Prevalence, safety and effectiveness of oral anticoagulant use in people with and without dementia or cognitive impairment: a systematic review and meta-analysis

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Running title: Anticoagulation use and outcomes stratified by dementia

Abstract

Background

Differences in management and outcomes of oral anticoagulant (OAC) use may exist for people with and without dementia or cognitive impairment (CI).

Objective

To systematically review the prevalence and safety and effectiveness outcomes of OAC use in people with and without dementia or CI.

Methods

MEDLINE, EMBASE and CINAHL were searched for studies reporting prevalence or safety and effectiveness outcomes of OAC use for people with and without dementia, published between 2000 to September 2017. Study selection, data extraction and quality assessment were performed by two-reviewers.

Results

27 studies met pre-specified inclusion criteria (21 prevalence studies, six outcomes studies). People with dementia had 52% lower odds of receiving OAC compared to people without dementia. Mean OAC prevalence was 32% for people with dementia, compared to 48% without dementia. There was no difference in the composite outcome of embolic events, myocardial infarction, and all-cause death between dementia and non-dementia groups (adjusted hazard ratio (HR) 0.72, 95% CI, 0.45-1.14, p=0.155). Bleeding rate was lower for people without dementia (HR 0.56, 95% CI, 0.37-0.85). Adverse warfarin events were more common for residents of long-term care with dementia (adjusted incidence rate ratio 1.48, 95% CI, 1.20-1.82). Community-dwelling people with dementia treated with warfarin had poorer

anticoagulation control than those without dementia (mean time in therapeutic range (TTR) % ± SD, 38±26 (dementia), 61±27 (no dementia), p<0.0001).

Conclusion

A lower proportion of people with dementia received oral anticoagulation compared with people without dementia. People with dementia had higher bleeding risk and poorer anticoagulation control when treated with warfarin.

Key words: anticoagulant, atrial fibrillation, dementia, cognitive impairment, prevalence, ischaemic stroke, haemorrhage, warfarin

INTRODUCTION

Atrial fibrillation (AF), dementia and cognitive impairment (CI) are common in older adults, hence they often occur together [1]. AF is a key risk factor for stroke, and confers a nearly twofold increased probability of death [2-5]. Further, AF has been associated with an increased risk of developing dementia, with and without prior history of stroke [1, 6]. Diabetes, heart failure and hypertension are risk factors for both AF and CI [1, 6-9]. Between 26% and 51% of community and hospitalized individuals with AF have CI [10-12]. People with CI have longer durations of hospitalization, poorer post-discharge outcomes and increased risk of re-hospitalization than people without CI [13, 14].

The presence of dementia or CI affects the management of comorbid chronic disease [15, 16]. Prevention of long-term complications of chronic disease may be de-emphasized in the context of limited life expectancy and changing care goals [16]. Compared to people with AF and normal cognition people with dementia or CI and AF are less likely to receive vitamin K antagonists (VKA), even though people with dementia demonstrate similar or increased stroke risk [17-21] and increased mortality risk [22, 23]. People with dementia are at increased risk of haemorrhagic complications, such as bleeding linked to falls [24-26]. Further, due to the detrimental effects of amyloid-beta on arterial walls, people with dementia may experience increased rates of intracranial haemorrhage [27, 28]. European Society of Cardiology guidelines recommend withholding OAC in people with dementia only when medication non-adherence is suspected and cannot be assured by a caregiver [22]. American Academy of Neurology guidelines state insufficient evidence is available regarding the safety of OAC for stroke prevention in AF in moderate to severe dementia [29].

The introduction of four direct oral anticoagulants (DOACs): dabigatran, rivaroxaban, apixaban and edoxaban, has expanded the anticoagulant armamentarium for stroke

prevention in AF. Large phase III randomised controlled trials (RCTs) provide evidence of non-inferiority or superiority to warfarin for the prevention of cerebral and systemic embolic events in AF, but reduced risk of intracranial bleeding [30-34]. Well-conducted observational studies support the effectiveness and safety of DOACs compared with warfarin in more inclusive groups [35-39]. DOACs offer practical advantages over VKA therapy as DOAC dosing is based on clinical characteristics and fixed dosing regimens [40]. OAC utilization has increased considerably following DOAC introduction. There has been increasing uptake of DOACs, while the use of VKA has gradually reduced [41-45]. Increasing OAC use has been observed in women [41] and in older people, particularly octogenarians [41, 44]. However, comparative effectiveness and safety studies that include representative samples of people with dementia or CI are lacking [45]. Few people with dementia were eligible to participate in the pivotal DOAC trials [46]. The objective of this systematic review was to identify published data comparing the prevalence and safety and effectiveness outcomes of OAC use in people with AF with and without dementia or cognitive impairment, and to summarise the data using a meta-analysis.

METHODS

The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [47]. The review protocol was registered in the Prospero International Prospective Register of Systematic Reviews (PROSPERO Number CRD42017050663). Oral anticoagulant medications were defined as oral formulations of vitamin K antagonists, direct thrombin inhibitors and factor Xa inhibitors (Anatomical Therapeutic Chemical (ATC) codes of the World Health Organization: B01AA03 (warfarin), B01AE07 (dabigatran etexilate), B01AF01 (rivaroxaban), B01AF01 (apixaban) and B01AF03 (edoxaban) [48]. Studies of all forms of cognitive impairment and

dementia were considered, including mild cognitive impairment, Alzheimer's disease, vascular dementia, mixed dementias and Lewy Body dementia.

Search strategy

Studies were identified through a literature search using MEDLINE, EMBASE and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases from 1 January 2000 until 30 September 2017. This date range was selected to cover eight to 10 years before and after the introduction of the DOACs. Medical subject headings (MeSH), Emtree terms, keywords and truncated search terms related to dementia or CI (dementia, Alzheimer's disease, cognitive impairment, cognitive aging) and anticoagulants (anticoagulant, novel oral anticoagulant, NOAC, direct oral anticoagulant, DOAC, apixaban, dabigatran, rivaroxaban, edoxaban, warfarin, vitamin K antagonist, direct thrombin inhibitor and factor Xa inhibitor) were combined. Searches were limited to English-language. Reference lists of identified articles were screened for any additional studies. Full search strategies are available in Appendix 1 of Supplemental Material.

Inclusion and exclusion criteria

Studies of all designs were eligible for inclusion. Studies were included in this review if they reported:

- original research reporting the prevalence or safety and effectiveness outcomes of oral anticoagulant use for people with and without dementia or CI;
- prevalence or safety and effectiveness outcomes data separately for people with and without dementia or CI drawn from the same study sample and presented within the study result, for example, sub-group analyses;

- prevalence data of specific oral anticoagulants or prevalence data for classes of oral anticoagulants such as vitamin K or non-vitamin K antagonists for people with and without dementia or CI;

Studies were excluded if they:

- reported the prevalence or safety and effectiveness outcomes of oral anticoagulant use in people with dementia or CI only;
- only reported aggregated results for oral and parenteral anticoagulants combined or antiplatelet and anticoagulant medications combined;
- did not present original data, or were case reports, conference proceedings, review articles, editorials or letters, or not available in English language.

Study selection

One reviewer (TRA) performed the full search strategy, removed duplicates and screened article titles. Abstracts were screened independently by two reviewers (TRA, LF). Full-text copies were obtained if studies appeared to meet inclusion criteria or if it was unclear if they met inclusion criteria. Full-text articles were independently reviewed by two investigators (TRA, LF) for inclusion. Discrepancies were discussed with a third investigator (JI) until consensus was reached.

