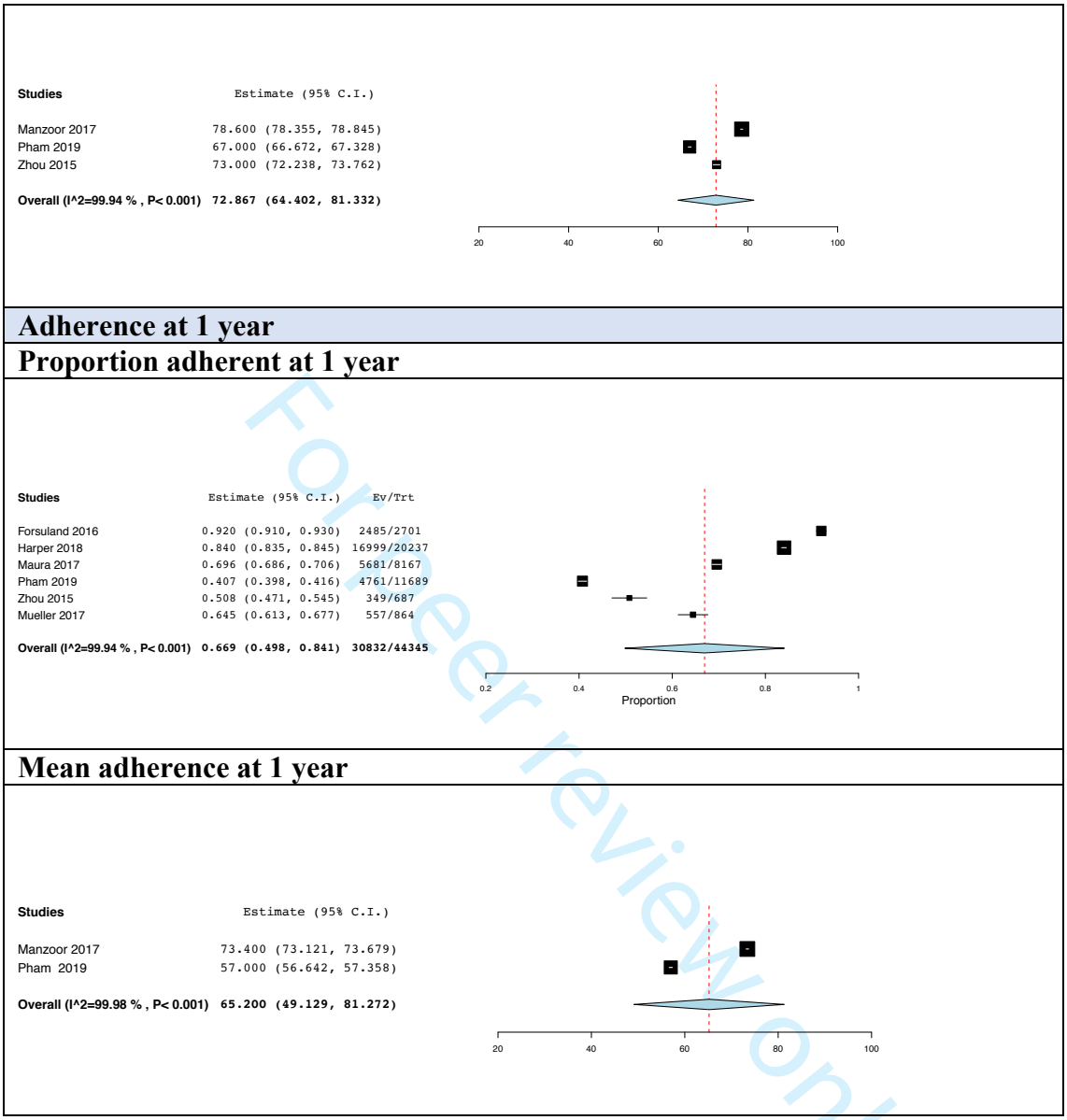
Dabigatran: Sub-analysis: Excluding studies with conflict of interest

Adherence at 6 months

Proportion adherent at 6 months



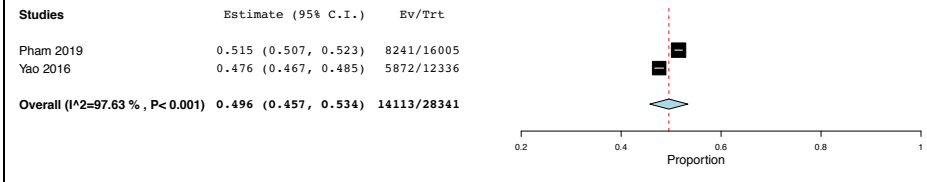
Mean adherence at 6 months



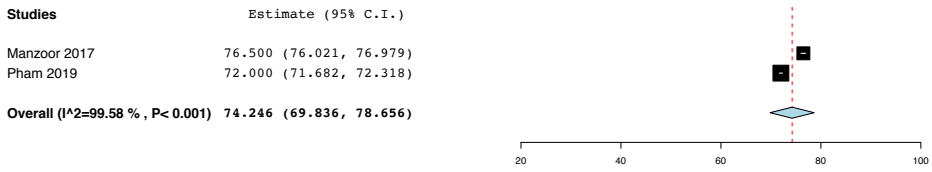
Rivaroxaban: Sub-analysis: Excluding studies with conflict of interest

Adherence at 6 months

Proportion adherent at 6 months

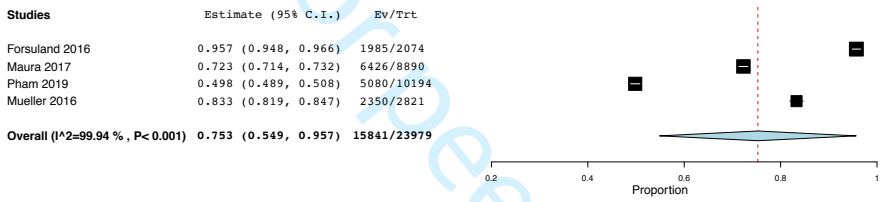


Mean adherence at 6 months

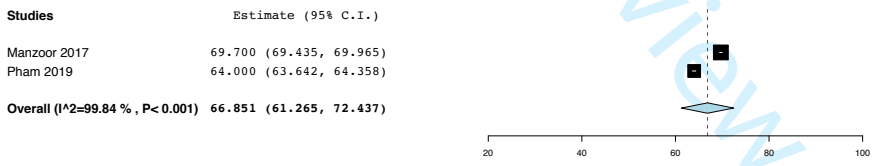


Adherence at 1 year

Proportion adherent at 1 year



Mean adherence at 1 year

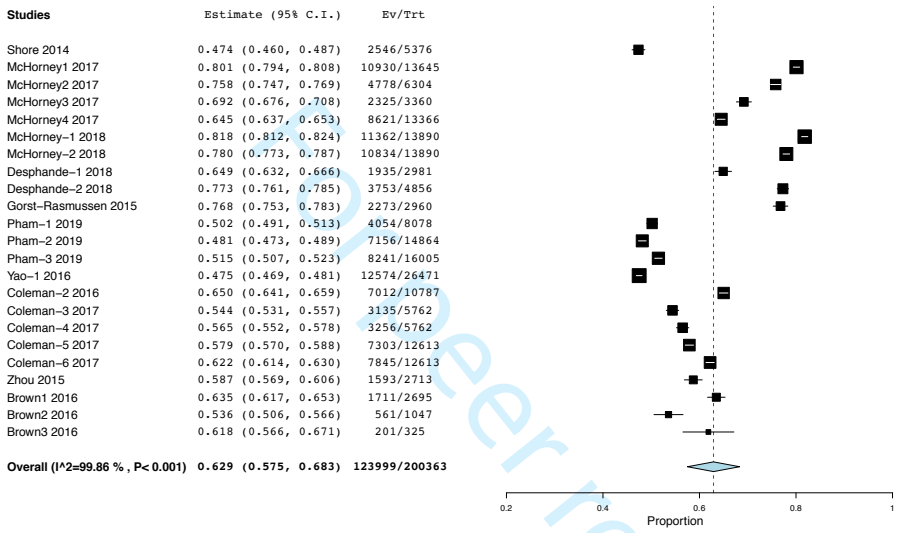


Supplementary 4.1.2: Sub-group analysis by excluding low and medium quality studies.

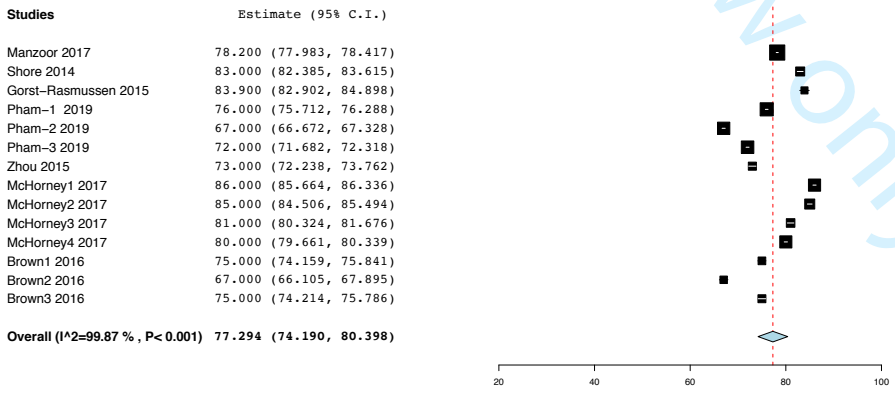
All OAC: Sub-analysis: Excluding low and medium quality studies

Adherence at 6 months

Proportion adherent at 6 months

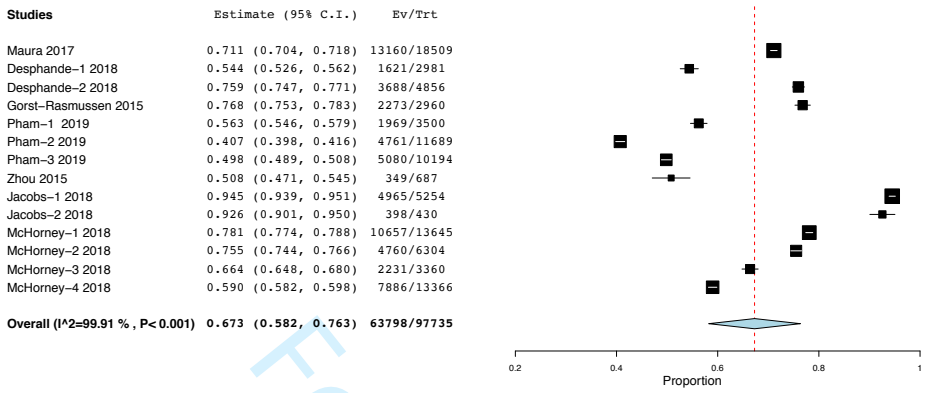


Mean adherence at 6 months

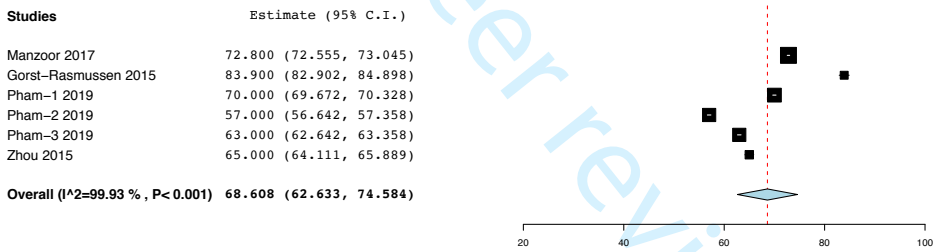


Adherence at 1 year

Proportion adherent at 1 year



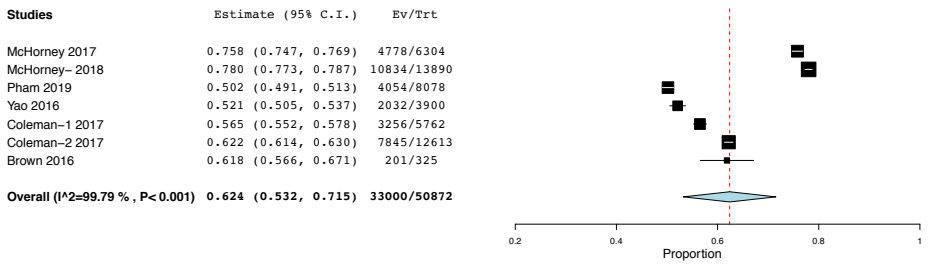
Mean adherence at 1 year



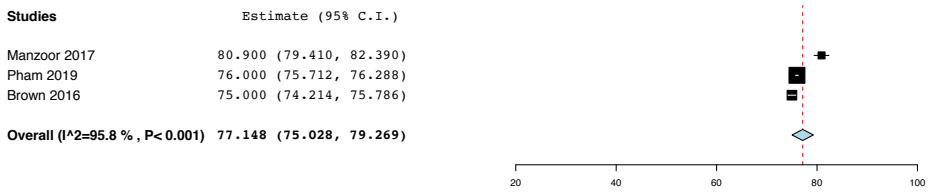
Apixaban: Sub-analysis: Excluding low and medium quality studies

Adherence at 6 months

Proportion adherent at 6 months

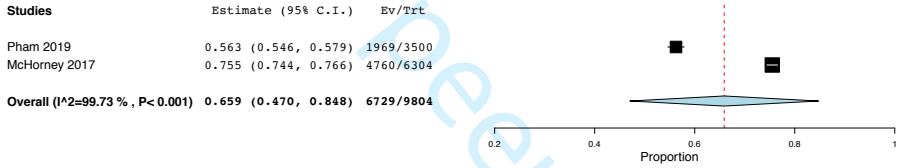


Mean adherence at 6 months

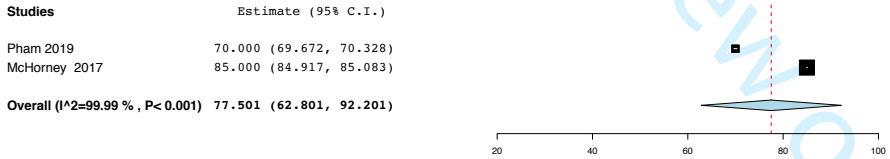


Adherence at 1 year

Proportion adherent at 1 year



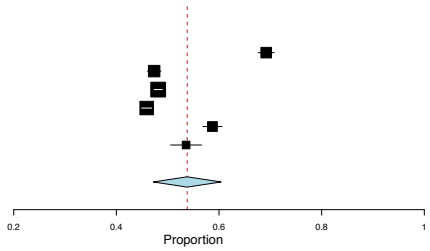
Mean adherence at 1 year



Dabigatran: Sub-analysis: Excluding low and medium quality studies

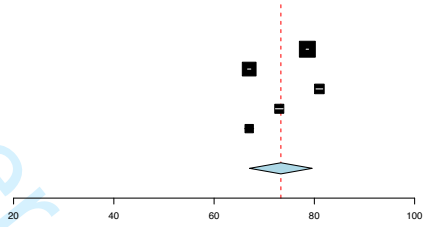
Adherence at 6 months

Proportion adherent at 6 months



Studies	Estimate (95% C.I.)	Ev/Trt
McHorney 2017	0.692 (0.676, 0.708)	2325/3360
Shore 2014	0.474 (0.460, 0.487)	2546/5376
Pham 2019	0.481 (0.473, 0.489)	7156/14864
Yao 2016	0.459 (0.449, 0.469)	4698/10235
Zhou 2015	0.587 (0.569, 0.606)	1593/2713
brown 2016	0.536 (0.506, 0.566)	561/1047
Overall (I^2=99.35 % , P< 0.001)	**0.538 (0.472, 0.604)**	**18879/37595**

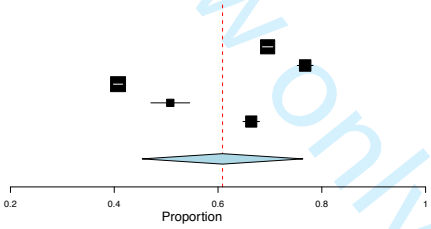
Mean adherence at 1 year



Studies	Estimate (95% C.I.)
Manzoor 2017	78.600 (78.355, 78.845)
Pham 2019	67.000 (66.672, 67.328)
McHorney 2017	81.000 (80.324, 81.676)
Zhou 2015	73.000 (72.238, 73.762)
Brown 2016	67.000 (66.105, 67.895)
Overall (I^2=99.89 % , P< 0.001)	**73.322 (67.076, 79.568)**

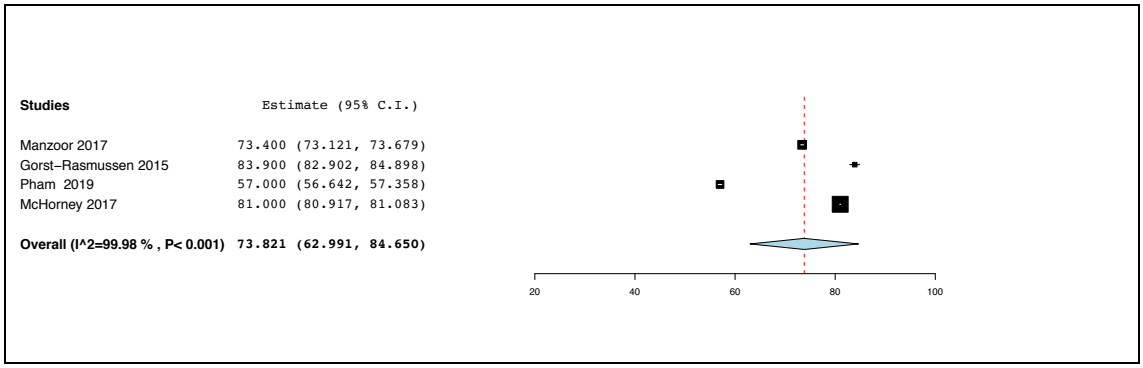
Adherence at 1 year

Proportion adherent at 1 year



Studies	Estimate (95% C.I.)	Ev/Trt
Maura 2017	0.696 (0.686, 0.706)	5681/8167
Gorst–Rasmussen 2015	0.768 (0.753, 0.783)	2273/2960
Pham 2019	0.407 (0.398, 0.416)	4761/11689
Zhou 2015	0.508 (0.471, 0.545)	349/687
McHorney 2017	0.664 (0.648, 0.680)	2231/3360
Overall (I^2=99.85 % , P< 0.001)	**0.609 (0.454, 0.764)**	**15295/26863**

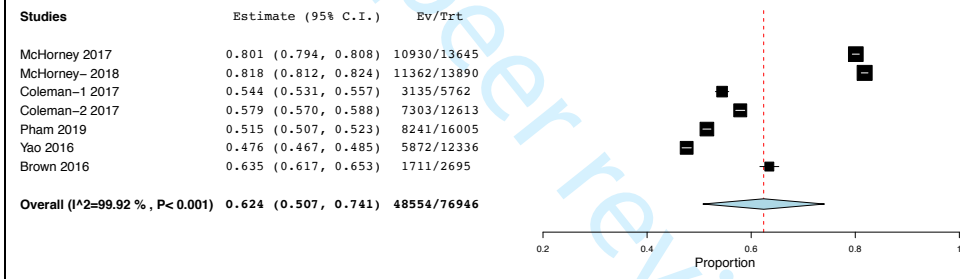
Mean adherence at 1 year



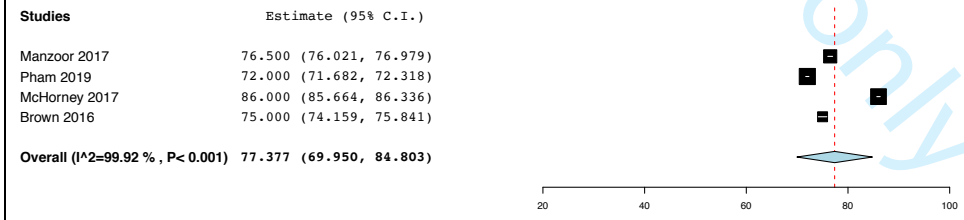
Rivaroxaban: Sub-analysis: Excluding low and medium quality studies

Adherence at 6 months

Proportion adherent at 6 months

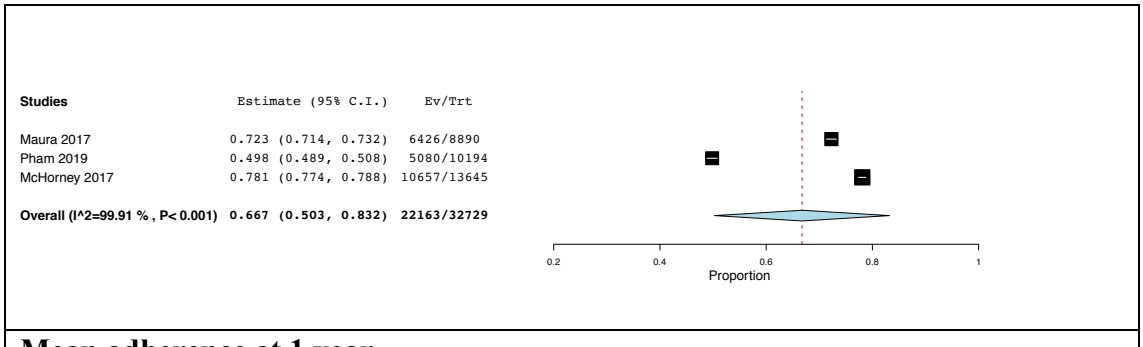


Mean adherence at 1 year

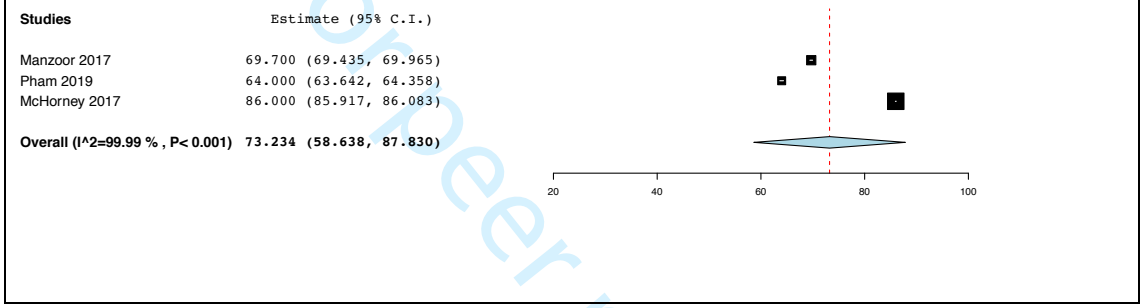


Adherence at 1 year

Proportion adherent at 1 year



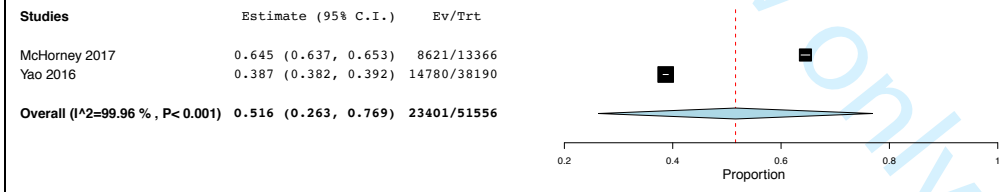
Mean adherence at 1 year



Warfarin: Sub-analysis: Excluding low and medium quality studies

Adherence at 6 months

Proportion adherent at 6 months



Mean adherence at 6 months

NA

Adherence at 1 year

Proportion adherent at 1 year

NA

Mean adherence at 1 year

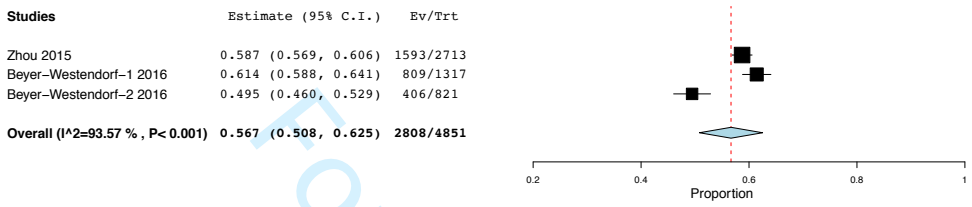
NA

Supplementary 4.1.3: Sub-group analysis by adherence measure

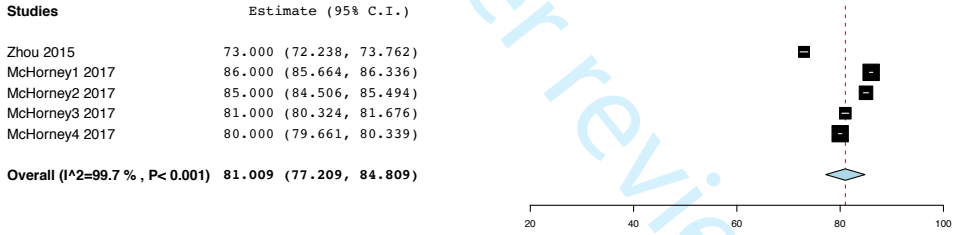
All OACs: Sub-analysis: stratified by adherence measure

Adherence at 6 months

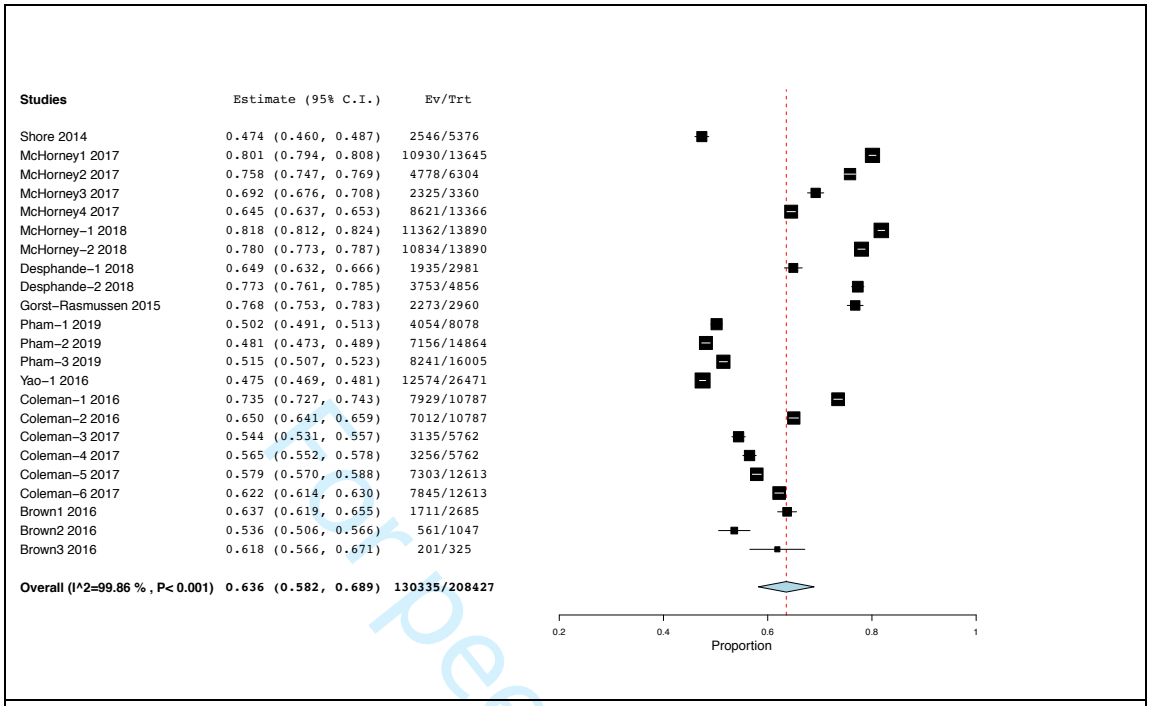
MPR: proportion adherent at 6 months



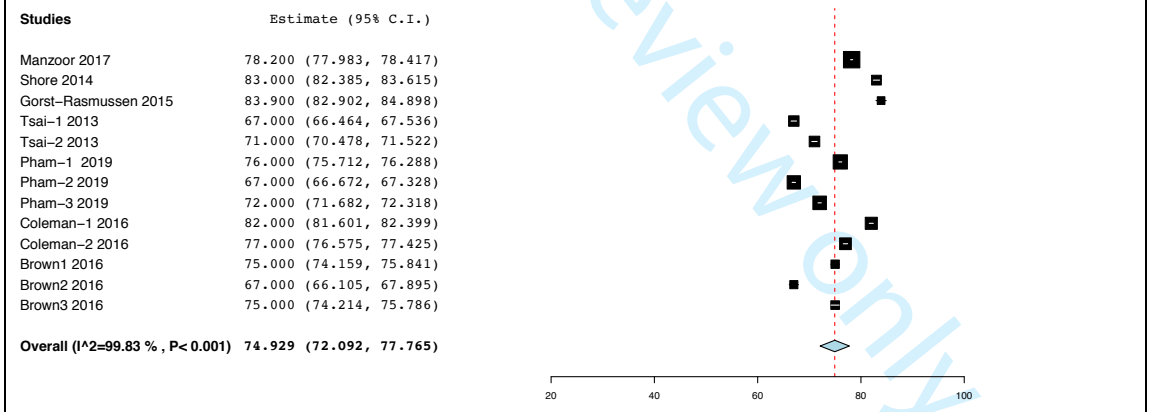
MPR: Mean (SD) adherence at 6 months



PDC: proportion adherent at 6 months

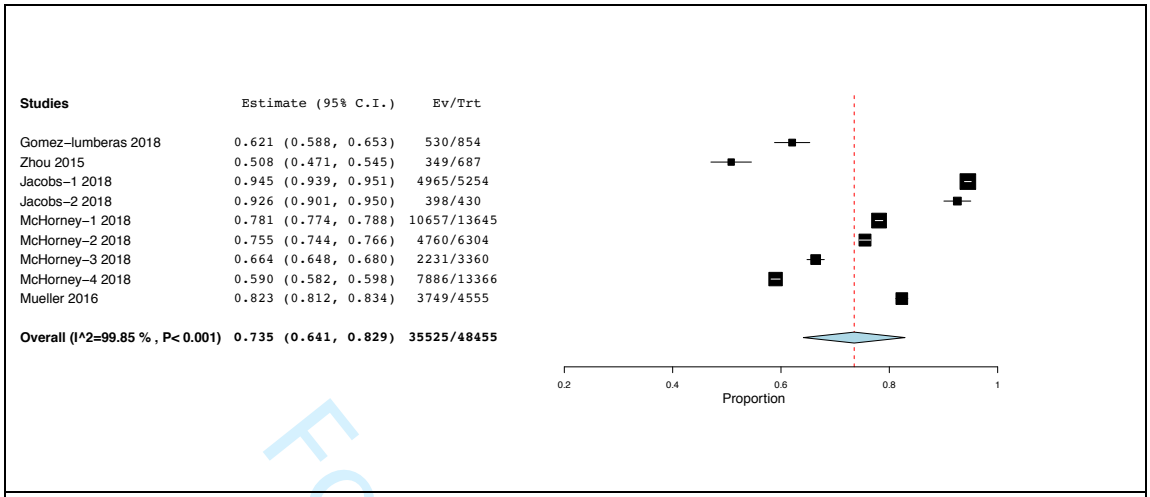


PDC: Mean (SD) adherence at 6 months



Adherence at 1 year

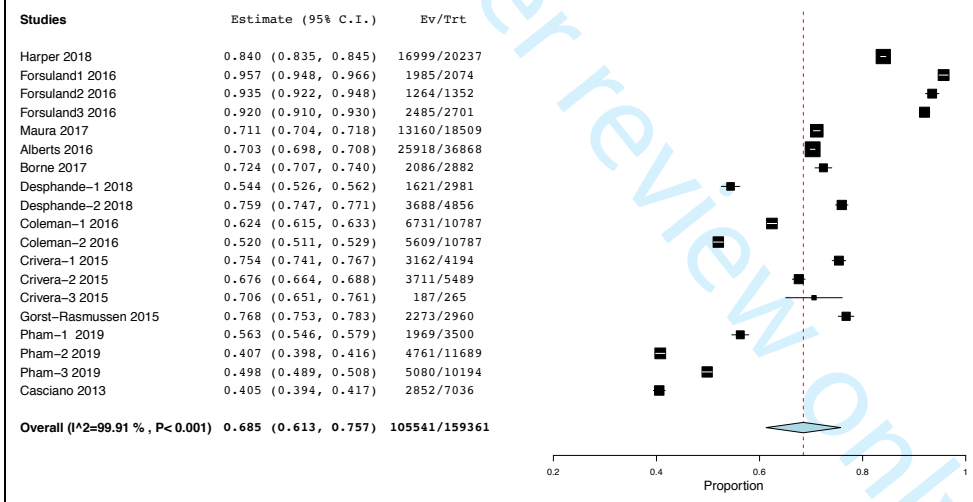
MPR: proportion adherent at 1 year



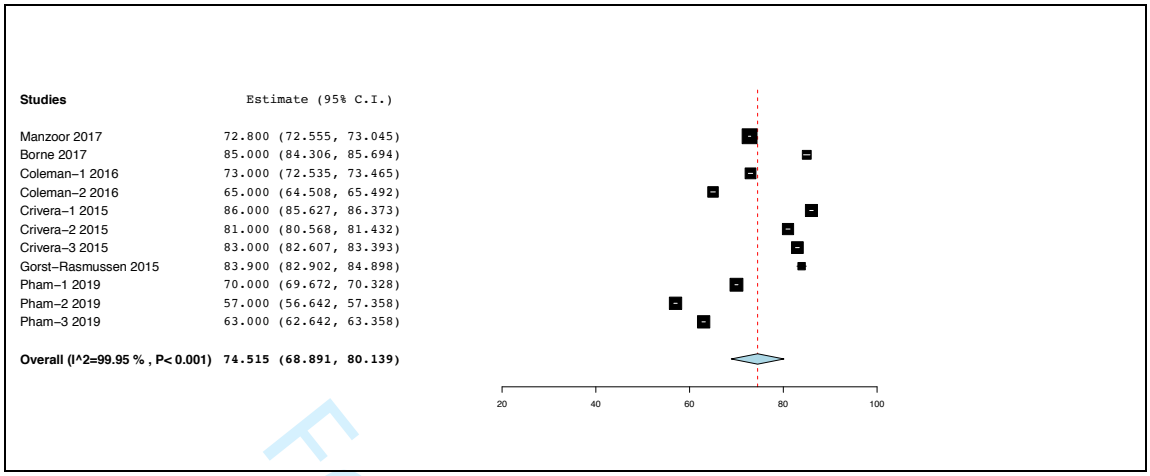
MPR: Mean (SD) adherence at 1 year

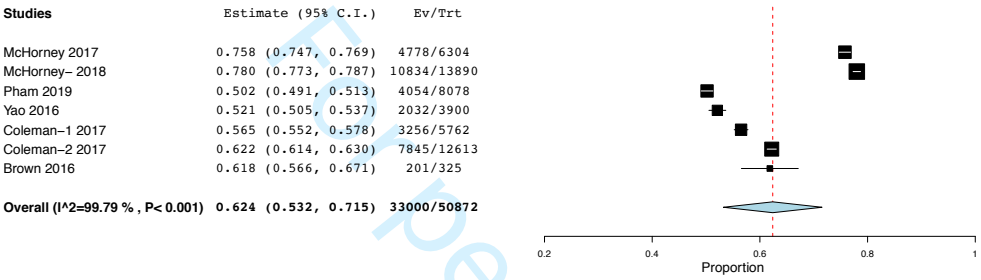
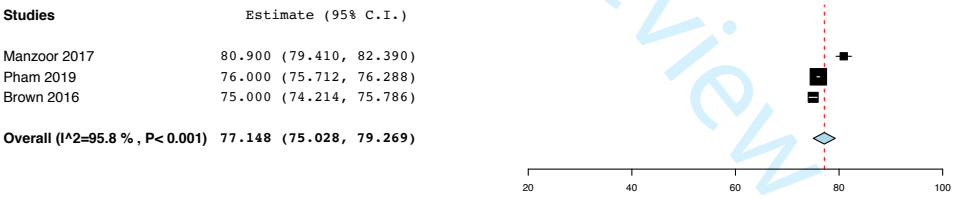
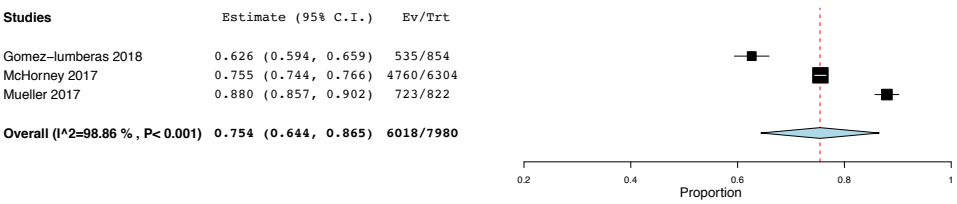
NA

