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# Oral Anticoagulants and Risk of Dementia: A Systematic Review and Meta-analysis of Observational Studies and Randomized Controlled Trials

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**Highlights**

- Use of Oral anticoagulants (OACs) is associated with reduced risk of dementia.
- Maximizing time in therapeutic range could improve cognitive function in warfarin users.
- OACs are useful not only for stroke prevention, but also for protection against dementia.
- Methodological issues and the small number of studies limit the evidence.

**Abstract**

Atrial fibrillation (AF) is a documented risk factor for dementia. However, it is unclear whether oral anticoagulant (OAC) treatment can reduce the development of dementia or cognitive impairment. We conducted a systematic review and meta-analysis of the association between OAC use and subsequent dementia development in AF patients by searching databases from their inception to February 2018 without language restriction. Six studies (one randomized

controlled trial and five observational studies) met the inclusion criteria. The pooled adjusted risk ratios (RRs) suggested a protective effect of OAC use in reducing dementia risk (RR 0.79 [95% CI: 0.67 – 0.93],  $I^2=59.7\%$ ;  $P=0.005$ ). Further, high percentage of time in therapeutic range (TTR) was associated with a decreased risk of dementia (RR 0.38 [95% CI 0.22-0.64],  $I^2=81.8\%$ ;  $P<0.001$ ). Our results support the hypothesis that AF-related dementia may be due to silent brain infarcts and micro-embolism that could be prevented by OAC use. Future studies with prospective follow-up with direct comparison of vitamin K antagonists and direct oral anticoagulants are needed.

**Abstract word count:** 165 words

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## 1. Introduction

Dementia is the development of severe cognitive decline that subsequently causes significant impairment in social and/or occupational functioning (American Psychiatric Association, 2013). In 2010, it was estimated that 35.6 million people were living with dementia worldwide. It is projected that an excess of 100 million people will have dementia by 2050 (Prince et al., 2013). The risks of developing dementia increases steadily with increasing age. Its prevalence doubles every 5 years after 65 years of age and incidence also increases

exponentially (Hugo and Ganguli, 2014). People living with dementia have a number of comorbidities which lead to considerable primary care consultations, hospital admissions, and increased risk of death (Browne et al., 2017). Cardiovascular disease is recognized as a risk factor for developing dementia or cognitive impairment, particularly atrial fibrillation (AF).

A growing body of evidence suggests a relationship between AF and cognitive impairment ranging from mild to severe dementia (Kalantarian et al., 2013; Kwok et al., 2011; Mead and Keir, 2001; Santangeli et al., 2012; Stefanidis et al., 2018). It is worth noting that AF is associated with a five-fold increased risk of stroke and AF patients with a history of stroke are at a greater risk for an occurrence of dementia or cognitive impairment (January et al., 2014). In addition, AF and dementia share several cardiovascular risk factors such as hypertension, heart failure, diabetes mellitus, and excessive alcohol intake (Aldrugh and Sardana, 2017). Therefore, it is not surprising that AF is associated with an increased risk of dementia. However, there was an evidence demonstrating that AF is a risk factor for cognitive decline that occurs independently of ischemic stroke (Bunch et al., 2010; Kalantarian et al., 2013). Accordingly, additional mechanisms may underlie the association between AF and dementia other than stroke and shared risk factors. One such mechanism is silent cerebral infarct (SCI). A previous systematic review suggested that AF is associated with more than two-fold increase in the odds of developing SCI (Kalantarian et al., 2014). Therefore, it is hypothesized that effective anticoagulation treatment in patients with AF should preserve cognitive function by reducing infarct burden.

Previous systematic reviews (Cheng et al., 2018; Moffitt et al., 2016) have investigated the role of oral anticoagulant (OAC) on the onset of dementia or cognitive impairment, but the results have been conflicting. One study (Moffitt et al., 2016) failed to show any significant reduction in dementia risk, while another study (Cheng et al., 2018) demonstrated an association between OAC use and reduced dementia occurrence. The major limitation of these previous reviews was the inclusion of cross-sectional studies, which could not confirm the temporal relationship between OAC treatment and the development of dementia or cognitive impairment.

Accordingly, there is no clear evidence on the direction of effect of anticoagulants in incident dementia. The aim of this systematic review and meta-analysis was to investigate the association between the use of OAC and the incidence of dementia or cognitive impairment in patients with AF.

## **2. Methods**

This systematic review was conducted in accordance with the principle outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins, 2011) and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). The systematic review protocol was registered in the Prospero International Prospective Register of Systematic Reviews (PROSPERO Number: CRD42018090955).

### ***2.1 Data sources and search strategy***

The following electronic databases were searched from their inception dates to the 21<sup>st</sup> February 2018: Cochrane library, Pubmed/MEDLINE, EMBASE, Web of Science (Science Citation Index), the Cumulative Index to Nursing and Allied Health Literature, ClinicalTrials.gov, and PsycINFO. The literature retrieval was supplemented by manually searching reference lists of all identified articles. There were no language restrictions. A comprehensive search strategy including the terms: atrial fibrillation, antithrombotics, anticoagulants, antithrombin, factor Xa inhibitors, platelet aggregation inhibitors, and dementia, as keywords, text words or Medical Subject Headings (MeSH) terms was used. Full search strategies for all database search are available in Supplementary eTable 1.