Data extraction

Data were extracted by two reviewers (TRA and LF) independently using a standardised data extraction tool. Data extracted included study details, publication year, study design, study country and setting, study sample characteristics (age, gender), sample size, data sources used, data collection period, prevalence of dementia or CI within study sample, prevalence of OAC use for the overall study sample, prevalence of OAC use among participants with dementia or

CI, prevalence of OAC use among participants without dementia or CI, safety and effectiveness outcomes of OAC use for participants with dementia, OAC investigated and OAC indications(s), safety and effectiveness outcomes from OAC use for participants without dementia, dementia type and the method used to identify dementia or CI. Data were extracted separately for participants with and without dementia or CI. Prevalence results include both estimates based on individual oral anticoagulants and grouped oral anticoagulants. When prevalence of OAC use data were clearly reported for these groups, results provided by the authors were used. When data were not clearly reported, but stratification and calculations were possible using the published data, calculations were undertaken to determine prevalence of OAC use among participants with dementia or CI and those without dementia or CI. Data for safety and effectiveness outcomes from OAC use were descriptively extracted from each study and reported separately.

Quality assessment

Two investigators (LF, TRA) independently assessed the methodological quality of prevalence and outcomes studies using adapted versions of the Joanna Briggs Institute critical appraisal tools for analytical cross-sectional studies and cohort studies, respectively [49] (Appendix 2). Quality assessment tools were selected based on study designs of included studies. No RCTs were identified in this systematic review. For cross-sectional prevalence studies, the definition of dementia and medication use, were assessed against pre-specified quality criteria. These quality criteria were applied even when comparing the prevalence of OAC use in people with and without dementia was not the primary objective of each included study (Appendix 2). Any disagreements in assessments were resolved by a third investigator (JI).

Mean OAC prevalence and time trends

The mean OAC prevalence for cardioembolic stroke prevention in AF for dementia/CI and non-dementia/CI groups was calculated by averaging OAC prevalence for all studies combined and stratified by community, hospital and long term care settings. Trends in OAC prevalence for cardioembolic stroke prevention in AF over the time period 2000 to 2016 were examined by plotting OAC prevalence for dementia/CI and non-dementia/CI groups by mid-year of study observation period. A linear trend line was fit to examine changes in OAC prevalence over time. Two studies did not report time of study observation period and were excluded [50, 51].

Meta-analysis

The prevalence of OAC use for people with AF both with and without dementia or CI and crude odds ratios (OR) were calculated from study data of included articles. Meta-analyses were conducted by pooling all studies, and then stratifying by healthcare settings: community, hospital and long-term care (e.g: residential aged care facilities). Meta-analyses were performed using Review Manager 5.3 [52]. Data were pooled using a random effect model as described by DerSimonian-Laird [53]. The pooled-effect of OAC use for people with and without dementia are reported as OR and 95% confidence intervals (CI). Statistical heterogeneity was assessed among studies by the I^2 statistic. To account for both clinical and statistical heterogeneity between studies we utilised a random-effects model. Sensitivity analyses were conducted to investigate the influence of individual studies and characteristics in the pooled ORs for OAC prevalence.

RESULTS

Electronic database searches yielded 4081 articles, of which 27 were finally included in this review (figure 1). Of the included 27 studies, 21 studies provided results for prevalence of OAC use for cardioembolic stroke prevention in AF and six studies provided results for

safety and effectiveness outcomes from OAC use for cardioembolic stroke prevention in AF among people with and without dementia or CI.

Study characteristics

Study characteristics are summarised in table 1. Studies were conducted in United States of America (n=8) [20, 23, 51, 54-58], Canada (n=3) [17, 59, 60], United Kingdom (n=4) [19, 24, 61, 62] and rest of Europe (n=11) [50, 63-72], and one study was a multicentre international study [18]. Three prevalence studies utilised data from the Stroke in Atrial Fibrillation Ensemble II (SAFE II) study (multi-site European study) [65, 66, 68].

Of the 21 studies reporting the prevalence of OAC use, 11 were conducted in a hospital setting [17, 20, 50, 55, 59, 64-68, 70], seven in a community setting [19, 24, 54, 60-62, 69] and three in long-term care [51, 57, 63]. Fifteen of the studies were cross-sectional designs, four were retrospective cohort studies, one study was a prospective cohort study and one was a series of cross-sectional studies (table1). Data from prevalence studies involved 14,734 people with dementia and 307,961 people without dementia.

Of the six studies that presented safety and effectiveness outcomes data of OAC use, four were conducted in community settings [18, 23, 56, 72], one in a hospital [71] and one in long-term care setting [58]. Four of the studies were retrospective cohort designs [23, 56, 71, 72], one study was a prospective cohort study [58] and one study undertook post-hoc analysis of a subset of data collected in a randomised controlled trial (table 1) [18].

Warfarin was the anticoagulant investigated for 20 of the 27 studies. One study included dabigatran, rivaroxaban, apixaban and warfarin [17], one study reviewed warfarin and phenprocoumaron [70], one study reviewed warfarin and acenocoumarol [71] and one study reviewed acenocoumarol alone [72]. Three studies did not specify the exact anticoagulant [50, 62, 64] but stated vitamin K antagonists were used.

The indication for OAC for 24 of the 27 studies was stroke prevention in AF alone. Further, one study included thromboembolic disease, mechanical valve replacement and stroke prevention in AF indications [58], one study included treatment of venous thromboembolism (VTE) and stroke prevention in AF indications [56] and one study did not specify the indication [50].

Study participant characteristics

The included studies selected their patients based on the presence of AF (n=13), AF plus incident- or prior-stroke and/or TIA (n=7), AF/thromboembolic disease/mechanical valve replacement (n=2), AF plus an additional risk factor for stroke (n=1), received treatment from a cardiac provider (n=1), had sustained hip fracture secondary to high-energy fall (n=1), admitted to a geriatric unit and were receiving OAC (n=1), were aged 75 years and older with a history of cardiovascular disease (n=1) (table 1).

Age was reported as mean with standard deviation, median with range or interquartile range (IQR) and by proportions for specified age groups. Mean age ranged from 70.9 ± 9.5 years to 87.1 ± 5.3 years [18, 63]. Median age ranged from 73 (IQR: 64-81) to 85 years [57, 62]. Three studies stratified by age groups and included 21% of participants aged between 60-69 years [24], 9.4% aged less than 65 years [66], and 16% between 65-75 years [23]. The proportion of females ranged from 45% to 75%. The proportion of participants within each study with dementia or CI ranged from 1% to 75%.

The presence of dementia or CI was variably defined across studies. Dementia was reported for 14 studies, cognitive impairment/disorders/dysfunction was reported for 10 studies, and three studies considered both terms as distinct clinical classifications. Eleven studies identified the presence of dementia from information available in administrative data: International Classification of Diseases and Health Related Problems (ICD) codes for

dementia [60, 70], Quality and Outcome Read Codes for dementia [19, 24, 61, 62], dementia diagnosis within the Minimum Data Set [57] or comorbid information/problem lists from hospital electronic medical records [54, 59], electronic nursing home database [57], or stroke registry [17]. Nine studies identified people with dementia or cognitive impairment via medical diagnoses found in medical charts and histories, where some studies specified a formal dementia or geriatric assessment and others did not [20, 23, 51, 55, 58, 63-66, 68]. Seven studies described dementia diagnosis ascertainment from validated methods such as the full or modified Mini Mental State Examination (MMSE) or Short Portable Mental Status questionnaire [18, 50, 56, 67, 69, 71, 72] (table 1).