PDC: proportion adherent at 1 year

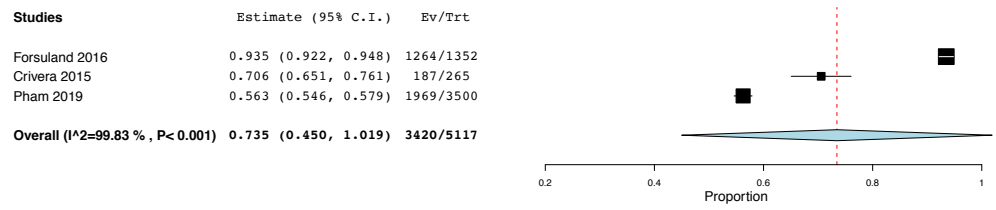


PDC: Mean (SD) adherence at 1 year

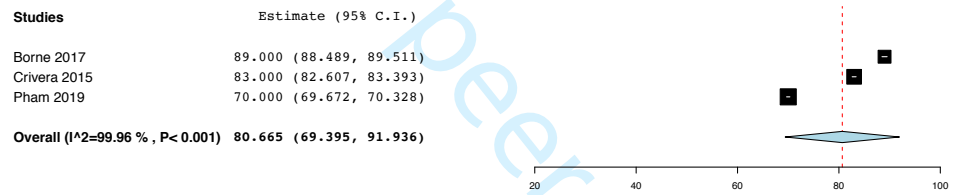


Apixaban: Sub-analysis: stratified by adherence measure
Adherence at 6 months
MPR: proportion adherent at 6 months
NA
MPR: Mean (SD) adherence at 6 months
NA
PDC: proportion adherent at 6 months

PDC: Mean (SD) adherence at 6 months

Adherence at 1 year
MPR: proportion adherent at 1 year

MPR: Mean (SD) adherence at 1 year
NA

PDC: proportion adherent at 1 year



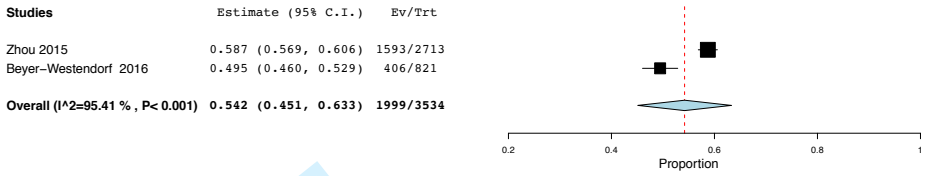
PDC: Mean (SD) adherence at 1 year



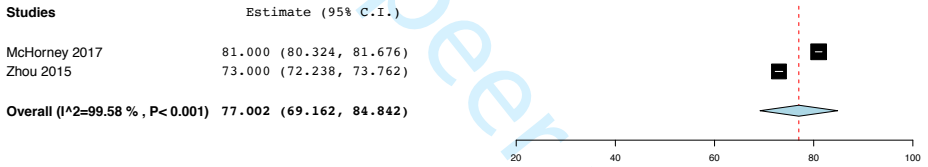
Dabigatran: Sub-analysis: stratified by adherence measure

Adherence at 6 months:

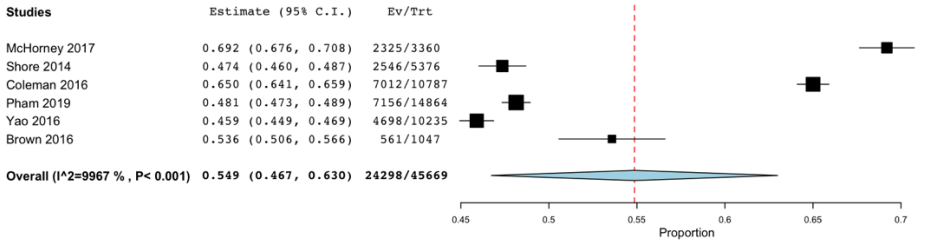
MPR: proportion adherent at 6 months



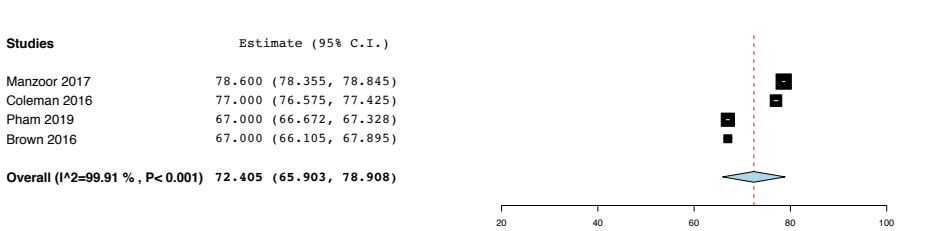
MPR: Mean (SD) adherence at 6 months



PDC: proportion adherent at 6 months

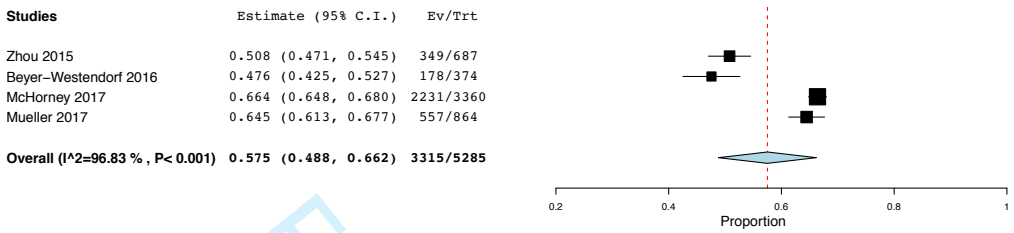


PDC: Mean (SD) adherence at 6 months



Adherence at 1 year

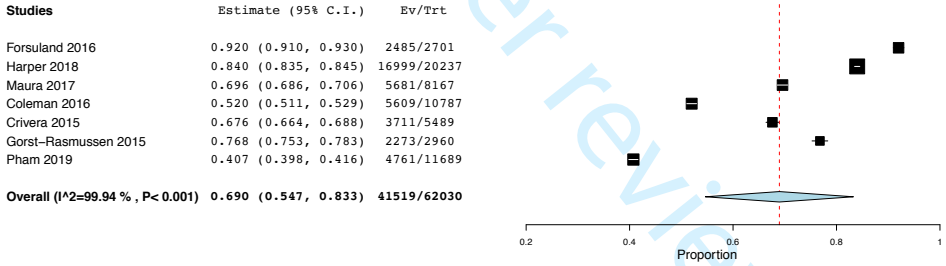
MPR: proportion adherent at 1 year



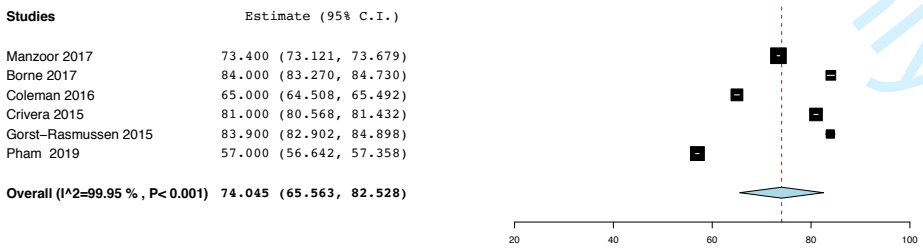
MPR: Mean (SD) adherence at 1 year

NA

PDC: proportion adherent at 1 year



PDC: Mean (SD) adherence at 1 year



Rivaroxaban: Sub-analysis: stratified by adherence measure.

Adherence at 6 months:

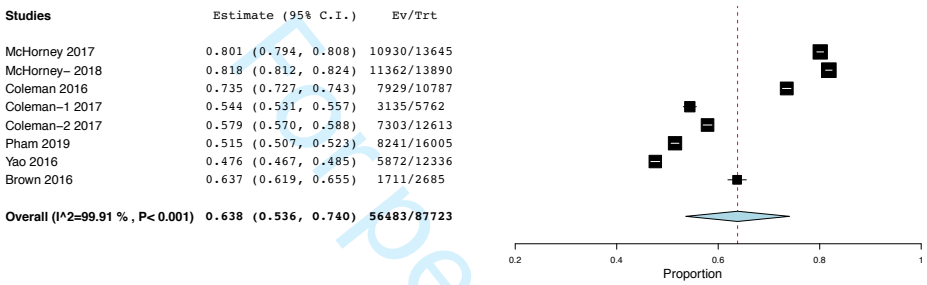
MPR: proportion adherent at 6 months

NA

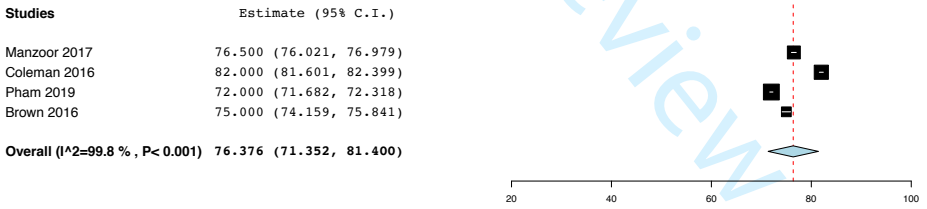
MPR: Mean (SD) adherence at 6 months

NA

PDC: proportion adherent at 6 months

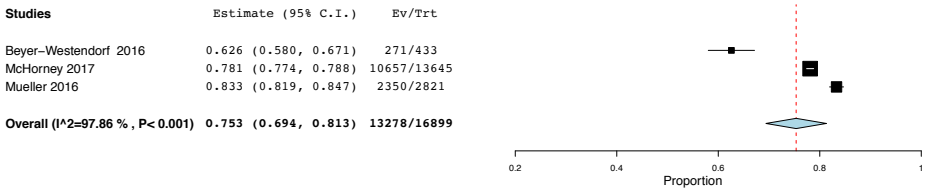


PDC: Mean (SD) adherence at 6 months



Adherence at 1 year:

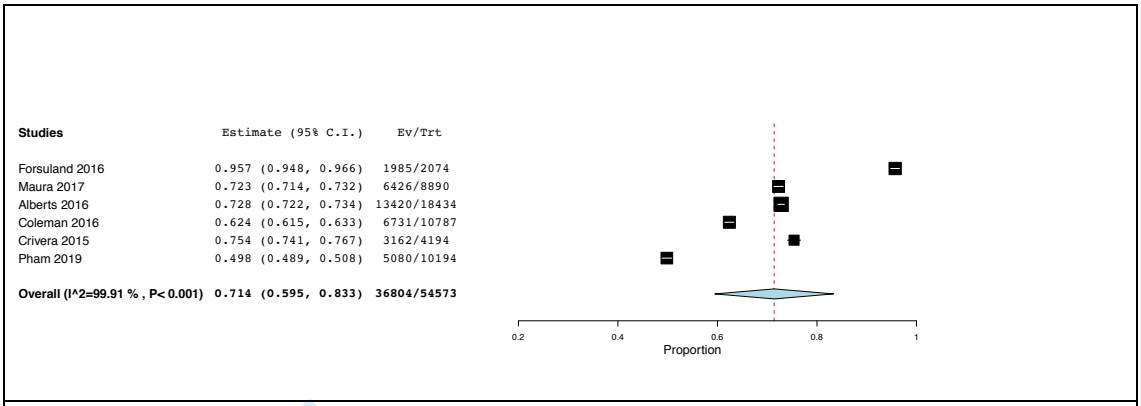
MPR: proportion adherent at 1 year



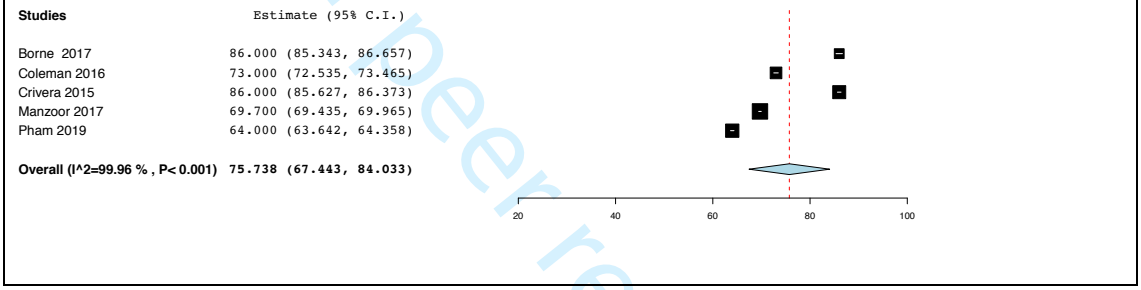
MPR: Mean (SD) adherence at 1 year

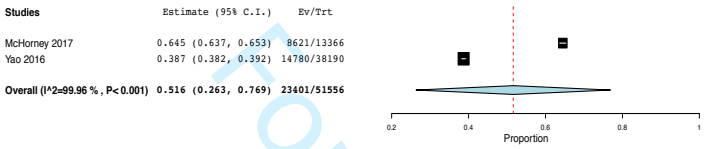
NA

PDC: proportion adherent at 1 year

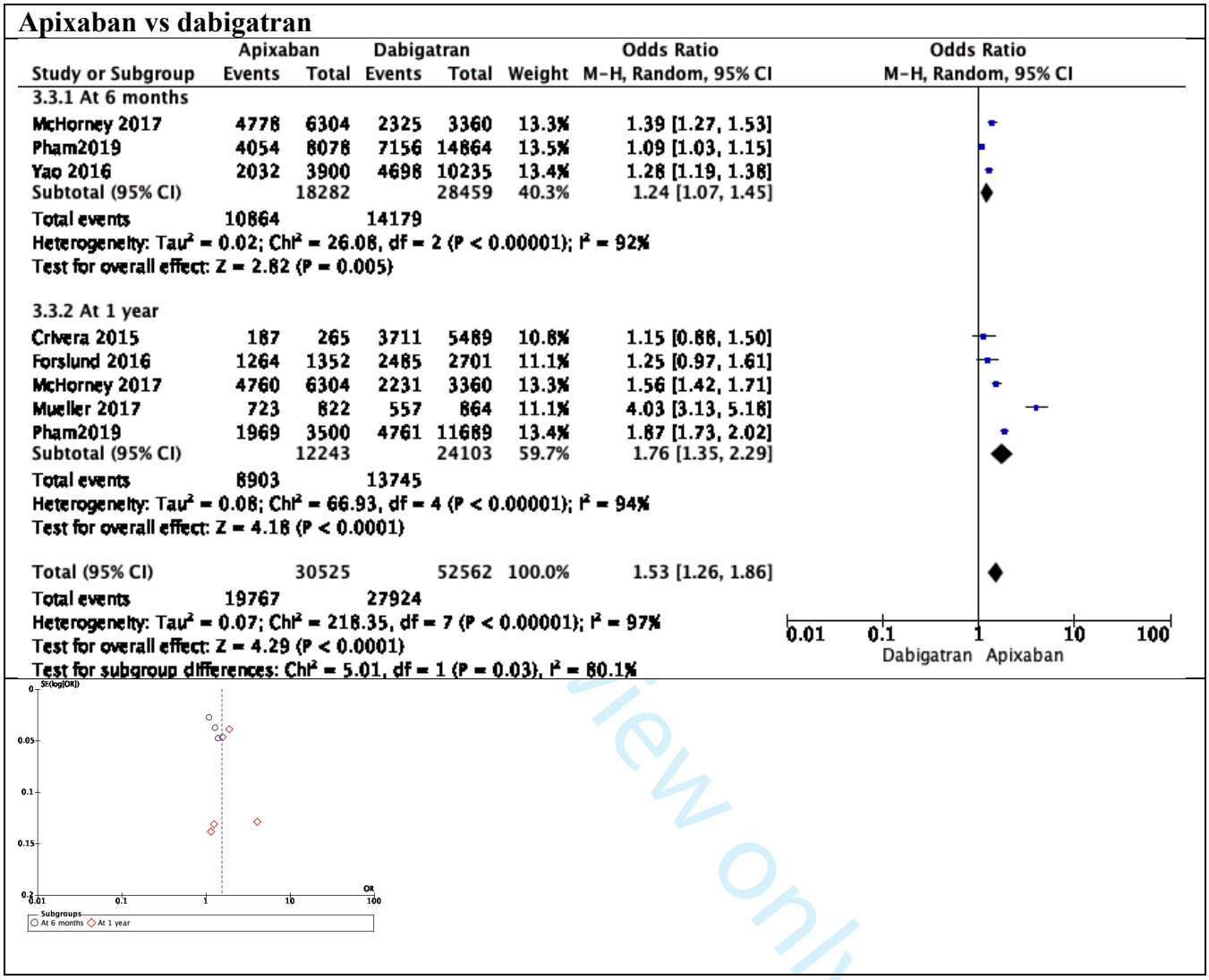


PDC: Mean (SD) adherence at 1 year



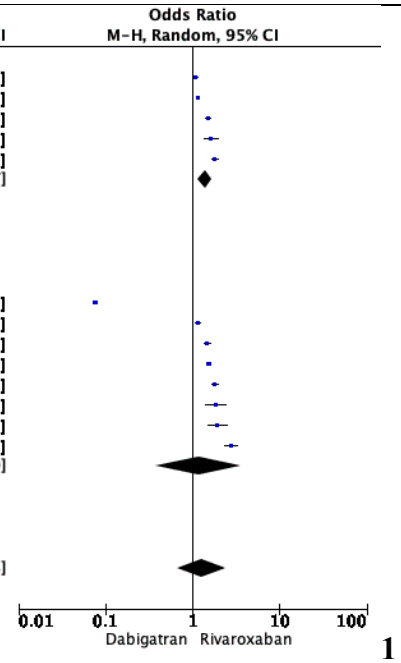
Warfarin: Sub-analysis: stratified by adherence measure
Adherence at 6 months:
MPR: proportion adherent at 6 months
NA
MPR: Mean (SD) adherence at 6 months
NA
PDC: proportion adherent at 6 months

PDC: Mean (SD) adherence at 6 months
NA
Adherence at 1 year
MPR: proportion adherent at 1 year
NA
MPR: Mean (SD) adherence at 1 year
NA
PDC: proportion adherent at 1 year
NA
PDC: Mean (SD) adherence at 1 year
NA

Supplementary 4.2: studies reporting adherence to different medications in the same cohort.



Rivaroxaban vs dabigatran

Study or Subgroup	Rivaroxaban Events	Rivaroxaban Total	Dabigatran Events	Dabigatran Total	Weight	Odds Ratio M-H, Random, 95% CI
5.3.1 At 6 months						
Yao 2016	5872	12336	4698	10235	7.7%	1.07 [1.02, 1.13]
Pham2019	8241	16005	7156	14864	7.7%	1.14 [1.09, 1.20]
Coleman 2016	7929	10787	7012	10787	7.7%	1.49 [1.41, 1.58]
Beyer-Westendorf 2016	809	1317	406	821	7.7%	1.63 [1.36, 1.94]
McHorney 2017	10930	13645	2325	3360	7.7%	1.79 [1.65, 1.95]
Subtotal (95% CI)		54090		40067	38.5%	1.39 [1.15, 1.67]
Total events	33781		21597			
Heterogeneity: Tau² = 0.04; Chi² = 162.85, df = 4 (P < 0.00001); I² = 98%						
Test for overall effect: Z = 3.46 (P = 0.0005)						
5.3.2 At 1 year						
Pham2019	5080	101940	4761	11689	7.7%	0.08 [0.07, 0.08]
Maura 2017	6426	8890	5681	8167	7.7%	1.14 [1.07, 1.22]
Crivera 2015	3162	4194	3711	5489	7.7%	1.47 [1.34, 1.61]
Coleman 2016	6731	10787	5609	10787	7.7%	1.53 [1.45, 1.62]
McHorney 2017	10657	13645	2231	3360	7.7%	1.80 [1.66, 1.96]
Beyer-Westendorf 2016	271	433	178	374	7.6%	1.84 [1.39, 2.44]
Forslund 2016	1985	2074	2485	2701	7.6%	1.94 [1.50, 2.50]
Mueller 2017	2350	2821	557	864	7.7%	2.75 [2.32, 3.26]
Subtotal (95% CI)		144784		43431	61.5%	1.17 [0.38, 3.60]
Total events	36662		25213			
Heterogeneity: Tau² = 2.64; Chi² = 10724.75, df = 7 (P < 0.00001); I² = 100%						
Test for overall effect: Z = 0.27 (P = 0.79)						
Total (95% CI)		198874		83498	100.0%	1.25 [0.66, 2.38]
Total events	70443		46810			
Heterogeneity: Tau² = 1.39; Chi² = 12603.04, df = 12 (P < 0.00001); I² = 100%						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%						



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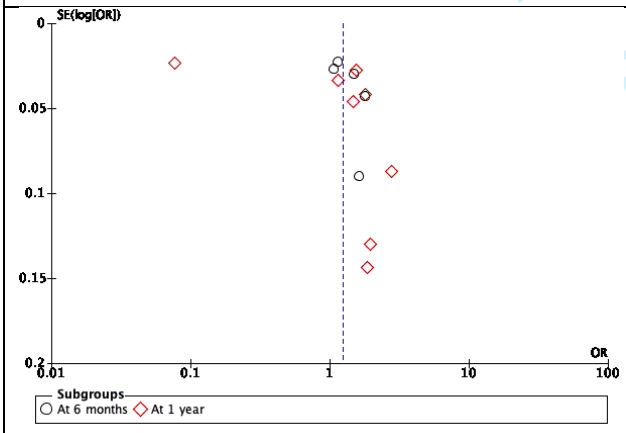

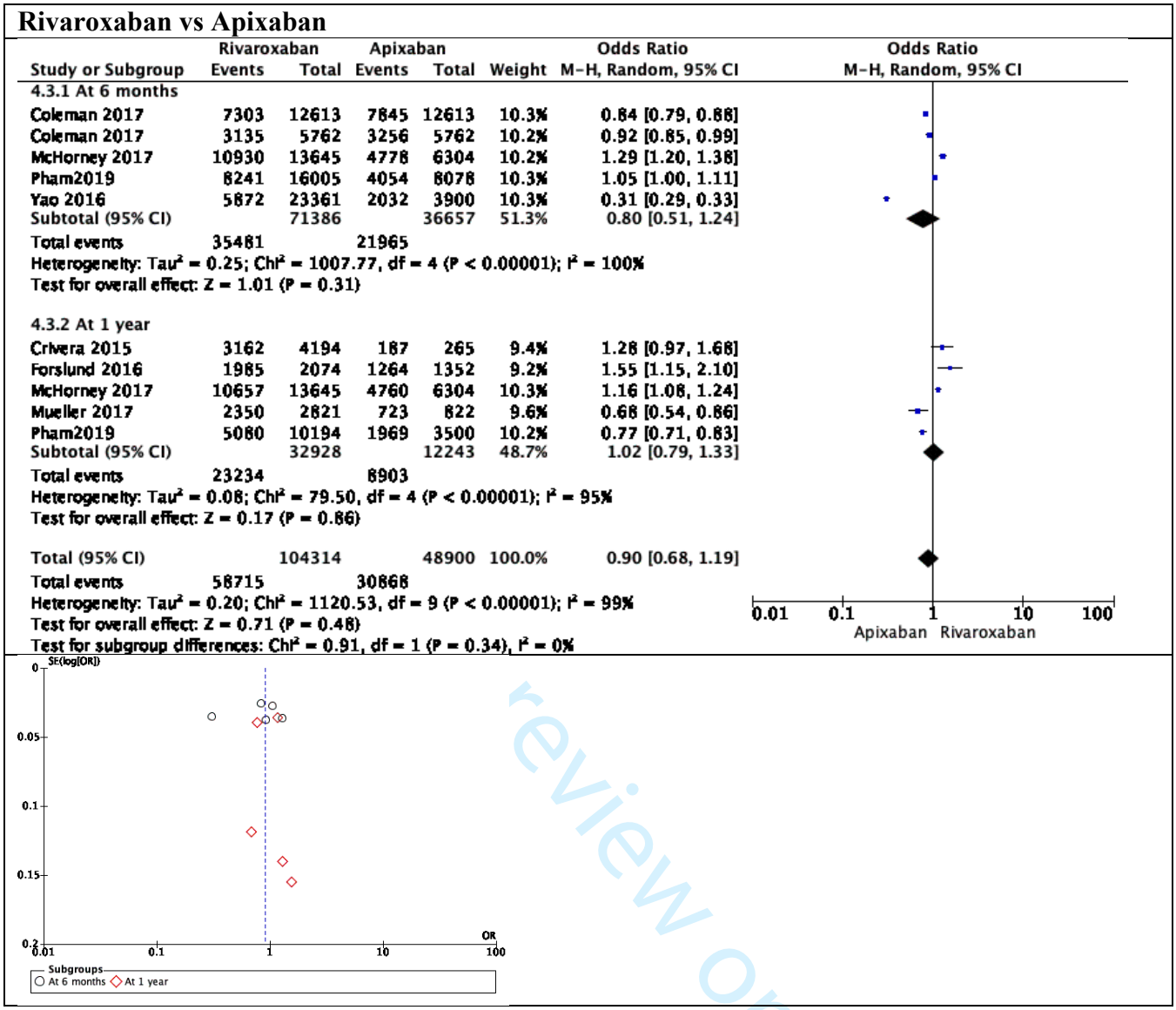

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Adherence to oral anticoagulants among patients with atrial fibrillation:

A systematic review and meta-analysis of observational studies

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Short title: Adherence to anticoagulants in patients with AF.

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ABSTRACT

INTRODUCTION

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

METHODS

We systematically searched 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 six months and one 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 six months and one 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 to 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.

Keywords: Atrial fibrillation, anticoagulants, medication adherence, stroke.

Strengths and limitations of this study

- This is a timely systematic review that synthesizes 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 synthesize 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 five-fold, 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 summarize the medication taking behavior 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, summarize evidence from randomized controlled trials (which do not reflect the day to day behaviors of patients), and provide a narrative summary of results with no meta-analysis.[19-21] Further, no studies have summarized 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 summarize 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 (PRISMA) and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (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 (Supplementary 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 utilized 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 (NVAF), 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 standard deviation (SD) of patients' adherence over six- or twelve- 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 (e.g. 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 analyzed to minimize 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 World Health Organization's (WHO) 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 Der Simonian & Laird random-effects models to determine the pooled mean adherence and the corresponding pooled proportion of adherent patients over six months and one 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, and 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 odds ratio (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, WA) or RevMan5 (version 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 (e.g. OR).[30,31] Clinical and economic impacts of poor adherence were summarized 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 STROBE.[33] Studies received a point for each checklist item they met and a zero 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 categorized 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.

Ethical approval

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

RESULTS

Initial search led to 1,122 studies, all of which were in English (Figure 1.0). 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 (Supplementary 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 six months or one year post index date (Table 2). The majority of the included studies focused on adherence to DOACs with only 4 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] to 86[55] over six months and 57[58] to 86[41] over one year post index date, with corresponding reported proportion of adherent patients ranging between 47%[59] to 82%[56] over six months and 41%[58] to 95%[45] over one year. A wide range of adherence results were observed even at the individual OAC level (Table 2).

Pooled mean adherence scores over six month and one 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 2 studies only (as illustrated in tables 2 and 3). Due to the limited data in warfarin, no drug class comparison could be made. Figure 2.0 illustrates the forest plots for patients' mean adherence score over six months and one 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 supplementary 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 versus MPR), or country (USA versus others) had only minor impacts on pooled adherence results and the detected heterogeneity (Supplementary 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 to dabigatran over both six months (Odds Ratio (OR):1.24, 95% CI: 1.07-1.45) and one year post index date (OR:1.76, 95% CI: 1.35-2.29). Odds of adherence was significantly

higher for rivaroxaban compared to dabigatran over six months (OR:1.39, 95% CI: 1.15-1.67), but not one year (OR:1.17, 95% CI: 0.38-3.60). Odds of adherence did not differ between apixaban and rivaroxaban over six months (OR:0.80, 95% CI: 0.51-1.24) or one 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 to 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 to 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 to naïve users over six months (83.3±24.6 vs 72.3±31.3; p< 0.05), nine months (81.2±26.4 vs 67.3±33.8); p< 0.05) and one year (79.9±27.6 vs 63.7±35.2; p <0.05).[50]

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 to those prescribed after discharge at three months (84.5% vs 12.3%; P<0.001) and one 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. Summarizing 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], angiotensin converting enzyme 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 ischemic 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 ischemic stroke compared to adherent patients, over six 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 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 compare to adherent patients and Deshpande et al. reported significantly higher annual adjusted per-patient medical cost (inpatient and outpatient) for non-adherent users compared to adherent ones ($30,485 versus $23,544; p≤0.001).[38,43]

DISCUSSION

In this systematic review, we synthesized 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 to 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 six months and one 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 to 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-, regimen- 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, angiotensin converting enzyme 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 utilization and costs. Our findings confirm the results of a 2017 systematic review of 79 studies across 14 disease groups which reported that $3,347-19,472 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 summarize 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, 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 (Supplementary 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 (e.g. OAC naïve versus experienced); methods for handling and defining medication switches, stockpiling, refill gaps, and hospitalization dates; fixed versus variable observational periods and adherence measure used (PDC versus 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 behavior, calculating and reporting it using a single summary measure. This methodological approach does not provide a complete picture of adherence, which is a dynamic behavior that changes over time.[25,81] Characterization 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 characterize 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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COMPETING INTERESTS

Authors have no competing interests to declare.

CONTRIBUTIONS

Conceived the study: SS, PL, MDV; Designed the search strategy: SS, MDV, PL; 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): MDV, SS; Analyzed the data: SS; Conducted quality assessment; SS, RT; Interpreted the results: SS, PL, JGA, MDV; Prepared the manuscript first draft: SS, MDV, PL, RT; Reviewed the manuscript and provided critical feedback: JGA, MDV, PL; Revised the manuscript: SS, PL, RT, MDV.

DATA AVAILABILITY STATEMENT

No additional data available.

FIGURE LEGENDS

Figure 1.0: PRISMA flow diagram that details the number of studies identified by our search strategy, screened, and included in the final analysis.

Figure 2.0: Forest plots illustrating patients' mean adherence scores over six months and one year post index date. See Supplementary 4 for additional forest plots for each OAC and subgroup analyses.

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TABLES

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	2016	Retrospective	USA	36,868 (55%)	76%>65 years	NVAF	NA	Both	Yes	61%	67%
Beyer-Westendorf	2016	Retrospective	Germany	7,265 (52%)	NA	NVAF	Index OAC	Naïve	Yes	73%	74%
Borne	2017	Retrospective	USA	2,882 (97%)	67.4 (9.5)	NVAF	NA	Naïve to DOACs‡	Yes	73%	78%
Brown	2016	Retrospective	USA	5,223 (40%)	59%≥65 years	NVAF	Both	Naïve	Yes	77%	84%
Casciano	2013	Retrospective	USA	13,289 (47%)	78% ≥75 years	AF	NA	Naïve	Yes	63%	79%
Coleman	2016	Retrospective	USA	21,756 (54%)	66.5 (12.2)	NVAF	NA	Naïve	Yes	55%	50%
Coleman	2017	Retrospective	USA	106,227 (63%)	71.1 (11.0)	NVAF	Index OAC	Naïve	Yes	77%	84%
Crivera	2015	Retrospective	USA	9,948 (53%)	75.5 (8.3)	NVAF	Both	Naïve	Yes	73%	61%
Deshpande PMID: 29694285	2018	Retrospective	USA	2,981 (70%)	64.4 (10.7)	AF	NA	Naïve to DOACs‡	No	77%	83%
Deshpande PMID: 29334815	2018	Retrospective	USA	4,856 (52%)	65.0 (10.5)	AF	NA	Naïve	No	81%	83%
Kapen	2014	Retrospective	USA	2,691 (43%)	100%>65 years	AF	NA	Both	No	76%	74%
Forsuland	2016	Retrospective	Sweden	16,096 (52%)	75.45 (SD not reported)	NVAF	Current OAC	Both	No	63%	61%
Gomez-Iumberas	2018	Retrospective	Spain	854 (NA%)	73.2 (11.0)	NVAF	NA	Both	Yes	50%	67%
Gorst-Rasmussen	2015	Retrospective	Denmark	2,960 (54%)	72.1 (10.8)	NVAF	Index OAC	Naïve	Yes	80%	100%
Harper	2018	Retrospective	New Zealand	20,237 (NA%)	83%>60	NVAF	NA	NA	No	47%	53%
Jacobs	2018	Retrospective	Sweden & Netherlands	5,684 (60%)	78%≥65 years	AF	Current OAC	Both	Yes	80%	83%
Manzoor	2017	Retrospective	USA	66,090 (62%)	68.7 (12.1)	AF	Index OAC	Both	Missing	70%	85%
Márquez-Contrera	2016	Prospective	Spain	412 (42%)	75.2 (7.5)	NVAF	NA	Experienced	Yes	63%	83%
Maura	2017	Retrospective	France	22,267 (53%)	74.0 (10.8)	NVAF	Index	Naïve	No	79%	100%
McAlister	2018	Retrospective	Canada	57,669 (56%)	100%>65 years	NVAF	Current OAC	Naïve	No	87%	94%
McCormick	2001	Retrospective	USA	429 (22%)	87 (7.1)	AF	Current OAC	Experienced	No	60%	82%
McHorney	2017	Retrospective	USA	36,675 (67%)	63.1 (SD not reported)	NVAF	Index OAC	Naïve	Yes	87%	89%
McHorney	2018	Retrospective	USA	41,201 (58%)	NA	NVAF	Index OAC	Both	Yes	84%	100%
Mueller	2017	Retrospective	Scotland	5,398 (54%)	74.4 (11.3)	AF	NA	NA	No	70%	53%
Pham	2019	Retrospective	USA	38,947 (60%)	100%>65 years	NVAF	Index OAC & any OAC	Naïve	No	77%	89%
Shore	2014	Retrospective	USA	5,376 (98%)	71.3 (9.7)	NVAF	Index OAC	NA	No	90%	94%
Sørensen	2017	Retrospective	Denmark	46,675 (58%)	79%>65 years	NVAF	Current OAC	Naïve	Yes	67%	79%

Tsai	2013	Retrospective	USA	17,691 (49%)	76.4 (8.7)	NA	Current OAC	Warfarin Naïve and warfarin experienced	No	60%	78%
Yao	2016	Retrospective	USA	64,661 (56%)	75% >65	AF	Index OAC	Naïve	No	77%	84%
Zhou	2015	Retrospective	USA	5,951 (34%)	36.1%>65	AF	Index OAC	Naïve	No	80%	79%

Footnote:

USA: United States of America; NVAF: non-valvular atrial fibrillation; AF: atrial fibrillation (valvular and non-valvular); NA: not applicable (no data reported)

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 (2016)	PDC (>80%)	NA	NA	NA	Overall: 0.70 A and D: 0.68 R: 0.73
Borne (2017)	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 (2016)	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 (2013)	PDC (>80%)	NA	NA	NA	W: 0.41
Coleman (2016)	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 (2017)	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 (2015)	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 (2018) PMID: 29694285	PDC (≥80%)	NA	R and D: 0.65	NA	R and D: 0.54
Deshpande (2018) PMID: 29334815	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 (2016)	PDC (>80%)	NA	NA	NA	A: 0.93 D: 0.92 R: 0.96
Gorst-Rasmussen (2015)	PDC (>80%)	0.84 ± 0.28	NA	NA	D: 0.77
Harper (2018)	PDC (>80%)	NA	NA	NA	D: 0.84
Manzoor (2017)	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 (2017)	PDC>80	NA	NA	NA	**Index OAC:** Overall: 0.71 D: 0.70

					R: 0.72
McHorney (2017)	PDC (>80% & >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 (2018)	PDC (>80% & >90%)	NA	**PDC80:** A:0.78 R: 0.82 **PDC90:** A: 0.60 R: 0.67	NA	NA
Pham (2019)	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 (2014)	PDC (>80%)	NA	D: 0.28	NA	NA
Sørensen (2017)	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 (2013)	PDC (no threshold)	D: warfarin-naïve: 0.67 ± 0.36 warfarin-experienced: 0.71 ± 0.35	NA	NA	NA
Yao (2016)	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 (2016)	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 (2014)	MPR (no threshold)	NA	NA	Median (IQR): 0.77 (0.51- 0.98)	NA
Gomez-lumberas (2018)	MPR (>0.8)	NA	NA	NA	A: 0.62
Jacobs (2018)	MPR (≥0.8)	NA	NA	NA	Sweden: 0.95 Netherlands: 0.93
McHorney (2017)	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 (2015)	MPR (>0.8)	D: 0.73 ± 0.30	D: 0.59	D: 0.65 ± 0.35	D: 0.51
Mueller (2017)	MPR>80‡	NA	NA	NA	DOACs: 0.82 A: 0.88 D: 0.65 R: 0.83

Márquez-Contrera (2016)	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 (2018)	TTR>65% (INR2-3)	NA	W: Percent patients with time in therapeutic range: 4.11%	NA	NA

Footnote:
PDC: proportions days covered; MPR: medication possession ratio; CP: Compliance percentage; TTR: Time in therapeutic range; USA: United States of America; NA: Not available/not applicable; aHR: adjusted Hazard ratio; VKA: Vitamin K antagonist. A: apixaban; D: dabigatran; R: rivaroxaban; W: warfarin.
Drug specific proportion of adherent patients was calculated as the percent 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

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)
Sub-analysis: 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)
Sub-analysis: 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)
Sub-analysis: 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)

[*]I^2 <80%.
[+] Not pooled. Based on one study
[++] Pooled results of only two studies

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	
	Number of unique studies	**Odds ratio (95% CI)**	**Number of unique studies**	**Odds ratio (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)
Sub-analysis: 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)

***I^2 <80%.**
+ Not pooled. Based on one study

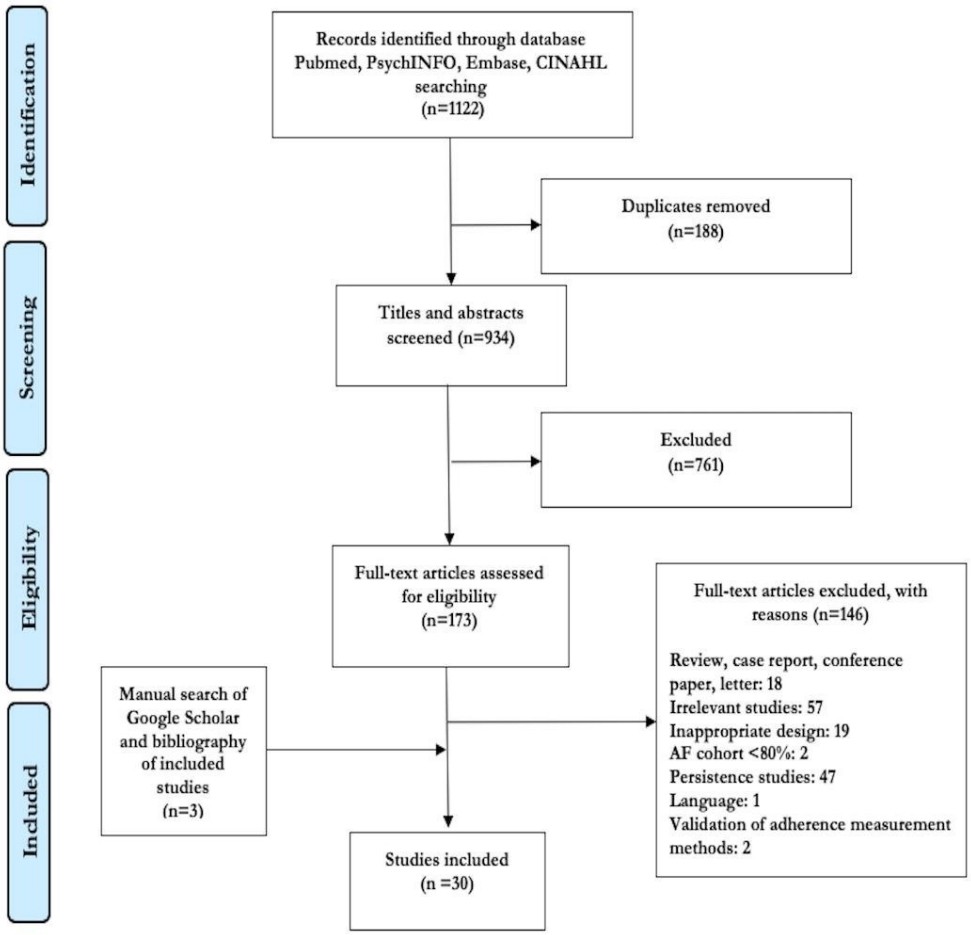


Figure 1.0: PRISMA flow diagram that details the number of studies identified by our search strategy, screened, and included in the final analysis.