### ***2.2 Inclusion and exclusion criteria***

The following criteria were used for including studies in our systematic review: (i) randomized controlled trials (RCTs) or observational studies (ii) conducted in patients with AF who were  $\geq 18$  years and had no history of dementia; (iii) investigated the effects of OACs on the

incidence of dementia/cognitive decline; and (iv) reported the outcomes as hazard ratio (HR), risk ratio (RR) or odd ratio (OR), with 95% confidence intervals (CIs). Both vitamin K antagonists (VKAs) and non-vitamin K oral anticoagulants (NOACs) were considered as OACs of interest. Non-OAC users were defined as AF patients who did not receive OAC at study baseline. All studies of any forms of dementia (Alzheimer's/Lew-body/vascular dementia) and cognitive decline were eligible. For studies with overlapping participants, the information with the longest follow-up and the most detailed information were included. The PICOS (Participants, Intervention, Comparators, Outcomes, Study Design) criteria are shown in Supplementary eTable 2.

We excluded studies that were a cross-sectional design (which cannot establish a reliable relationship between OAC use and onset of dementia/cognitive decline), and did not present original data, or were editorials, conference meeting abstracts, expert opinions, case reports, case series, or systematic reviews. Studies that provided only crude RR or unadjusted results may be affected by potential confounding factors and thus were also excluded.

Eligible titles, abstracts and full-text articles were screened by two independent investigators (PM and AN). Any disagreements were resolved through discussion.

### **2.3 Outcome measurement**

The primary outcome was the incidence of dementia or cognitive impairment among AF patients with and without OACs. Dementia or cognitive impairment had to be diagnosed based on clinical judgement, results from mental state examinations, cognitive status testing, neuropsychological and physiological testing, established diagnostic criteria for dementia including the Diagnostic and Statistical Manual of Mental Disorders (DSM) -III, DSM-IV, DSM-V, diagnosis based on international classification of diseases codes (ICD), or United Kingdom (UK) Read codes. The secondary outcome was the association between time in therapeutic range (TTR) during warfarin treatment and the risk of dementia. High TTR and low TTR were compared to determine the effect on dementia. We considered high TTR as percentage of TTR  $\geq 75\%$  or in quartile 4, and low TTR as TTR  $\leq 25\%$  or in quartile 1.

## **2.4 Data extraction and risk of bias assessment**

Information were independently extracted from the studies meeting the eligibility criteria by two investigators (PM and AN) using a pre-designed data extraction form. The following information was extracted: country of study, study setting, study design, duration of follow-up, sample size, study sample characteristics (age and gender), AF ascertainment, definition of dementia or cognitive impairment, antiplatelet/non-steroidal anti-inflammatory drugs (NSAIDs) use, CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc score, OAC used, and comparison group. We also contacted authors when primary outcome data was missing. If the authors did not respond, the study was excluded. Disagreements were resolved by discussion between the two investigators (PM and AN).

Two investigators (PM and AN) independently appraised the risk of bias for the included studies using the Cochrane risk of bias tool for RCTs (Higgins, 2011). This tool includes seven domains for methodological evaluation: i) sequence generation, ii) allocation concealment, iii) blinding of participants, personnel and outcome assessors, iv) incomplete outcome data, v) selective outcome reporting, and vi) other sources of bias. The RCT was classified as low risk of bias (low risk of bias for all domains), high risk (high risk of bias for one or more domains), or unclear risk (unclear risk of bias for one or more key domains). For observational studies, we used the Newcastle–Ottawa Scale (NOS) (Wells et al., 2014). Criteria included: selection of the exposed/unexposed cohort, comparability of the study group and the outcome assessment. Studies with a total score of 8 or more were defined as high quality. Any disagreements were resolved by discussion.

## **2.5 Strength of evidence grading**

The Grading of Recommended Assessment, Development and Evaluation (GRADE) system, was used to classify the strength of evidence (SOE) based on five key domains; study limitations, directness, consistency, precision, and reporting bias (Berkman et al., 2015). The



ratings classified evidence as high-quality, moderate-quality, low-quality, or insufficient-quality. PM and AN independently evaluated SOE domains for outcomes with different comparisons.