Methodological quality of studies

Fifteen of 21 cross-sectional prevalence studies scored the maximum on quality assessment. Comparative prevalence of OAC use in people with and without dementia was not the main outcome of interest in all 21 studies included in this review. For this reason we did not assess whether confounding factors were adequately addressed when investigating the difference in prevalence among people with and without dementia or CI. All studies for which prevalence results were obtained compared characteristics of people receiving OAC with those not receiving OAC, which was stratified by presence of dementia (sub-group analyses). Five of the 21 studies from which prevalence data were obtained did not indicate how OAC use was measured which precludes rigorous assessment of whether this was measured validly [50, 62, 64, 67, 70]. For studies that compared safety and effectiveness outcomes of OAC use between dementia and non-dementia groups, three studies scored 10 out of a maximum of 11 points [18, 58, 72] while three studies scored 7 or less points on quality assessment [23, 56, 71]. These three studies were descriptive and did not deal with confounding factors. One study did not provide adequate information to measure OAC use [23]. Full quality assessment results are available in appendix 3 of supplemental material.

Prevalence of oral anticoagulant use

The prevalence of OAC use for cardioembolic stroke prevention in AF was 29% (4221/14539) for people with dementia or CI and 47% (144254/306751) for people without dementia or CI when all study data were combined. Prevalence of OAC use for cardioembolic stroke prevention in AF in people with and without dementia or CI ranged from 8.3% to 64.0% and 7.0% and 75.6%, respectively (table 2). Mean prevalence of OAC use for cardioembolic stroke prevention in AF for people with dementia was 32% compared with 48% for people without dementia (figure 2). For the time period 1998 to 2014, OAC prevalence for cardioembolic stroke prevention in AF increased for both dementia and non-dementia groups across all health care settings combined (figure 3).

An overall meta-analysis for all healthcare settings revealed that people with dementia or CI had a significantly lower prevalence of OAC use for cardioembolic stroke prevention in AF compared to people without dementia or CI (OR 0.48, 95% CI=0.40–0.58, p<0.00001) (figure 4 (1.1.1)). Significant statistical heterogeneity between studies was found (I^2=93%). When stratified by healthcare setting, people with dementia or CI residing in the community had a significantly lower prevalence of OAC use (OR 0.40, 95% CI=0.31–0.52, p<0.00001) (figure 4 (1.1.2)), followed by the people with dementia or CI receiving care in hospital (OR 0.49, 95% CI=0.33–0.73, p<0.00001) (figure 4 (1.1.3)), then followed by residents in long-term care (OR 0.66, 95% CI=0.45–0.95, p<0.00006) (figure 4 (1.1.4)) when compared to people without dementia or CI. Sensitivity analysis revealed no significant influence of any individual studies, study characteristics or dementia classification on the prevalence of OAC in people with and without dementia (Figures 1-5 and 8-9 within Appendix 4 of Supplemental Material). Additionally, to assess increasing prevalence of OAC over time, a sensitivity analysis was conducted that included studies published during or after 2010 only which showed a similar pooled odds ratio to the overall odds ratio (Figure 2, Appendix 4 in

Supplemental Material). However, sensitivity analysis that included studies with ≥ 30% of the study sample with a prior history of stroke or TIA demonstrated a higher prevalence of OAC use for cardioembolic stroke prevention in AF compared to people without dementia or CI (OR 0.58, 95% CI=0.43–0.79, p<0.00001) (Figure 6 of Appendix 4 in Supplemental Material).

Safety and effectiveness outcomes of oral anticoagulant use

Safety and effectiveness outcomes of oral anticoagulant use for cardioembolic stroke prevention in AF for people with and without dementia or CI are summarised in table 3. Differences in effectiveness and safety were reported for dementia/CI and non-dementia/CI groups. It was not possible to conduct a meta-analysis on the safety and effectiveness of OACs. Data on the safety and effectiveness of OACs from each study were reported separately.

Effectiveness outcomes

One study reported that the composite outcome of stroke, non-central nervous system (CNS) embolism, myocardial infarction (MI), vascular death, and all-cause death was significantly lower for people without dementia than for people with dementia (HR 0.46, 95% CI, 0.27-0.78, p=0.002). When controlled for TTR, there was no increased risk for the composite outcome in the dementia group (adjusted HR 0.72, 95% CI, 0.45-1.14, p=0.155) [18]. Results for studies of smaller samples suggested that rates of thrombosis [56], stroke, and mortality [23] were not different for dementia and non-dementia groups (table 3).

Safety outcomes: anticoagulation control

Four studies reported varied results regarding anticoagulation control. One study found that people with CI residing in the community had poorer anticoagulation control than people without CI. People with CI (MMSE score <24) demonstrated lower mean percentage of TTR

(mean ± standard deviation (SD) 38±26) compared to people without cognitive impairment (MMSE score >27), (mean (SD) 61±27), p< 0.0001) [71]. Results of another study demonstrated that long-term warfarin users with CI monitored within a pharmacist-managed anticoagulation clinic also spent reduced TTR compared with warfarin users without CI, but the result was not statistically significant (TTR % mean (SD) 61±16 (MMSE ≤26), 65±20 (MMSE >26), p=0.36 [56]. Further descriptive results in another study indicated patients monitored in an anticoagulation clinic with an MMSE score less than 23 spent 68% of TTR compared with 76% for those with an MMSE 23 and above [72]. In addition, no differences for percentage of days with subtherapeutic, therapeutic and supratherapeutic INR values were found for people with and without dementia in long-term care [58].

Safety outcomes: adverse events

Total bleeding (minor and major) was found to be significantly lower for people without dementia than for those with dementia (HR) 0.56, 95% CI, 0.37-0.85) [18]. Although, in two studies, no significant differences were found for rates of minor and major bleeding and haemorrhage between dementia and non-dementia groups [23, 56]. Adverse warfarin events (AWEs) (injuries from warfarin) were significantly higher for residents in long-term care with dementia (adjusted incidence rate ratio (IRR) 1.48, 95% CI, 1.20-1.82). Risk of potential or preventable AWEs which constituted an INR value greater than 4.5 was also higher (adjusted IRR 1.36, 95% CI, 1.06-1.76) [58] (table 3).