90x90mm (300 x 300 DPI)

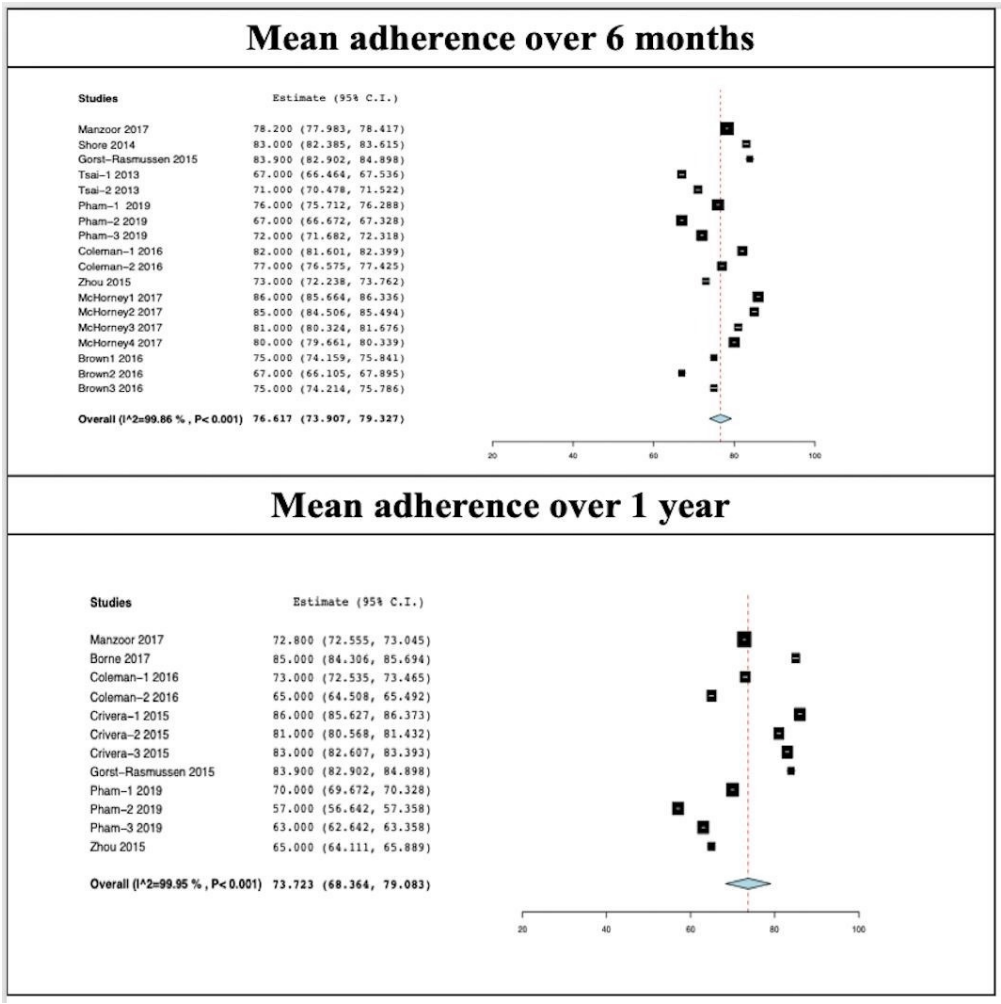


Figure 2.0: Forest plots illustrating patients' mean adherence scores over six-month and one-year post index date. See Supplementary 4 for additional forest plots for each OAC and subgroup analyses.

90x90mm (300 x 300 DPI)

PRISMA 2009 Checklist (Supplementary 1a)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Cover page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Inclusion criteria and study selection 5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Search strategy 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary File 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Inclusion criteria and study selection, Data extraction and synthesis 5, 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Inclusion criteria and study selection, Data extraction and synthesis 5, 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Inclusion criteria and study selection, Data extraction and synthesis 5, 6

PRISMA 2009 Checklist (Supplementary 1a)

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Supplementary File 3, Quality assessment, Data analysis 6, 7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Data analysis 6, 7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Data analysis 6, 7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Supplementary File 3, Quality assessment, Data analysis 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Data analysis 6, 7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results 9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1 31, 32
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary File 3, Quality assessment 7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2 33, 34
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 3,4 37, 37
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary File 4.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 3 36
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion 12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Limitations 14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion, Future directions

PRISMA 2009 Checklist (Supplementary 1a)

			12, 13, 14, 15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding 16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

MOOSE Guidelines (Supplementary 1b)

MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies	
Background	
Problem definition	Introduction 4
Hypothesis statement	NA- The study is mostly descriptive
Description of study outcomes	Introduction, Data extraction and synthesis 4, 6
Type of exposure or intervention used	Introduction, Inclusion criteria and study selection 4, 5
Type of study design used	Inclusion criteria and study selection 5
Study population	Inclusion criteria and study selection 5
Search Strategy	
Qualification of searchers	Search strategy 5
Search strategy including time periods included in the synthesis and keywords	Supplementary File 2, Search strategy 5
Effort to include all available studies, including contact with authors	Inclusion criteria and study selection 5, Authors were not contacted
Databases and registries searched	Search strategy 5
Search software used, name and version, including special features used	NA
Use of hand searching	Search strategy 5
List of citations located and those excluded	Figure 1.0: PRISMA flow chart
Method of addressing articles published in languages other than English	Inclusion criteria and study selection 5
Method of handling abstracts and unpublished studies	Inclusion criteria and study selection 5
Description of any contact with authors	All relevant information for this systematic review could be found in the published reports. There was no need to contact the respective authors
Methods	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Introduction, Supplementary File 3 4

MOOSE Guidelines (Supplementary 1b)

Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Introduction, Inclusion criteria and study selection, Data extraction and synthesis, Data analysis 4, 5, 6, 7
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Inclusion criteria and study selection, Data extraction and synthesis, Data analysis 5, 6, 7
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	NA
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Data analysis. Quality assessment 6, 7
Assessment of heterogeneity	Data analysis 7
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Data analysis 6, 7
Provision of appropriate tables and graphics	Figure 1
Results	
Graphic summarizing individual study estimates and overall estimate	Figures 2 and 3
Table giving descriptive information for each study included	Tables 1 and 2
Results of sensitivity testing (eg, subgroup analysis)	Table 3
Indication of statistical uncertainty of findings	Results 10
Discussion	
Quantitative assessment of bias (eg, publication bias)	Supplementary File 3
Justification for exclusion (eg, exclusion of non–English-language citations)	Inclusion criteria and study selection. Limitations 5, 14
Assessment of quality of included studies	Supplementary File 3, Results, Table 1 9, 31, 32
Conclusion	
Consideration of alternative explanations for observed results	Discussion 12, 13, 14
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Limitations 14
Guidelines for future research	Future directions 15
Disclosure of funding sources	Funding 16

Supplementary file 1: Literature search

Concept	Keywords	MeSH terms (Pubmed)
Medications	Anticoagulant* OR "blood thinner" OR "Vitamin K antagonists"OR "new oral anticoagulants" OR VKA OR NOAC OR DOAC OR Apixaban OR Eliquis OR dabigatran OR "dabigatran etexilate" mesylate OR pradaxa OR edoxaban OR lixiana OR rivaroxaban OR xarelto OR warfarin OR coumadin OR betrixaban OR bevyxxa OR acenocoumarol OR phenprocoumon OR fluindione	Warfarin Anticoagulants Dabigatran Rivaroxaban
Adherence	Adherence OR persistence OR compliance "Medication taking" OR "discontinuation" OR "nonpersistence" OR "nonadherence" OR "noncompliance"	Treatment Adherence and Compliance"[Mesh])
Atrial fibrillation	"atrial fibrillation" OR NVAF OR "non-valvular atrial fibrillation"	atrial fibrillation

Complete search example for Pubmed:
(((((((("atrial fibrillation") OR NVAF) OR "non-valvular atrial fibrillation")) AND (((((((Adherence) OR noncompliance) OR discontinuation) OR nonpersistence) OR nonadherence) OR persistence) OR "Medication taking") OR compliance)) AND ((((((((((((((((((((((((Anticoagulant*) OR "blood thinner") OR "Vitamin K antagonists") OR "new oral anticoagulants") OR VKA) OR NOAC) OR DOAC) OR Apixaban) OR Eliquis) OR dabigatran) OR "dabigatran etexilate") OR "dabigtaran mesylate") OR pradaxa) OR edoxaban) OR lixiana) OR rivaroxaban) OR xarelto) OR warfarin) OR coumadin) OR betrixaban) OR bevyxxa) OR acenocoumarol) OR phenprocoumon) OR fluindione))) AND "Atrial Fibrillation"[Mesh]) AND (("Treatment Adherence and Compliance"[Mesh]) OR ("Warfarin"[Mesh] OR "Anticoagulants"[Mesh] OR "Dabigatran"[Mesh] OR "Rivaroxaban"[Mesh]))):

STROBE	CODE	Alberts 2016	Beyer - Westendorf 2016	Borne 2017	Brown 2016	Casciano 2013	Coleman 2016	Coleman 2017	Civera 2015	Deshpande 2018 PMID: 29694285	Deshpande 2018 PMID: 29334815	Eapen 2014	Forsuland 2016	Gomez-Lumberas 2018	Gorst - Rasmussen 2015	Harper 2018	Jacobs 2018	Manzoor 2017	Marquez 2016	Maura 2017	McAlister 2018	McCormick 2001	McHorney 2017	McHorney 2018	Mueller 2017	Pham 2019	Shore 2014	Sorensen 2017	Tsai 2013	Yao 2016	Zhou 2015
Title and abstract																															
Indicate the study's design with a commonly used term in the title or the abstract	1a	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0
Provide in the abstract an informative and balanced summary of what was done and what was found.	1b	0	1	1	1	1	0	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Background/rationale: Explain the scientific background and rationale for the investigation being reported	2	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1
Objective: State specific objectives, including any prespecified hypothesis.	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Study design: Present key elements of study design early in the paper	4	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Setting: Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	5	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1
Participants: Give the eligibility criteria, and the sources and methods of selection of participants	6a	1	1	1	1	0	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1
For matched studies, give matching criteria and number of exposed and unexposed	6b	1	NA	NA	NA	NA	1	1	NA	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	NA	NA	NA	NA	NA	1	NA
Variables: Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	7	0	1	0	1	0	0	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
Data sources/measurement: For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one grou	8	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Bias: Describe any efforts to address potential sources of bias (e.g. Propensity scores)	9	1	0	0	0	0	1	1	0	1	1	0	0	0	0	0	1	1	1	1	0	1	1	1	0	1	1	0	0	0	0
Study size: Explain how the study size was arrived at.	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Quantitative variables/ statistical analysis:																															
Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why. (categorizing)	11	0	1	1	1	1	0	0	0	0	0	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1
Describe all statistical methods, including those used to control for confounding	12a	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1
Describe any methods used to examine subgroups and interactions	12b	1	0	1	1	0	0	1	1	1	1	1	0	0	1	0	1	1	0	1	1	0	1	1	0	0	1	0	1	1	1
Explain how missing data were addressed	12c	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0	0	0	0
Cohort study: If applicable, describe how loss to follow-up was addressed.	12d	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Describe any sensitivity analyses	12e	0	1	1	0	0	0	0	0	0	0	0	1	0	1	0	1	1	0	1	1	0	1	1	0	0	1	1	0	1	1
Participants:																															
Report the numbers of individuals at each stage of the study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed.	13a	0	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	0	0	1	1	0	1	1	1	1	1	1	0	0	1
Give reasons for non-participation at each stage	13b	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Consider use of a flow diagram	13c	0	1	1	1	1	0	1	1	1	1	1	1	0	1	0	0	0	0	1	1	0	1	1	1	1	1	1	0	0	1
Descriptive data:																															
Give characteristics of study participants (e.g. demographic, clinical, social) and	14a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

information on exposures and potential confounders																														
Indicate the number of participants with missing data for each variable of interest.	**14b**	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0
Summarise follow-up time (eg, average and total amount)	**14c**	1	1	1	0	1	1	1	1	0	1	1	0		0	0	1	0	1	1	0	0	1	0	1	0	1	0	0	1	0
Outcome data: Report numbers of outcome events or summary measures over time	**15**	0	1	0	1	0	1	0	0	1	1	1	0	0	0	0	0	1	0	0	1	0	1	1	1	1	1	0	0	1	1
Main results																															
Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**16a**	1	0	0	1	0	0	0	1	1	1	1	0	0	1	0	1	0	1	NA	1	1	1	1	0	0	1	1	0	1	1
Report category boundaries when continuous variables were categorized.	**16b**	1	1	1	1	1	1	1	1	1	1	NA	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**16c**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Other analysis: Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses.	**17**	1	1	1	1	1	0	1	1	1	1	1	0	1	0	1	1	0	1	1	0	1	1	1	1	1	0	1	1	1	1
Key results: Summarize key results with reference to study objectives.	**18**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Limitations: Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	**19**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Interpretation: Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**20**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Generalizability: Discuss the generalizability (external validity) of the study results	**21**	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1
Funding: Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**22**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1		1	1	1	1
Sum		19	22	22	23	19	17	24	22	23	25	22	19	15	24	14	24	21	20	23	26	18	26	26	21	23	27	20	18	24	24
Total applicable		31	30	30	30	30	31	31	30	30	31	29	30	30	30	30	30	30	32	29	30	30	30	31	30	30	30	30	30	31	30
Score		0.612903	0.733333	0.73333	0.766667	0.633333	0.548387	0.774193	0.733333	0.766667	0.806451	0.75862	0.633333	0.5	0.8	0.466667	0.8	0.7	0.625	0.793103	0.866667	0.6	0.866667	0.838709	0.7	0.766667	0.9	0.666667	0.6	0.774193	0.8
Percent		61	73	73	77	63	55	77	73	77	81	76	63	50	80	47	80	70	63	79	87	60	87	84	70	77	90	67	60	77	80

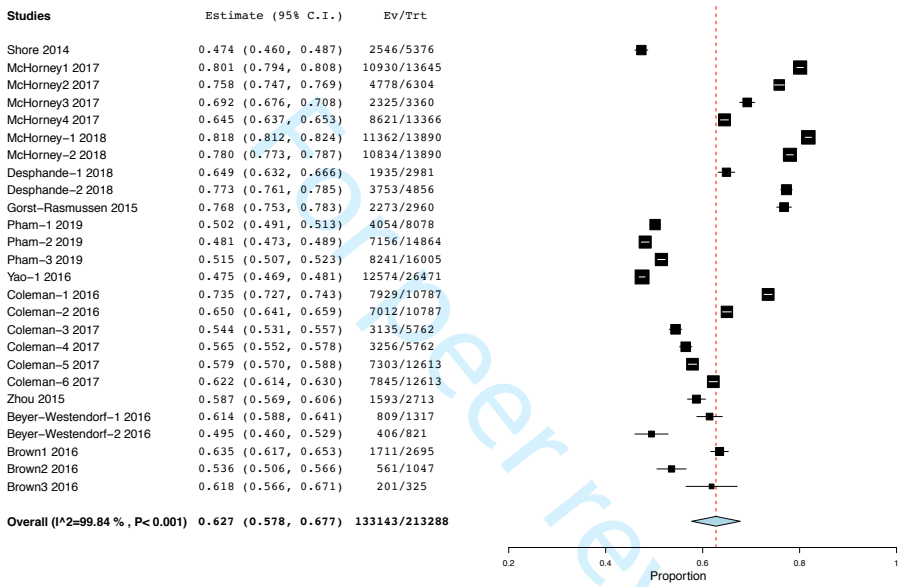
Item No	ISPOR	Alberts 2016	Beyer-Westendorf 2016	Borne 2017	Brown 2016	Cascia no 2013	Coleman 2016	Coleman 2017	Civera 2015	Deshpande 2018 PMID: 29694285	Deshpande 2018 PMID: 29334815	Eapen 2014	Forsuland 2016	Gomez-Lumberas 2018	Gorst-Rassussen 2015	Harper 2018	Jacobs 2018	Manzoor 2017	Marquez 2006	Maura 2017	McAlister 2018	McCormick 2001	McHorney 2017	McHorney 2018	Mueller 2017	Pharm 2019	Shore 2014	Sorenson 2017	Tsai 2013	Yao 2016	Zhou 2015
	Title / Abstract																														
1	Title is descriptive and reflective of study purpose	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	1	1	0	1	1	0	0	1	0	0	0	0
2	Abstract is a concise and accurate, reflecting contents of the study	0	1	1	1	1	0	1	0	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Introduction																														
	Clear review of fundamental literature related to topic	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Objectives and Definitions																														
	Objective(s) stated?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Design and Methods																														
	Study design appropriate for objectives	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Data sources adequately described	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1
	Evidence provided for reliability / accuracy of data	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0
	Sampling methods described	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Well describe patient population and Subject inclusion / exclusion criteria stated	1	1	1	1	0	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1
	Sufficient data to make valid estimate of compliance (i.e. Continuous eligibility for drug during study period verified)	0	1	1	1	1	1	1	0	1	1	1	0	1	1	0	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1
	Sufficient pre-enrollment period to ensure drug naivety? (If applicable)	NA	1	NA	1	1	NA	1	NA	NA	NA	1	NA	NA	NA	0	NA	1	NA	1	1	NA	1	1	0	1	NA	1	NA	1	1
	Explanation of how patients who switched drugs within or between therapeutic classes were handled	0	0	0	1	0	0	1	1	0	0	0	1	0	1	0	1	1	0	1	NA	NA	0	1	0	1	1	0	1	1	1
	Explicit definition of compliance/persistence based on published, accepted definition?	1	1	1	1	1	0	1	0	1	1	1	0	1	1	0	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1
	Methods for calculating compliance / persistence clearly described (and matches operational definition)	1	1	1	0	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1
	Was handling of medication gaps described	0	0	0	1	1	0	0	0	1	1	0	0	0	1	1	0	0	1	1	1	0	0	1	0	1	1	0	0	0	0
	Follow-up period specified	1	1	1	1	1	1	1	0	1	1	1	0	0	1	0	0	1	1	1	1	1	1	1	1	0	1	1	1	1	0
	Statistics appropriate to design and data	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Test statistics are reported appropriately (i.e. CIs, p-values reported)	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1
	Appropriate descriptive data on study sample are presented	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Distribution of compliance/persistence variable is presented (i.e. proportion of discontinuers)	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1
	Sum	12	14	14	16	15	9	16	11	15	15	14	11	12	18	10	15	17	15	19	17	14	17	19	10	17	17	15	14	16	15
	Total Applicable	18	19	18	19	19	18	19	18	18	18	19	18	18	18	19	18	20	18	19	18	17	19	19	19	19	18	19	18	19	19
	Score	0.666667	0.736842	0.777778	0.842105	0.789473	0.5	0.842105	0.611111	0.833333	0.833333	0.736842	0.611111	0.666667	1	0.5263	0.833	0.85	0.833333	1	0.944444	0.823529	0.894736	1	0.526315	0.895	0.944	0.789473	0.778	0.842	0.789
	Percent	67	74	78	84	79	50	84	61	83	83	74	61	67	100	53	83	85	83	100	94	82	89	100	53	89	94	79	78	84	79

Supplementary 4.0: Forest plots

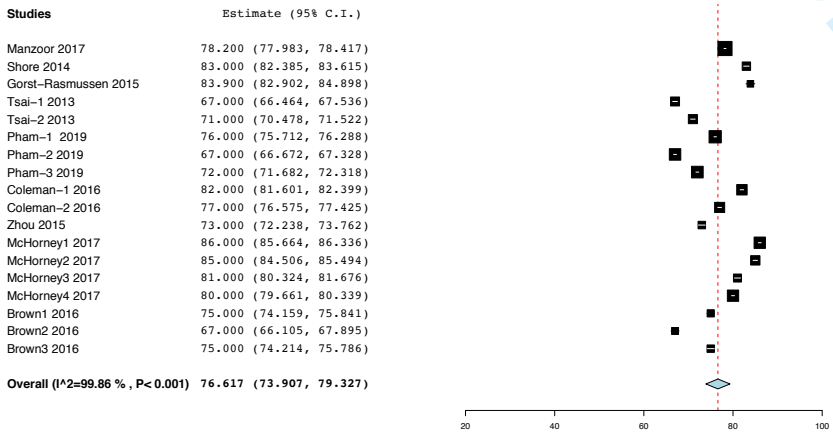
All OACs

Adherence at 6 months

Proportion adherent at 6 months

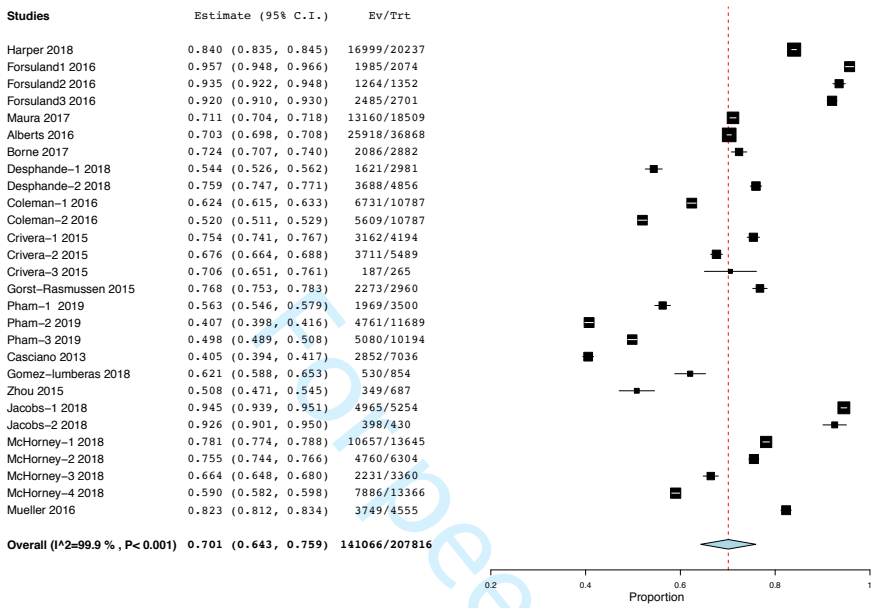


Mean adherence score at 6 months

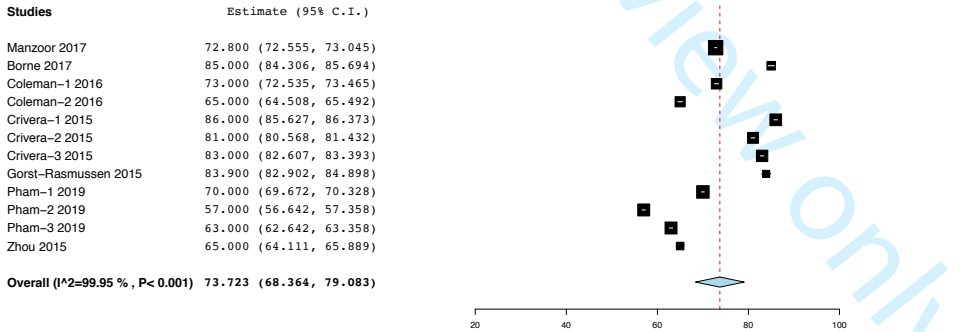


Adherence at 1 year

Proportion adherent at 1 year



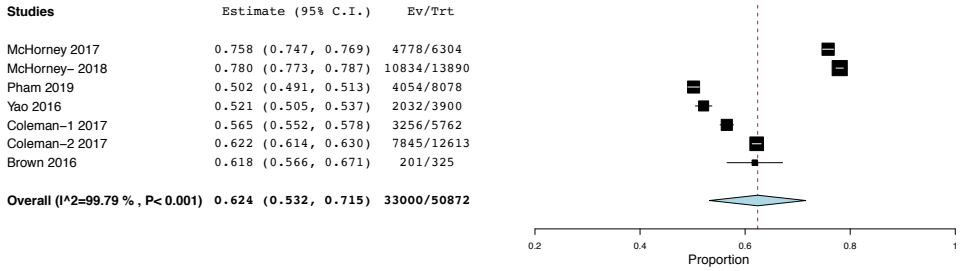
Mean adherence at 1 year



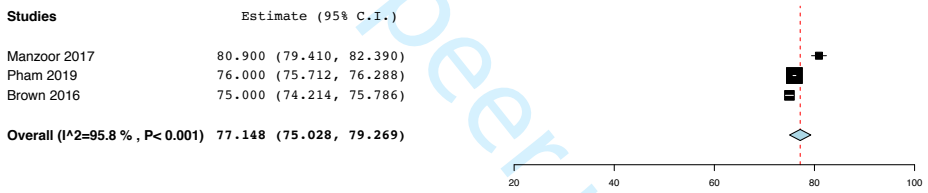
Apixaban

Adherence at 6 months

Proportion adherent at 6 months

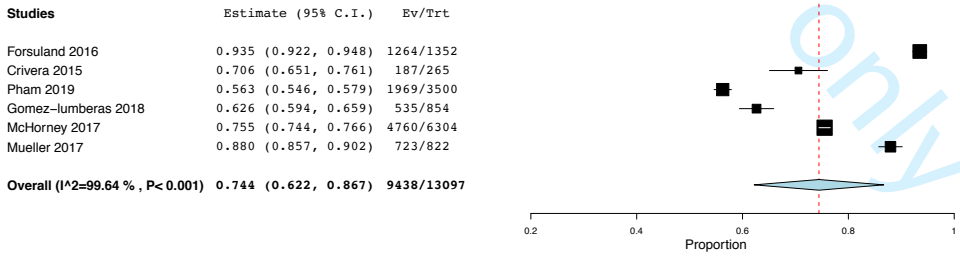


Mean adherence at 6 months

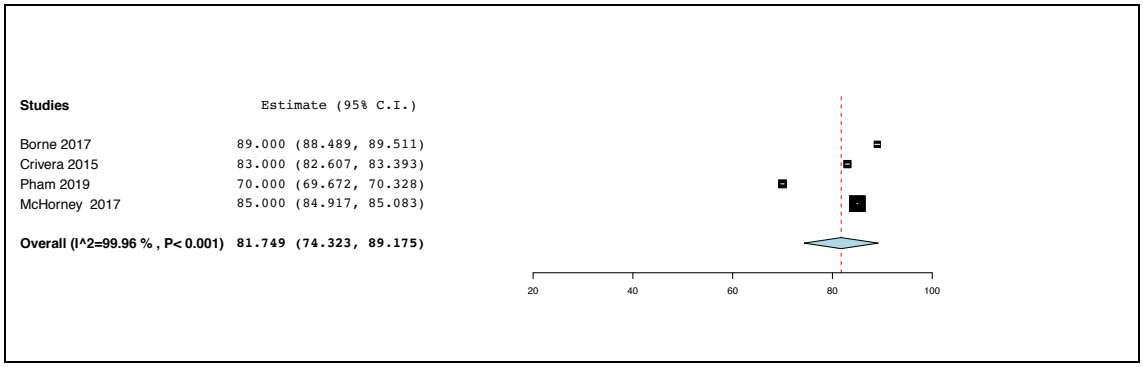


Adherence at 1 year

Proportion adherent at 1 year



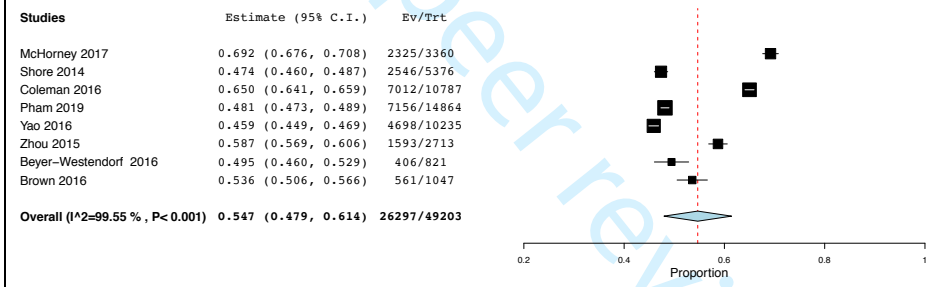
Mean adherence at 1 year



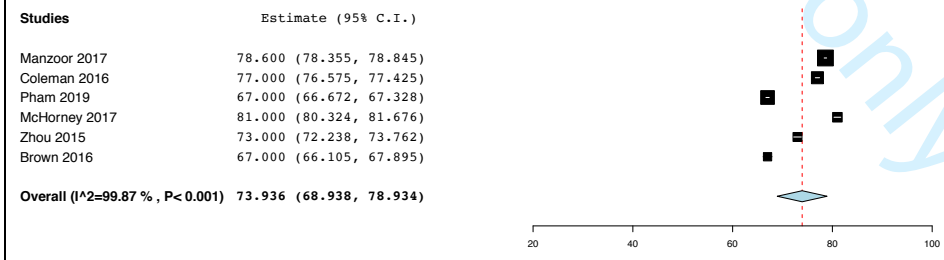
Dabigatran:

Adherence at 6 months

Proportion adherent at 6 months

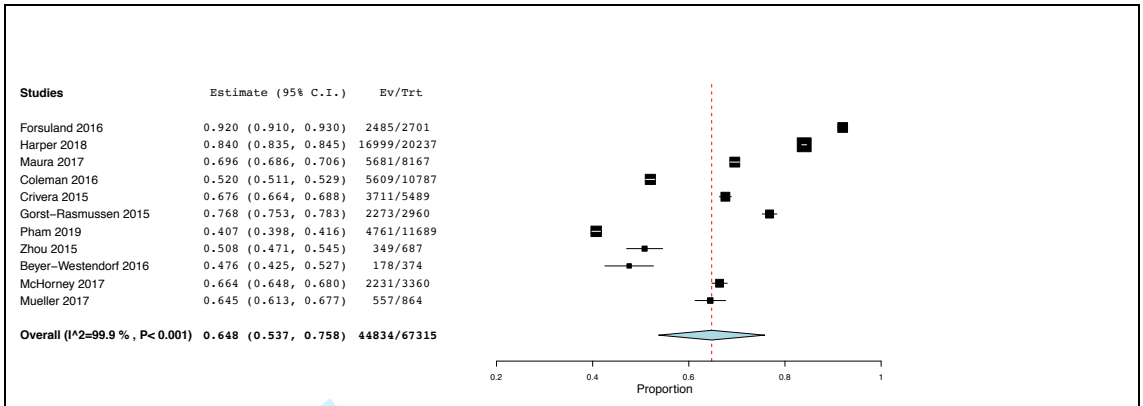


Mean adherence at 6 months

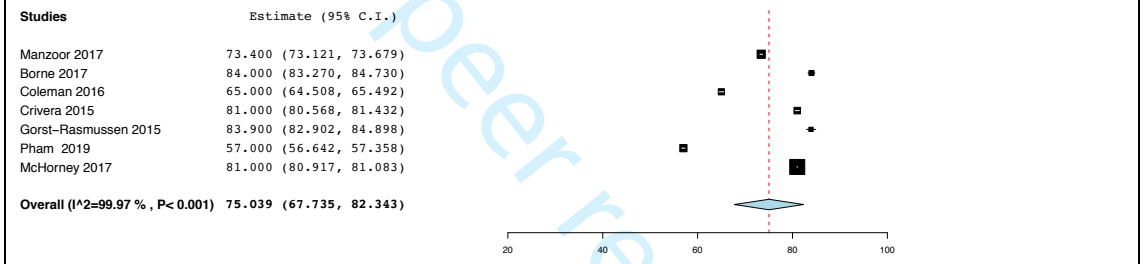


Adherence at 1 year

Proportion adherent at 1 year



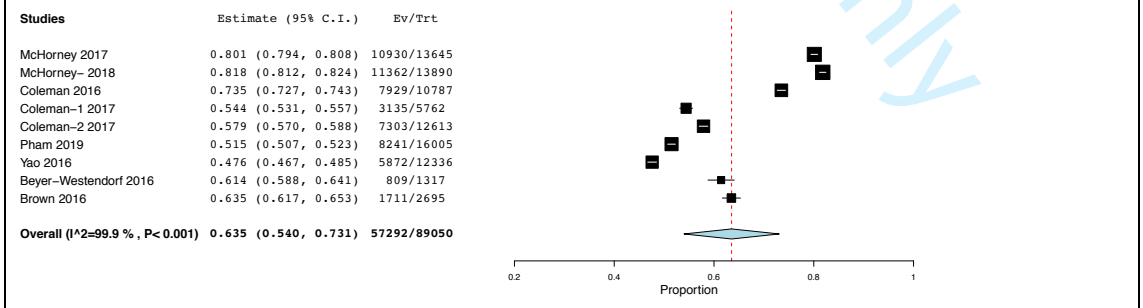
Mean adherence at one year



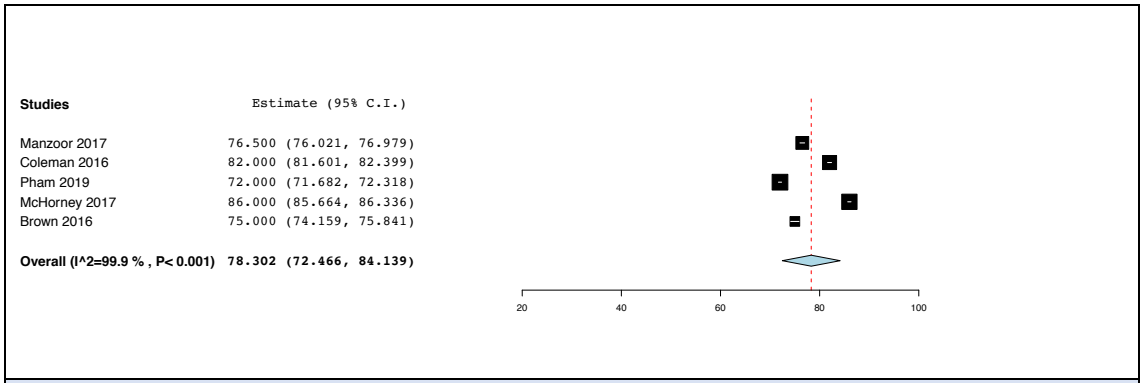
Rivaroxaban:

Adherence at 6 months

Proportion adherent at 6 months

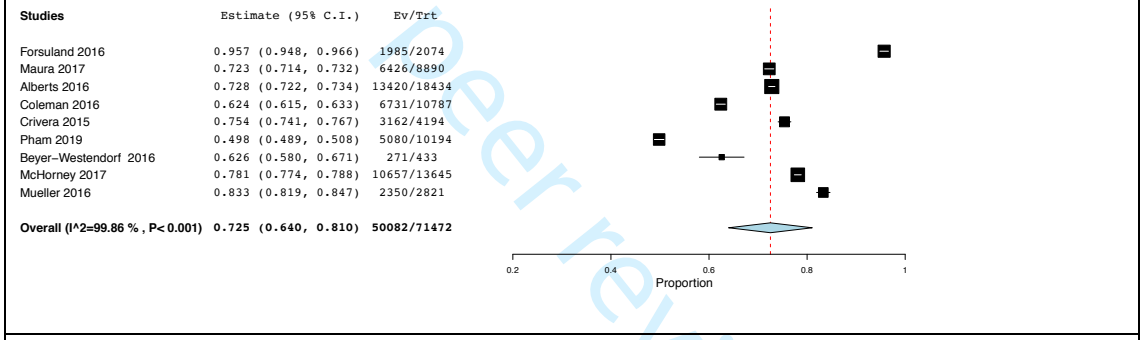


Mean adherence at 6 months

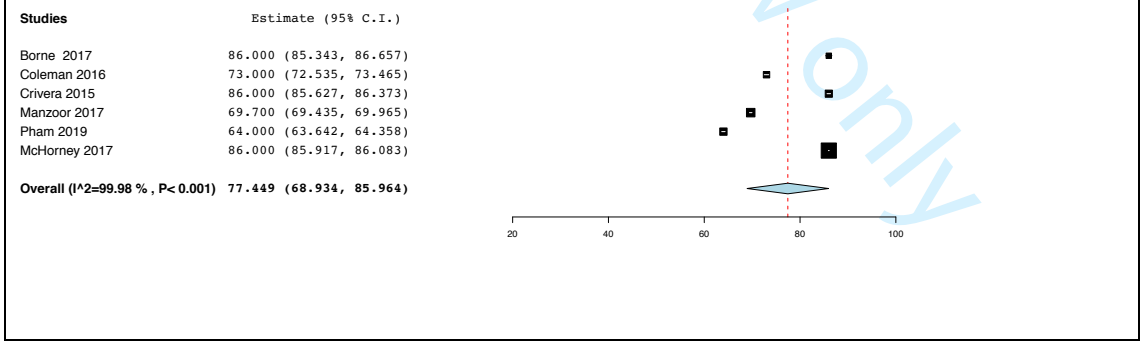


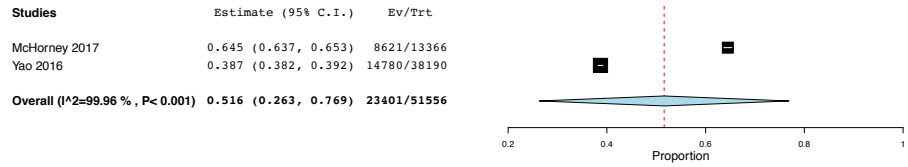
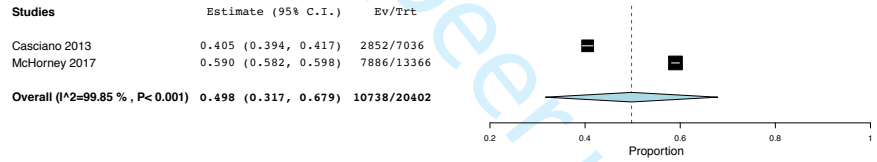
Adherence at 1 year

Proportion adherent at 1 year



Mean adherence at 1 year



Warfarin:
Adherence at 6 months
Proportion adherent at 6 months

Mean adherence at 6 months
NA
Adherence at 1 year
Proportion adherent at 1 year

Mean adherence at 1 year
NA

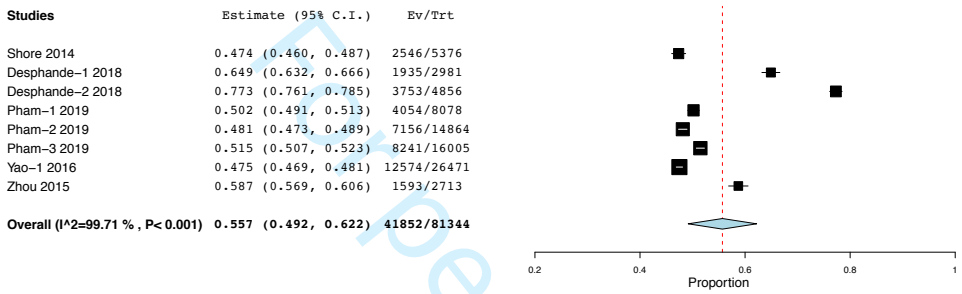
Supplementary 4.1: Sub-group analysis

Supplementary 4.1.1: Sub-group analysis by excluding studies with conflict of interest:

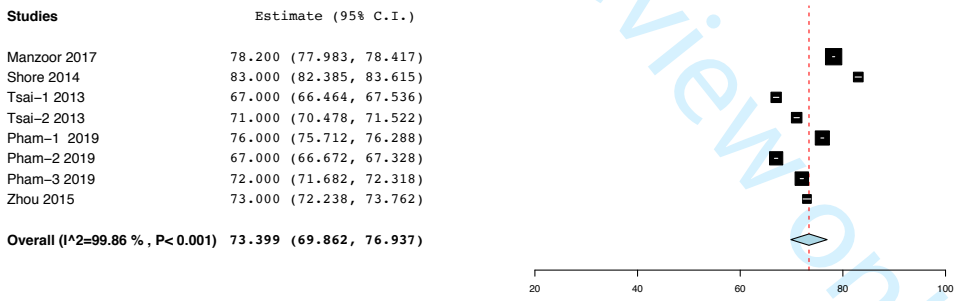
All OACs: Sub-analysis: Excluding studies with conflict of interest

Adherence at 6 months

Proportion adherent at 6 months

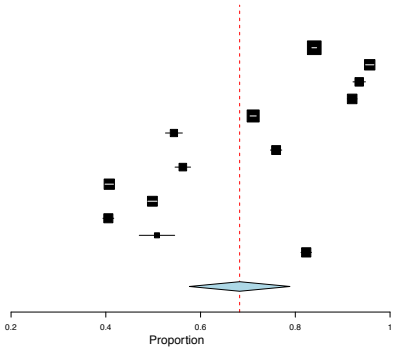


Mean adherence at 6 months

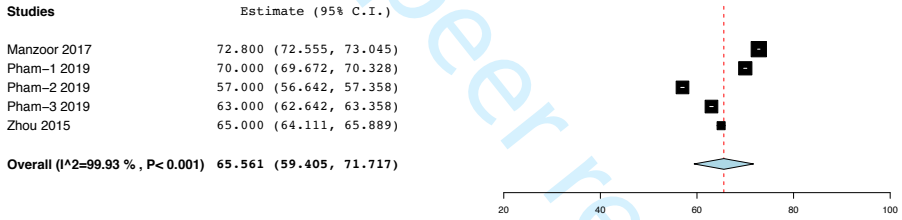


Adherence at 1 year

Proportion adherent at 1 year



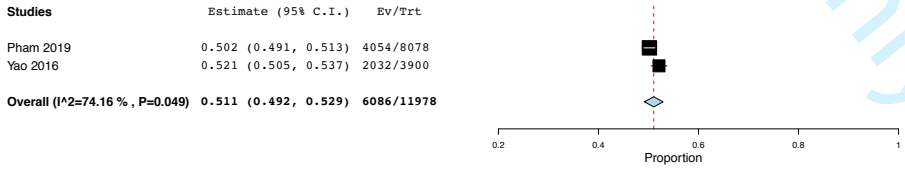
Mean adherence at 1 year



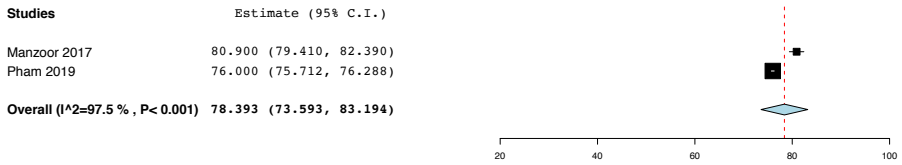
Apixaban: Sub-analysis: Excluding studies with conflict of interest

Adherence at 6 months

Proportion adherent at 6 months

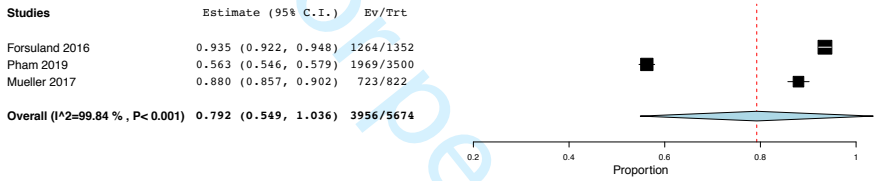


Mean adherence at 1 year



Adherence at 1 year:

Proportion adherent at 1 year



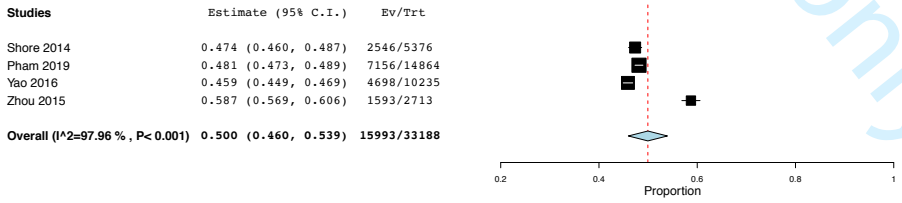
Mean adherence at 1 year

NA (one study)

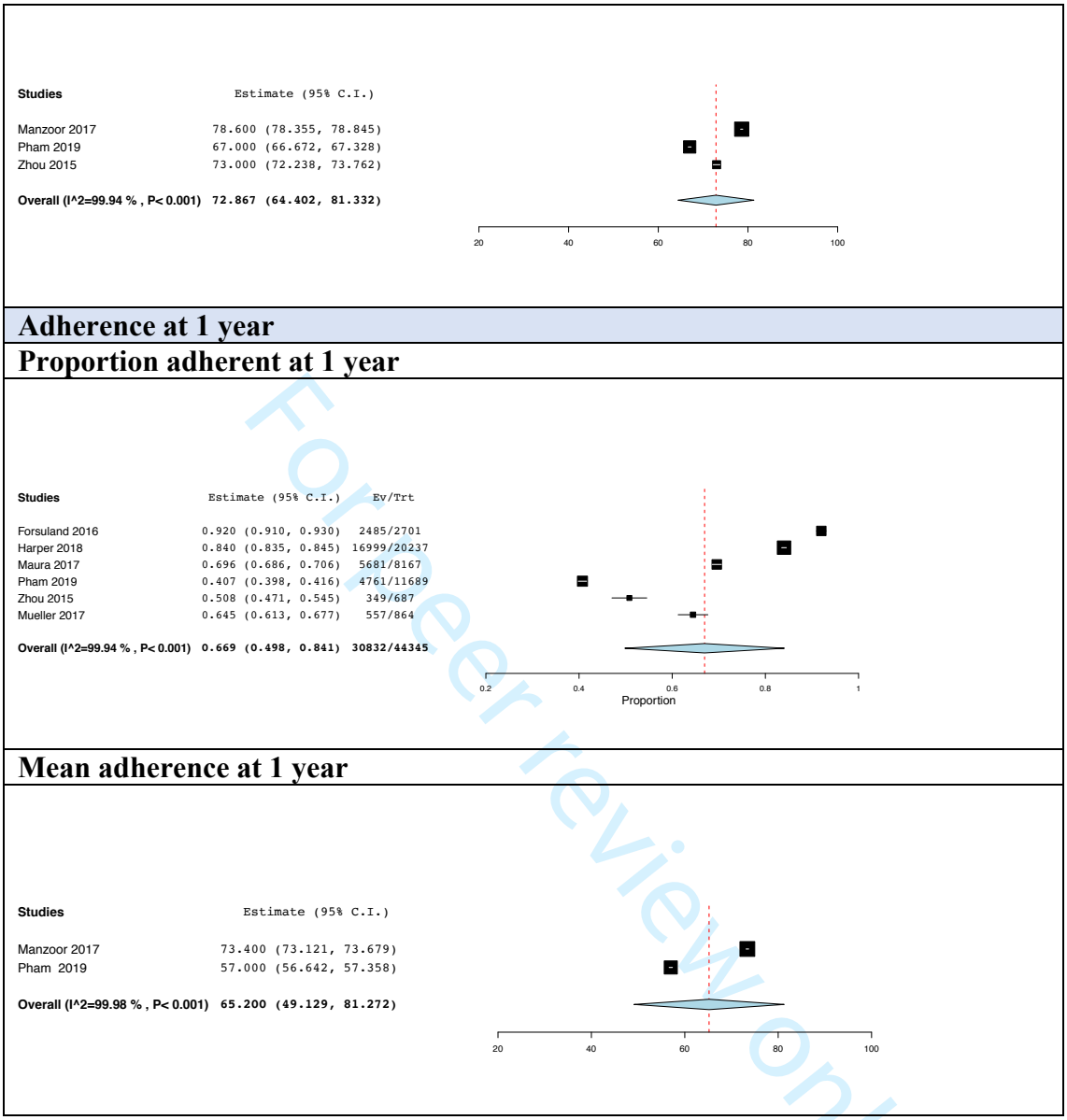
Dabigatran: Sub-analysis: Excluding studies with conflict of interest

Adherence at 6 months

Proportion adherent at 6 months



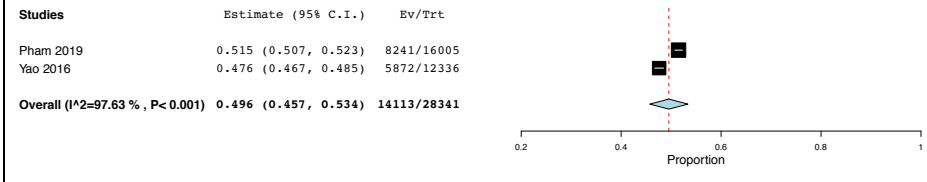
Mean adherence at 6 months



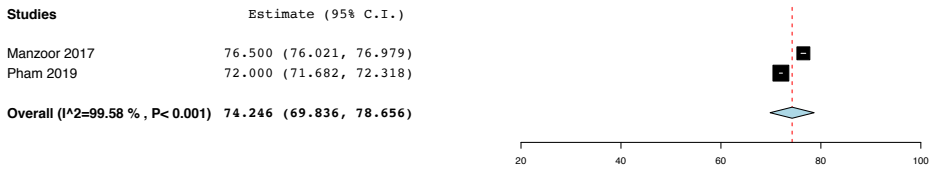
Rivaroxaban: Sub-analysis: Excluding studies with conflict of interest

Adherence at 6 months

Proportion adherent at 6 months

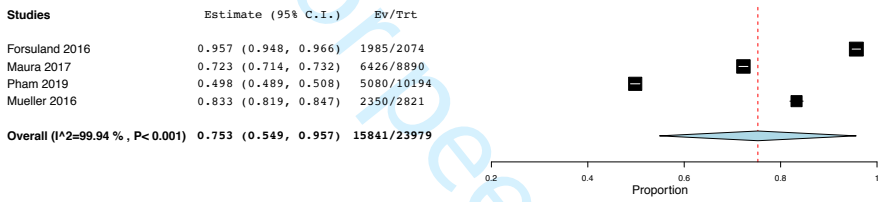


Mean adherence at 6 months

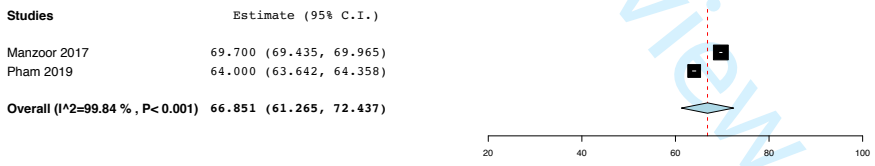


Adherence at 1 year

Proportion adherent at 1 year



Mean adherence at 1 year

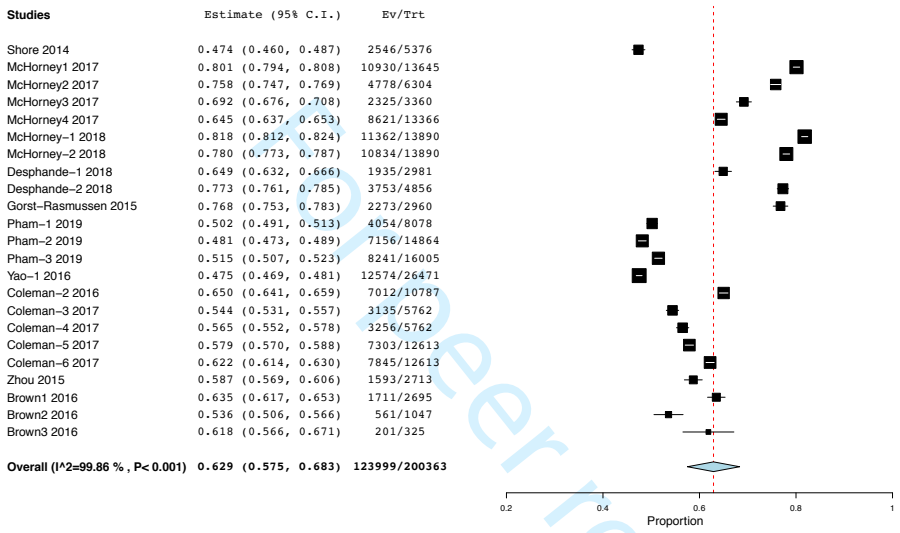


Supplementary 4.1.2: Sub-group analysis by excluding low and medium quality studies.

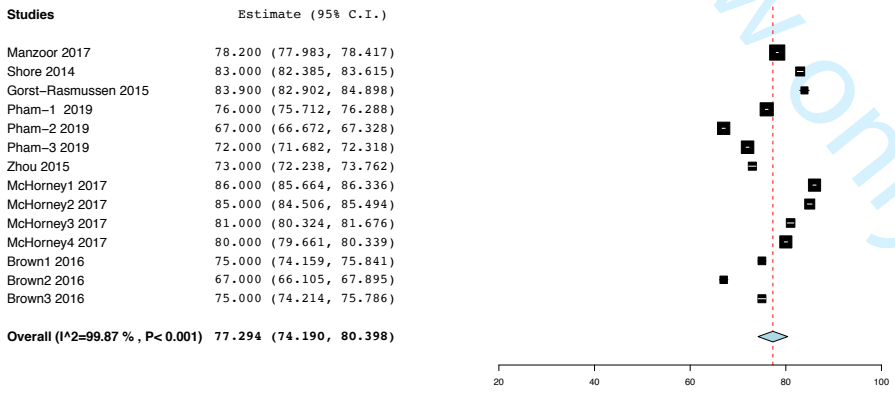
All OAC: Sub-analysis: Excluding low and medium quality studies

Adherence at 6 months

Proportion adherent at 6 months

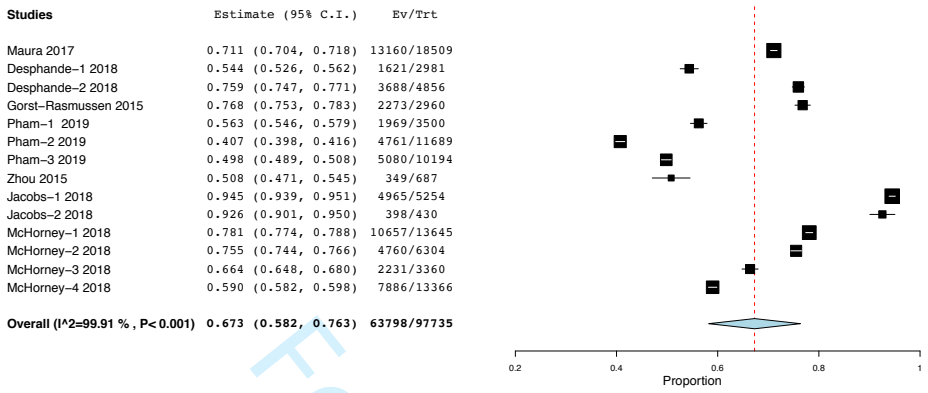


Mean adherence at 6 months

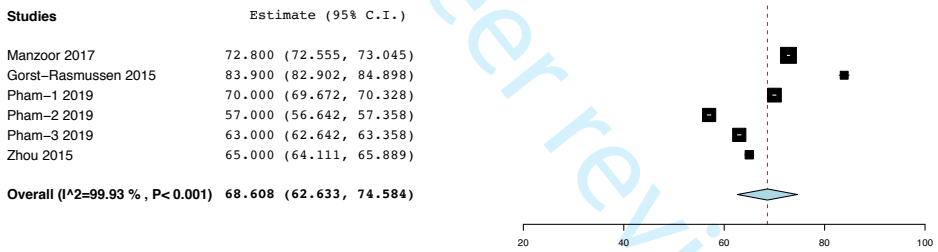


Adherence at 1 year

Proportion adherent at 1 year



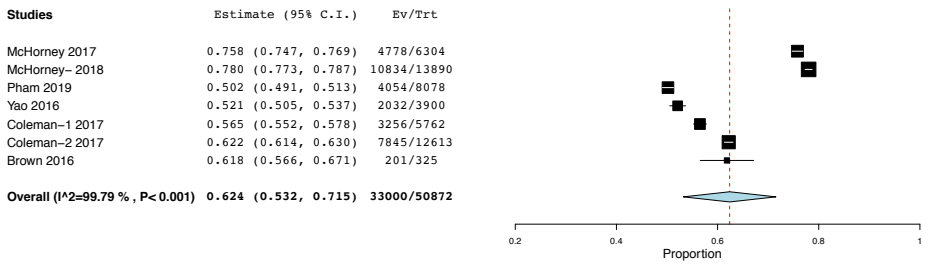
Mean adherence at 1 year



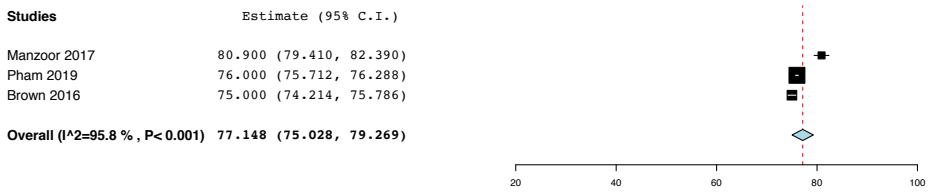
Apixaban: Sub-analysis: Excluding low and medium quality studies

Adherence at 6 months

Proportion adherent at 6 months

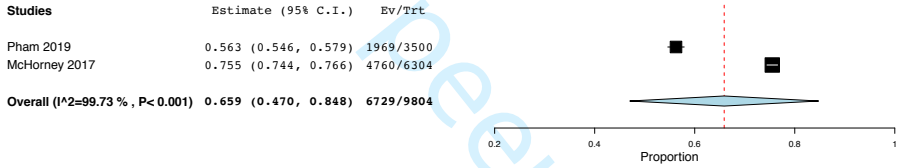


Mean adherence at 6 months

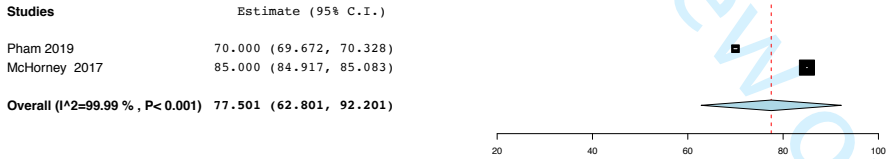


Adherence at 1 year

Proportion adherent at 1 year



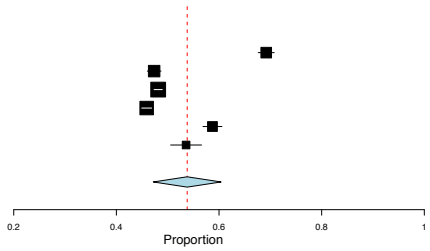
Mean adherence at 1 year



Dabigatran: Sub-analysis: Excluding low and medium quality studies

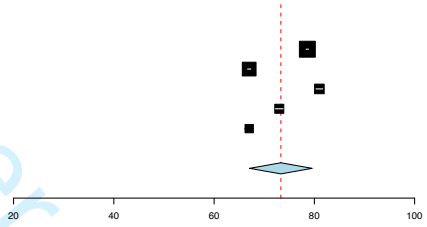
Adherence at 6 months

Proportion adherent at 6 months



Studies	Estimate (95% C.I.)	Ev/Trt
McHorney 2017	0.692 (0.676, 0.708)	2325/3360
Shore 2014	0.474 (0.460, 0.487)	2546/5376
Pham 2019	0.481 (0.473, 0.489)	7156/14864
Yao 2016	0.459 (0.449, 0.469)	4698/10235
Zhou 2015	0.587 (0.569, 0.606)	1593/2713
brown 2016	0.536 (0.506, 0.566)	561/1047
Overall (I^2=99.35 % , P< 0.001)	**0.538 (0.472, 0.604)**	**18879/37595**

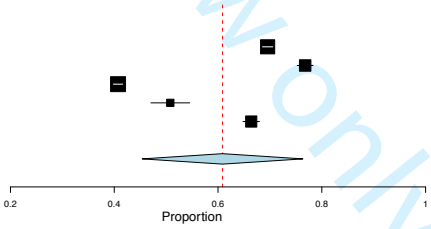
Mean adherence at 1 year



Studies	Estimate (95% C.I.)
Manzoor 2017	78.600 (78.355, 78.845)
Pham 2019	67.000 (66.672, 67.328)
McHorney 2017	81.000 (80.324, 81.676)
Zhou 2015	73.000 (72.238, 73.762)
Brown 2016	67.000 (66.105, 67.895)
Overall (I^2=99.89 % , P< 0.001)	**73.322 (67.076, 79.568)**

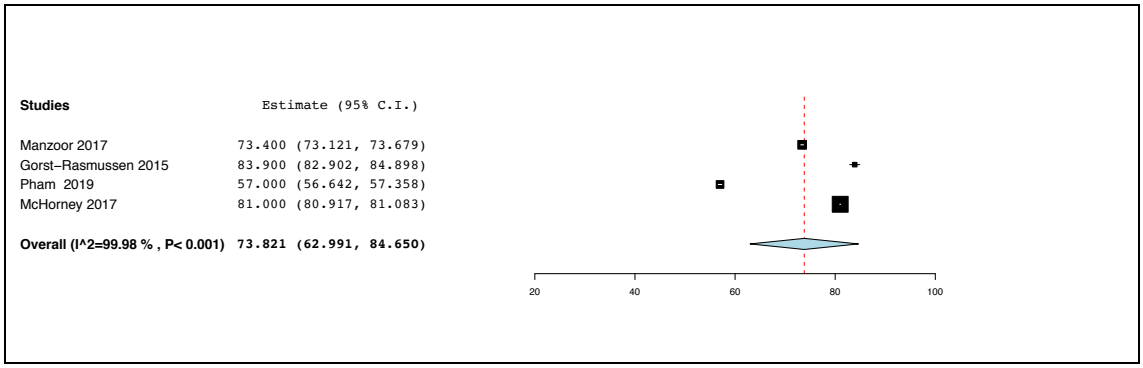
Adherence at 1 year

Proportion adherent at 1 year



Studies	Estimate (95% C.I.)	Ev/Trt
Maura 2017	0.696 (0.686, 0.706)	5681/8167
Gorst–Rasmussen 2015	0.768 (0.753, 0.783)	2273/2960
Pham 2019	0.407 (0.398, 0.416)	4761/11689
Zhou 2015	0.508 (0.471, 0.545)	349/687
McHorney 2017	0.664 (0.648, 0.680)	2231/3360
Overall (I^2=99.85 % , P< 0.001)	**0.609 (0.454, 0.764)**	**15295/26863**

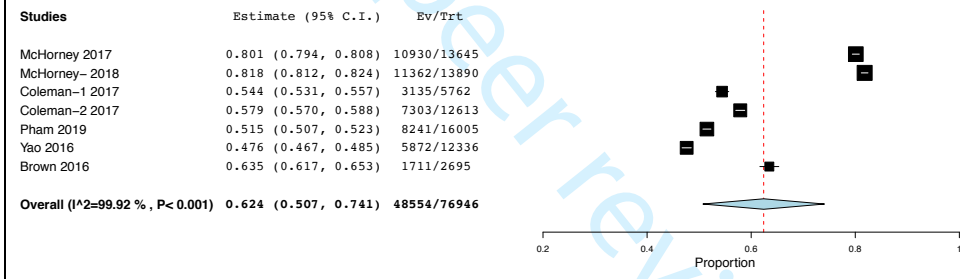
Mean adherence at 1 year



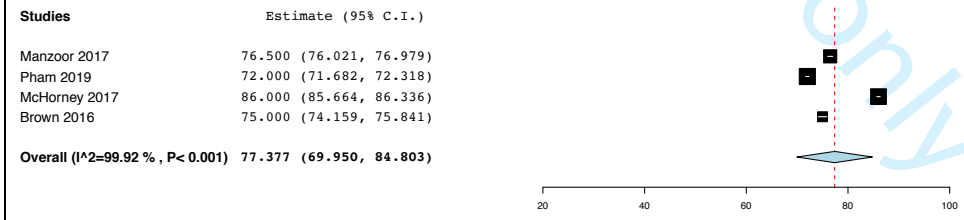
Rivaroxaban: Sub-analysis: Excluding low and medium quality studies

Adherence at 6 months

Proportion adherent at 6 months

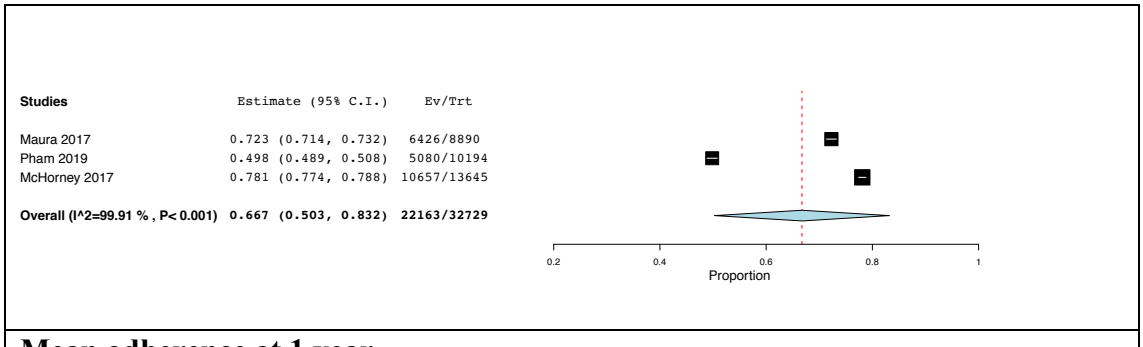


Mean adherence at 1 year

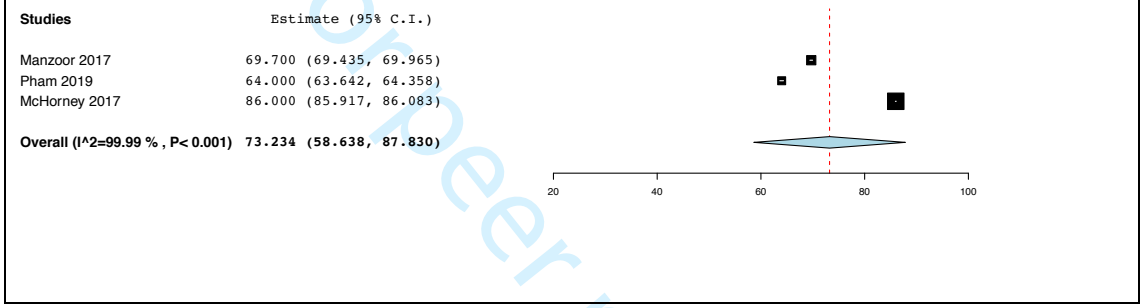


Adherence at 1 year

Proportion adherent at 1 year



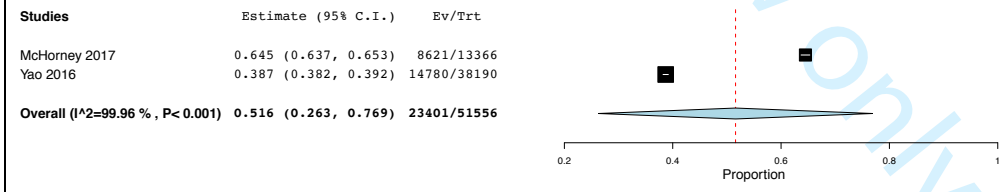
Mean adherence at 1 year



Warfarin: Sub-analysis: Excluding low and medium quality studies

Adherence at 6 months

Proportion adherent at 6 months



Mean adherence at 6 months

NA

Adherence at 1 year

Proportion adherent at 1 year

NA

Mean adherence at 1 year

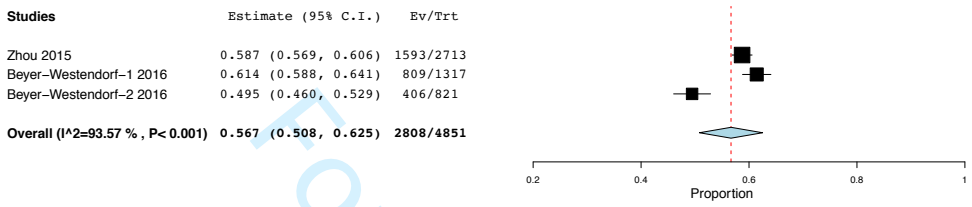
NA

Supplementary 4.1.3: Sub-group analysis by adherence measure

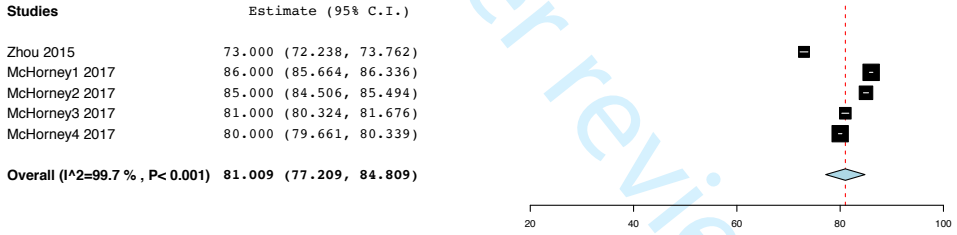
All OACs: Sub-analysis: stratified by adherence measure