## **2.6 Statistical analysis**

The primary analysis compared the incidence of dementia/cognitive impairment between users and non-users of OAC. Results from included studies were expressed as HR, RR, or OR. The RRs were used as the common effect estimates of association across studies. The HRs were considered comparable to RRs (Stare and Maucourt-Boulch, 2016.). However, for studies that provided ORs, a corrected RR was computed using the methods described by (Zhang and Yu, 1998). We performed meta-analyses under the DerSimonian-Laird random-effects model to pool RR with 95% CIs for the incidence of dementia assuming that the true effect size varied between studies. Homogeneity was assessed using the Cochran Q test, with  $p < 0.10$  (Higgins et al., 2003). The degree of heterogeneity was estimated by  $I^2$ .  $I^2$  value  $< 25\%$  indicated low,  $25\text{--}75\%$  moderate, and  $> 75\%$  high heterogeneity (Higgins et al., 2003). To explore possible sources of heterogeneity, subgroup analyses were carried out for different study designs (RCTs versus observational studies), prospective studies versus retrospective studies, and a history of stroke (mixed patients with and without prior stroke versus patients with a prior stroke). Sensitivity analyses were performed by adding unpublished studies and using the 'leave-one-out' approach. A funnel plot was used to investigate any evidence of publication bias, and was statistically assessed by the Begg's and Egger's tests. In addition, the trim-and-fill method was performed to calibrate for publication bias. Statistical tests were two-sided and used a significance threshold of  $p < 0.05$ . All analyses were conducted using STATA, v14.1 (StataCorp, Stata Statistical Software. College Station, TX: StataCorp LP; 2015).

## **3. Results**

### **3.1 Search results**

Of the 1926 articles retrieved from electronic databases, 487 were duplicates and 1341 did not meet the eligibility criteria. The remaining 98 full-text articles were evaluated for eligibility. Finally, six studies (Barber et al., 2004; Bunch et al., 2016; Douiri et al., 2013; Friberg and Rosenqvist, 2018; Madhavan et al., 2018; Mavaddat et al., 2014) were included in this systematic review and meta-analysis (Figure 1).

### **3.2 Study characteristics**

Of the six included studies, four (Barber et al., 2004; Bunch et al., 2016; Douiri et al., 2013; Mavaddat et al., 2014) were carried out in the UK, one (Friberg and Rosenqvist, 2018) in Sweden, and one (Madhavan et al., 2018) in the United States. One study (Mavaddat et al., 2014) was a RCT, two (Barber et al., 2004; Douiri et al., 2013) were prospective observational studies, and the other two (Friberg and Rosenqvist, 2018; Madhavan et al., 2018) were retrospective observational studies. Of the five included observational studies, one study (Douiri et al., 2013) specifically examined the association of anticoagulant use with dementia in patients with AF who had experienced a stroke. Four studies (Barber et al., 2004; Bunch et al., 2016; Friberg and Rosenqvist, 2018; Madhavan et al., 2018) reported the association in a broader population which included patients both with and without a history of stroke. Only three (Bunch et al., 2016; Madhavan et al., 2018; Mavaddat et al., 2014) studies reported the quality control of warfarin use based on TTR (Supplementary eTable 3).

The measurement of dementia or cognitive impairment varied across studies. Two studies (Douiri et al., 2013; Mavaddat et al., 2014) used the Mini-Mental State Examination (MMSE) for cognitive assessment, three studies (Bunch et al., 2016; Friberg and Rosenqvist, 2018; Madhavan et al., 2018) identified dementia using ICD-9 or ICD-10 codes, and one study (Barber et al., 2004) applied the modified 13-item version of the Telephone Interview for Cognitive Status (TICS<sub>m</sub>) and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). The main characteristics and the outcomes of the included studies are shown in Table 1.

Based on the quality assessment by NOS, five of the included studies (Barber et al., 2004; Bunch et al., 2016; Douiri et al., 2013; Friberg and Rosenqvist, 2018; Madhavan et al., 2018) were judged as high quality with a score ranging from 8 to 9 (Supplementary eTable 4). One RCT (Mavaddat et al., 2014) was included in the review and it was judged as high risk of bias due to lack of outcome assessment blinding (Supplementary eTable 5). Practitioner recording of MMSE might have influenced treatment allocation.

### ***3.3 The use of oral anticoagulation and risk of dementia***

#### ***3.3.1 OAC use versus non-OAC use and risk of dementia***

The use of OAC was associated with decreased risk of dementia or cognitive impairment compared with no OAC use (RR 0.79 [95% CI: 0.67 – 0.93],  $I^2=59.7\%$ ;  $P=0.005$ ) (Table 2, Figure 2). Furthermore, five studies (Barber et al., 2004; Douiri et al., 2013; Friberg and Rosenqvist, 2018; Madhavan et al., 2018; Mavaddat et al., 2014) reported the risk of dementia separately for VKA use and non OAC use. The results from meta-analysis demonstrated significant protective effect of VKA use in reducing dementia risk by 23% compared with no OAC treatment (RR 0.77 [95% CI: 0.66 – 0.90],  $I^2=48.3\%$ ;  $P=0.001$ ) (Table 2, Figure 2). There was one study (Friberg and Rosenqvist, 2018) comparing NOACs to no OAC treatment. The risk of dementia was lower with NOAC treatment (RR 0.40; [95% CI 0.30 – 0.54];  $P<0.001$ ).