Table 1. Methodological characteristics of included studies of prevalence and outcomes of oral anticoagulant use in people with and without dementia or cognitive impairment (by year of publication)

First author (year)	Study design, country and health care setting	Population (N), description of study sample and study data source(s)	Anticoagulant reviewed and main indication(s)	Dementia type reported, data source and measurement method	Time of data collection
Articles relating to prevalence of oral anticoagulant use (by year of publication)					
Deplanque (2004)[65]	Cross-sectional Five countries: Austria, Belgium, France, Italy and Portugal Hospital	N=370 Patients diagnosed with an acute stroke or TIA with known AF (paroxysmal or permanent) – on admission to hospital Medical histories from a variety of sources: GP, patient interview, family, cardiologist	Warfarin Stroke prevention in AF	Condition reported: Cognitive impairment Data source and measurement method: Ascertainment of documentation of cognitive impairment diagnosis from study data (derived from medical history taking)	September 2001 – June 2002
Latif (2005)[51]	Cross-sectional USA Residential Aged Care Facility	N=117 Nursing home residents with AF Medical charts and administrative data	Warfarin Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Dementia diagnosis within the nursing home medical charts	Not specified
Choudhry (2006)[60]	Cross-sectional Canada Community	N=116200[a] Patients with an identifiable cardiac provider Data sources: 1. Canadian Institutes of Health Information database 2. The Ontario Drug Benefits claims database 3. Ontario Health Insurance Plan 4. Ontario Registered Persons database 5. Corporate Providers Database of the Ontario Ministry of Health 6. Southam Medical database	Warfarin Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Presence of dementia diagnosis coding (hospital ICD-9 codes 290.1 to 290.4, 290.8, 290.9, 294.1, 331.0, 331.1, 331.2 046.1, 046.2) in hospital administrative data	1 January, 1994 – March 31, 2002
Deplanque (2006)[66]	Cross-sectional Five countries: Austria, Belgium, France, Italy and Portugal Hospital	N=320 (subset of Deplanque 2004[65]) Patients with AF who have suffered ischaemic stroke and were being discharged from hospital Medical histories from a variety of sources: GP, patient interview, family, cardiologist	Warfarin Stroke prevention in AF	Condition reported: Cognitive impairment Data source and measurement method: Ascertainment of documentation of cognitive impairment diagnosis from study data (derived from medical history taking)	September 2001 – June 2002
Hylek (2006)[55]	Cross-sectional USA Hospital	N=405 Hospitalized patients with AF Hospital medical records	Warfarin Stroke prevention in AF	Condition reported: Cognitive impairment/dementia Data source and measurement method: Medical diagnosis of dementia within the hospital medical record	January 2001 – June 2003
Lefebvre (2006)[68]	Prospective cohort France and Italy Hospital	N=204 Patients diagnosed with an acute stroke or TIA with known AF (paroxysmal or permanent) Medical histories from a variety of sources:	Warfarin Stroke prevention in AF	Condition reported: Cognitive impairment Data source and measurement method: Ascertainment of documentation of cognitive impairment diagnosis from	September 2001 – June 2002

		GP, patient interview, family, cardiologist		study data (derived from medical history taking)	
Lopponen (2006)[69]	Cross-sectional Finland Community	N=409 Patients aged 75 years and older with CVD Patient interview, laboratory and clinical examinations	Warfarin Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Two stage process: 1) MMSE, 2) Interview covering items of the Hachinski Ischaemic Scale and the Clinical Dementia Rating. Dementia was also assessed in clinical examination according to DSM-IV criteria, diagnosis of possible Alzheimer's disease according to the NINCDS-ADRDA criteria and diagnosis of possible vascular dementia according to the NINDS-AIREN criteria	1998 – 1999
Partington (2007)[59]	Cross-sectional Canada Hospital	N=196 (entire study sample) N=106 (patients eligible for anticoagulation in which dementia stratification presented) Patients with AF and acute ischaemic stroke EMR data	Warfarin Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Dementia documentation in primary diagnoses and comorbid conditions from the hospital's EMR	1999 – 2004
Doucet (2008)[67]	Cross-sectional France Hospital	N=209 Patients ≥ 65 years with chronic AF Medical charts	Warfarin Stroke prevention in AF	Condition reported: Dementia (mean MMSE for anticoagulant and aspirin groups provided) Data source: Medical charts	January 2004 – April 2005
De Breucker (2010)[64]	Cross-sectional Belgium Hospital	N=111 Patients admitted to an acute geriatric unit at an academic hospital Computerized medical charts	Vitamin K Antagonist (exact medication not specified) Stroke prevention in AF	Condition reported: Cognitive disorders Data source and measurement method: Documentation of cognitive disorders within comprehensive geriatric assessments	April 2006 – November 2008
Ewen (2012)[54]	Retrospective longitudinal cohort study USA Community	N=1141 Patients with AF EMR data, hospital administrative data	Warfarin Stroke prevention in AF	Condition reported: Cognitive dysfunction Data source and measurement method: EMR problem list, hospital administrative data	January 1, 1998 – June 30, 2010
Holt (2012)[62]	Longitudinal series of cross-sectional surveys United Kingdom Community	N=59804 Patients with AF QResearch database	Specific anticoagulant(s) not specified Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Read code for dementia within the QResearch database	2007-2010 (2010 data only presented in this paper)
Scowcroft (2012)[24]	Retrospective cohort United Kingdom General Practice	N=81381 Patients aged >60 years with a new diagnosis of AF United Kingdom General Practice Research Database	Warfarin Stroke prevention in AF	Condition reported: Alzheimer's disease/dementia Data source and measurement method: Presence of dementia Read Code in the United Kingdom General Practice Research Database	2000 – 2009
Mohammed	Cross-sectional	N=50361	Warfarin	Condition reported: Dementia	1 May 2010

(2013)[19]	United Kingdom General Practice	Patients with a diagnosis of AF (≥ 35 years of age). The Health Improvement Network (THIN) database	Stroke prevention in AF	Data source and measurement method: Dementia Read Code present within patient records of the Health Improvement Network (THIN) database	
Reardon (2013)[57]	Cross-sectional USA Long-term care	N=5211 Long-term care residents with AF National Nursing Home Survey and the AnalytiCare Long-Term Care databases	Warfarin Stroke prevention in AF	Condition reported: Dementia/cognitive impairment Data source and measurement method: Presence of dementia or cognitive impairment diagnosis within the minimum data set of the AnalytiCare Long-Term Care database or from comorbid condition information in the National Nursing Home Survey database	2004 and 1 January 2007 – 30 June 2009
Dreischulte (2014)[61]	Cross-sectional Scotland Community	N=21096 Patients with AF Scottish General Practice data	Warfarin Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Quality and Outcomes defined Read Codes for dementia or prescription for acetylcholinesterase inhibitor) with the population database of Scottish general practices	31 March 2007
Tanislav (2014)[70]	Cross-sectional Germany Hospital	N=1828 Patients >18 years with index event of stroke or TIA; and diagnosed AF and a minimal physical impairment and direct discharge after acute treatment or referral to a rehabilitation facility. Registry data of the Institute of Quality Assurance Hesse and Claims data from a nationwide statutory health insurance company	Phenprocoumaron, warfarin and coumadin Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Presence of dementia ICD-10 codes within the claims data from a nationwide statutory health insurance company (F00, F01, F02, F03, G30)	2004 – 2010
Bahri (2015)[63]	Cross-sectional France Long-term care	N=1085 Nursing home residents over 75 years with a documented history of AF Medical charts	Warfarin Stroke prevention in AF	Condition reported: Cognitive impairment Data source and measurement method: Documentation of dementia/cognitive impairment with or without formal assessment from medical records	March 2012
Formiga (2016)[50]	Cross-sectional Spain Hospital	N=1225 Patients with hip fracture secondary to a high energy impact Hospital medical records	Chronic anticoagulation therapy (CAT) (exact medication not provided) Indication not provided	Condition reported: Dementia Data source and measurement method: Short Portable Mental Status questionnaire from the comprehensive geriatric assessment	Not provided
Shah (2016)[17]	Retrospective cohort Canada Hospital	N=5781 Patients ≥ 65 years with AF hospitalized from ischaemic stroke or TIA Databases: Ontario Stroke Registry, Canada	Warfarin, dabigatran, rivaroxaban and apixaban Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Presence of dementia diagnosis within the comorbid condition information in Ontario Stroke Registry	1 July 2003 – 31 December 2011