Adherence at 6 months

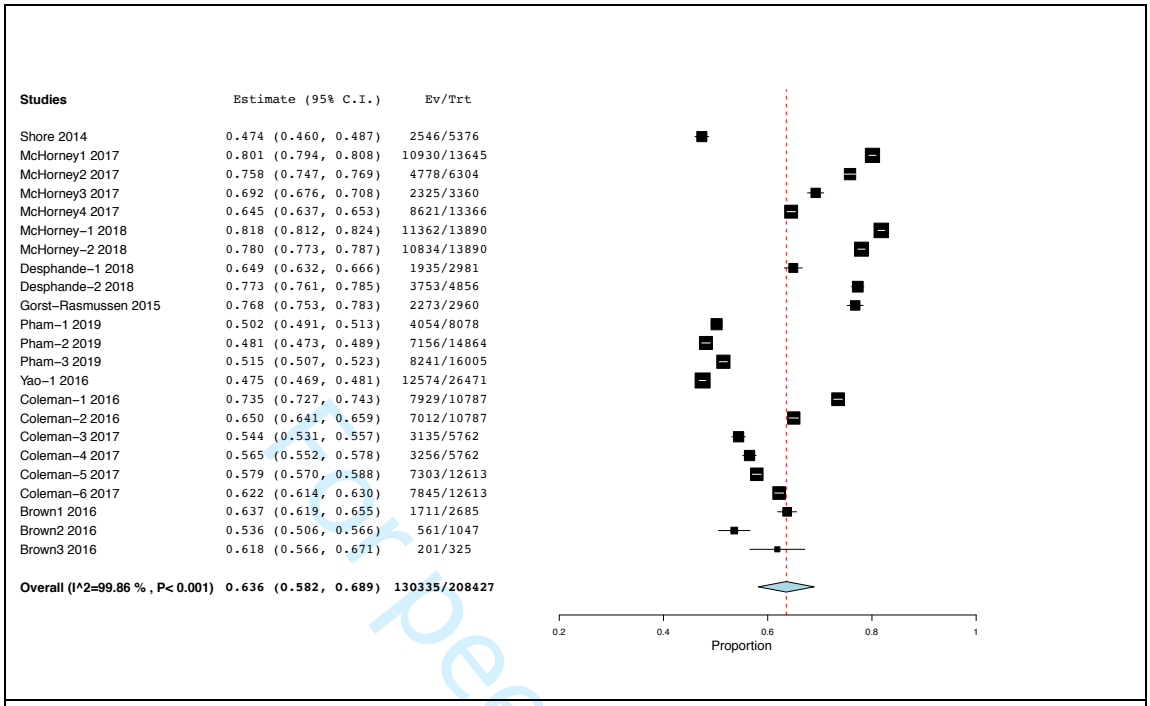
MPR: proportion adherent at 6 months



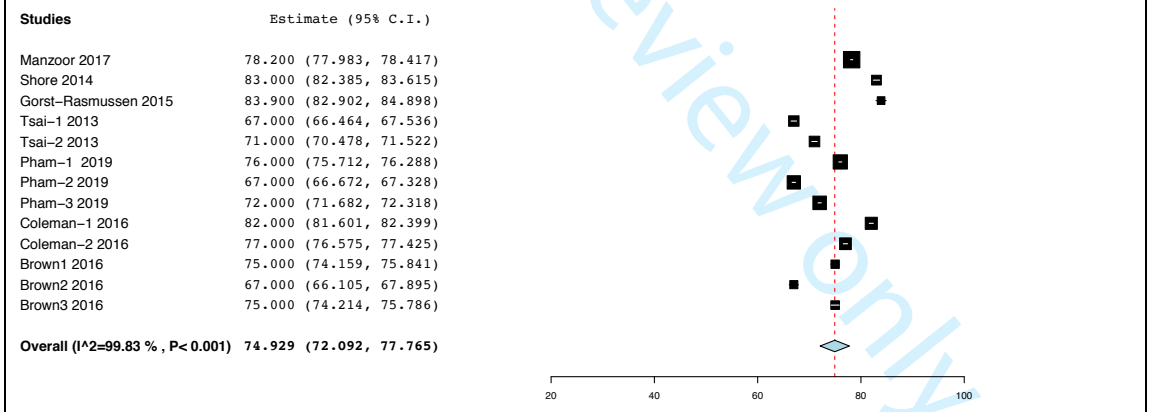
MPR: Mean (SD) adherence at 6 months



PDC: proportion adherent at 6 months

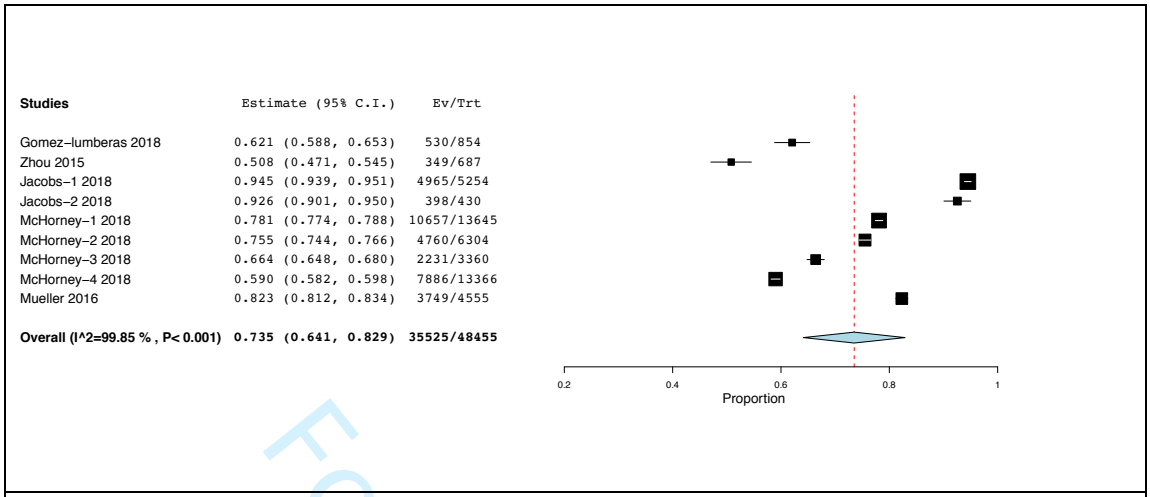


PDC: Mean (SD) adherence at 6 months



Adherence at 1 year

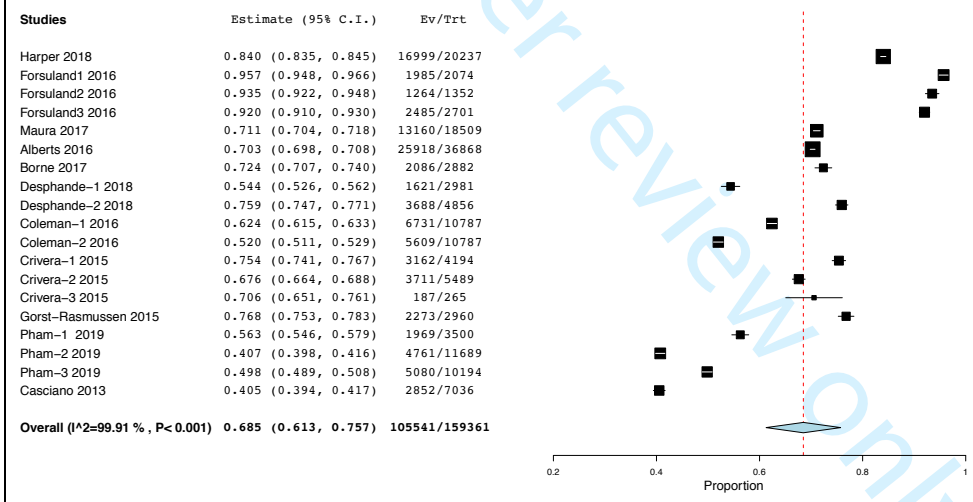
MPR: proportion adherent at 1 year



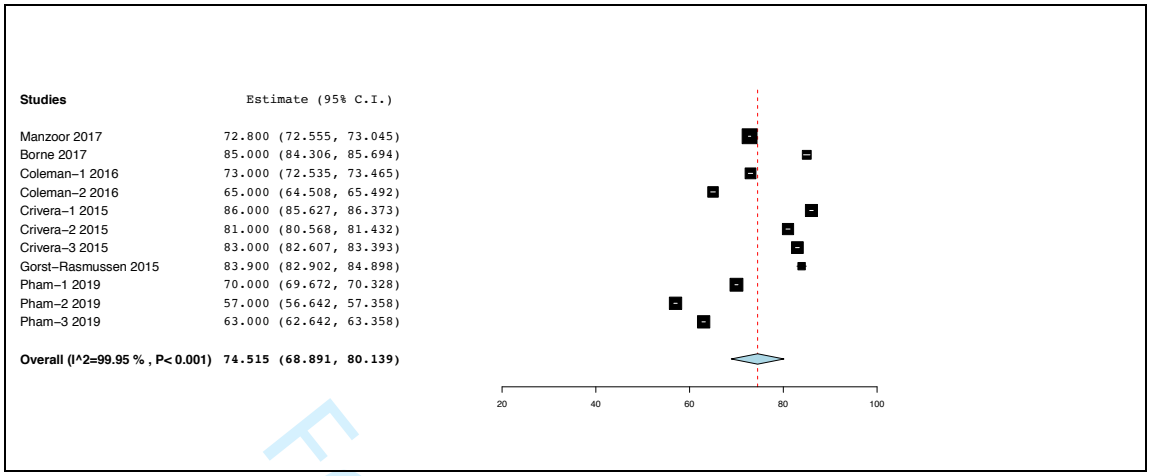
MPR: Mean (SD) adherence at 1 year

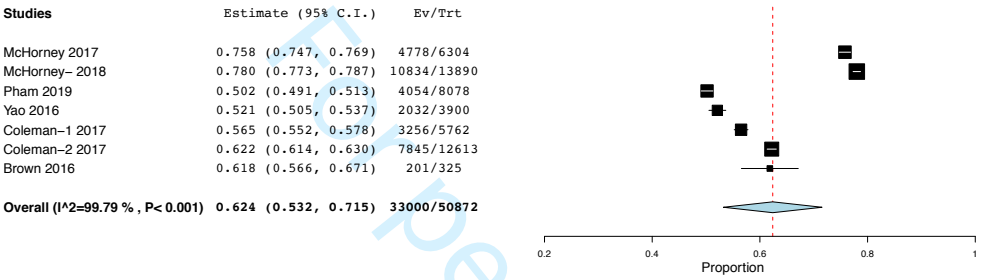
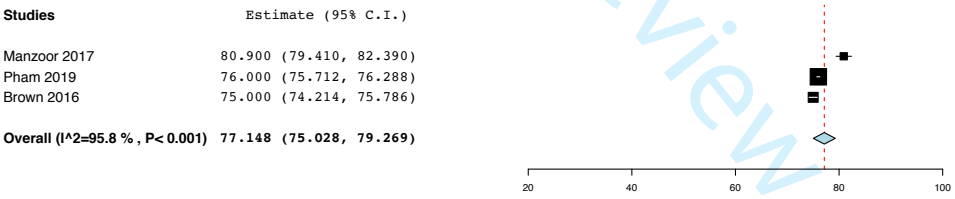
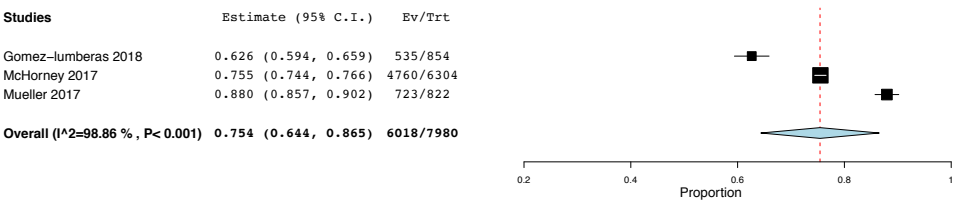
NA

PDC: proportion adherent at 1 year

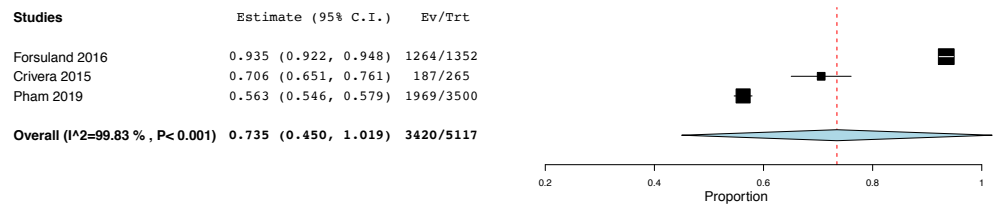


PDC: Mean (SD) adherence at 1 year

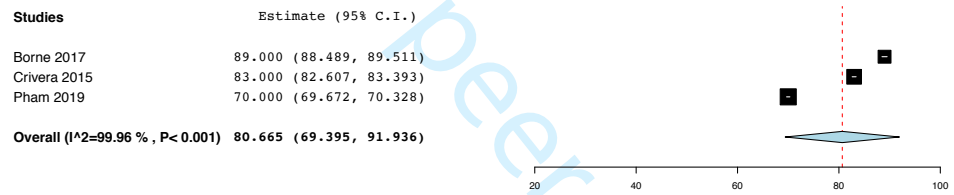


Apixaban: Sub-analysis: stratified by adherence measure
Adherence at 6 months
MPR: proportion adherent at 6 months
NA
MPR: Mean (SD) adherence at 6 months
NA
PDC: proportion adherent at 6 months

PDC: Mean (SD) adherence at 6 months

Adherence at 1 year
MPR: proportion adherent at 1 year

MPR: Mean (SD) adherence at 1 year
NA

PDC: proportion adherent at 1 year



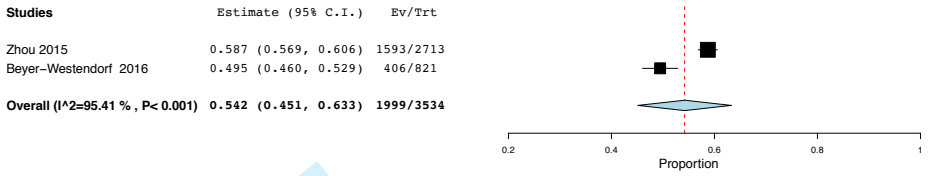
PDC: Mean (SD) adherence at 1 year



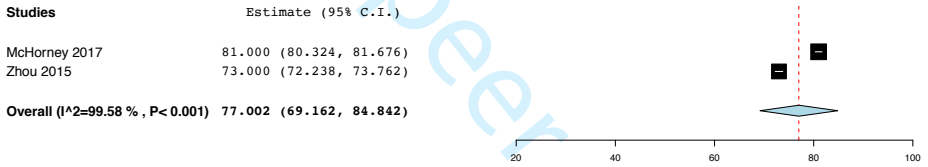
Dabigatran: Sub-analysis: stratified by adherence measure

Adherence at 6 months:

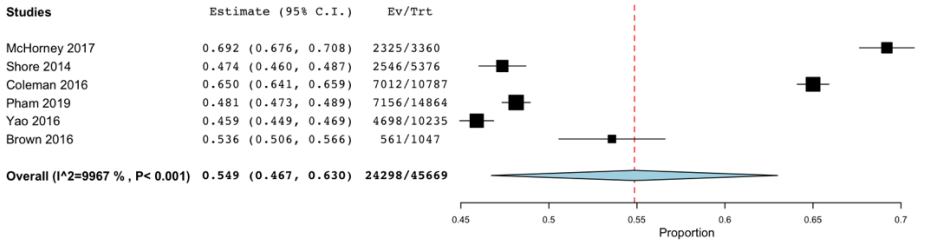
MPR: proportion adherent at 6 months



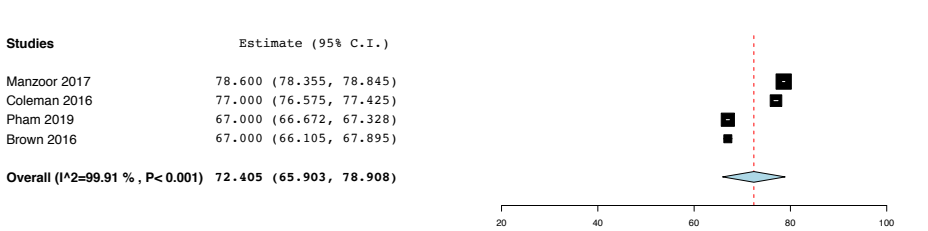
MPR: Mean (SD) adherence at 6 months



PDC: proportion adherent at 6 months

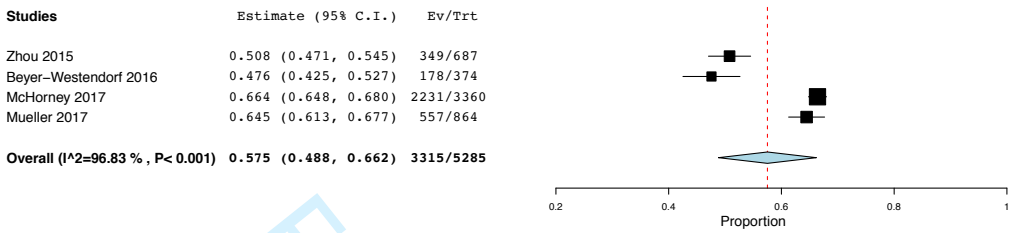


PDC: Mean (SD) adherence at 6 months



Adherence at 1 year

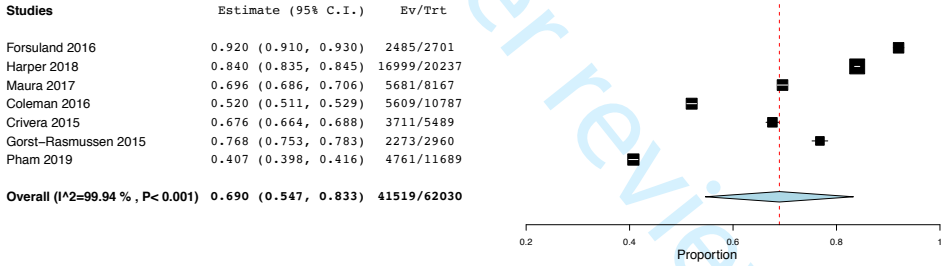
MPR: proportion adherent at 1 year



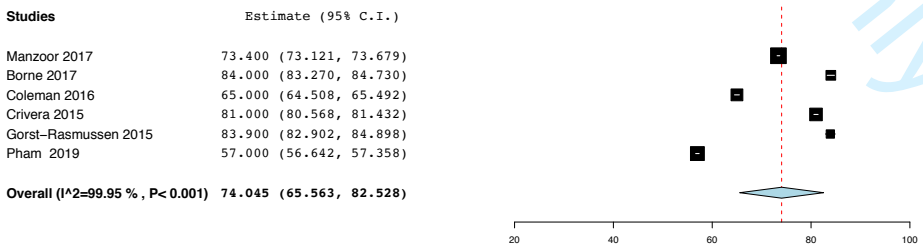
MPR: Mean (SD) adherence at 1 year

NA

PDC: proportion adherent at 1 year



PDC: Mean (SD) adherence at 1 year



Rivaroxaban: Sub-analysis: stratified by adherence measure.

Adherence at 6 months:

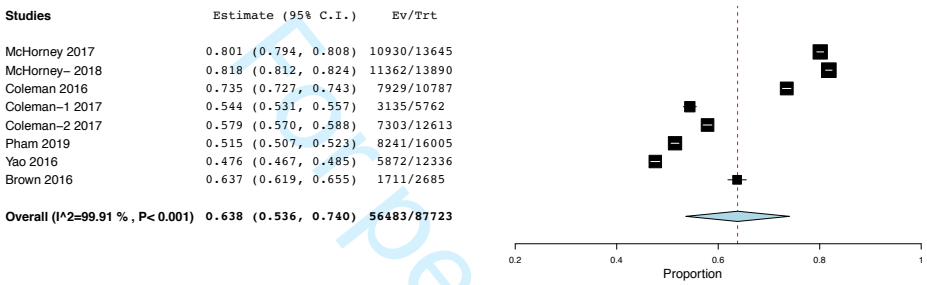
MPR: proportion adherent at 6 months

NA

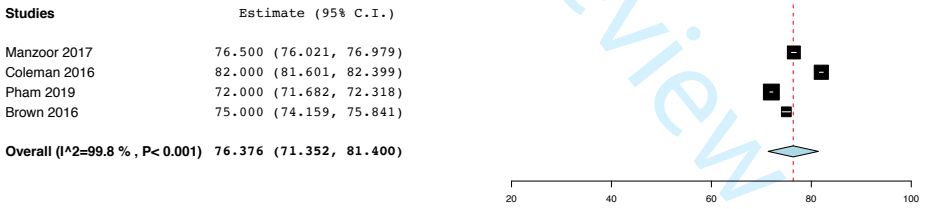
MPR: Mean (SD) adherence at 6 months

NA

PDC: proportion adherent at 6 months

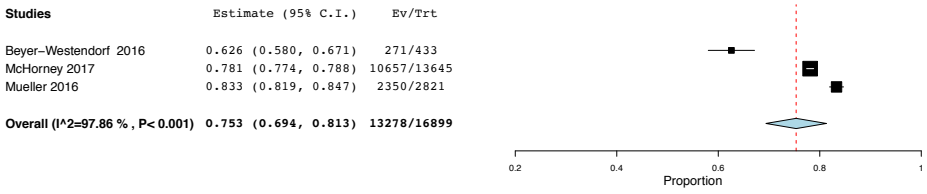


PDC: Mean (SD) adherence at 6 months



Adherence at 1 year:

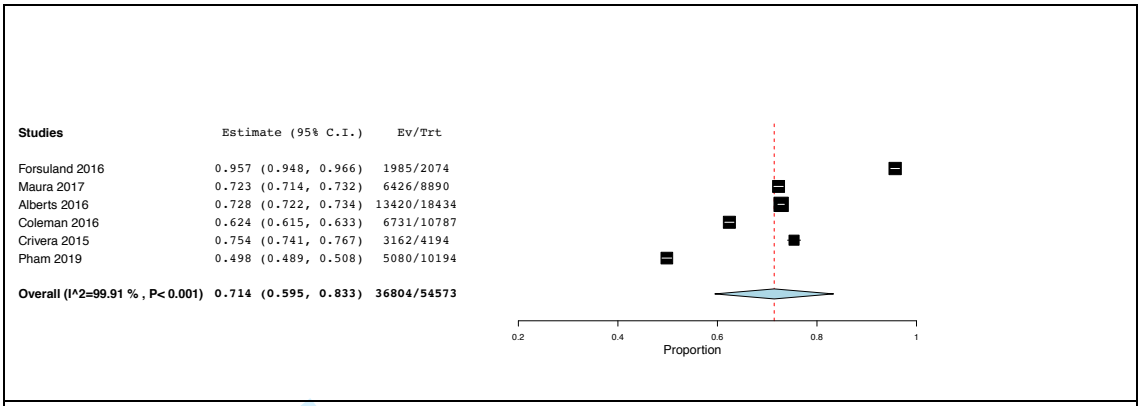
MPR: proportion adherent at 1 year



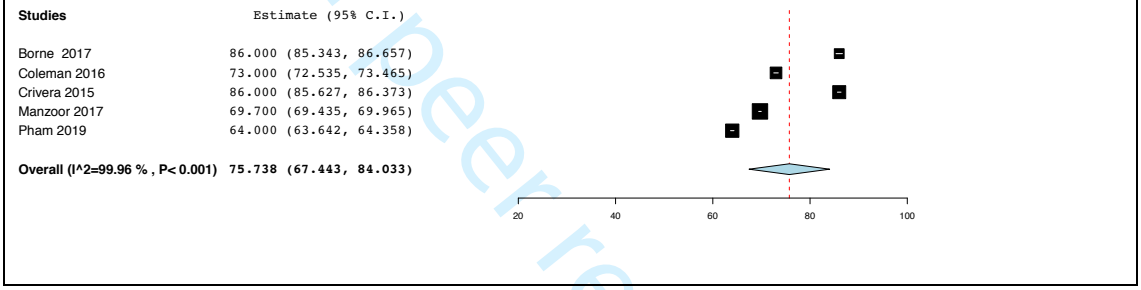
MPR: Mean (SD) adherence at 1 year

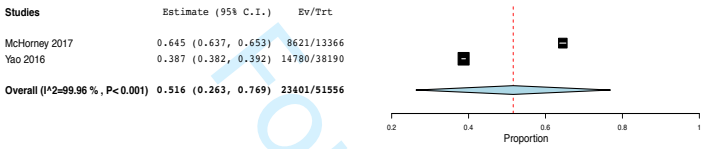
NA

PDC: proportion adherent at 1 year

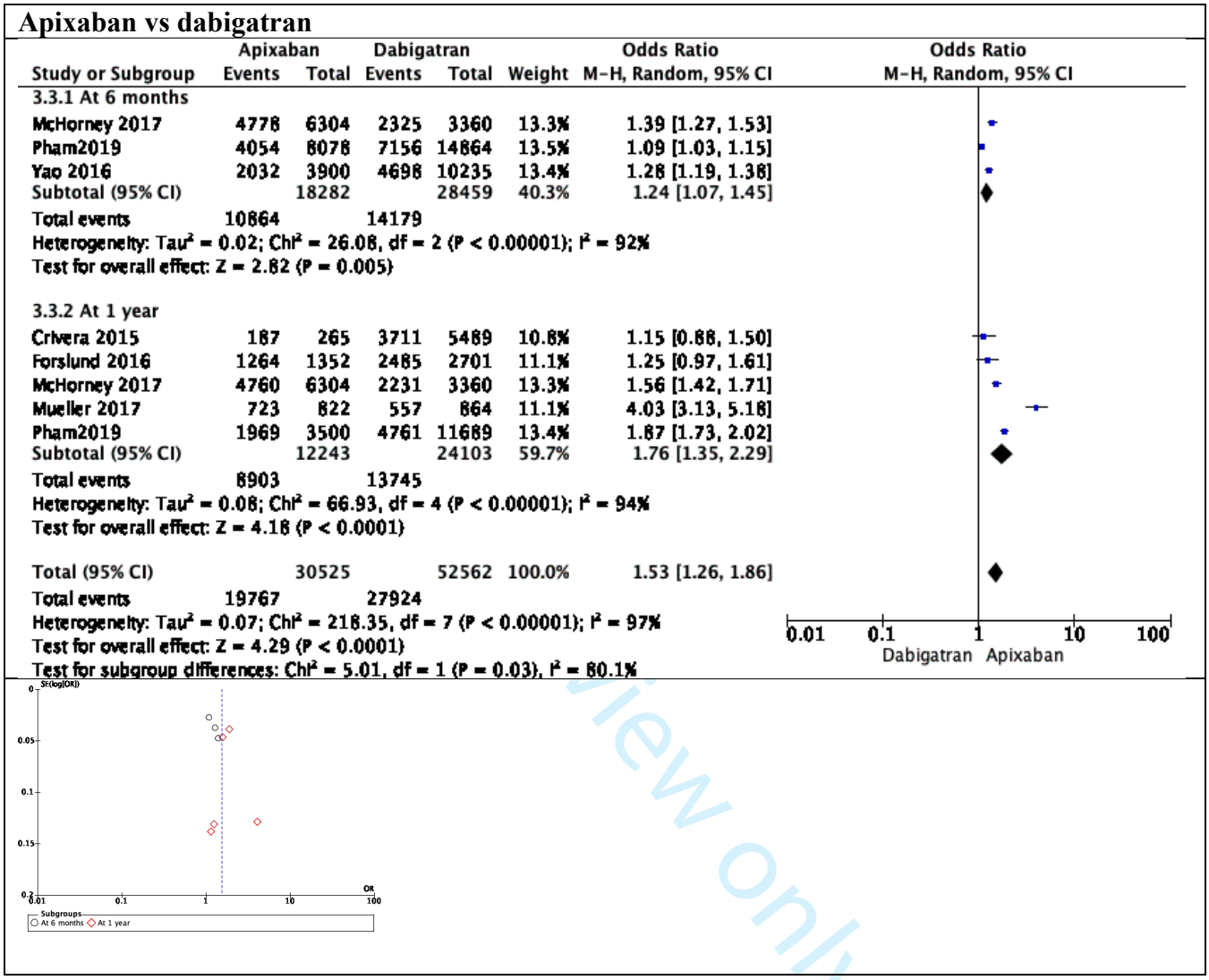


PDC: Mean (SD) adherence at 1 year



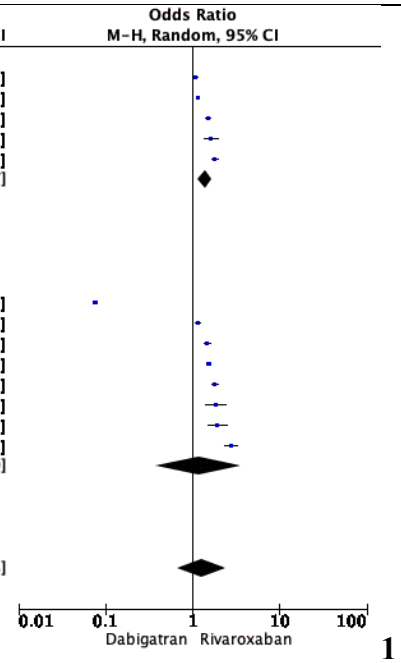
Warfarin: Sub-analysis: stratified by adherence measure
Adherence at 6 months:
MPR: proportion adherent at 6 months
NA
MPR: Mean (SD) adherence at 6 months
NA
PDC: proportion adherent at 6 months

PDC: Mean (SD) adherence at 6 months
NA
Adherence at 1 year
MPR: proportion adherent at 1 year
NA
MPR: Mean (SD) adherence at 1 year
NA
PDC: proportion adherent at 1 year
NA
PDC: Mean (SD) adherence at 1 year
NA

Supplementary 4.2: studies reporting adherence to different medications in the same cohort.



Rivaroxaban vs dabigatran

Study or Subgroup	Rivaroxaban Events	Rivaroxaban Total	Dabigatran Events	Dabigatran Total	Weight	Odds Ratio M-H, Random, 95% CI
5.3.1 At 6 months						
Yao 2016	5872	12336	4698	10235	7.7%	1.07 [1.02, 1.13]
Pham2019	8241	16005	7156	14864	7.7%	1.14 [1.09, 1.20]
Coleman 2016	7929	10787	7012	10787	7.7%	1.49 [1.41, 1.58]
Beyer-Westendorf 2016	809	1317	406	821	7.7%	1.63 [1.36, 1.94]
McHorney 2017	10930	13645	2325	3360	7.7%	1.79 [1.65, 1.95]
Subtotal (95% CI)		54090		40067	38.5%	1.39 [1.15, 1.67]
Total events	33781		21597			
Heterogeneity: Tau² = 0.04; Chi² = 162.85, df = 4 (P < 0.00001); I² = 98%						
Test for overall effect: Z = 3.46 (P = 0.0005)						
5.3.2 At 1 year						
Pham2019	5080	101940	4761	11689	7.7%	0.08 [0.07, 0.08]
Maura 2017	6426	8890	5681	8167	7.7%	1.14 [1.07, 1.22]
Crivera 2015	3162	4194	3711	5489	7.7%	1.47 [1.34, 1.61]
Coleman 2016	6731	10787	5609	10787	7.7%	1.53 [1.45, 1.62]
McHorney 2017	10657	13645	2231	3360	7.7%	1.80 [1.66, 1.96]
Beyer-Westendorf 2016	271	433	178	374	7.6%	1.84 [1.39, 2.44]
Forslund 2016	1985	2074	2485	2701	7.6%	1.94 [1.50, 2.50]
Mueller 2017	2350	2821	557	864	7.7%	2.75 [2.32, 3.26]
Subtotal (95% CI)		144784		43431	61.5%	1.17 [0.38, 3.60]
Total events	36662		25213			
Heterogeneity: Tau² = 2.64; Chi² = 10724.75, df = 7 (P < 0.00001); I² = 100%						
Test for overall effect: Z = 0.27 (P = 0.79)						
Total (95% CI)		198874		83498	100.0%	1.25 [0.66, 2.38]
Total events	70443		46810			
Heterogeneity: Tau² = 1.39; Chi² = 12603.04, df = 12 (P < 0.00001); I² = 100%						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%						



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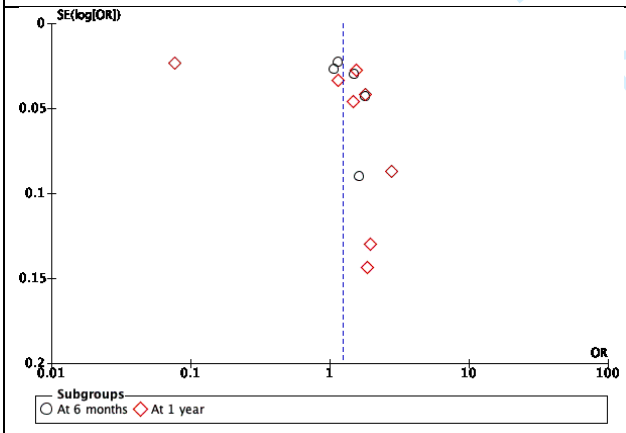

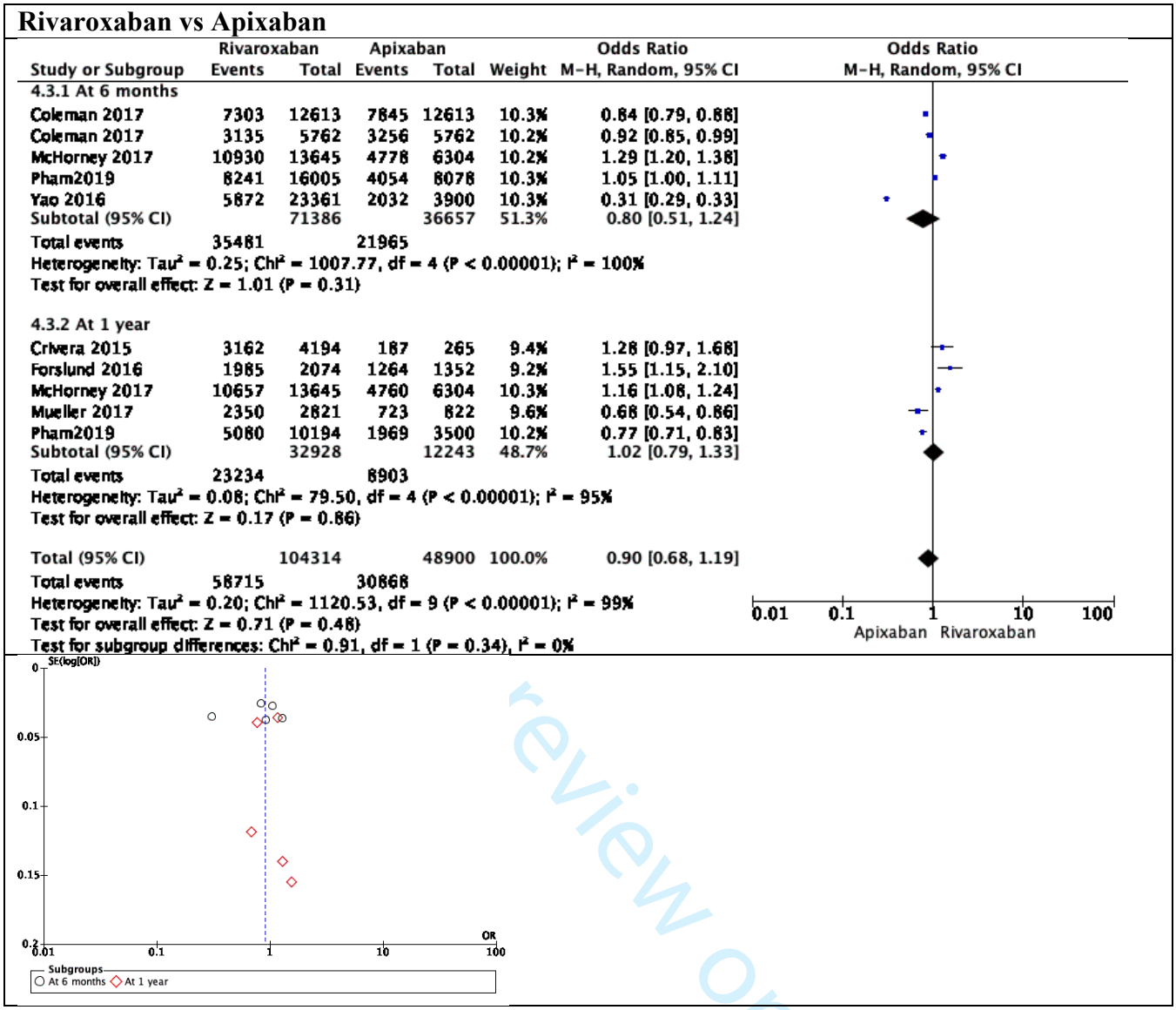

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Adherence to oral anticoagulants among patients with atrial fibrillation:

A systematic review and meta-analysis of observational studies

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Short title: Adherence to anticoagulants in patients with AF.

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ABSTRACT

INTRODUCTION

Medications cannot exert their effect if not taken as prescribed by patients. Our objective was to summarize 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 six months and one 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 six months and one 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 to 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.

Keywords: Atrial fibrillation, anticoagulants, medication adherence, stroke.

Strengths and limitations of this study

- This is a timely systematic review that synthesizes 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 synthesize 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 five-fold, 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 summarize the medication taking behavior 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, summarize evidence from randomized controlled trials (which do not reflect the day to day behaviors of patients), and provide a narrative summary of results with no meta-analysis.[19-21] Further, no studies have summarized 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 summarize 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 (PRISMA) and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (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 (Supplementary 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 utilized 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 (NVAF), 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 standard deviation (SD) of patients' adherence over six- or twelve- 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 (e.g. 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 analyzed to minimize 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 World Health Organization's (WHO) 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 Der Simonian & Laird random-effects models to determine the pooled mean adherence and the corresponding pooled proportion of adherent patients over six months and one 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, and 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 odds ratio (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, WA) or RevMan5 (version 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 (e.g. OR).[30,31] Clinical and economic impacts of poor adherence were summarized 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 STROBE.[33] Studies received a point for each checklist item they met and a zero 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 categorized 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.

Ethical approval

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

RESULTS

Initial search led to 1,122 studies, all of which were in English (Figure 1.0). 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 (Supplementary 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 six months or one year post index date (Table 2). The majority of the included studies focused on adherence to DOACs with only 4 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] to 86[55] over six months and 57[58] to 86[41] over one year post index date, with corresponding reported proportion of adherent patients ranging between 47%[59] to 82%[56] over six months and 41%[58] to 95%[45] over one year. A wide range of adherence results were observed even at the individual OAC level (Table 2).

Pooled mean adherence scores over six month and one 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 2 studies only (as illustrated in tables 2 and 3). Due to the limited data in warfarin, no drug class comparison could be made. Figure 2.0 illustrates the forest plots for patients' mean adherence score over six months and one 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 supplementary 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 versus MPR), or country (USA versus others) had only minor impacts on pooled adherence results and the detected heterogeneity (Supplementary 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 to dabigatran over both six months (Odds Ratio (OR):1.24, 95% CI: 1.07-1.45) and one year post index date (OR:1.76, 95% CI: 1.35-2.29). Odds of adherence was significantly

higher for rivaroxaban compared to dabigatran over six months (OR:1.39, 95% CI: 1.15-1.67), but not one year (OR:1.17, 95% CI: 0.38-3.60). Odds of adherence did not differ between apixaban and rivaroxaban over six months (OR:0.80, 95% CI: 0.51-1.24) or one 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 to 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 to 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 to naïve users over six months (83.3±24.6 vs 72.3±31.3; p< 0.05), nine months (81.2±26.4 vs 67.3±33.8); p< 0.05) and one year (79.9±27.6 vs 63.7±35.2; p <0.05).[50]

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 to those prescribed after discharge at three months (84.5% vs 12.3%; P<0.001) and one 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. Summarizing 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], angiotensin converting enzyme 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 ischemic 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 ischemic stroke compared to adherent patients, over six 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 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 compare to adherent patients and Deshpande et al. reported significantly higher annual adjusted per-patient medical cost (inpatient and outpatient) for non-adherent users compared to adherent ones ($30,485 versus $23,544; p≤0.001).[38,43]

DISCUSSION

In this systematic review, we synthesized 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 to 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 six months and one 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 to 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-, regimen- 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, angiotensin converting enzyme 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 utilization and costs. Our findings confirm the results of a 2017 systematic review of 79 studies across 14 disease groups which reported that $3,347-19,472 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 summarize 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, 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 (Supplementary 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 (e.g. OAC naïve versus experienced); methods for handling and defining medication switches, stockpiling, refill gaps, and hospitalization dates; fixed versus variable observational periods and adherence measure used (PDC versus 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 behavior, calculating and reporting it using a single summary measure. This methodological approach does not provide a complete picture of adherence, which is a dynamic behavior that changes over time.[25,81] Characterization 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 characterize 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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COMPETING INTERESTS

Authors have no competing interests to declare.