#### ***3.3.2 NOAC use versus VKA use and risk of dementia***

One study was included comparing NOACs and VKAs (Friberg and Rosenqvist, 2018) in this systematic review. The results showed that there was no statistically significant difference between the two groups with respect to the occurrence of dementia (RR 0.97; [95% CI 0.67-1.40];  $P=0.871$ ).

#### ***3.3.3 Time in therapeutic range (TTR) and risk of dementia***

There were two included studies (Bunch et al., 2016; Madhavan et al., 2018) examining the risk of dementia based on warfarin efficacy. The pooled RR showed that a high percentage

of TTR was associated with a significantly decreased risk of dementia (RR 0.38, [95% CI 0.22-0.64],  $I^2$  81.8%;  $P<0.001$ ) (Table 2, Figure 3).

### **3.4 Subgroup analysis**

In subgroup analyses by study design, the pooled RR for observational studies showed a significant association between OAC use and decreased risk of dementia, (RR 0.75 [95% CI: 0.67 – 0.83],  $I^2$ =33.6%;  $P<0.001$ ), while RCT results demonstrated no significant association with OAC use (RR 1.31 [95% CI: 0.79 - 2.18];  $P=0.297$ ). In addition, there was no significant association between OAC use and incidence of dementia in prospective studies and similar results were observed in studies conducted in AF patients with prior stroke (Table 3).

### **3.5 Sensitivity analysis**

After adding unpublished data which was obtained from conference abstracts, the results illustrated that OAC use was not associated with decreased risk of dementia or cognitive impairment. However, there was a trend towards a protective effect with OAC use. The results are shown in supplementary eFigure1. We also carried out a leave-one-out sensitivity analysis. After the removal of Friberg and Rosenqvist, 2018 and Madhavan et al., 2018, dementia or cognitive impairment was no longer associated with OAC therapy: RR=0.85 [95% CI 0.68 – 1.05], and RR=0.80 [95% CI 0.64 – 1.01], respectively. The summary is displayed in Supplementary eTable 6.

### **3.6 Publication bias**

A publication bias assessment using the data of any OAC use and risk of dementia was performed (n=5 studies). No evidence of publication bias was detected by Begg's test ( $p=0.221$ ) and Egger's test ( $p=0.219$ ). A well-proportioned funnel plot was formed in a sensitivity analysis using the trim-and-fill method. After the performance of trim-and-fill method, the RR remained unchanged (RR 0.79, 95% CI 0.67 – 0.93;  $P=0.005$ ). The corresponding funnel plots are displayed in Supplementary eFigure 2-4.

### **3.7 Strength of the body of evidence**

Using the GRADE system, we graded the SOE for the association between OAC/VKA treatment and incidence of dementia as low due to moderate study limitations, inconsistency and plausible confounding factors for the included studies. Meanwhile, the comparison between NOAC use and non-OAC use, or direct comparison of NOAC and warfarin and the subsequent of dementia were graded as insufficient because the number of studies were limited. Details of GRADE evidence are shown in Table 2 and supplementary eTable 7.

## **4. Discussion**

This systematic review and meta-analysis demonstrated that in patients with AF, oral anticoagulant use was significantly associated with a decreased risk of developing dementia or cognitive impairment by 20% compared with no treatment, but considerable heterogeneity was observed. In addition, in patients using warfarin, an increased TTR correlated with lower risk of dementia. According to GRADE system, the SOE for the association was low or insufficient.

The findings from this study are in line with a recent meta-analysis (Cheng et al., 2018), which was based on five studies and suggested there was an association between anticoagulant use and reduced incidence of dementia. However, the limitations of previous meta-analysis were the results relied on cross sectional studies, which may introduce bias and confounding, and the effects of VKA alone versus no treatment on dementia were not examined. Furthermore, even though the authors demonstrated a significant association between the use of NOACs versus warfarin and the risk of dementia, one included study (Jacobs et al., 2016) reported a composite outcome of stroke/TIA/dementia which reduces the certainty of this result. Our present study provided additional information regarding the association between VKA users and non-VKA users, and included a recently published study (Madhavan et al., 2018).

Given that OAC reduces the risk of thromboembolism, the findings of this study is supportive of the potential role of subclinical cerebral ischemic lesions in increasing the risk of developing dementia in patients with AF (Gaita et al., 2013; Graff-Radford et al., 2016; Kalantarian

et al., 2013). A high prevalence of silent cerebral ischemia in patients with both paroxysmal and persistent AF has been associated with worse cognitive impairment (Gaita et al., 2013). Further, there is evidence of elevated markers of hemostatic activation (F1 +2, TAT, and D-dimer) in patients with AF and dementia compared to those without dementia (Barber et al., 2004). Moreover, AF is a key risk factor for ischemic stroke (Wolf et al., 1991). Prior data have demonstrated that the occurrence of stroke in patients with AF was significantly associated with the development of cognitive impairment (RR =2.7, 95% CI: 1.82-4.00) (Kalantarian et al., 2013). The absence of OAC was also an independent factor for dementia development in the context of AF (Friberg and Rosenqvist, 2018). OAC treatment for cardioembolic stroke prevention in AF may confer a decreased risk for the development of dementia or cognitive impairment, which was demonstrated in this meta-analysis. Furthermore, our results suggest that the quality of anticoagulation control with maintaining INRs in the therapeutic range could preserve cognitive function and decrease dementia incidence. This result also supports the hypothesis that chronic cerebral injury or silent cerebral infarct is one of the most likely factors leading to the occurrence of dementia or cognitive impairment in patients with AF.