		Census, Ontario Drug Benefits, Canadian Institute for Health Information Discharge Abstract and the National Ambulatory Reporting System			
McGrath (2017)[20]	Retrospective cohort United States of America Hospital	N=1405 Individuals with AF and acute ischaemic stroke surviving hospitalization Kaiser Permanente database	Warfarin Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Dementia documentation in medical records extracted from structured chart review	July 1996 – September 2003
Articles relating to outcomes from oral anticoagulant use (by year of publication)					
Van Deelen (2005)[72]	Retrospective cohort study The Netherlands Community	N=152 Patients ≥ 70 years with AF treated with acenocoumarol managed by an anticoagulation service	Acenocoumarol (nicoumalone) Stroke prevention in AF	Condition reported: Cognitive impairment Data source and measurement method: MMSE during home visit on index date. Patients with MMSE < 23 were considered cognitively impaired.	March – May 2003
Jacobs (2009)[23]	Retrospective cohort study United State of America Community	N=106 Patients ≥ 65 years with chronic AF receiving warfarin or aspirin Medical records	Warfarin Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Documentation of dementia in medical records	2003
Flaker (2010)[18]	Post-hoc analysis of a randomized controlled trial 522 centres/31 countries Community	N=2510 Community patients with AF and an additional risk factor for stroke ACTIVE-W study data [73]	Warfarin Stroke prevention in AF	Condition reported: Cognitive impairment Data source and measurement method: Presence of cognitive impairment within clinical trial data which used a modified MMSE	June 2003 and December 2004
Khreizat (2012)[56]	Retrospective cohort study United States of America Community	N=57 Community patients aged ≥ 60 years on warfarin with target INR of 2-3. Medical charts	Warfarin Stroke prevention in AF and treatment of VTE	Condition reported: Cognitive impairment Data source and measurement method: Cognitive assessment was part of routine care using the Folstein MMSE. Cognitive impairment was defined as having a MMSE ≤ 26 . A lower cut point of MMSE ≤ 23 was also used to see if it impacted results	2006-2010
Tija (2012)[58]	Prospective cohort study (embedded within a clinical trial) United States of America Long-term care	N=435 Nursing home residents prescribed warfarin Clinical trial data (included medical charts and data abstraction by trained investigators)	Warfarin Stroke prevention in AF Thromboembolic disease Mechanical valve replacement	Condition reported: Dementia Data source and measurement method: Medical record review for dementia diagnosis	1 October 2007 to 31 December 2008
Gorzelak-Pabis (2016)[71]	Retrospective cohort study Poland Community	N=154 Persons with AF and dementia and indications for OAC ($CHA_2DS_2VAS_C \geq 1$ and HASBLED < 3)	Warfarin and acenocoumarol Stroke prevention in AF	Condition reported: Cognitive impairment Data source and measurement method: Cognitive skills were assessed using the Polish version of the correct MMSE.	2013-2015

		Medical charts		MMSE scores were corrected using Mungas adjustments for age and education level. MMSE < 27 was considered cognitive impairment.	

a - study sample was larger, but this group (n-value) were people with an identifiable provider in which dementia information was available

Abbreviations: AF = atrial fibrillation; CVD = cardiovascular disease; DOAC = direct oral anticoagulant; TIA = transient ischemic attack; MMSE = Mini-Mental State Examination; VTE = venous thromboembolism; INR = international normalised ratio; GP = general practitioner: ICD-9/ICD-10 = International Classification of Diseases and Health Related Problems, 9th edition or 10 edition; EMR = Electronic Medical Record; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th edition; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NINDS-AIREN = National Institute of Neurological and Communicative Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences.

Table 2. Prevalence of oral anticoagulant use in studies of persons with and without dementia – stratified by healthcare setting (by year of publication)

Author (year)	Age[a] and gender, % female	Prevalence of dementia (study sample)	Prevalence of anticoagulant use (study sample)	Prevalence of anticoagulant use in persons with dementia	Prevalence of anticoagulant use in persons without dementia	Odds ratio[b] (95% CI)
Community or General Practice						
Choudhry (2006)[60]	Warfarin users (n=50551) with identifiable providers = 76.2 (6.5), 48.3% Warfarin non-users (n=65649) with identifiable providers = 77.2 (7.1) 49% female	1738/116200 (2%)	50551/116200 (44%)	556/1738 (32%)	49995/114462 (43.7%)	0.61 (0.55 – 0.67)
Lopponen (2006)[69]	CVD+dem: 84.4 (5.7) CVD+no dem: 79.8 (4.4) 66% female	85/409 (21%)	Warfarin use only[d] 24/64 (38%)	5/20 (25%)	19/44 (43.2%)	0.44 (0.14 – 1.42)
Ewen (2012)[54]	70 (13.3) 48% female	87/1141 (8%)	764/1141 (67%)	55/87 (63%)	709/1054 (67.3%)	0.84 (0.53 – 1.32)
Holt (2012)[62]	Median age[c] (at AF diagnosis): 73.0 (IQR=64.0-81.0), median age (in 2010, of 69762 registered in 2010): 80.0 years (IQR=71.0-87.0) 47% female	374/34041 (1%)	18042/34041 (53%)	108/374 (29%)	17934/33667 (53.2%)	0.36 (0.28 – 0.45)
Scowcroft (2012)[24]	60-69=17054 (21%) 70-79=30350 (37%) 80+=33977 (42%) 52% female	53825/81381 (7%)	37119/81381 (46%)	1376/5382 (26%)	35761/75999 (47.0%)	0.39 (0.36 – 0.41)
Mohammed (2013)[19]	75.6 (11.7), 44% female	2255/50361 (4%)	24064/50361 (48%)	567/2255 (25%)	23497/48106 (48.8%)	0.35 (0.32 – 0.39)
Dreischulte (2014)[61]	75.5 (no SD) 45% female	1034/21096 (5%)	8852/20443 (43% - all current anticoagulation), 11959/20443 (59% - anticoagulant ever since diagnosis)	144/1006 (14%)	8717/19437 (44.8%)	0.21 (0.17 – 0.25)
Total prevalence: community setting	--	**Data combined: 59398/304629 (20%)** **Mean (%) (Std Dev): 15 (23)**	**Data combined: 142523/303631 (47%)** **Mean (%) (Std Dev): 50 (10)**	**Data combined: 2811/10862 (26%)** **Mean (%) (Std Dev): 31 (15)**	**Data combined: 136632/292769 (47%)** **Mean (%) (Std Dev): 50 (8)**	**0.40 (0.31 – 0.52)**
Hospital						
Deplanque (2004)[65]	Median age: 78 (range 29-101) 58% female	82/370 (22%)	82/288 (29%)	4/41 (10%)	78/329 (24%)	0.35 (0.12 – 1.01)