CONTRIBUTIONS

Conceived the study: SS, PL, MDV; Designed the search strategy: SS, MDV, PL; 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): MDV, SS; Analyzed the data: SS; Conducted quality assessment; SS, RT; Interpreted the results: SS, PL, JGA, MDV; Prepared the manuscript first draft: SS, MDV, PL, RT; Reviewed the manuscript and provided critical feedback: JGA, MDV, PL; Revised the manuscript: SS, PL, RT, MDV.

DATA AVAILABILITY STATEMENT

No additional data available.

FIGURE LEGENDS

Figure 1.0: PRISMA flow diagram that details the number of studies identified by our search strategy, screened, and included in the final analysis.

Figure 2.0: Forest plots illustrating patients' mean adherence scores over six months and one year post index date. See Supplementary 4 for additional forest plots for each OAC and subgroup analyses.

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TABLES

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	2016	Retrospective	USA	36,868 (55%)	76%>65 years	NVAF	NA	Both	Yes	61%	67%
Beyer-Westendorf	2016	Retrospective	Germany	7,265 (52%)	NA	NVAF	Index OAC	Naïve	Yes	73%	74%
Borne	2017	Retrospective	USA	2,882 (97%)	67.4 (9.5)	NVAF	NA	Naïve to DOACs‡	Yes	73%	78%
Brown	2016	Retrospective	USA	5,223 (40%)	59%≥65 years	NVAF	Both	Naïve	Yes	77%	84%
Casciano	2013	Retrospective	USA	13,289 (47%)	78% ≥75 years	AF	NA	Naïve	Yes	63%	79%
Coleman	2016	Retrospective	USA	21,756 (54%)	66.5 (12.2)	NVAF	NA	Naïve	Yes	55%	50%
Coleman	2017	Retrospective	USA	106,227 (63%)	71.1 (11.0)	NVAF	Index OAC	Naïve	Yes	77%	84%
Crivera	2015	Retrospective	USA	9,948 (53%)	75.5 (8.3)	NVAF	Both	Naïve	Yes	73%	61%
Deshpande PMID: 29694285	2018	Retrospective	USA	2,981 (70%)	64.4 (10.7)	AF	NA	Naïve to DOACs‡	No	77%	83%
Deshpande PMID: 29334815	2018	Retrospective	USA	4,856 (52%)	65.0 (10.5)	AF	NA	Naïve	No	81%	83%
Kapen	2014	Retrospective	USA	2,691 (43%)	100%>65 years	AF	NA	Both	No	76%	74%
Forsuland	2016	Retrospective	Sweden	16,096 (52%)	75.45 (SD not reported)	NVAF	Current OAC	Both	No	63%	61%
Gomez-Iumberas	2018	Retrospective	Spain	854 (NA%)	73.2 (11.0)	NVAF	NA	Both	Yes	50%	67%
Gorst-Rasmussen	2015	Retrospective	Denmark	2,960 (54%)	72.1 (10.8)	NVAF	Index OAC	Naïve	Yes	80%	100%
Harper	2018	Retrospective	New Zealand	20,237 (NA%)	83%>60	NVAF	NA	NA	No	47%	53%
Jacobs	2018	Retrospective	Sweden & Netherlands	5,684 (60%)	78%≥65 years	AF	Current OAC	Both	Yes	80%	83%
Manzoor	2017	Retrospective	USA	66,090 (62%)	68.7 (12.1)	AF	Index OAC	Both	Missing	70%	85%
Márquez-Contrera	2016	Prospective	Spain	412 (42%)	75.2 (7.5)	NVAF	NA	Experienced	Yes	63%	83%
Maura	2017	Retrospective	France	22,267 (53%)	74.0 (10.8)	NVAF	Index	Naïve	No	79%	100%
McAlister	2018	Retrospective	Canada	57,669 (56%)	100%>65 years	NVAF	Current OAC	Naïve	No	87%	94%
McCormick	2001	Retrospective	USA	429 (22%)	87 (7.1)	AF	Current OAC	Experienced	No	60%	82%
McHorney	2017	Retrospective	USA	36,675 (67%)	63.1 (SD not reported)	NVAF	Index OAC	Naïve	Yes	87%	89%
McHorney	2018	Retrospective	USA	41,201 (58%)	NA	NVAF	Index OAC	Both	Yes	84%	100%
Mueller	2017	Retrospective	Scotland	5,398 (54%)	74.4 (11.3)	AF	NA	NA	No	70%	53%
Pham	2019	Retrospective	USA	38,947 (60%)	100%>65 years	NVAF	Index OAC & any OAC	Naïve	No	77%	89%
Shore	2014	Retrospective	USA	5,376 (98%)	71.3 (9.7)	NVAF	Index OAC	NA	No	90%	94%
Sørensen	2017	Retrospective	Denmark	46,675 (58%)	79%>65 years	NVAF	Current OAC	Naïve	Yes	67%	79%

Tsai	2013	Retrospective	USA	17,691 (49%)	76.4 (8.7)	NA	Current OAC	Warfarin Naïve and warfarin experienced	No	60%	78%
Yao	2016	Retrospective	USA	64,661 (56%)	75% >65	AF	Index OAC	Naïve	No	77%	84%
Zhou	2015	Retrospective	USA	5,951 (34%)	36.1%>65	AF	Index OAC	Naïve	No	80%	79%

Footnote:

USA: United States of America; NVAF: non-valvular atrial fibrillation; AF: atrial fibrillation (valvular and non-valvular); NA: not applicable (no data reported)

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 (2016)	PDC (>80%)	NA	NA	NA	Overall: 0.70 A and D: 0.68 R: 0.73
Borne (2017)	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 (2016)	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 (2013)	PDC (>80%)	NA	NA	NA	W: 0.41
Coleman (2016)	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 (2017)	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 (2015)	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 (2018) PMID: 29694285	PDC (≥80%)	NA	R and D: 0.65	NA	R and D: 0.54
Deshpande (2018) PMID: 29334815	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 (2016)	PDC (>80%)	NA	NA	NA	A: 0.93 D: 0.92 R: 0.96
Gorst-Rasmussen (2015)	PDC (>80%)	0.84 ± 0.28	NA	NA	D: 0.77
Harper (2018)	PDC (>80%)	NA	NA	NA	D: 0.84
Manzoor (2017)	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 (2017)	PDC>80	NA	NA	NA	**Index OAC:** Overall: 0.71 D: 0.70

					R: 0.72
McHorney (2017)	PDC (>80% & >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 (2018)	PDC (>80% & >90%)	NA	**PDC80:** A:0.78 R: 0.82 **PDC90:** A: 0.60 R: 0.67	NA	NA
Pham (2019)	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 (2014)	PDC (>80%)	NA	D: 0.28	NA	NA
Sørensen (2017)	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 (2013)	PDC (no threshold)	D: warfarin-naïve: 0.67 ± 0.36 warfarin-experienced: 0.71 ± 0.35	NA	NA	NA
Yao (2016)	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 (2016)	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 (2014)	MPR (no threshold)	NA	NA	Median (IQR): 0.77 (0.51- 0.98)	NA
Gomez-lumberas (2018)	MPR (>0.8)	NA	NA	NA	A: 0.62
Jacobs (2018)	MPR (≥0.8)	NA	NA	NA	Sweden: 0.95 Netherlands: 0.93
McHorney (2017)	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 (2015)	MPR (>0.8)	D: 0.73 ± 0.30	D: 0.59	D: 0.65 ± 0.35	D: 0.51
Mueller (2017)	MPR>80‡	NA	NA	NA	DOACs: 0.82 A: 0.88 D: 0.65 R: 0.83

Márquez-Contrera (2016)	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 (2018)	TTR>65% (INR2-3)	NA	W: Percent patients with time in therapeutic range: 4.11%	NA	NA

Footnote:
PDC: proportions days covered; MPR: medication possession ratio; CP: Compliance percentage; TTR: Time in therapeutic range; USA: United States of America; NA: Not available/not applicable; aHR: adjusted Hazard ratio; VKA: Vitamin K antagonist. A: apixaban; D: dabigatran; R: rivaroxaban; W: warfarin.
Drug specific proportion of adherent patients was calculated as the percent 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

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)
Sub-analysis: 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)
Sub-analysis: 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)
Sub-analysis: 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)

[*]I^2 <80%.
[+] Not pooled. Based on one study
[++] Pooled results of only two studies

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	
	Number of unique studies	**Odds ratio (95% CI)**	**Number of unique studies**	**Odds ratio (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)
Sub-analysis: 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)

***I^2 <80%.**
+ Not pooled. Based on one study

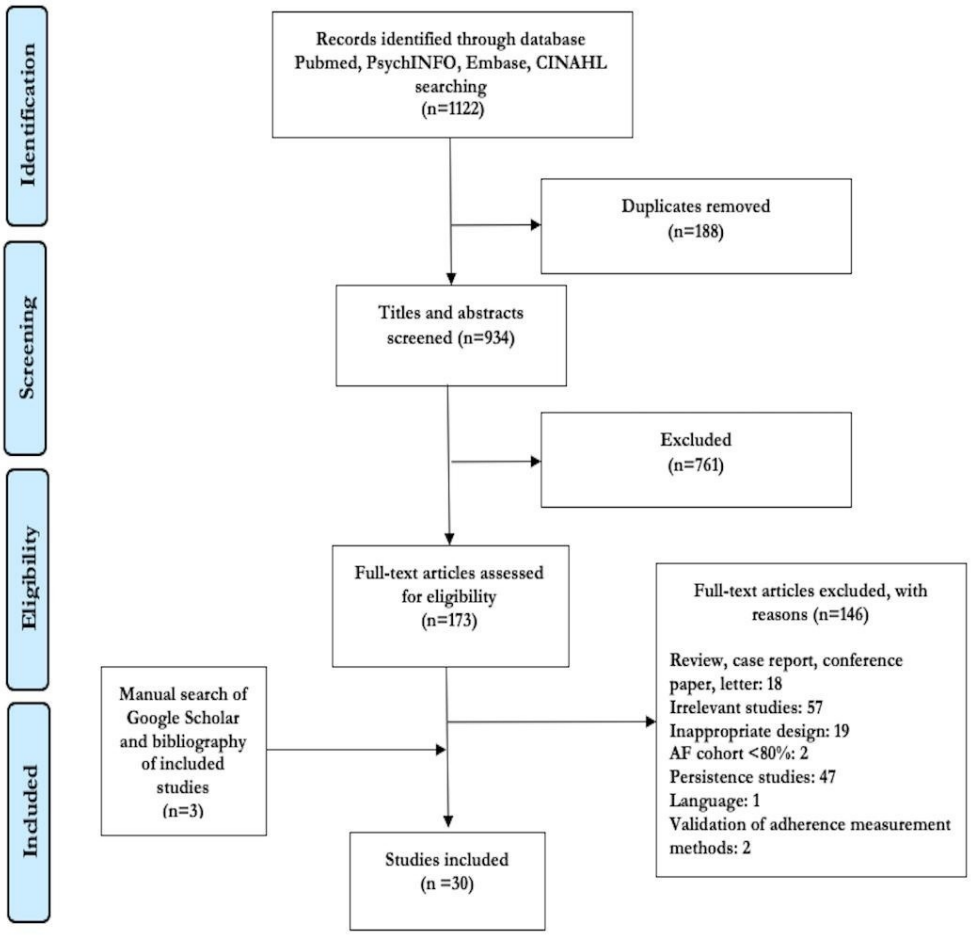


Figure 1.0: PRISMA flow diagram that details the number of studies identified by our search strategy, screened, and included in the final analysis.

90x90mm (300 x 300 DPI)

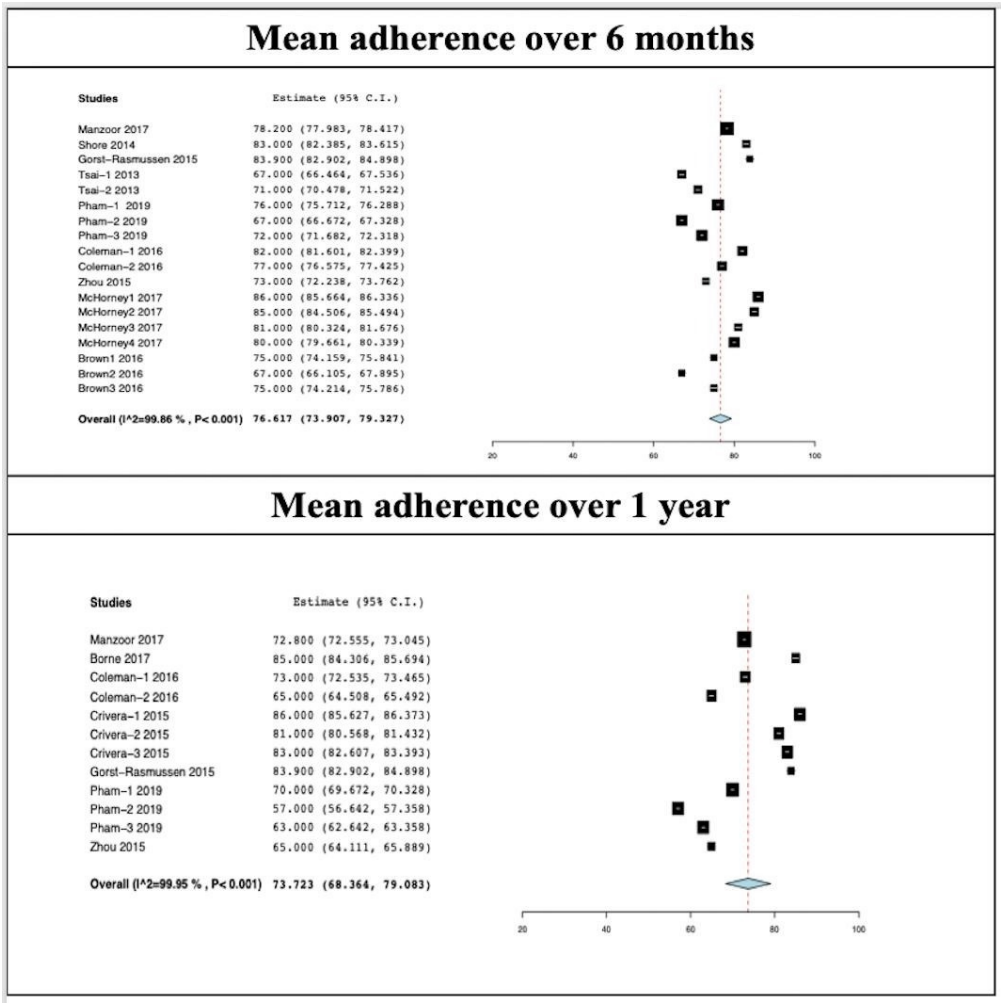


Figure 2.0: Forest plots illustrating patients' mean adherence scores over six-month and one-year post index date. See Supplementary 4 for additional forest plots for each OAC and subgroup analyses.

90x90mm (300 x 300 DPI)

PRISMA 2009 Checklist (Supplementary 1a)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Cover page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Inclusion criteria and study selection 5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Search strategy 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary File 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Inclusion criteria and study selection, Data extraction and synthesis 5, 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Inclusion criteria and study selection, Data extraction and synthesis 5, 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Inclusion criteria and study selection, Data extraction and synthesis 5, 6

PRISMA 2009 Checklist (Supplementary 1a)

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Supplementary File 3, Quality assessment, Data analysis 6, 7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Data analysis 6, 7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Data analysis 6, 7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Supplementary File 3, Quality assessment, Data analysis 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Data analysis 6, 7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results 9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1 31, 32
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary File 3, Quality assessment 7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2 33, 34
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 3,4 37, 37
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary File 4.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 3 36
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion 12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Limitations 14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion, Future directions

PRISMA 2009 Checklist (Supplementary 1a)

			12, 13, 14, 15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding 16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

MOOSE Guidelines (Supplementary 1b)

MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies	
Background	
Problem definition	Introduction 4
Hypothesis statement	NA- The study is mostly descriptive
Description of study outcomes	Introduction, Data extraction and synthesis 4, 6
Type of exposure or intervention used	Introduction, Inclusion criteria and study selection 4, 5
Type of study design used	Inclusion criteria and study selection 5
Study population	Inclusion criteria and study selection 5
Search Strategy	
Qualification of searchers	Search strategy 5
Search strategy including time periods included in the synthesis and keywords	Supplementary File 2, Search strategy 5
Effort to include all available studies, including contact with authors	Inclusion criteria and study selection 5, Authors were not contacted
Databases and registries searched	Search strategy 5
Search software used, name and version, including special features used	NA
Use of hand searching	Search strategy 5
List of citations located and those excluded	Figure 1.0: PRISMA flow chart
Method of addressing articles published in languages other than English	Inclusion criteria and study selection 5
Method of handling abstracts and unpublished studies	Inclusion criteria and study selection 5
Description of any contact with authors	All relevant information for this systematic review could be found in the published reports. There was no need to contact the respective authors
Methods	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Introduction, Supplementary File 3 4

MOOSE Guidelines (Supplementary 1b)

Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Introduction, Inclusion criteria and study selection, Data extraction and synthesis, Data analysis 4, 5, 6, 7
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Inclusion criteria and study selection, Data extraction and synthesis, Data analysis 5, 6, 7
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	NA
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Data analysis. Quality assessment 6, 7
Assessment of heterogeneity	Data analysis 7
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Data analysis 6, 7
Provision of appropriate tables and graphics	Figure 1
Results	
Graphic summarizing individual study estimates and overall estimate	Figures 2 and 3
Table giving descriptive information for each study included	Tables 1 and 2
Results of sensitivity testing (eg, subgroup analysis)	Table 3
Indication of statistical uncertainty of findings	Results 10
Discussion	
Quantitative assessment of bias (eg, publication bias)	Supplementary File 3
Justification for exclusion (eg, exclusion of non–English-language citations)	Inclusion criteria and study selection. Limitations 5, 14
Assessment of quality of included studies	Supplementary File 3, Results, Table 1 9, 31, 32
Conclusion	
Consideration of alternative explanations for observed results	Discussion 12, 13, 14
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Limitations 14
Guidelines for future research	Future directions 15
Disclosure of funding sources	Funding 16

Supplementary file 2: Literature

Concept	Keywords	MeSH terms (Pubmed)
Medications	Anticoagulant* OR "blood thinner" OR "Vitamin K antagonists"OR "new oral anticoagulants" OR VKA OR NOAC OR DOAC OR Apixaban OR Eliquis OR dabigatran OR "dabigatran etexilate" mesylate OR pradaxa OR edoxaban OR lixiana OR rivaroxaban OR xarelto OR warfarin OR coumadin OR betrixaban OR bevyxxa OR acenocoumarol OR phenprocoumon OR fluindione	Warfarin Anticoagulants Dabigatran Rivaroxaban
Adherence	Adherence OR persistence OR compliance "Medication taking" OR "discontinuation" OR "nonpersistence" OR "nonadherence" OR "noncompliance"	Treatment Adherence and Compliance"[Mesh])
Atrial fibrillation	"atrial fibrillation" OR NVAF OR "non-valvular atrial fibrillation"	atrial fibrillation

Complete search example for Pubmed:
(((((((("atrial fibrillation")) OR NVAF) OR "non-valvular atrial fibrillation")) AND (((((((Adherence) OR noncompliance) OR discontinuation) OR nonpersistence) OR nonadherence) OR persistence) OR "Medication taking") OR compliance)) AND ((((((((((((((((((((((((Anticoagulant*) OR "blood thinner") OR "Vitamin K antagonists") OR "new oral anticoagulants") OR VKA) OR NOAC) OR DOAC) OR Apixaban) OR Eliquis) OR dabigatran) OR "dabigatran etexilate") OR "dabigtaran mesylate") OR pradaxa) OR edoxaban) OR lixiana) OR rivaroxaban) OR xarelto) OR warfarin) OR coumadin) OR betrixaban) OR bevyxxa) OR acenocoumarol) OR phenprocoumon) OR fluindione))) AND "Atrial Fibrillation"[Mesh]) AND (("Treatment Adherence and Compliance"[Mesh]) OR ("Warfarin"[Mesh] OR "Anticoagulants"[Mesh] OR "Dabigatran"[Mesh] OR "Rivaroxaban"[Mesh]))):

STROBE	CODE	Alberts 2016	Beyer - Westendorf 2016	Borne 2017	Brown 2016	Casciano 2013	Coleman 2016	Coleman 2017	Civera 2015	Deshpande 2018 PMID: 29694285	Deshpande 2018 PMID: 29334815	Eapen 2014	Forsuland 2016	Gomez-Lumberas 2018	Gorst - Rasmussen 2015	Harper 2018	Jacobs 2018	Manzoor 2017	Marquez 2016	Maura 2017	McAlister 2018	McCormick 2001	McHorney 2017	McHorney 2018	Mueller 2017	Pham 2019	Shore 2014	Sorensen 2017	Tsai 2013	Yao 2016	Zhou 2015
Title and abstract																															
Indicate the study's design with a commonly used term in the title or the abstract	1a	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0
Provide in the abstract an informative and balanced summary of what was done and what was found.	1b	0	1	1	1	1	0	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Background/rationale: Explain the scientific background and rationale for the investigation being reported	2	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1
Objective: State specific objectives, including any prespecified hypothesis.	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Study design: Present key elements of study design early in the paper	4	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Setting: Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	5	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1
Participants: Give the eligibility criteria, and the sources and methods of selection of participants	6a	1	1	1	1	0	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1
For matched studies, give matching criteria and number of exposed and unexposed	6b	1	NA	NA	NA	NA	1	1	NA	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	NA	NA	NA	NA	NA	1	NA
Variables: Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	7	0	1	0	1	0	0	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
Data sources/measurement: For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one grou	8	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Bias: Describe any efforts to address potential sources of bias (e.g. Propensity scores)	9	1	0	0	0	0	1	1	0	1	1	0	0	0	0	0	1	1	1	1	0	1	1	1	0	1	1	0	0	0	0
Study size: Explain how the study size was arrived at.	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Quantitative variables/ statistical analysis:																															
Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why. (categorizing)	11	0	1	1	1	1	0	0	0	0	0	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1
Describe all statistical methods, including those used to control for confounding	12a	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1
Describe any methods used to examine subgroups and interactions	12b	1	0	1	1	0	0	1	1	1	1	1	0	0	1	0	1	1	0	1	1	0	1	1	0	0	1	0	1	1	1
Explain how missing data were addressed	12c	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0	0	0	0
Cohort study: If applicable, describe how loss to follow-up was addressed.	12d	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Describe any sensitivity analyses	12e	0	1	1	0	0	0	0	0	0	0	0	1	0	1	0	1	1	0	1	1	0	1	1	0	0	1	1	0	1	1
Participants:																															
Report the numbers of individuals at each stage of the study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed.	13a	0	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	0	0	1	1	0	1	1	1	1	1	1	0	0	1
Give reasons for non-participation at each stage	13b	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Consider use of a flow diagram	13c	0	1	1	1	1	0	1	1	1	1	1	1	0	1	0	0	0	0	1	1	0	1	1	1	1	1	1	0	0	1
Descriptive data:																															
Give characteristics of study participants (e.g. demographic, clinical, social) and	14a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

information on exposures and potential confounders																														
Indicate the number of participants with missing data for each variable of interest.	**14b**	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0
Summarise follow-up time (eg, average and total amount)	**14c**	1	1	1	0	1	1	1	1	0	1	1	0		0	0	1	0	1	1	0	0	1	0	1	0	1	0	0	1	0
Outcome data: Report numbers of outcome events or summary measures over time	**15**	0	1	0	1	0	1	0	0	1	1	1	0	0	0	0	0	1	0	0	1	0	1	1	1	1	1	0	0	1	1
Main results																															
Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**16a**	1	0	0	1	0	0	0	1	1	1	1	0	0	1	0	1	0	1	NA	1	1	1	1	0	0	1	1	0	1	1
Report category boundaries when continuous variables were categorized.	**16b**	1	1	1	1	1	1	1	1	1	1	NA	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**16c**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Other analysis: Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses.	**17**	1	1	1	1	1	0	1	1	1	1	1	0	1	0	1	1	0	1	1	0	1	1	1	1	1	0	1	1	1	1
Key results: Summarize key results with reference to study objectives.	**18**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Limitations: Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	**19**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Interpretation: Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**20**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Generalizability: Discuss the generalizability (external validity) of the study results	**21**	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1
Funding: Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**22**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1		1	1	1	1
Sum		19	22	22	23	19	17	24	22	23	25	22	19	15	24	14	24	21	20	23	26	18	26	26	21	23	27	20	18	24	24
Total applicable		31	30	30	30	30	31	31	30	30	31	29	30	30	30	30	30	30	32	29	30	30	30	31	30	30	30	30	30	31	30
Score		0.612903	0.733333	0.73333	0.766667	0.633333	0.548387	0.774193	0.733333	0.766667	0.806451	0.75862	0.633333	0.5	0.8	0.466667	0.8	0.7	0.625	0.793103	0.866667	0.6	0.866667	0.838709	0.7	0.766667	0.9	0.666667	0.6	0.774193	0.8
Percent		61	73	73	77	63	55	77	73	77	81	76	63	50	80	47	80	70	63	79	87	60	87	84	70	77	90	67	60	77	80

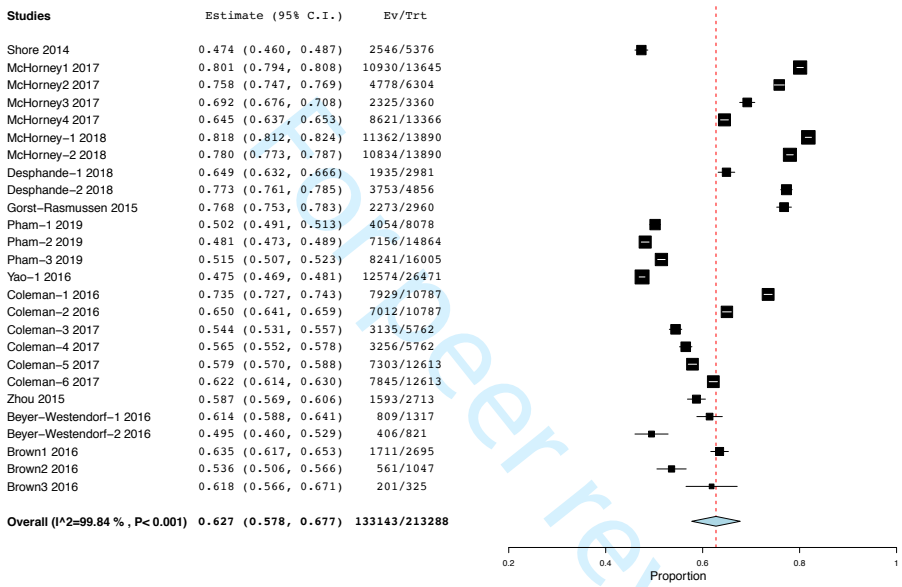
Item No	ISPOR	Alberts 2016	Beyer-Westendorf 2016	Borne 2017	Brown 2016	Cascia no 2013	Coleman 2016	Coleman 2017	Civera 2015	Deshpande 2018 PMID: 29694285	Deshpande 2018 PMID: 29334815	Eapen 2014	Forsuland 2016	Gomez-Lumberas 2018	Gorst-Rassussen 2015	Harper 2018	Jacobs 2018	Manzoor 2017	Marquez 2006	Maura 2017	McAlister 2018	McCormick 2001	McHorney 2017	McHorney 2018	Mueller 2017	Pharm 2019	Shore 2014	Sorenson 2017	Tsai 2013	Yao 2016	Zhou 2015
	Title / Abstract																														
1	Title is descriptive and reflective of study purpose	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	1	1	0	1	1	0	0	1	0	0	0	0
2	Abstract is a concise and accurate, reflecting contents of the study	0	1	1	1	1	0	1	0	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Introduction																														
	Clear review of fundamental literature related to topic	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Objectives and Definitions																														
	Objective(s) stated?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Design and Methods																														
	Study design appropriate for objectives	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Data sources adequately described	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1
	Evidence provided for reliability / accuracy of data	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0
	Sampling methods described	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Well describe patient population and Subject inclusion / exclusion criteria stated	1	1	1	1	0	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1
	Sufficient data to make valid estimate of compliance (i.e. Continuous eligibility for drug during study period verified)	0	1	1	1	1	1	1	0	1	1	1	0	1	1	0	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1
	Sufficient pre-enrollment period to ensure drug naivety? (If applicable)	NA	1	NA	1	1	NA	1	NA	NA	NA	1	NA	NA	NA	0	NA	1	NA	1	1	NA	1	1	0	1	NA	1	NA	1	1
	Explanation of how patients who switched drugs within or between therapeutic classes were handled	0	0	0	1	0	0	1	1	0	0	0	1	0	1	0	1	1	0	1	NA	NA	0	1	0	1	1	0	1	1	1
	Explicit definition of compliance/persistence based on published, accepted definition?	1	1	1	1	1	0	1	0	1	1	1	0	1	1	0	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1
	Methods for calculating compliance / persistence clearly described (and matches operational definition)	1	1	1	0	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1
	Was handling of medication gaps described	0	0	0	1	1	0	0	0	1	1	0	0	0	1	1	0	0	1	1	1	0	0	1	0	1	1	0	0	0	0
	Follow-up period specified	1	1	1	1	1	1	1	0	1	1	1	0	0	1	0	0	1	1	1	1	1	1	1	1	0	1	1	1	1	0
	Statistics appropriate to design and data	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Test statistics are reported appropriately (i.e. CIs, p-values reported)	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1
	Appropriate descriptive data on study sample are presented	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Distribution of compliance/persistence variable is presented (i.e. proportion of discontinuers)	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1
	Sum	12	14	14	16	15	9	16	11	15	15	14	11	12	18	10	15	17	15	19	17	14	17	19	10	17	17	15	14	16	15
	Total Applicable	18	19	18	19	19	18	19	18	18	18	19	18	18	18	19	18	20	18	19	18	17	19	19	19	19	18	19	18	19	19
	Score	0.666667	0.736842	0.777778	0.842105	0.789473	0.5	0.842105	0.611111	0.833333	0.833333	0.736842	0.611111	0.666667	1	0.5263	0.833	0.85	0.833333	1	0.944444	0.823529	0.894736	1	0.526315	0.895	0.944	0.789473	0.778	0.842	0.789
	Percent	67	74	78	84	79	50	84	61	83	83	74	61	67	100	53	83	85	83	100	94	82	89	100	53	89	94	79	78	84	79

Supplementary 4.0: Forest plots

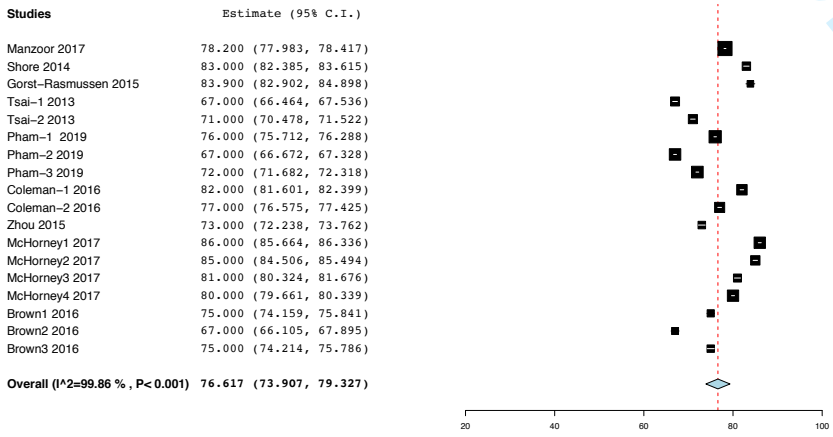
All OACs

Adherence at 6 months

Proportion adherent at 6 months

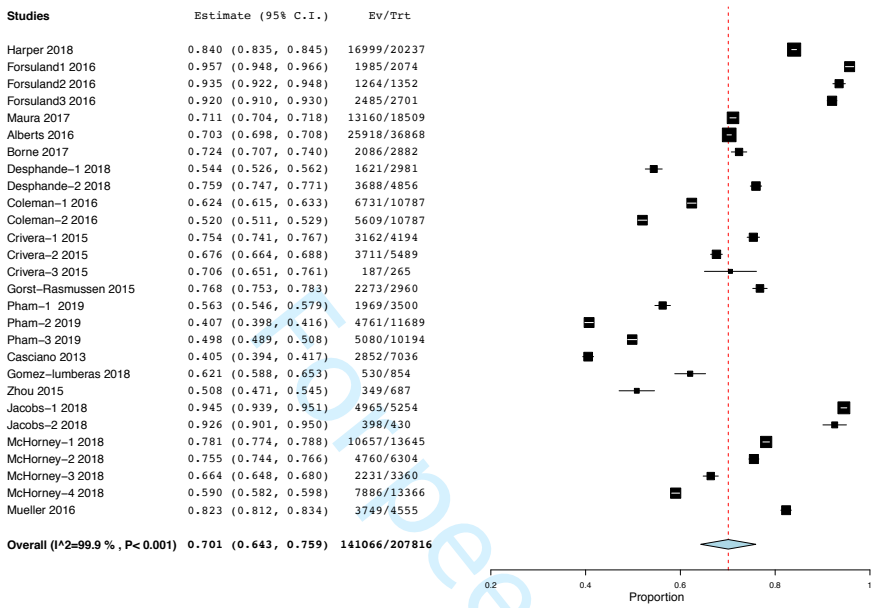


Mean adherence score at 6 months

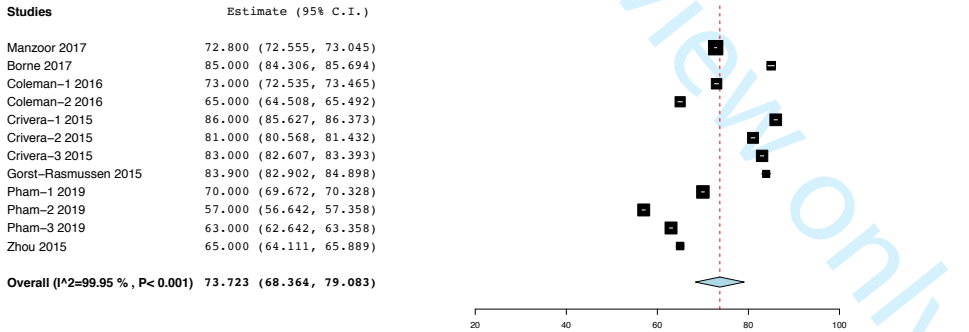


Adherence at 1 year

Proportion adherent at 1 year



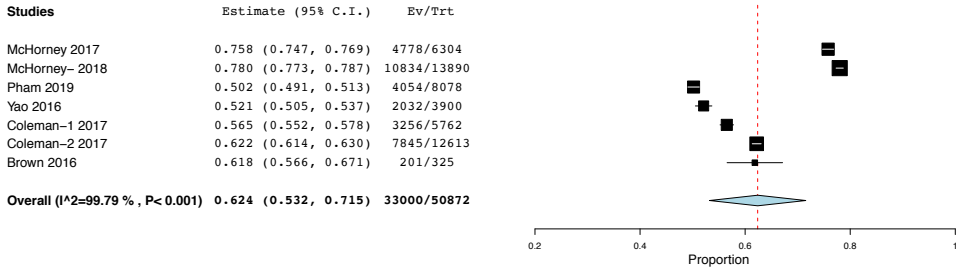
Mean adherence at 1 year



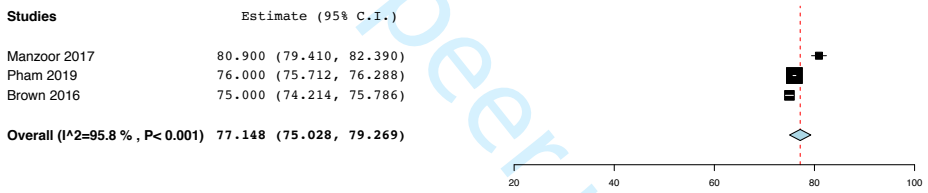
Apixaban

Adherence at 6 months

Proportion adherent at 6 months

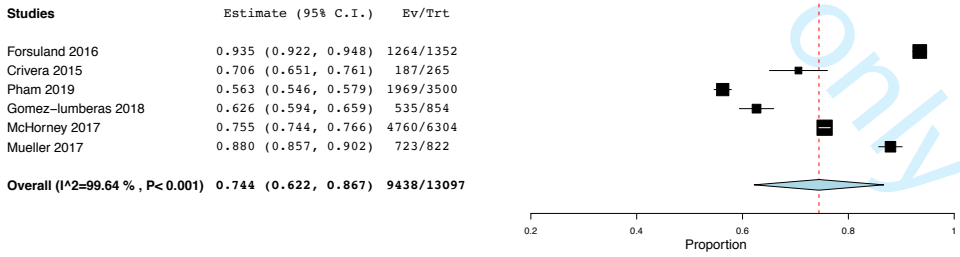


Mean adherence at 6 months

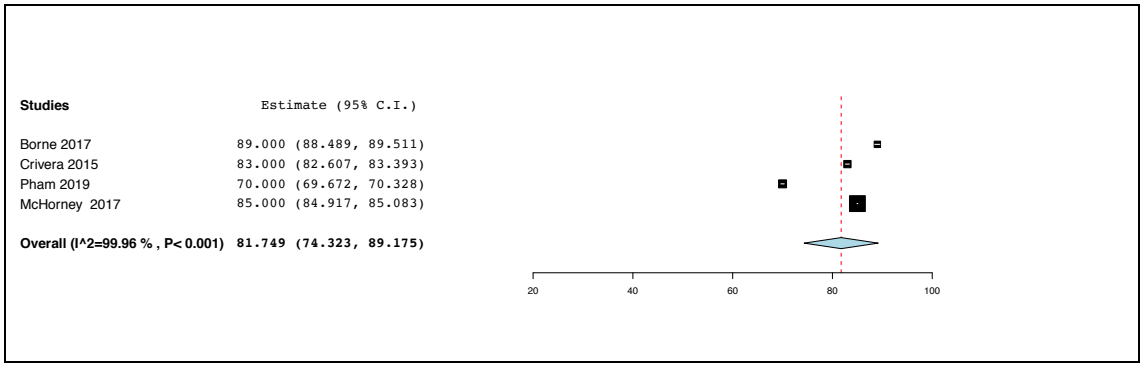


Adherence at 1 year

Proportion adherent at 1 year



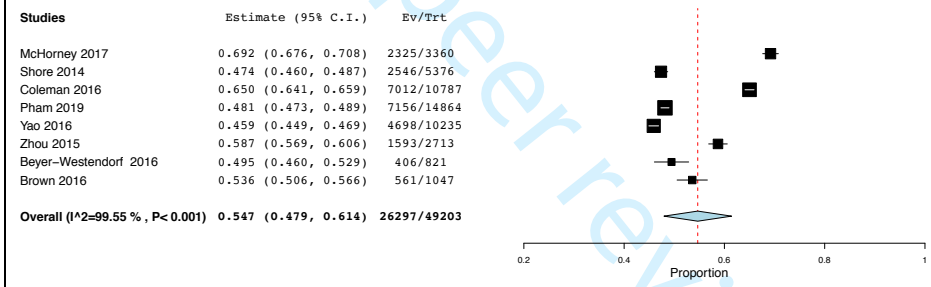
Mean adherence at 1 year



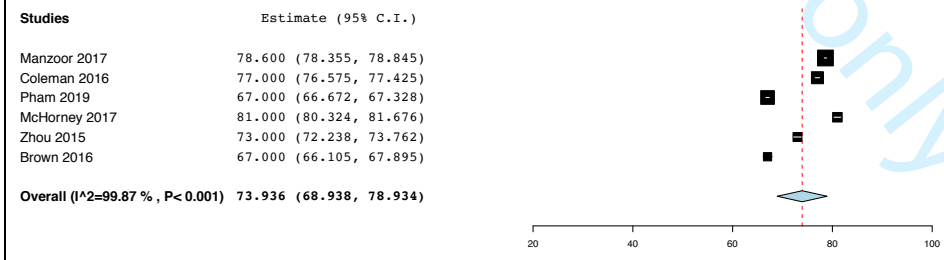
Dabigatran:

Adherence at 6 months

Proportion adherent at 6 months

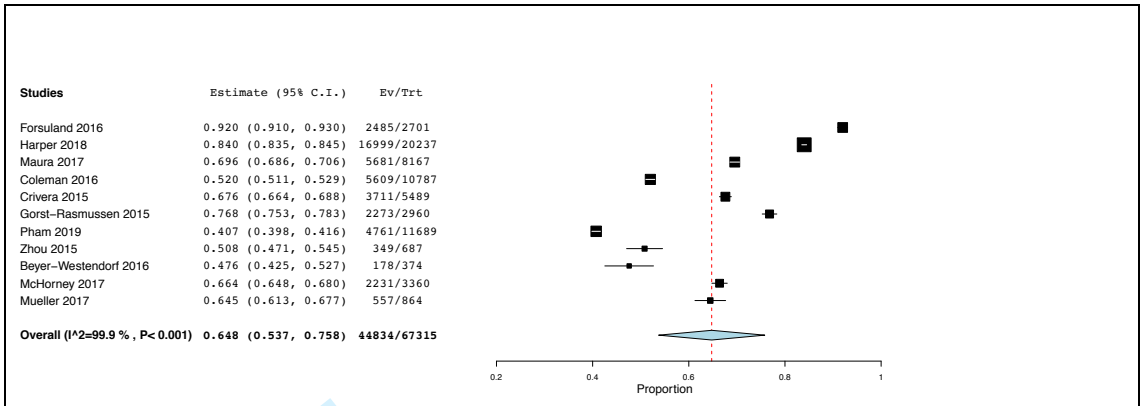


Mean adherence at 6 months

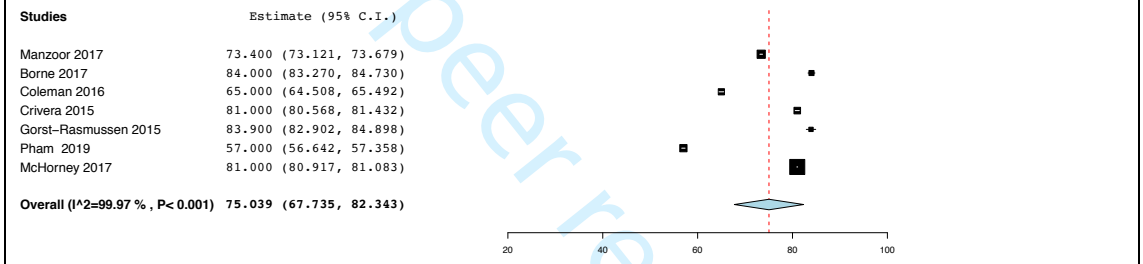


Adherence at 1 year

Proportion adherent at 1 year



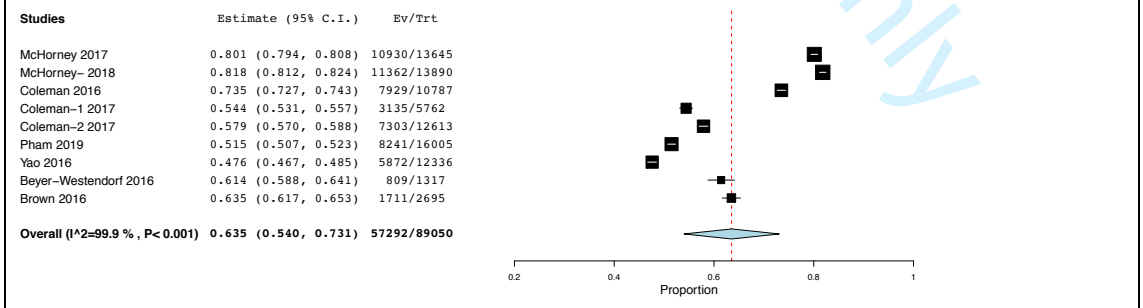
Mean adherence at one year



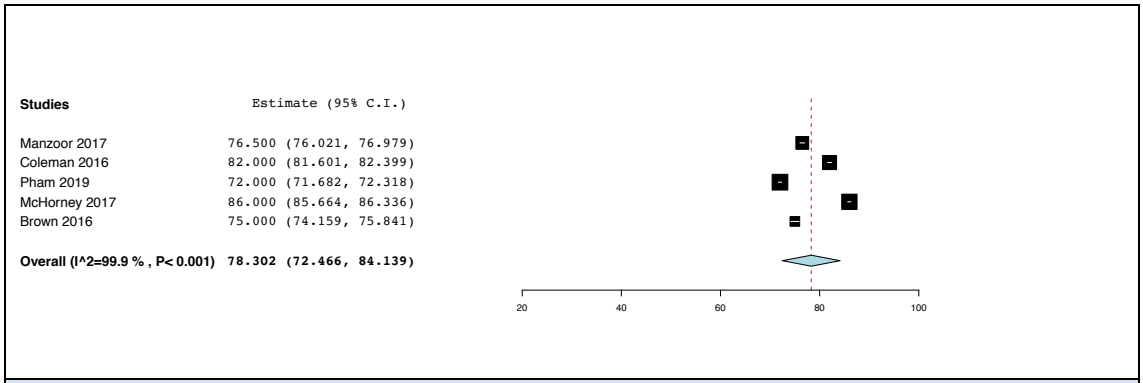
Rivaroxaban:

Adherence at 6 months

Proportion adherent at 6 months

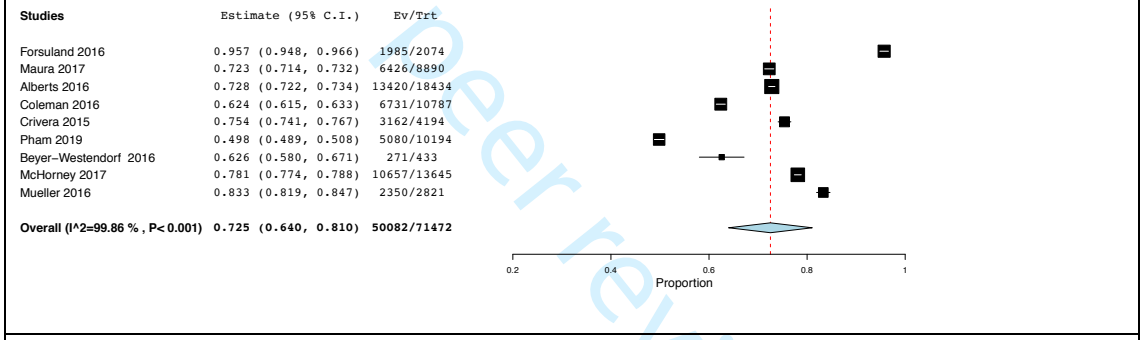


Mean adherence at 6 months

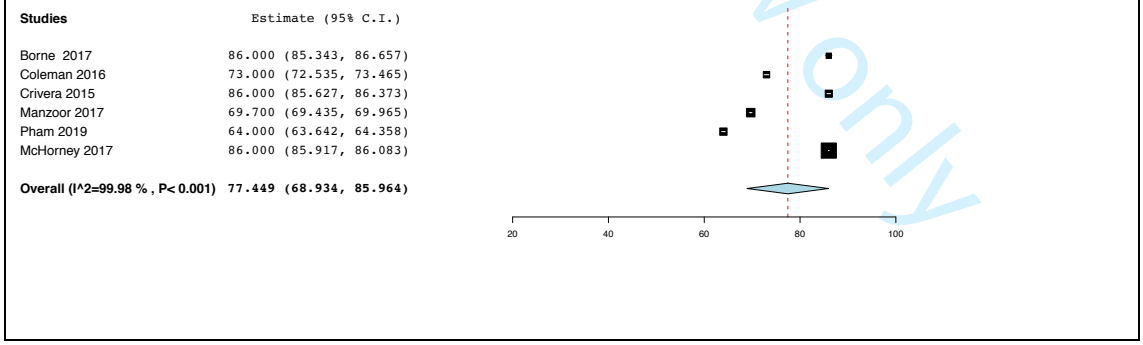


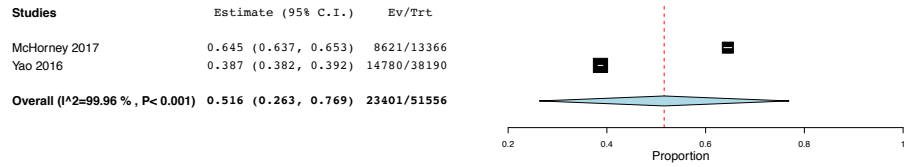
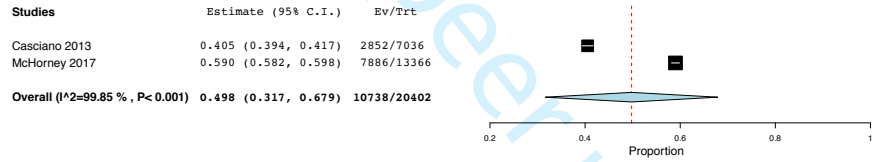
Adherence at 1 year

Proportion adherent at 1 year



Mean adherence at 1 year



Warfarin:
Adherence at 6 months
Proportion adherent at 6 months

Mean adherence at 6 months
NA
Adherence at 1 year
Proportion adherent at 1 year

Mean adherence at 1 year
NA

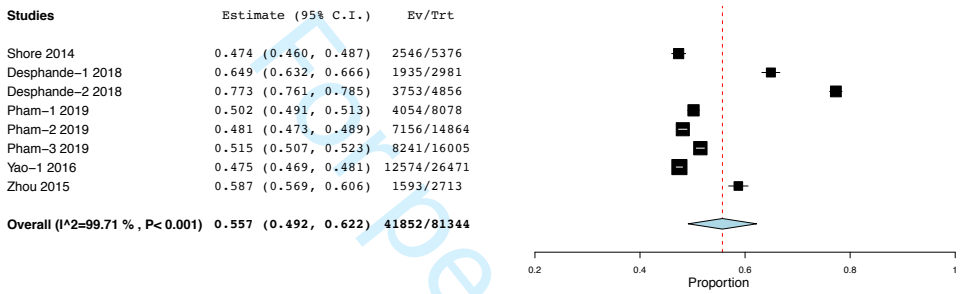
Supplementary 4.1: Sub-group analysis

Supplementary 4.1.1: Sub-group analysis by excluding studies with conflict of interest:

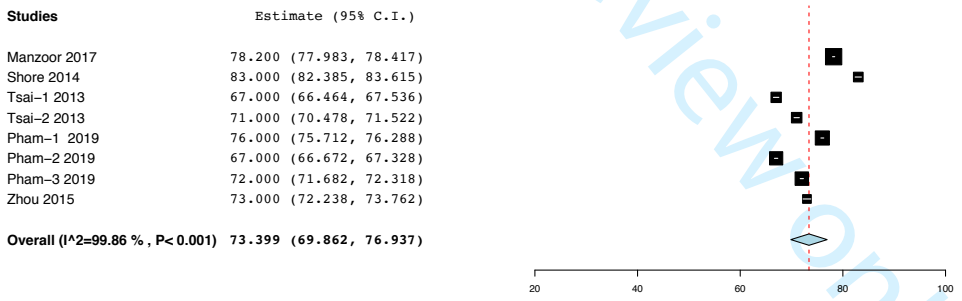
All OACs: Sub-analysis: Excluding studies with conflict of interest

Adherence at 6 months

Proportion adherent at 6 months

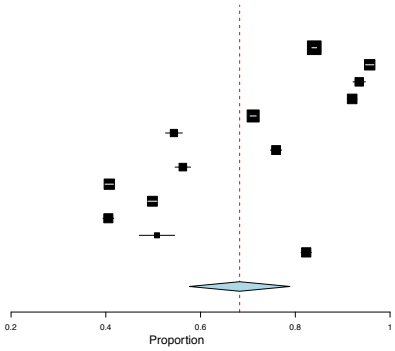


Mean adherence at 6 months

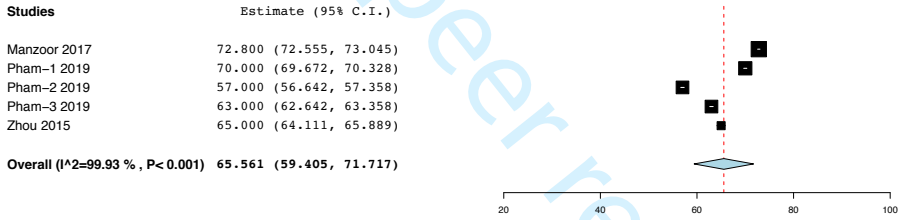


Adherence at 1 year

Proportion adherent at 1 year



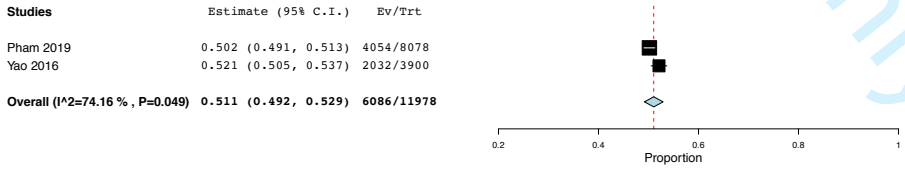
Mean adherence at 1 year



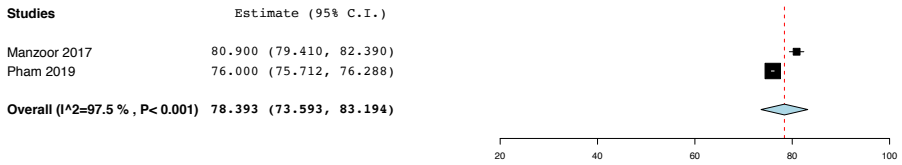
Apixaban: Sub-analysis: Excluding studies with conflict of interest

Adherence at 6 months

Proportion adherent at 6 months

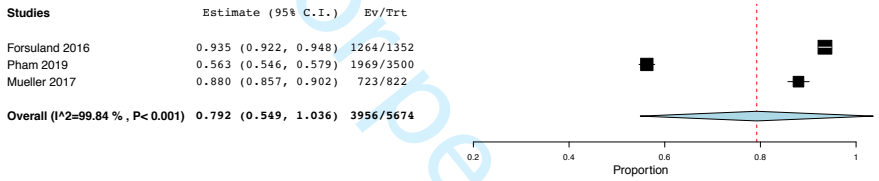


Mean adherence at 1 year



Adherence at 1 year:

Proportion adherent at 1 year



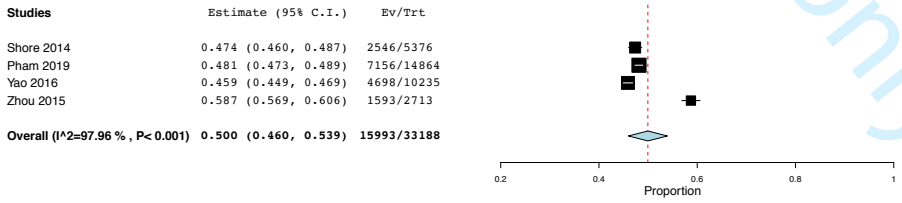
Mean adherence at 1 year

NA (one study)

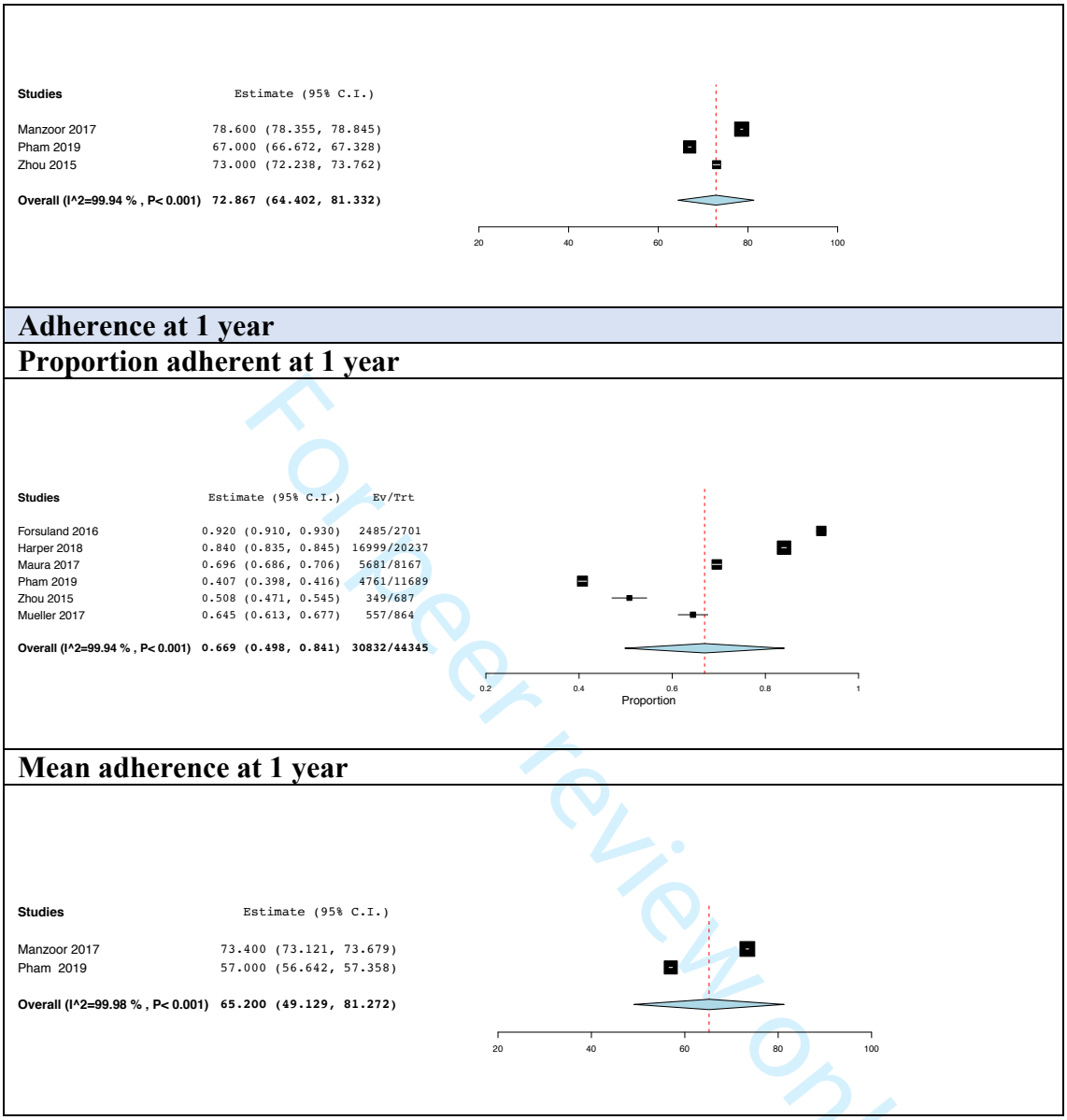
Dabigatran: Sub-analysis: Excluding studies with conflict of interest

Adherence at 6 months

Proportion adherent at 6 months



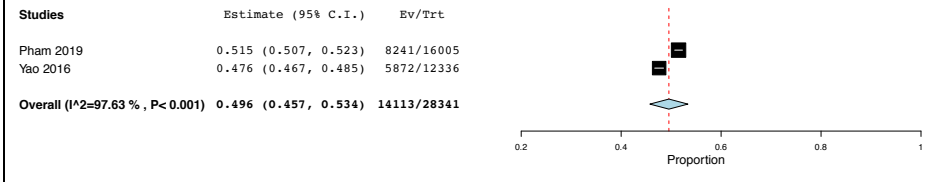
Mean adherence at 6 months



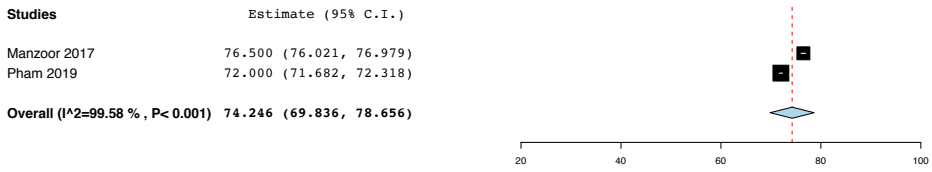
Rivaroxaban: Sub-analysis: Excluding studies with conflict of interest

Adherence at 6 months

Proportion adherent at 6 months

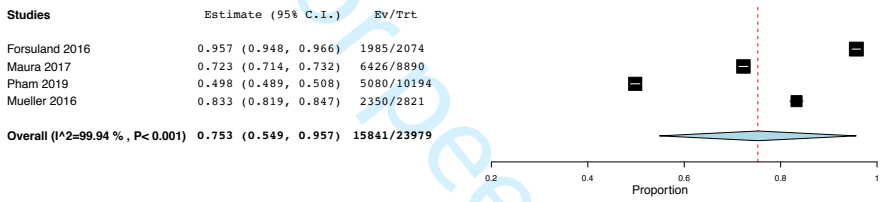


Mean adherence at 6 months

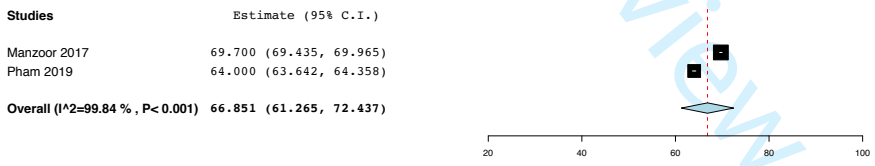


Adherence at 1 year

Proportion adherent at 1 year



Mean adherence at 1 year

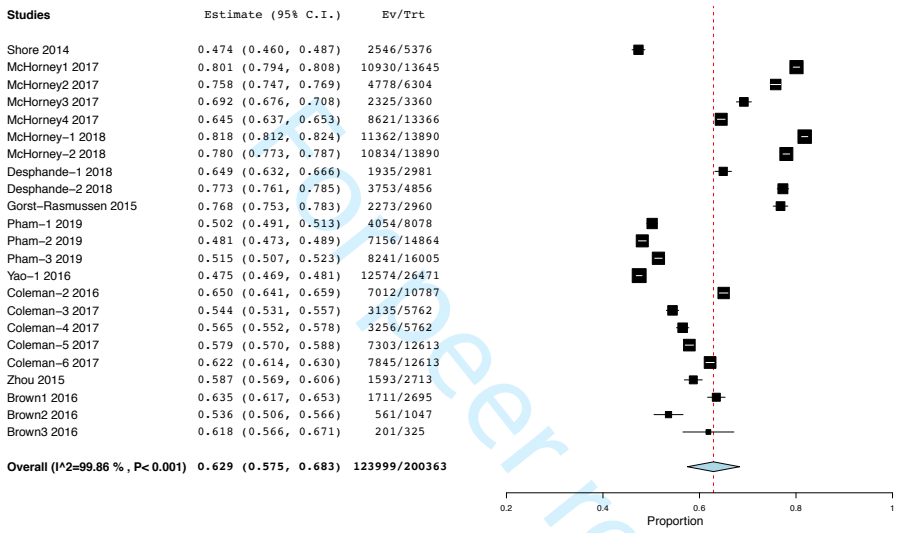


Supplementary 4.1.2: Sub-group analysis by excluding low and medium quality studies.

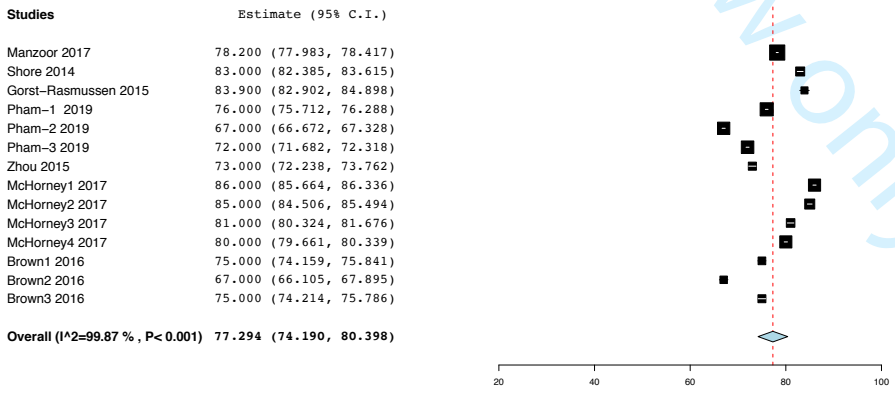
All OAC: Sub-analysis: Excluding low and medium quality studies

Adherence at 6 months

Proportion adherent at 6 months

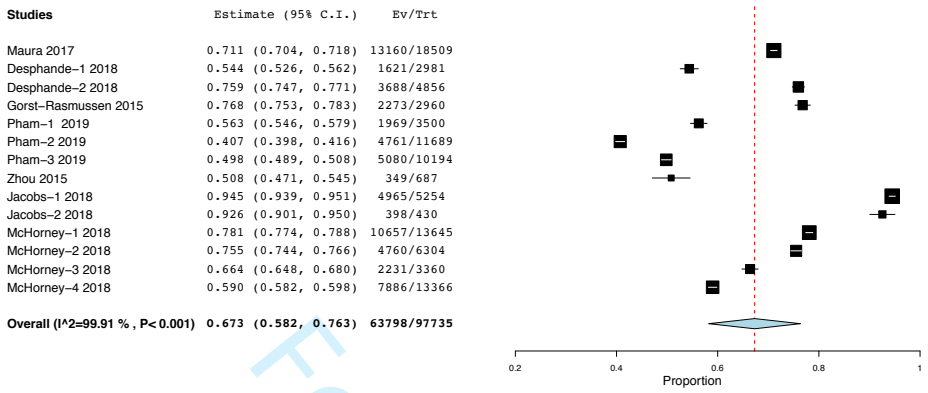


Mean adherence at 6 months

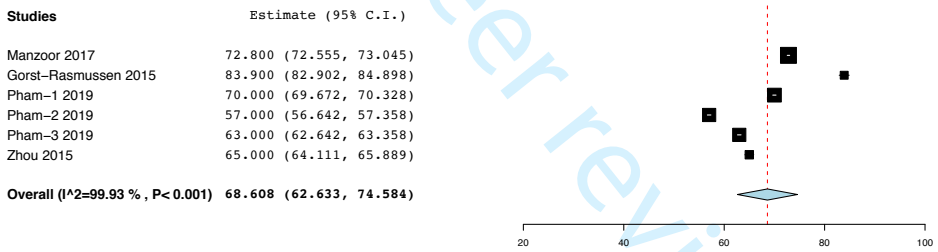


Adherence at 1 year

Proportion adherent at 1 year



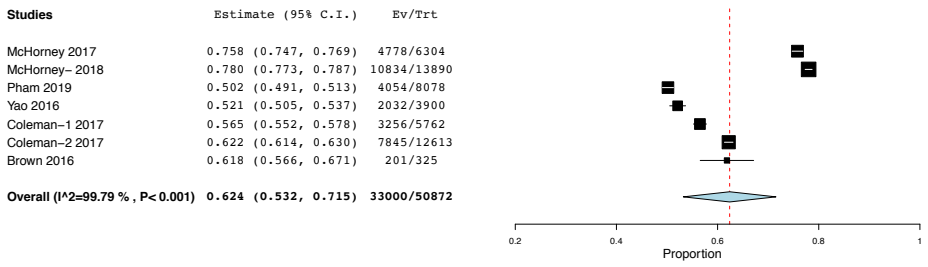
Mean adherence at 1 year



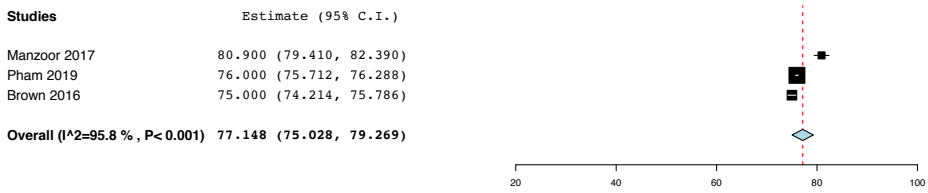
Apixaban: Sub-analysis: Excluding low and medium quality studies

Adherence at 6 months

Proportion adherent at 6 months

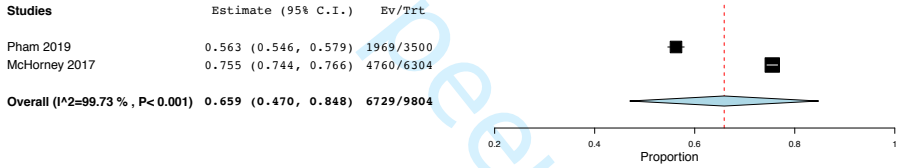


Mean adherence at 6 months

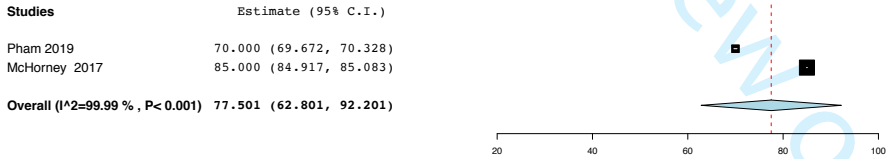


Adherence at 1 year

Proportion adherent at 1 year



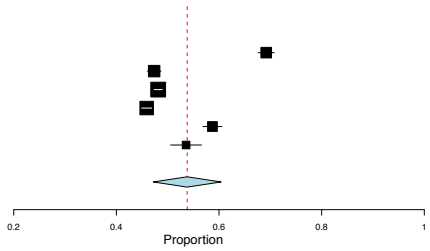
Mean adherence at 1 year



Dabigatran: Sub-analysis: Excluding low and medium quality studies

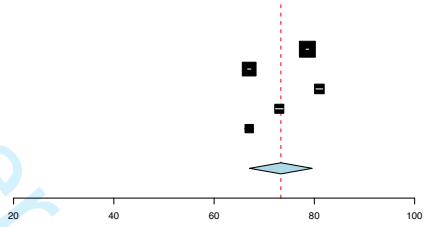
Adherence at 6 months

Proportion adherent at 6 months



Studies	Estimate (95% C.I.)	Ev/Trt
McHorney 2017	0.692 (0.676, 0.708)	2325/3360
Shore 2014	0.474 (0.460, 0.487)	2546/5376
Pham 2019	0.481 (0.473, 0.489)	7156/14864
Yao 2016	0.459 (0.449, 0.469)	4698/10235
Zhou 2015	0.587 (0.569, 0.606)	1593/2713
brown 2016	0.536 (0.506, 0.566)	561/1047
Overall (I^2=99.35 % , P< 0.001)	**0.538 (0.472, 0.604)**	**18879/37595**

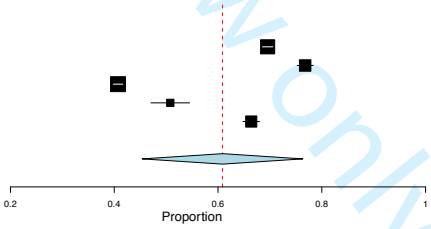
Mean adherence at 1 year



Studies	Estimate (95% C.I.)
Manzoor 2017	78.600 (78.355, 78.845)
Pham 2019	67.000 (66.672, 67.328)
McHorney 2017	81.000 (80.324, 81.676)
Zhou 2015	73.000 (72.238, 73.762)
Brown 2016	67.000 (66.105, 67.895)
Overall (I^2=99.89 % , P< 0.001)	**73.322 (67.076, 79.568)**

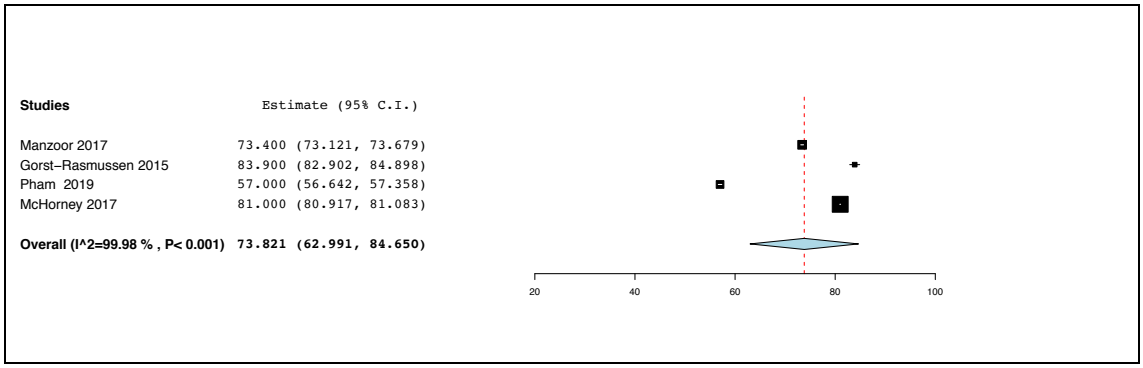
Adherence at 1 year

Proportion adherent at 1 year



Studies	Estimate (95% C.I.)	Ev/Trt
Maura 2017	0.696 (0.686, 0.706)	5681/8167
Gorst–Rasmussen 2015	0.768 (0.753, 0.783)	2273/2960
Pham 2019	0.407 (0.398, 0.416)	4761/11689
Zhou 2015	0.508 (0.471, 0.545)	349/687
McHorney 2017	0.664 (0.648, 0.680)	2231/3360
Overall (I^2=99.85 % , P< 0.001)	**0.609 (0.454, 0.764)**	**15295/26863**

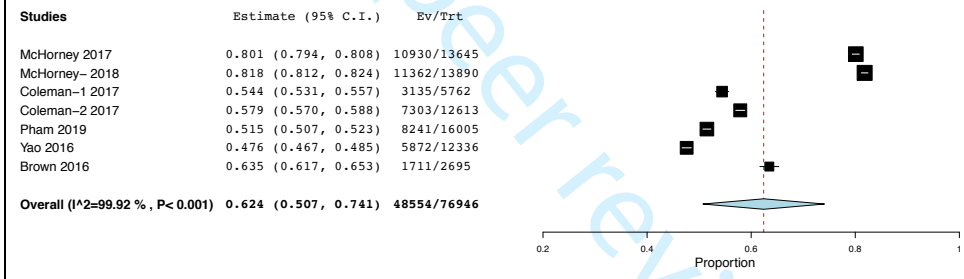
Mean adherence at 1 year



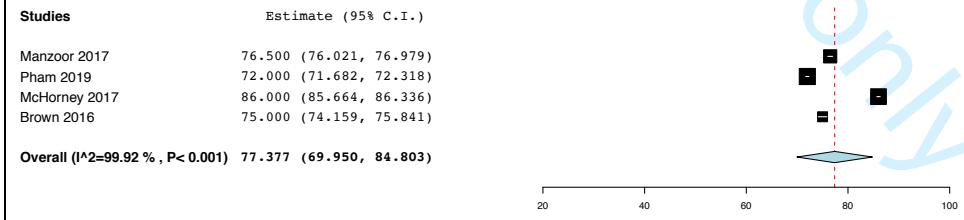
Rivaroxaban: Sub-analysis: Excluding low and medium quality studies