Although this study found a significant association between OAC use and reduced risk of developing dementia or cognitive impairment, several limitations of the included studies are worthy of mention. Firstly, the majority of included studies in the meta-analysis were observational studies. The decision to prescribe OAC was not randomized which could lead to confounding by indication (Salas et al., 1999). Characteristics of patients who were prescribed OACs may be different from those who were not prescribed OAC in terms of comorbidities and risk of thromboembolic complications. Indeed, it should be noted that individual characteristics including age, the presence of heart failure, hypertension, diabetes, history of stroke and higher CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc score, have been associated with increased dementia risk (Duron and Hanon, 2008; Graves et al., 2017; Liao et al., 2015). Although some studies adjusted for baseline covariates, residual confounders may remain. Secondly, cognitive status of patients might influence clinician decision-making regarding OAC prescribing. Physicians are more likely to

prescribe OACs to patients with normal cognitive status (Gussoni et al., 2013), meanwhile patients with normal cognitive status may be less likely to develop dementia compared to those with cognitive impairment. Therefore, this could overestimate the protective effects of OACs on dementia. Indeed, patients with cognitive impairment may be more likely to go on to develop dementia. Given that non-OAC users are more likely to have worse cognitive function than OAC users at baseline, a more rapid development of dementia in non-OAC users may be observed during study follow-up periods. This is consistent with the study conducted by (Friberg and Rosenqvist, 2018) – of which the results showed a rapid increase of incident dementia among non-users of OAC within the first year of follow-up. Thirdly, cases of early-stage dementia could have gone undetected, which may underestimate the incidence of dementia identified in the studies. Finally, baseline medication use was not obtained across all included studies. NSAIDs or statin have been found to be associated with a reduction in incident dementia (Chao et al., 2015; de Craen et al., 2005; Swiger et al., 2013). However, only two studies (Bunch et al., 2016; Friberg and Rosenqvist, 2018) provided these data. Indeed, concomitant medication use might affect the association between OAC use and dementia, as well as lifestyle, genetic and socio-economic factors, which were not adequately examined in the literature available.

For a direct comparison of NOAC and VKA on risk of dementia, it has been proposed that NOAC could preserve the cognitive function better than VKA as they have a lower variability in anticoagulation effect and have a lower risk of intracranial bleeding (Lip et al., 2018; Ruff et al., 2014). A previous retrospective observational study included in this systematic review showed insignificant results with regards to the risk of dementia. Thus, due to the limited number of studies, we have insufficient evidence to draw a conclusion on which group of oral anticoagulant medication has a better protective effect against dementia. To confirm such a hypothesis, this comparison needs to be investigated with rigorous long-term studies or RCTs. Currently, there are two ongoing RCTs (ClinicalTrials.gov Identifier: NCT01994265 and NCT03061006) that aim to determine the impact of NOACs and VKAs on neurocognitive decline or dementia.

#### **4.1 Strengths and limitations**

The strengths of this study should be highlighted. First, we applied a comprehensive search strategy without language restriction to ensure that the included studies were representative. Second, the meta-analysis covered updated evidence and reflect real-world practices. In addition, the analyses were performed using rigorous statistical approaches. Finally, our study adheres to the standard methodology of systematic review and meta-analysis as required by the Cochrane and PRISMA checklist (Higgins, 2011; Moher et al., 2009).

Our study also has limitations. First, it is possible that publication bias exists. Although no evidence of publication bias was found by the Begg's and Egger's test, these methods may be underpowered to detect publication bias due to the small number of included studies. However, after calibration with the trim and fill method, the direction of findings remained unchanged. Second, despite a rigorous and comprehensive search, the majority of included studies in this meta-analysis are observational studies which are prone to bias and unmeasured confounders. On this point, we suggested that the causality of OAC usage and the reduction of dementia cannot be established. Therefore, the results should be interpreted with caution. Third, a moderate degree of heterogeneity may limit our findings. However, we conducted subgroup analyses and found that study design and prior history of stroke/TIA were potential factors contributing to heterogeneity. We conducted a sensitivity analysis where unpublished data from conference abstracts was included. Results demonstrate OAC use was not associated with decreased dementia risk, however a protective trend was apparent. Further, we also conducted sensitivity analyses using the leave-one-out method. Results become statistically non-significant after omitting studies conducted by Friberg et al., 2017 and Madhavan et al., 2018. One explanation for this is that these two studies comprised large cohorts and might have sufficient power to detect an association, and removal of these two studies reduced the statistical power. By contrast, these studies differ from the remaining, as they were retrospective studies. This was also apparent when we did a subgroup analysis by study design which showed that studies of retrospective designs had a significant protective association between OAC use and incidence of dementia. These variable results indicate that a well-designed RCT with a large sample size or sufficiently powered



cohort study is needed to help confirm the associations presented in this review. Finally, we found that risk of dementia was lower with NOACs treatment, but no differences were found when comparing NOACs and warfarin. However, this result was based on only a single study, thus, caution should be applied when interpreting this finding.