Deplanque (2006)[66]	< 65: 30 (9.4%) 65-74: 85 (26.6%) ≥ 75: 205 (64.1%) 57% female	38/320 (12%)	186/320 (58%)	7/38 (18%)	179/282 (64%)	0.13 (0.06 – 0.31)
Hylek (2006)[55]	80 (no SD) 58% female	51/405 (13%)	206/405 (51%)	8/51 (16%)	198/354 (56%)	0.15 (0.07 – 0.32)
Lefebvre (2006)[68]	Median age: 78.5 years (range: 54-101), 59% female	24/204 (12%)	53/204 (26%)	2/24 (8%)	51/180 (28%)	0.23 (0.05 – 1.01)
Partington (2007)[59],e	OAC 77.7 (8.6), 47% female No OAC 82.0 (9.2), 42% female	22/106 (21%)	57/106 (29%)	12/22 (55%)	45/84 (54%)	1.04 (0.41 – 2.67)
Doucet (2008)[67]	84.7 (7) 61% female	57/209 (27%)	102/209 (49%)	23/57 (40%)	79/152 (52%)	0.63 (0.34 – 1.16)
De Breucker (2010)[64]	84 (5), 72% female	65/111 (59%)	57/111 (51%)	35/65 (54%)	22/46 (48%)	1.27 (0.60 – 2.71)
Tanislav (2014)[70]	77.61 (8.6) 58% female	241/1828 (13%)	827/1828 (45%)	67/241 (28%)	760/1587 (48%)	0.42 (0.31 – 0.56)
Formiga (2016)[50]	82.7 (6) 74% female	249/1225 (20%)	99/1225 (8%)	30/249 (12%)	69/976 (7%)	1.80 (1.14 – 2.83)
McGrath (2016)[20]	79 (9) 54% female	195/1405 (14%)	786/1405 (56%)	67/195 (34%)	719/1210 (59%)	0.36 (0.26 – 0.49)
Shah (2016)[17]	Median age (IQR) No OAC=82 (75-87), OAC=79 (73-85) Females No OAC 54.9% OAC 53%	589/5781 (10%)	4235/5781 (73%)	377/589 (64%)	3858/5102 (76%)	0.57 (0.48 – 0.69)
Total prevalence: Hospital setting	--	**Data combined: 1613/11964 (13%)** **Mean (%) (Std Dev): 20 (14)**	**Data combined: 6690/11882 (56%)** **Mean (%) (Std Dev): 45 (18)**	**Data combined: 632/1572 (40%)** **Mean (%) (Std Dev): 31 (20)**	**Data combined: 6058/10302 (59%)** **Mean (%) (Std Dev): 47 (20)**	**0.49 (0.33 – 0.73)**
Long-Term Care						
Latif (2005)[51]	84.6 (no SD) 71% female	66/117 (56%)	54/117 (46%)	26/66 (39%)	28/51 (55%)	0.53 (0.25 – 1.12)
Reardon (2013)[57]	NNHS database - median age 85 years 70% female AnalytiCare database - median age 83 years 63% female	1457/5211 (28%)	2176/5211 (42%)	462/1457 (32%)	1714/3754 (46%)	0.55 (0.49 – 0.63)

Bahri (2015)[63]	87.1 (5.3) 73% female	777/1085 (72%)	541/1085 (50%)	357/777 (46%)	541/1085 (50%)	0.86 (0.71 – 1.03)
Total prevalence: Long-Term Care setting	--	**Data combined: 2300/6413 (36%)** **Mean (%) (Std Dev): 52 (22)**	**Data combined: 2771/6413 (43%)** **Mean (%) (Std Dev): 46 (4)**	**Data combined: 845/2300 (37%)** **Mean (%) (Std Dev): 39 (7)**	**Data combined: 2283/4890 (47%)** **Mean (%) (Std Dev): 50 (5)**	**0.66 (0.45 – 0.95)**
TOTAL FOR ALL STUDIES COMBINED	--	**Data combined: 63311/323006 (20%)** **Mean (%) (Std Dev): 23 (21)**	**Data combined: 151984/321926 (47%)** **Mean (%) (Std Dev): 47 (14)**	**Data combined: 4288/14734 (29%)** **Mean (%) (Std Dev): 32 (17)**	**Data combined: 144793/307961 (47%)** **Mean (%) (Std Dev): 48 (15)**	**0.48 (0.40 – 0.58)**

a – presented as mean (years) ± standard deviation unless otherwise indicated

b – Odds ratios are crude unless otherwise specified. Crude odds ratios were calculated with data extracted from sub-group analysis of results within research papers

c – Holt et al (2012) – age data are based on the full cohort of 99351 persons. Prevalence data include persons with a CHADS2 score >2 (n=34041) in which dementia stratification was available.

d – Includes patients using warfarin. Patients using antiplatelets excluded

e – Results provided reflect the 106 patients eligible for OAC in which dementia/no dementia stratification was available (n=196 for entire study sample)

Abbreviations: CVD = cardiovascular disease; Dem = dementia; OAC = oral anticoagulation; CI = confidence interval; Std Dev = standard deviation.

Table 3. Outcomes for oral anticoagulant use in persons with and without dementia (by year of publication)

Author (year)	Age[a] and gender, % female	Prevalence of dementia (study sample)	Outcomes reported that were stratified by dementia/non-dementia	Outcome results
Van Deelen (2005)[72]	Age and gender stratified by %TTR INR 2-3.4 > 70% TT: 78.8 (5.3), 48.5% female INR 2-3.4 > 70% TT: 79.5 (5.3), 50% female	24/152 (15.8%)	Treatment time in therapeutic range	<u>INR with therapeutic range</u> MMSE < 23: 68% of treatment time MMSE ≥23: 76% of treatment time
Jacobs (2009)[23]	65-75 years, n=17 (16%); 75-85, n=51 (48%); >85, n=38 (36%), 75% female	22/106[b] (21%)	Mortality, haemorrhage and stroke (17 people with dementia were receiving warfarin and 73 without dementia or falls were receiving warfarin). *Results are descriptive.*	<u>Mortality</u> Dementia: 8/17 (47.1%) No dementia: 10/73 (13.7%) <u>Haemorrhage</u> Dementia: 1/17 (5.9%) No dementia: 4/73 (5.5%) <u>Stroke</u> Dementia: 0/17 (0%) No dementia: 2/73 (2.7%)
Flaker (2010)[18]	70.9 ± 9.5, 65.5% female	365/2510 (14.5%)	Stroke, non-CNS embolism, vascular events, myocardial infarction, total bleeding (minor and major)	<u>Composite of stroke, vascular death, MI or non-CNS embolism</u> MMSE < 26: 6.7 per 100 person-years MMSE ≥ 26: 3.6 per 100 person-years Unadjusted HR (95% CI) = 0.46 (0.27-0.78), p=0.002 Adjusted HR (95% CI) = 0.72 (0.45-1.14), p=0.155 <u>Total bleeding (includes major and minor)</u> MMSE < 26: 42 per 100 person-years MMSE ≥ 26: 7 per 100 person-years HR (95% CI) = 0.56 (0.37-0.85), p=0.04
Khreizat (2012) [56]	**New warfarin users** MMSE score >26: 79.4 ± 9.5, 92% female MMSE score ≤ 26: 75.6 ± 6.3, 75% female **Long-term warfarin users** MMSE score >26: 81.0 ± 6.9, 68% female	30/57 (53%)	*Outcomes were stratified by new warfarin users and long-term users with and without dementia/cognitive impairment* Visits/days required to achieve therapeutic anticoagulation (new users); TTR/long-term anticoagulation stability; percentage of clinic visits with reported dose mishaps; frequency of in-range INRs following dose	**New warfarin users (n=20; dementia=12, no dementia=8)** <u>Visits to achieve therapeutic anticoagulation</u> MMSE score >26: 5.8 ± 4.3 MMSE score ≤ 26: 4.6 ± 2.4 (p=0.44). <u>Days to reach therapeutic anticoagulation</u> MMSE score >26: 35.8 ± 30.5 MMSE score ≤ 26: 51.6 ± 45.7