Adherence at 6 months

Proportion adherent at 6 months

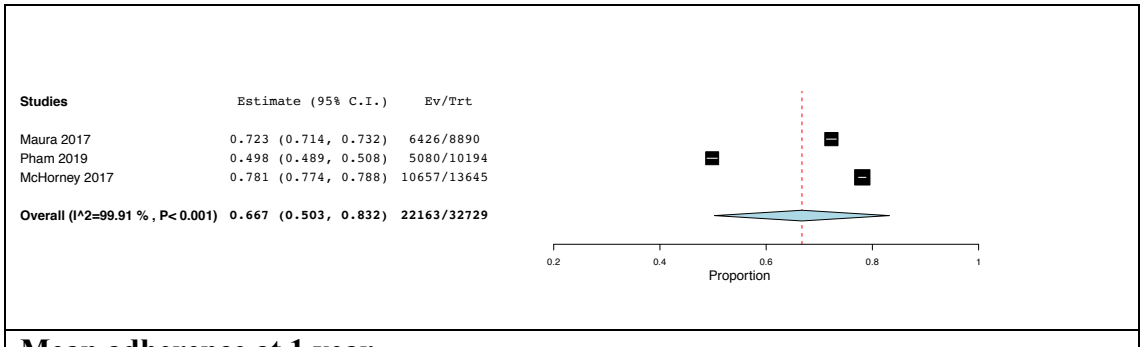


Mean adherence at 1 year

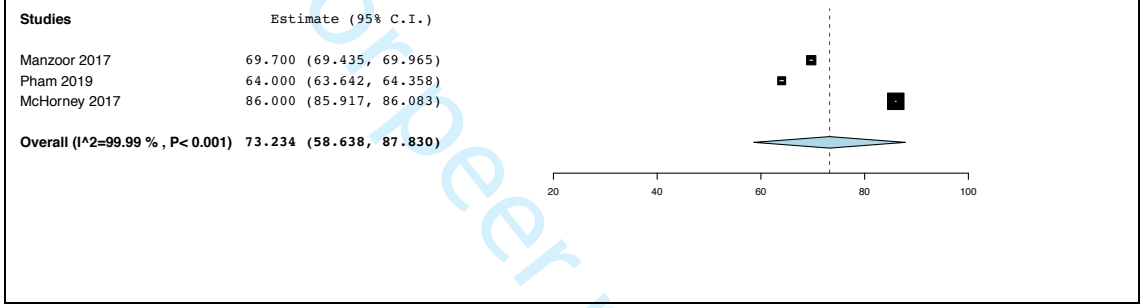


Adherence at 1 year

Proportion adherent at 1 year



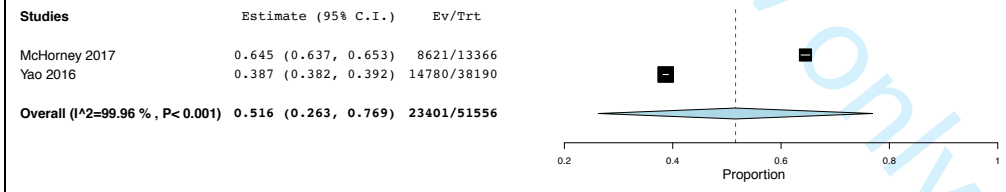
Mean adherence at 1 year



Warfarin: Sub-analysis: Excluding low and medium quality studies

Adherence at 6 months

Proportion adherent at 6 months



Mean adherence at 6 months

NA

Adherence at 1 year

Proportion adherent at 1 year

NA

Mean adherence at 1 year

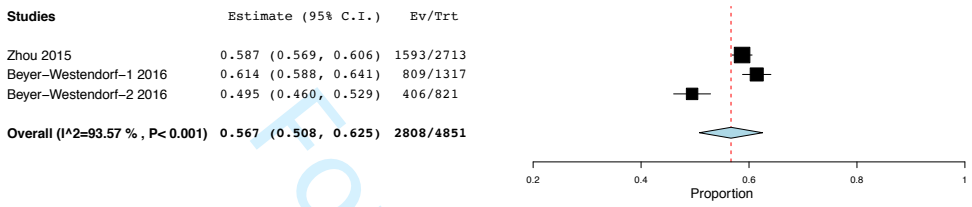
NA

Supplementary 4.1.3: Sub-group analysis by adherence measure

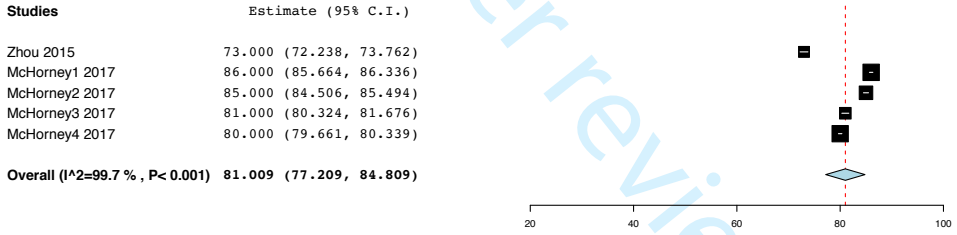
All OACs: Sub-analysis: stratified by adherence measure

Adherence at 6 months

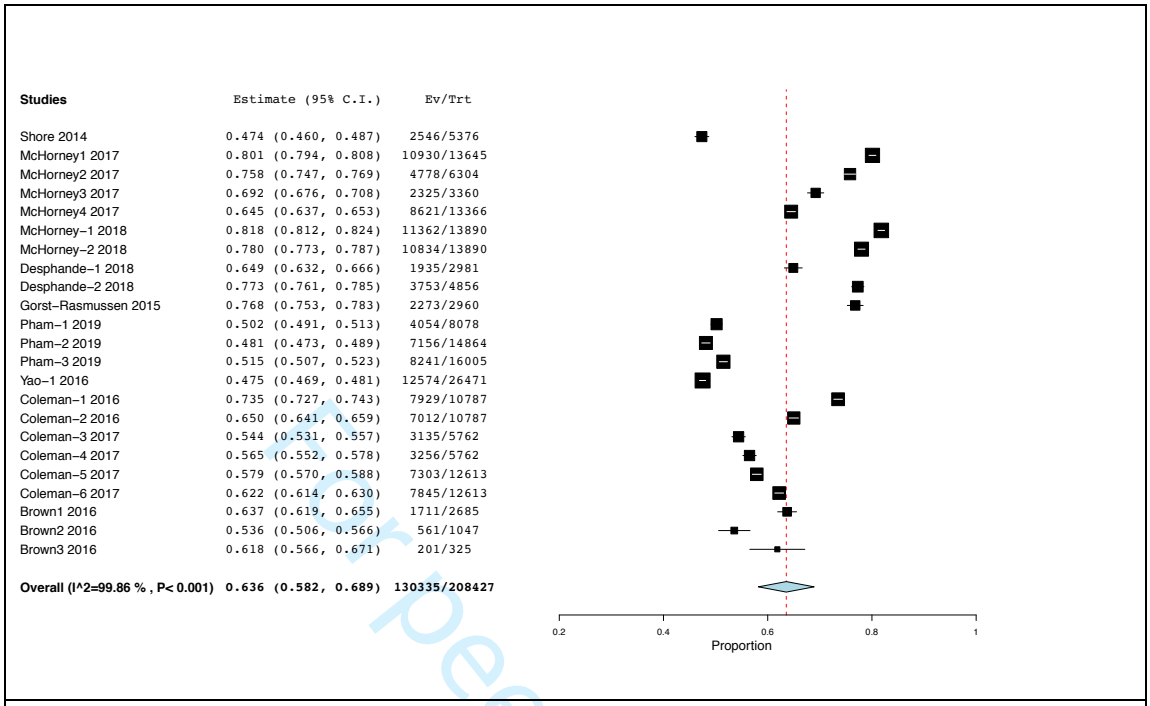
MPR: proportion adherent at 6 months



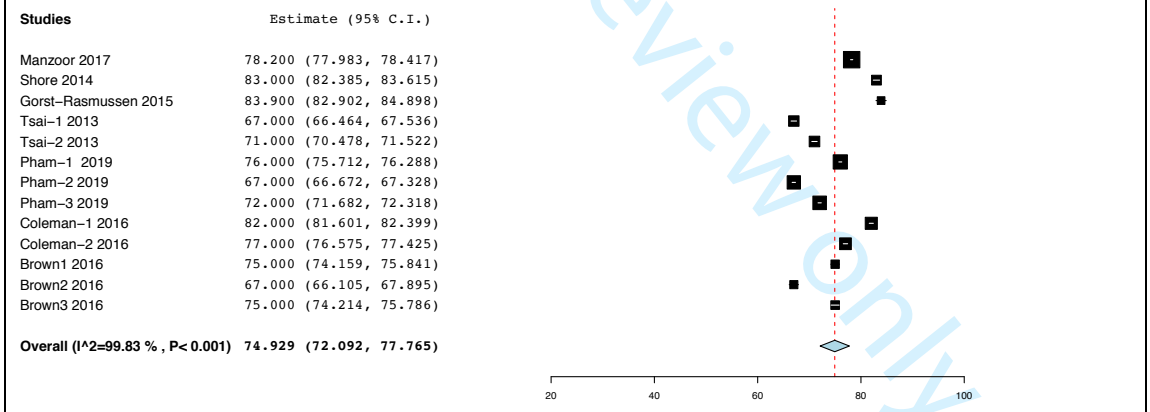
MPR: Mean (SD) adherence at 6 months



PDC: proportion adherent at 6 months

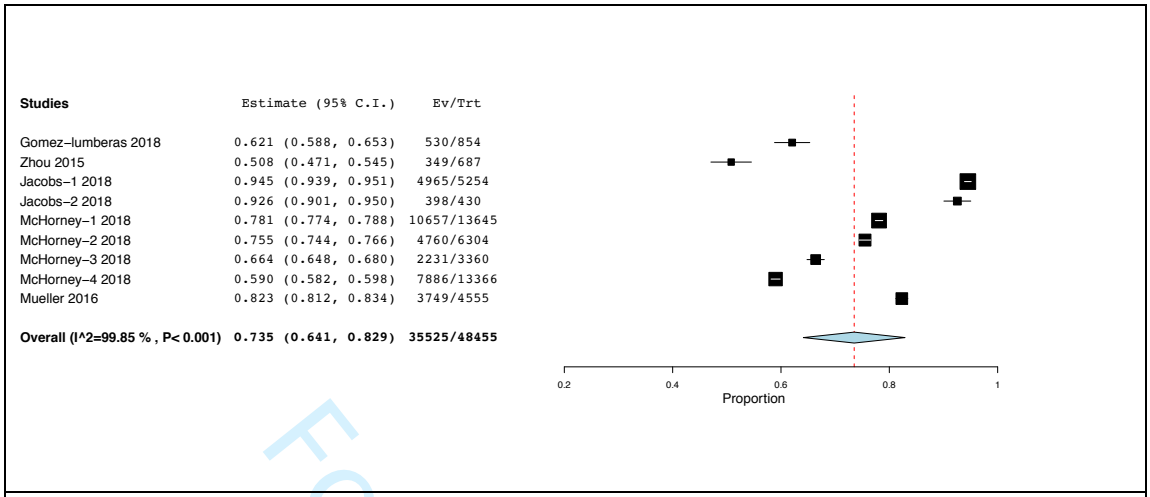


PDC: Mean (SD) adherence at 6 months



Adherence at 1 year

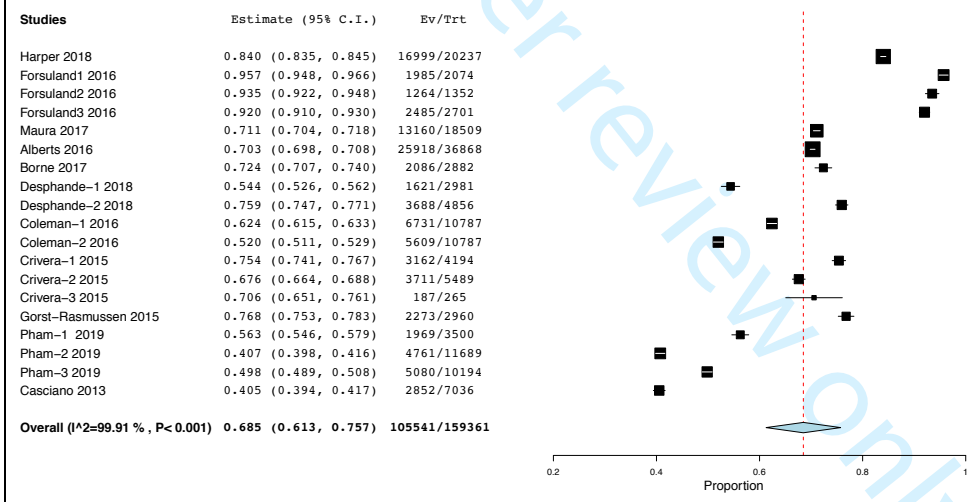
MPR: proportion adherent at 1 year



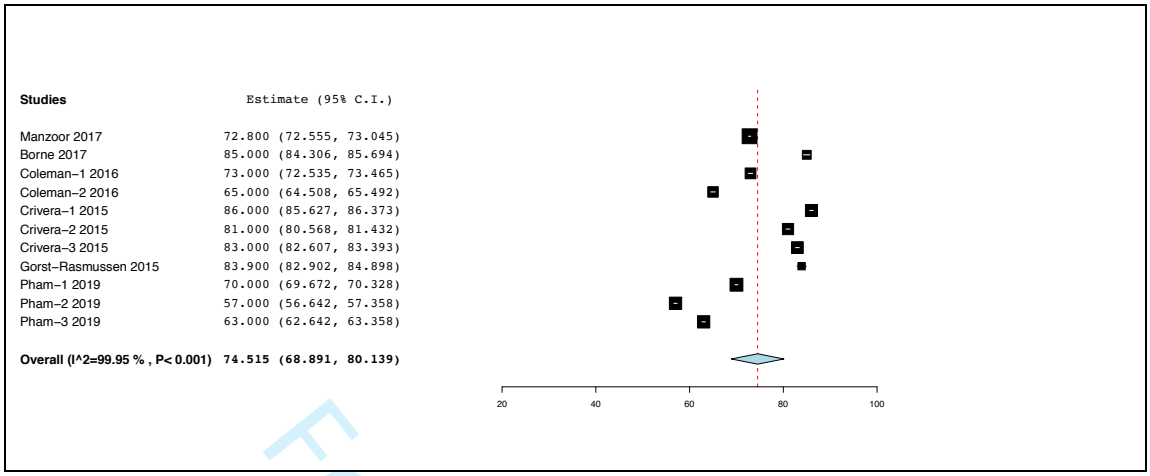
MPR: Mean (SD) adherence at 1 year

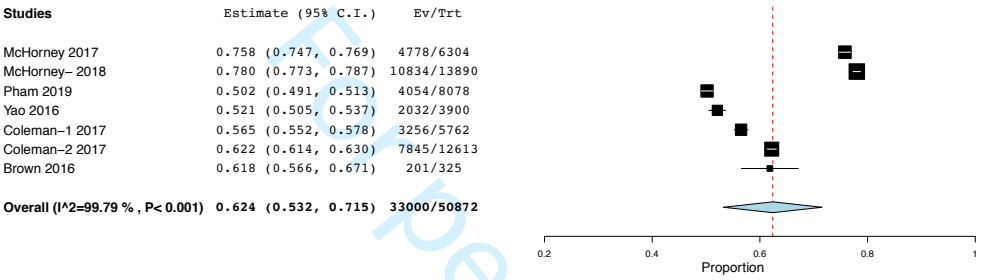
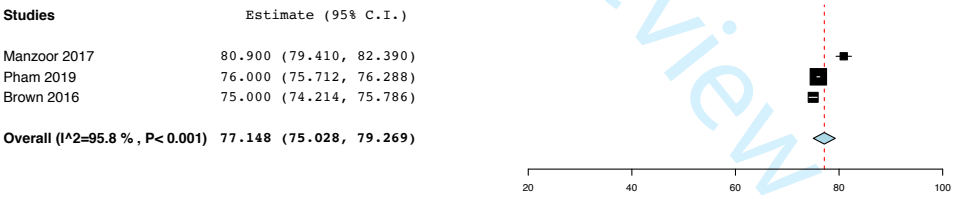
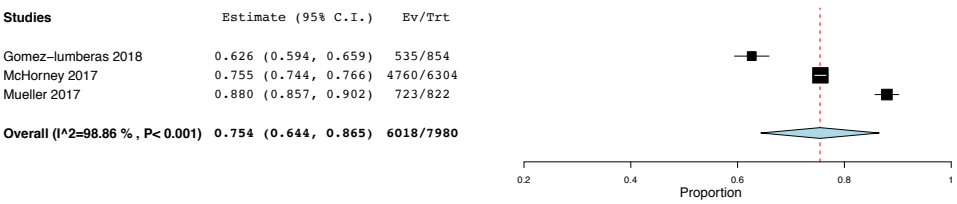
NA

PDC: proportion adherent at 1 year

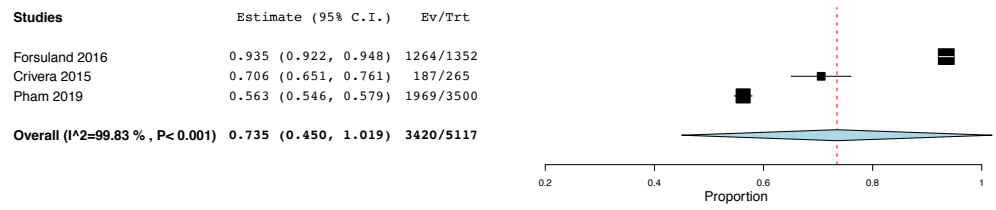


PDC: Mean (SD) adherence at 1 year

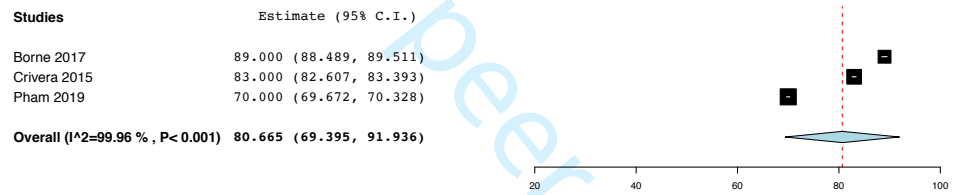


Apixaban: Sub-analysis: stratified by adherence measure
Adherence at 6 months
MPR: proportion adherent at 6 months
NA
MPR: Mean (SD) adherence at 6 months
NA
PDC: proportion adherent at 6 months

PDC: Mean (SD) adherence at 6 months

Adherence at 1 year
MPR: proportion adherent at 1 year

MPR: Mean (SD) adherence at 1 year
NA

PDC: proportion adherent at 1 year



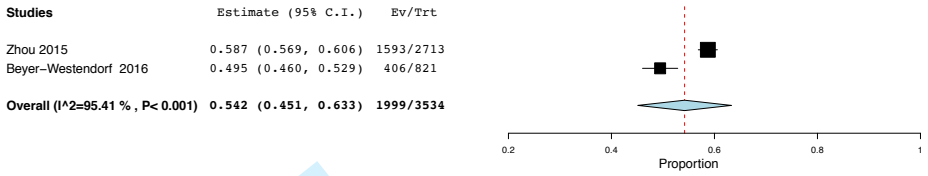
PDC: Mean (SD) adherence at 1 year



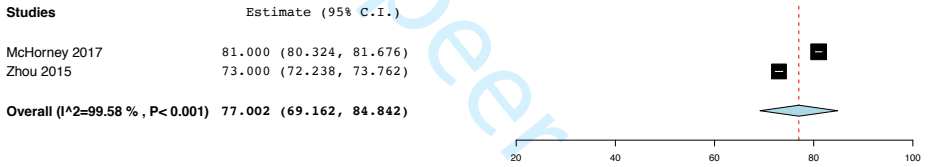
Dabigatran: Sub-analysis: stratified by adherence measure

Adherence at 6 months:

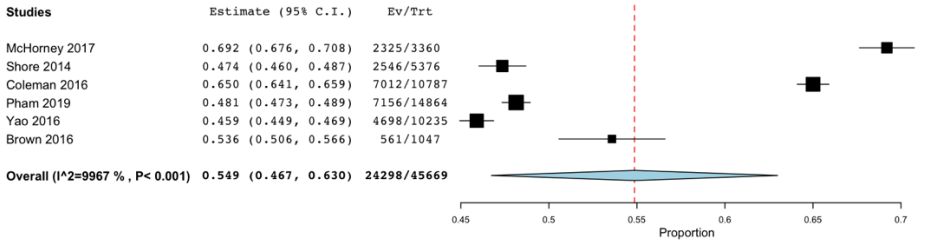
MPR: proportion adherent at 6 months



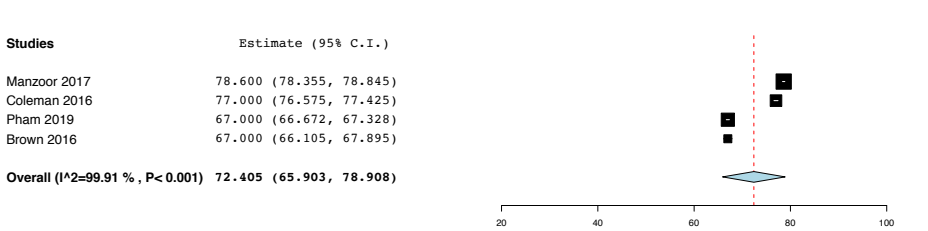
MPR: Mean (SD) adherence at 6 months



PDC: proportion adherent at 6 months

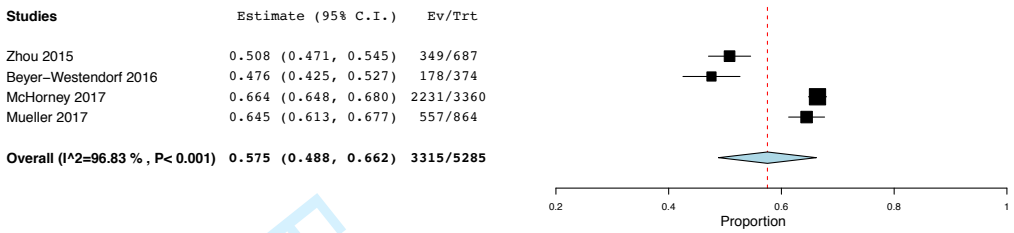


PDC: Mean (SD) adherence at 6 months



Adherence at 1 year

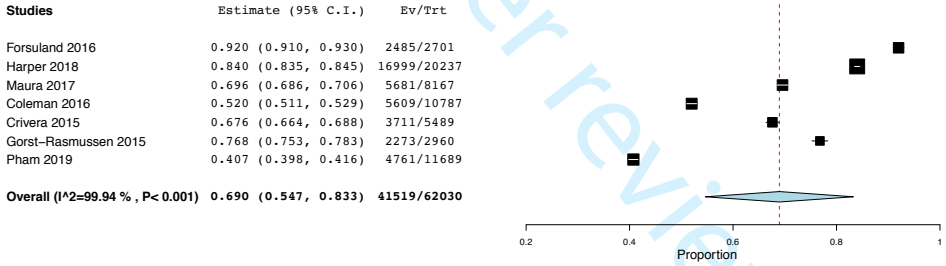
MPR: proportion adherent at 1 year



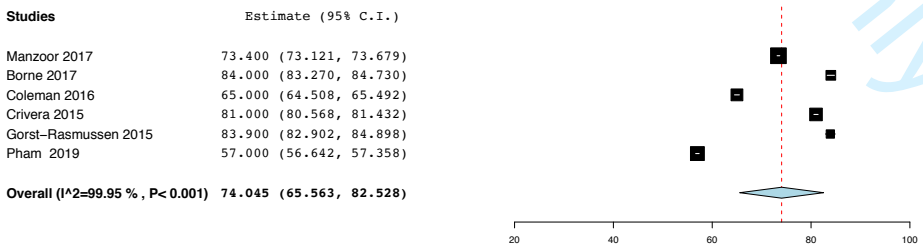
MPR: Mean (SD) adherence at 1 year

NA

PDC: proportion adherent at 1 year



PDC: Mean (SD) adherence at 1 year



Rivaroxaban: Sub-analysis: stratified by adherence measure.

Adherence at 6 months:

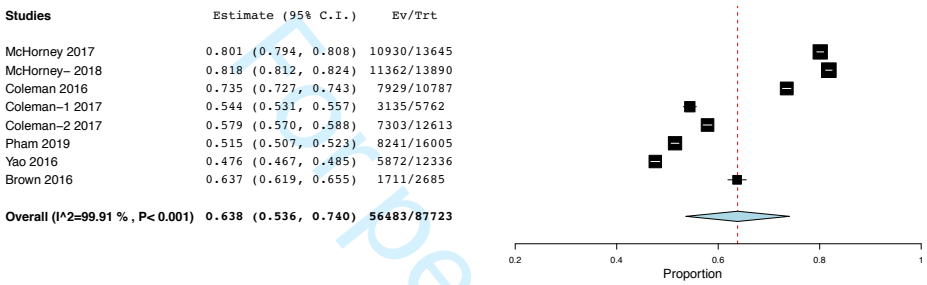
MPR: proportion adherent at 6 months

NA

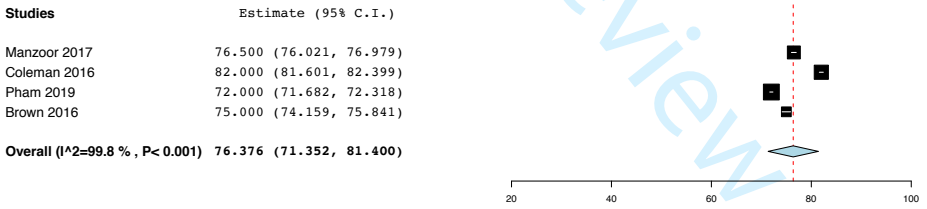
MPR: Mean (SD) adherence at 6 months

NA

PDC: proportion adherent at 6 months

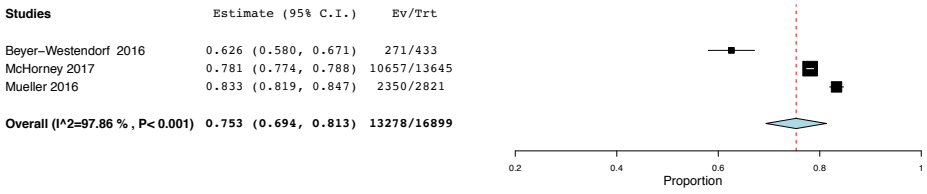


PDC: Mean (SD) adherence at 6 months



Adherence at 1 year:

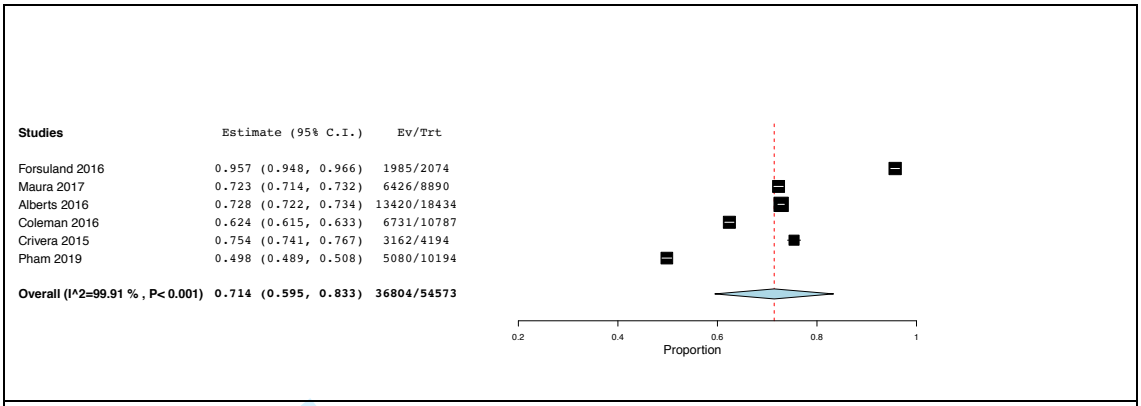
MPR: proportion adherent at 1 year



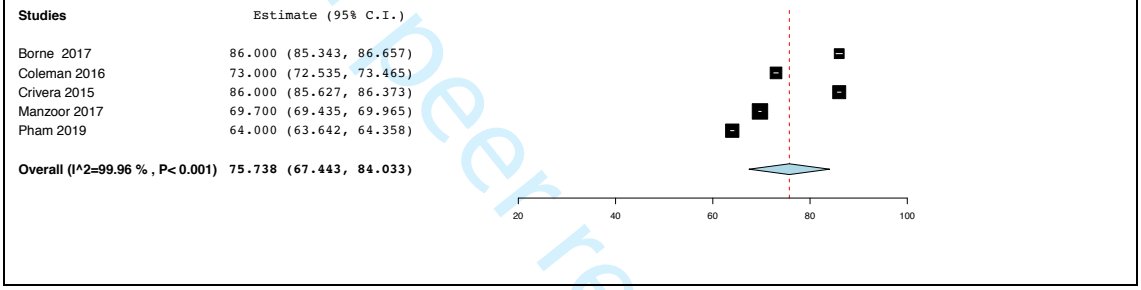
MPR: Mean (SD) adherence at 1 year

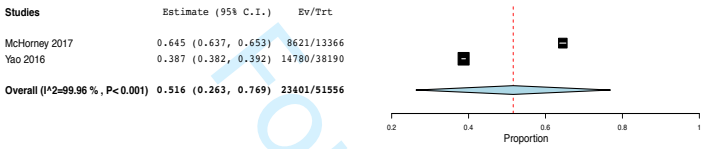
NA

PDC: proportion adherent at 1 year

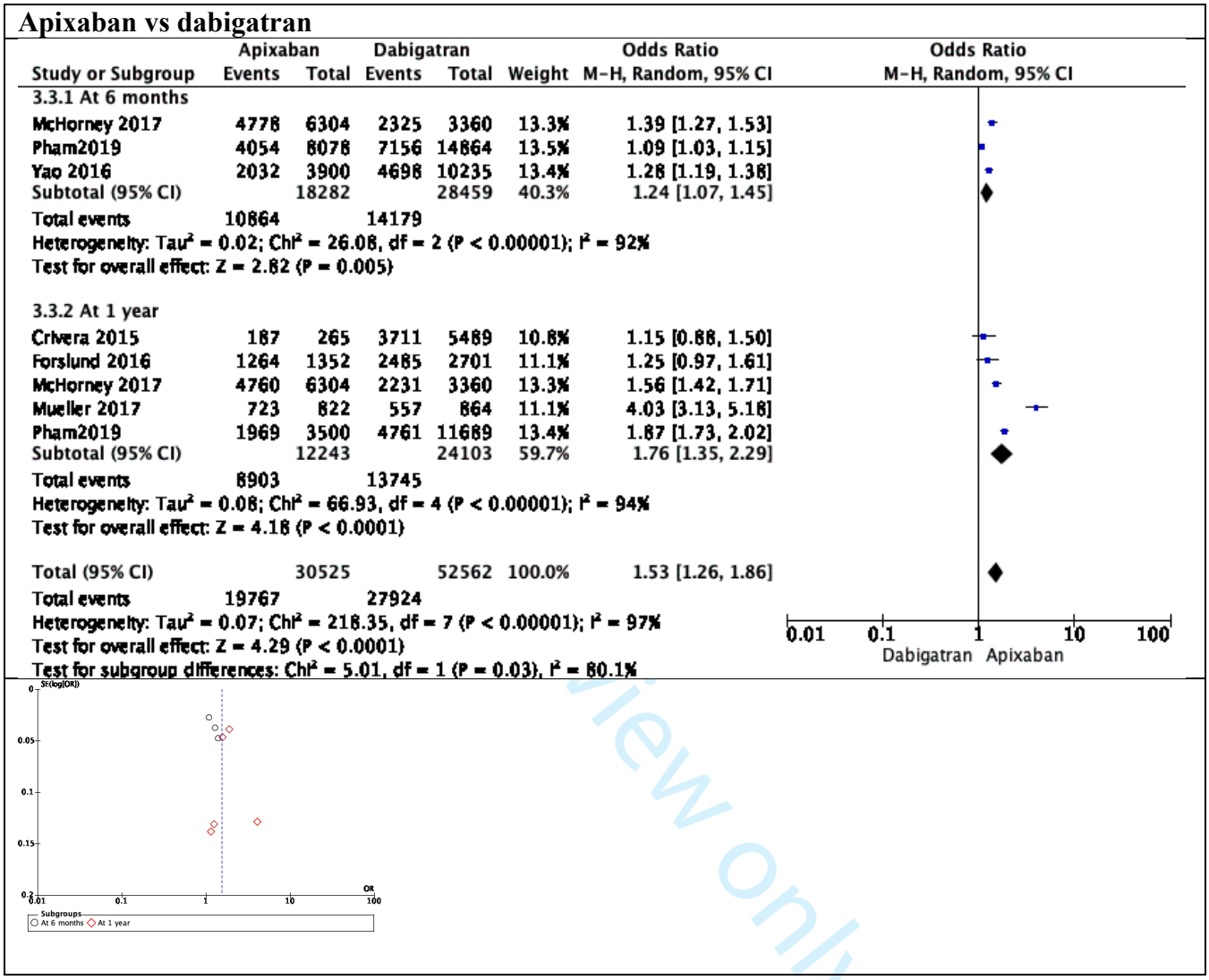


PDC: Mean (SD) adherence at 1 year



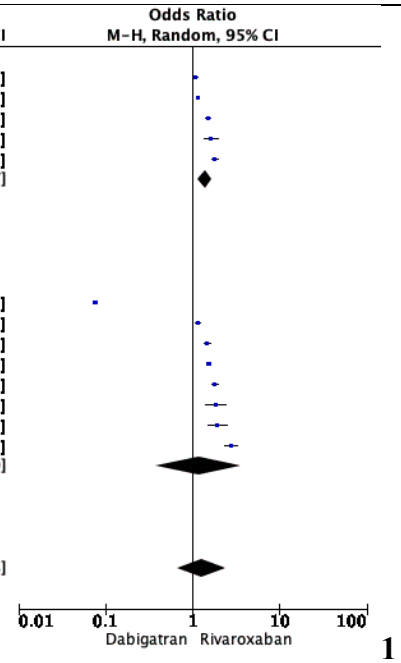
Warfarin: Sub-analysis: stratified by adherence measure
Adherence at 6 months:
MPR: proportion adherent at 6 months
NA
MPR: Mean (SD) adherence at 6 months
NA
PDC: proportion adherent at 6 months

PDC: Mean (SD) adherence at 6 months
NA
Adherence at 1 year
MPR: proportion adherent at 1 year
NA
MPR: Mean (SD) adherence at 1 year
NA
PDC: proportion adherent at 1 year
NA
PDC: Mean (SD) adherence at 1 year
NA

Supplementary 4.2: studies reporting adherence to different medications in the same cohort.



Rivaroxaban vs dabigatran

Study or Subgroup	Rivaroxaban Events	Rivaroxaban Total	Dabigatran Events	Dabigatran Total	Weight	Odds Ratio M-H, Random, 95% CI
5.3.1 At 6 months						
Yao 2016	5872	12336	4698	10235	7.7%	1.07 [1.02, 1.13]
Pham2019	8241	16005	7156	14864	7.7%	1.14 [1.09, 1.20]
Coleman 2016	7929	10787	7012	10787	7.7%	1.49 [1.41, 1.58]
Beyer-Westendorf 2016	809	1317	406	821	7.7%	1.63 [1.36, 1.94]
McHorney 2017	10930	13645	2325	3360	7.7%	1.79 [1.65, 1.95]
Subtotal (95% CI)		54090		40067	38.5%	1.39 [1.15, 1.67]
Total events	33781		21597			
Heterogeneity: Tau² = 0.04; Chi² = 162.85, df = 4 (P < 0.00001); I² = 98%						
Test for overall effect: Z = 3.46 (P = 0.0005)						
5.3.2 At 1 year						
Pham2019	5080	101940	4761	11689	7.7%	0.08 [0.07, 0.08]
Maura 2017	6426	8890	5681	8167	7.7%	1.14 [1.07, 1.22]
Crivera 2015	3162	4194	3711	5489	7.7%	1.47 [1.34, 1.61]
Coleman 2016	6731	10787	5609	10787	7.7%	1.53 [1.45, 1.62]
McHorney 2017	10657	13645	2231	3360	7.7%	1.80 [1.66, 1.96]
Beyer-Westendorf 2016	271	433	178	374	7.6%	1.84 [1.39, 2.44]
Forslund 2016	1985	2074	2485	2701	7.6%	1.94 [1.50, 2.50]
Mueller 2017	2350	2821	557	864	7.7%	2.75 [2.32, 3.26]
Subtotal (95% CI)		144784		43431	61.5%	1.17 [0.38, 3.60]
Total events	36662		25213			
Heterogeneity: Tau² = 2.64; Chi² = 10724.75, df = 7 (P < 0.00001); I² = 100%						
Test for overall effect: Z = 0.27 (P = 0.79)						
Total (95% CI)		198874		83498	100.0%	1.25 [0.66, 2.38]
Total events	70443		46810			
Heterogeneity: Tau² = 1.39; Chi² = 12603.04, df = 12 (P < 0.00001); I² = 100%						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%						



1