#### ***4.2 Implications for practice and future research***

This review provides the best available and up-to-date evidence which has implications for clinical decision-making. These findings support the importance of OAC use in AF patients, not only for the prevention of thromboembolic complications, but also for reducing the risk of developing dementia in patients with AF. Physicians should assess the benefits of OAC use and set these against the risks, such as bleeding.

Future directions and improvements to research in the area of the use of OAC in reducing the risk of developing dementia or cognitive impairment could include i) well-designed studies that adjust for confounding factors and include periods of longer follow-up, ii) assess associations between OAC use and dementia/cognitive impairment stratified by age, risk of thromboembolic complications, and medical history, iii) assess the dose-response relationship between the duration of untreated AF and the development of dementia, and iv) assess the benefits of individual OACs, in particular, the NOACs. The effects of these medications on cognitive function still need to be thoroughly investigated.

#### ***4.3 Conclusions***

Oral anticoagulant therapy was associated with a reduced risk of dementia/cognitive impairment in patients with AF. A higher TTR of warfarin treatment had a significant association with decreased risk of dementia compared with patients with lower TTR. However, the results were limited by the lack of adjusted effect ratios and heterogeneity of included studies. More rigorous studies are needed to explore the impact of oral anticoagulant use on dementia.

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## Conflict of interest disclosures

The authors have no conflicts of interest to declare.

## Author's contributions

ICKW, CK, PM, LF, and WL were involved in the study concept and design. All authors involved in the acquisition, analysis or interpretation of data. PM and AYN were involved in data screening, data extraction, quality assessment, and statistical analysis. PM drafted the manuscript with input from all authors. All authors were involved in the critical revision of the manuscript for important intellectual content. CK and ICKW were involved in the study supervision. All authors have read and approved the final manuscript.

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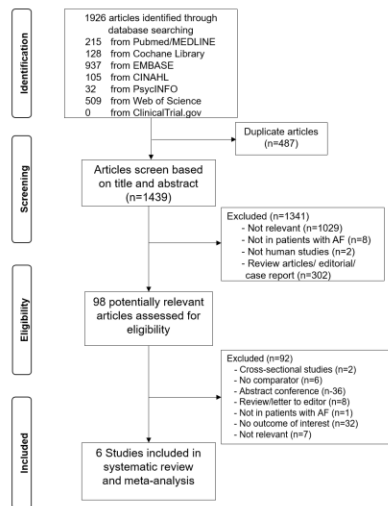
## Figure Captions

**Figure 1.** PRISMA flow chart

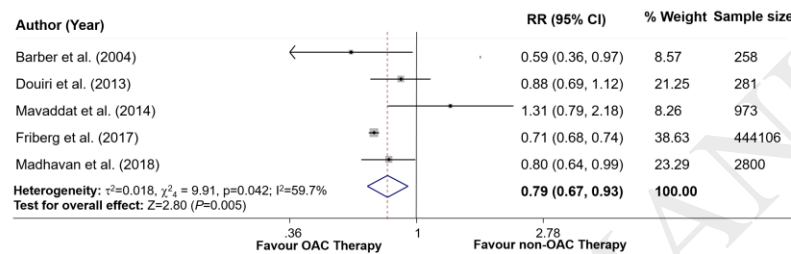
**Figure 2.** Forest plots showing risk ratio of dementia or cognitive impairment in patients with atrial fibrillation (A) Oral anticoagulant (OAC) therapy compared with non-OAC therapy B) Vitamin K antagonist (VKA) compared with non-OAC therapy. **Abbreviations:** CI=confidence interval; RR=risk ratio

**Figure 3.** Forest plots showing risk ratio of dementia or cognitive impairment in patients with atrial fibrillation comparing high time in therapeutic range (TTR) and low TTR. **Abbreviations:** CI=confidence interval; RR=risk ratio; TTR=time in therapeutic range