	MMSE score ≤ 26: 74.6 ± 9.3, 77% female		mishaps; minor bleeding; major bleeding; thrombosis (long-term users).	(p=0.36). **Long term warfarin users (n=54; dementia=28, no dementia=26)** TTR [mean ± SD] MMSE ≤ 26: 61 ± 16% MMSE > 26: 65 ± 20% (p=0.36) Frequency of dose mishaps MMSE ≤ 26: 86/691 visits MMSE > 26: 74/705 visits (p=0.18) In-range INRs following dose mishaps MMSE ≤ 26: 16% MMSE > 26: 32% (p=0.013) Minor bleeding (per patient-year) MMSE ≤ 26: 0.20±0.42 MMSE > 26: 0.28±0.54 (p=0.51) Major bleeding (per patient-year) MMSE ≤ 26: 0.02±0.10 MMSE > 26: 0.07±0.25 (p=0.29) Thrombosis (per patient-year) MMSE ≤ 26: 0 MMSE > 26: 0.01±0.06 (p=N/A)
Tija (2012)[58]	**Dementia** 83.6 ± 9.3, 74% female **No dementia** 80.4 ± 11.6, 61% female	218/435 (50%)	Number of INR tests; percentage of days with subtherapeutic, therapeutic and supratherapeutic INRs; incidence of AWEs (injuries from warfarin), incidence of preventable and potential AWEs (INRs >	Number of INR tests, mean (SD) Dementia: 24.2 (13.9) No dementia: 26.0 (14.5) (p=0.017)

			4.5), adjusted association of dementia with AWEs and preventable and potential AWEs	<u>INR < 2, % (SD)</u> Dementia: 37.8 (23.2) No dementia: 37.7 (20.4) (p=0.95) <u>INR < 2-3, % (SD)</u> Dementia: 49.5 (22.2) No dementia: 48.6 (19.9) (p=0.72) <u>INR < 3-4.5, % (SD)</u> Dementia: 10.7 (9.8) No dementia: 11.7 (12.2) (p=0.34) <u>INR >4.5, % (SD)</u> Dementia: 2.1 (6.7) No dementia: 2.0 (7.1) (p=0.82) <u>Incidence rates of AWEs (injuries from warfarin, events per 100 resident-months)</u> Dementia: 12.8 No dementia: 9.99 IRR (95% CI) = 1.40 (1.14-1.72) – after adjustment for resident characteristics IRR (95% CI) = 1.48 (1.20-1.82) – after adjustment for nursing home characteristics and case mix <u>Incidence of preventable and potential AWEs (INR >4.5, events per 100 resident-months)</u> Dementia:8.09 No dementia: 6.50 IRR (95% CI) = 1.35 (1.04-1.74) – after adjustment for resident characteristics IRR (95% CI) = 1.36 (1.06-1.76) – after adjustment for nursing home characteristics and case mix
Gorzelak-Pabis (2016)[71]	MMSE score ≥ 27: 73 ± 9, 61% female MMSE score < 27: 77 ± 11, 69% female	42/104 (40%)	Mean TTR and INR values	<u>Mean TTR, % (mean ± SD):</u> MMSE < 27: 38±26 MMSE ≥ 27: 61±27 (p<0.0001)

				TTR > 60, n (%): MMSE < 27: 12/42 (28%) MMSE ≥ 27: 38/62 (61%) (p<0.0001) *INR < 2*, n (%): MMSE < 27: 19/42 (46%) MMSE ≥ 27: 37/62 (59%) (p<0.05) *INR 2-3*, n (%): MMSE < 27: 11/42 (26%) MMSE ≥ 27: 37/62 (60%) (p<0.05) *INR > 3*, n (%): MMSE < 27: 12/42 (28%) MMSE ≥ 27: 14/62 (22%) (p<0.05)

a – presented as mean (years) ± standard deviation unless otherwise indicated

b – 112 patients in study sample, but 106 undergoing antithrombotic treatment

Abbreviations: TTR = time in therapeutic range; INR = international normalized ratio; OR = odds ratio; HR = Hazard Ratio; CI = confidence interval; N/A=not applicable; AWEs = adverse warfarin-associated events; IRR = incident rate ratio; TT = treatment time; CNS = central nervous system

DISCUSSION

To our knowledge, this is the first systematic review to investigate the prevalence and outcomes of OAC use for cardioembolic stroke prevention in AF in people with and without dementia or CI. There are three major findings from the review. First, people with dementia had 52% lower odds of receiving OAC for embolic stroke prevention associated with AF than people without dementia. Mean OAC prevalence for people with dementia was 32% compared with 48% for people without dementia. Over the time period 1998 to 2012, OAC prevalence increased for both groups for all healthcare settings combined. Second, six studies compared safety and effectiveness outcomes of OAC use among people with and without dementia, with all studies investigating diverse outcomes. This heterogeneity precludes a meta-analysis of outcomes data to accurately determine whether people with or without dementia have different outcomes of OAC treatment. Third, there is a paucity of data on the prevalence or outcomes of DOAC use in people with dementia. No DOAC safety or effectiveness studies identified by our search strategy have included representative samples of persons with dementia or presented sub-analyses for people with dementia.

People with dementia were less likely to receive OAC than people without dementia. Possible reasons for OAC underuse include: frailty, falls risk, active or prior bleeding, fear of bleeding complications, comorbidities, poor adherence, difficulties with self-monitoring, poor anticoagulation control and polypharmacy [10, 18, 51, 70, 71, 74]. Results from the European Heart Rhythm Association EP Wire survey found that 40% of respondents considered dementia as a key reason not to prescribe OAC. The only more important reason cited was prior or active bleeding or increased bleeding risk [74]. Yet it remains unclear to what extent dementia is associated with lower use of OAC independent of other factors that may contraindicate the prescription of OAC [75, 76]. Ultimately, people with dementia are more likely to experience substantial comorbidity, frailty and polypharmacy [75]. In a sample of

people with AF and dementia at high stroke risk but without increased bleeding risks or absolute contraindications to OAC, it was found that 22% of people received inadequate OAC and 39.5% received no OAC [76]. Further, at the time of dementia diagnosis, 26% of people with AF received warfarin, 37% antiplatelet therapy and 37% did not receive either antiplatelet or OAC [21]. While in people receiving warfarin therapy who were subsequently diagnosed with dementia, 16% remained on warfarin after dementia diagnosis compared with 96.7% of people who were not diagnosed with dementia [77]. Reluctance to prescribe OAC or an inclination to cease OAC in people with dementia could demonstrate that physicians perceive dementia as a limiting factor for OAC, possibly due to perceived increased bleeding risk or lack of adherence [74-76]. Moreover, high thromboembolic risk is often undervalued in ageing individuals with comorbid illness [78] and clinicians may be uncertain whether older, frail people, such as people with dementia could benefit from stroke reduction and whether this counterbalances the risk of bleeding [77, 78]. Our review demonstrates OAC under use in people with dementia and AF and possible higher bleeding risks. However, the risk-benefit of treatment for people with dementia may still provide net clinical benefit. Recent analysis of data from the Swedish Dementia Registry demonstrates lower risk of ischemic stroke and mortality, with only a small increase in any-cause haemorrhage in people with AF and dementia treated with warfarin [21]. Collectively, results may demonstrate that ~~patients~~ people with dementia and AF should not routinely be excluded from OAC treatment despite a slightly higher bleeding risk.