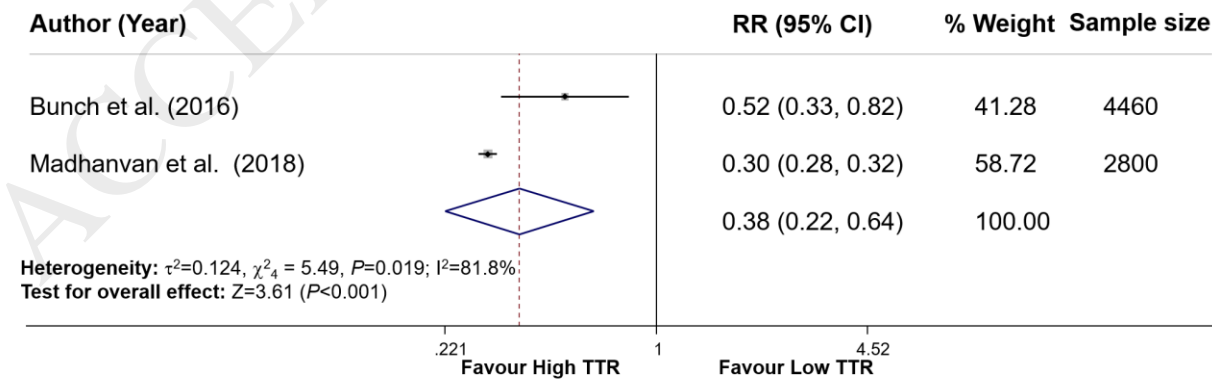
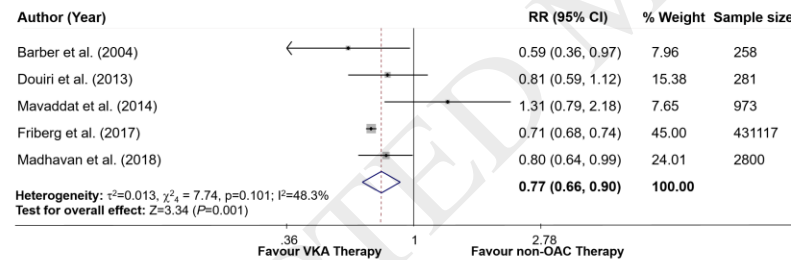




**A. Risk ratio (95% confident interval) for OAC therapy versus non-OAC therapy**



**B. Risk ratio (95% confident interval) for VKA therapy versus non-OAC therapy**



**Table 1.** Characteristics of studies included in the meta-analysis

First author, year	Setting	Country	Study design	Follow-up time	Sample size	Age (Median [IQR] or Mean [SD])	%Male	AF ascertainment	Dementia or cognitive impairment definition
Barber et al, 2004	General practice and anticoagulant clinics	United Kingdom	Prospective cohort study	3 yrs	258	Median 72 (IQR 66-78)	46%	NR	Dementia was defined TICS <sub>m</sub> ≤ 20 and IQCODE score of 3.12/3.19
Douiri et al, 2013	22 electoral wards in Lambeth and Southward	United Kingdom	Prospective cohort study	10 yrs	281 at 3 months	Median 71 (IQR18)	54%	Either self-reported or from medical histories	Cognitive impairment was defined as MMSE <24 or Abbreviated Mental Test <8
Mavaddat et al, 2014	260 general practices	United Kingdom	Randomized open-label trial	Mean 2.7 yrs (SD 1.2)	973	81.5 (4.3)	54.6%	ECG	Cognitive impairment was defined as MMSE <24
Bunch et al, 2016	The Intermountain Healthcare Clinical Pharmacist Anticoagulation Service (CPAS)	United States	Retrospective cohort study	Mean 2293.6 day (SD 1536.1)	4460	72.5 (11.2)	53.5%	ICD 9 and 10	Dementia was defined using ICD-9 and 10 codes entered by neurologists
Friberg et al, 2018	The Swedish Patient register and the Dispensed Drug register	Sweden	Retrospective cohort study	9 yrs	444106	Mean age: OAC users 73.7, non OAC users 75.7	OAC users 59.4%, non OAC users 51.9%	ICD-10	Dementia was defined using ICD-10
Madhavan et al, 2018	Olmsted County, Minnesota, Olmsted Medical Center, and their affiliated hospitals,	United States	Retrospective cohort	Mean 5 yr (SD 3.7)	2800	71.2 (14.6)	53.4%	ICD-9 or ECG	Dementia was defined using ICD-9

**Table 1.** Characteristics of studies included in the meta-analysis (continued)

First author, year	Antiplatelet/NSAIDs use (%)	CHADS <sub>2</sub> or CHA <sub>2</sub> DS <sub>2</sub> -VASc Score	OAC use defined as	OAC use (%)	Comparison group	Risk of bias
Barber et al, 2004	NR	NR	Warfarin use at baseline	Warfarin (n=166, 64.3%)	Non-OAC users (no warfarin)	High quality <sup>a</sup>
Douiri et al, 2013	NR	NR	Prescribed anticoagulants	NR	Non-OAC users (non-specify)	High quality <sup>a</sup>
Mavaddat et al, 2014	NR	NR	Assigned to receive warfarin	Warfarin (n=488, 50.2%)	Non-OAC users (aspirin)	High risk of bias <sup>b</sup>
Bunch et al, 2016	Antiplatelet (62.5)	CHADS <sub>2</sub> ≥2 (68.5%), CHA <sub>2</sub> DS <sub>2</sub> -VASc ≥ 2 (89.4%)	Warfarin use at baseline	Warfarin (n=4460), TTR≤25%, n=419, TTR>75%, n=1880	Low TTR (<25%)	High quality <sup>a</sup>
Friberg et al, 2018	OAC users (39.7), non-OAC users (67.7)	Mean CHA <sub>2</sub> DS <sub>2</sub> -VASc score: OAC users=3.43, non-OAC user =3.49	Prescriptions filled up to 30 days after the first contact with AF during the inclusion period	Warfarin (n=190570, 42.9%), phenprocoumon (n=199, 0.04%), NOAC (n=12916, 2.9%)	Non-OAC users (non-specify)	High quality <sup>a</sup>
Madhavan et al, 2018	NR	Median (IQR) CHA <sub>2</sub> DS <sub>2</sub> -VASc score 3 (2-4)	Warfarin use at baseline and had an INR measurement	Warfarin (n=1414, 50.5%)	Non-OAC users (no warfarin)	High quality <sup>a</sup>

**Abbreviations:** TICS<sub>m</sub>= the modified 13-item version of the Telephone Interview for Cognitive Status; IQCODE= the Informant Questionnaire on Cognitive Decline in the Elderly; MMSE= the Mini-Mental State Examination; OACs=oral anticoagulants; NOACs= non vitamin K oral anticoagulants; NR=not reported; CI=cumulative incidence; ICD = International Classification of Diseases and Health Related Problems; ECG= Electrocardiogram; TTR=time in therapeutic range; IQR=interquartile range, CHADS<sub>2</sub> =congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack; CHA<sub>2</sub>DS<sub>2</sub>-VASc= congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category

<sup>a</sup>risk of bias was evaluated using The Newcastle-Ottawa Scale (NOS)

<sup>b</sup>risk of bias was evaluated using Cochrane risk of bias tool for RCTs

**Table 2** Summary of findings from studies assessing oral anticoagulant use and the risk of dementia

Association between OAC use and risk of dementia	Number of studies included	Sample size	Risk ratio (95% CI)	P-value	Heterogeneity				SOE
					Q statistic	P-value	I <sup>2</sup> index	$\tau^2$	
OAC users vs. non-OAC users	5	448418	0.79 (0.67 – 0.93)	0.005	9.91	0.042	59.7%	0.018	Low
VKA users vs. non-OAC users	5	435429	0.77 (0.66 – 0.90)	0.001	7.74	0.101	48.3%	0.013	Low
NOAC users vs. non-OAC users	1	254149	0.40 (0.3 – 0.54)	<0.001	NA	NA	NA	NA	Insufficient
NOAC users vs. VKA users	1	202946	0.97 (0.67 – 1.40)	0.871	NA	NA	NA	NA	Insufficient
High TTR vs. low TTR	2	7260	0.38 (0.22 – 0.64)	<0.001	5.49	0.019	81.8%	0.124	Low

Abbreviations: OAC=oral anticoagulant, VKA=vitamin K antagonist, NNT=number needed to treat, SOE=strength of evidence, TTR=time in therapeutic range, NA=not applicable, CI=confident interval

**Table 3.** Subgroup Analyses: Oral anticoagulant (OAC) users and non-OAC users in patients with atrial fibrillation

Subgroup characteristics	Number of studies	Pooled RR (95% CI)	P-value	Heterogeneity			
				Q statistic	P-value	I <sup>2</sup> index	τ <sup>2</sup>
OAC users vs non-OAC users							
Study design							
• Observational studies	4	0.75 (0.67-0.83)	<0.001	4.52	0.211	33.6%	0.005
• RCTs	1	1.31 (0.79-2.18)	0.297	NA	NA	NA	NA
Prospective versus retrospective studies							
• Prospective studies	3	0.88 (0.61-1.26)	0.482	4.86	0.088	58.8%	0.062
• Retrospective studies	2	0.72 (0.67-0.76)	<0.001	1.11	0.292	9.8%	0.001
A history of stroke							
• Mixed patients with and without stroke	4	0.77 (0.64-0.93)	0.008	7.17	0.067	58.2	0.020
• Patients with prior stroke	1	0.88 (0.69-1.12)	0.301	NA	NA	NA	NA
VKA users vs non-VKA users							
Study design							
• Observational studies	4	0.71 (0.68-0.74)	<0.001	2.28	0.517	0%	<0.001
• RCTs	1	1.31 (0.79-2.18)	0.297	NA	NA	NA	NA
Prospective versus retrospective studies							
• Prospective studies	3	0.85 (0.57-1.26)	0.414	4.95	0.084	59.6%	0.073
• Retrospective studies	2	0.72 (0.67-0.76)	<0.001	1.11	0.292	9.8%	0.001
A history of stroke							
• Mixed patients with and without prior stroke	4	0.77 (0.64-0.93)	0.008	7.17	0.067	58.2	0.020
• Patients with prior stroke	1	0.81 (0.59-1.12)	0.198	NA	NA	NA	NA

**Abbreviations:** OAC=oral anticoagulant, RR=risk ratio, CI=confident interval, RCTs=randomized controlled trials, VKA=vitamin K antagonist, NA=not applicable