Over the time period of 1998 to 2012, increasing OAC prevalence was observed for both dementia and non-dementia groups. When stratified by healthcare setting, OAC prevalence for people with dementia in a hospital setting demonstrated the greatest increase. Medical practitioner characteristics and healthcare setting (hospital, community, long term care) have been found to influence OAC prescribing. It has been demonstrated that cardiologists have

increased guideline adherence, whereas General Practitioners (GPs) were less adherent [79]. Specialist therapeutic recommendations from neurology [70] facilitates the prescription of OAC, and follow-up by cardiologists and younger GPs were strong predictors of VKA treatment [65]. Patients treated at primary stroke centres and large academic hospitals were more likely to receive thromboprophylaxis than patients treated at smaller or general hospitals [34]. Residing in long term care is a negative predictor of being discharged from hospital with OAC [34, 66]. It is not possible to quantify the influence of practitioner characteristics and healthcare setting on our results, however future studies could confirm the effect of these factors on OAC use, particularly for people with dementia and since the introduction of the DOACs.

The results of this study reflect a low prevalence of OAC use for cardioembolic stroke prevention in AF in ~~patients~~ people with (48%) and without dementia or CI (32%). These results suggest possible under treatment in high risk populations for stroke. These results suggest limited compliance with current stroke prevention guidelines, especially among people with dementia. Alternatively, data included in this was averaged over an extended time period (2000-2017), which could mask the possible magnitude of changing rates of anticoagulation prevalence rates. Further, only one study included in this review provided data on DOAC use in dementia and non-dementia groups. Recent Australian and Norwegian studies have suggested that the overall prevalence of OAC use has increased since the availability of DOACs, particularly for octogenarians [41, 42].

Insufficient studies were identified in this present review to provide enough comparative information or to conduct a meta-analysis for outcomes of OAC use in persons with and without dementia. Two studies demonstrated that people with dementia have poorer anticoagulation control during treatment with VKA and spend more time below therapeutic range than people without dementia [56, 71]. Results that demonstrate a relationship between

CI and low TTR should not be directly interpreted as cause and effect, as other reasons could influence low TTR, although, it is clinically intuitive. Safe administration of thrombo-prophylaxis is heavily reliant on self-care. Poor self-care has been identified as a major contributor to hospital readmission and poor health outcomes in patients with heart failure [80]. This could also be expected for AF. People with dementia or CI could have difficulty in acquiring knowledge of chronic disease and medications. A thorough understanding of chronic illness and intact executive function are crucial for managing chronic disease [81, 82]. Limited executive functioning influences the ability to recognise symptoms and make decisions [83], which may result in poor in-range INRs and harm for people with dementia receiving OAC.

The composite outcome of stroke, non-CNS embolism, vascular death, MI and mortality was found to be significantly higher for people with dementia than those without, but when controlled for TTR, there was no increased risk [18]. This suggests that improving TTR for people with dementia could reduce embolic events. Further, two studies found that thrombosis [56], stroke and mortality [23] were not different for dementia and non-dementia groups, however these studies were limited by small numbers. Conflicting results were found for rates of bleeding events between dementia and non-dementia groups. One study demonstrated increased risk of total bleeding in people with dementia [18] and non-significant differences were found in a further two studies [23, 56].

Poor anticoagulation control is a known deterrent for prescribing OAC [75, 77, 84]. Poor anticoagulation control is closely correlated with embolic stroke, haemorrhage and mortality [85-87]. Given potential difficulties in achieving good anticoagulation control in persons with dementia receiving VKA, this may explain why proportionally less people with cognitive impairment receive anticoagulation than do people without cognitive impairment. DOACs circumvent some limitations of warfarin, such as the need for routine monitoring, and have

more predictable pharmacokinetics [40], and are simpler to use than VKA which may improve adherence [88], hence in people with cognitive impairment DOACs could alternatively be considered [89]. Indeed, the European Society of Cardiology guidelines recommend switching those with poor INR control to DOACs [22], but as yet there is little evidence to support this recommendation. DOACs directly inhibit thrombin (dabigatran) and factor Xa (apixaban, rivaroxaban and edoxaban) [90]. DOACs have a rapid onset of action, shorter half-lives and do not affect factor VII. These mechanisms could decrease bleeding risk; particularly limiting traumatic intracranial bleeding related to falls [91] which is critical when considering OAC for people with dementia. Dementia, per se, can impair medication adherence [92], but comorbidity burden [93] and polypharmacy [94] are known to reduce medication adherence, of which there is increased occurrence in persons with AF and dementia [94]. These areas require thorough investigation to understand the risks and benefits of DOACs in people with dementia.

Limitations

Our study has several limitations. First, the primary data sources have limitations in that comparisons are derived from sub-group analyses of observational studies. These studies did not examine anticoagulation in relation to cognitive status as the main objective. Crude ORs were therefore calculated and no adjustments have been made for variables confounding the prevalence of OAC in dementia/CI and non-dementia/CI groups. Further, information about cognitive status may be limited. For example, dementia and CI were defined in different ways in various studies, and the severity of dementia was not consistently reported. The effect of the use of data obtained from sub-groups of large studies and the heterogeneity of dementia definitions on our findings is unknown. Our meta-analyses showed substantial heterogeneity between studies demonstrated by high I^2 values and caution should be used when interpreting findings. Participants of the studies included in this review that were documented to have had

CI may have been more likely to have marked CI for it to have been documented. Hence, the observed results may not be generalizable to all people with CI, and this could underestimate the use of OAC in persons with dementia and CI. In addition, we did not assess how the diagnosis or detection of AF occurred for each study. Variability in AF detection rates could influence prescribing of OACs, which could impact the generalizability of the findings of this review to the general population. Further, given the heterogeneity of approaches taken and various safety and effectiveness outcomes reported in the outcomes studies, it was not possible to average or meta-analyse safety and effectiveness outcomes data. The methodological quality of included studies that determined prevalence of OAC use was generally sound. Five prevalence studies did not score maximum points of quality assessment as inclusion criteria were not clearly defined, exposure and outcomes measurements were unclear, and objective, standard criteria for measurement of diagnoses and conditions were not used. Three studies evaluating outcomes of OAC use for people with and without dementia did not provide adequate information to measure exposure (OAC use) and two studies were descriptive and therefore no adjustment for confounding factors was made, which limits the quality. Further, studies were conducted in the UK, the rest of Europe and North America which may limit the generalizability of results to other countries and healthcare systems.

CONCLUSION

People with atrial fibrillation who also have dementia are less likely to receive OAC for stroke prevention than people without dementia. There is a dearth of information regarding the outcomes of OAC use for stroke prevention in AF in people with dementia and CI. Given the increasing use of the DOACs, in particular within older age groups, the declining use of warfarin, and the limited generalizability of study findings from pivotal DOAC trials and various observational studies to people with dementia, there is an urgent need for more

information. Studies of the safety of OAC specifically in people with AF and dementia of various types, investigating the OAC type, dose, and adherence are urgently needed to guide treatment.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Figure 1. Literature flow diagram of studies identified, screened and included in the meta-analysis and systematic review; *OAC = oral anticoagulation.*

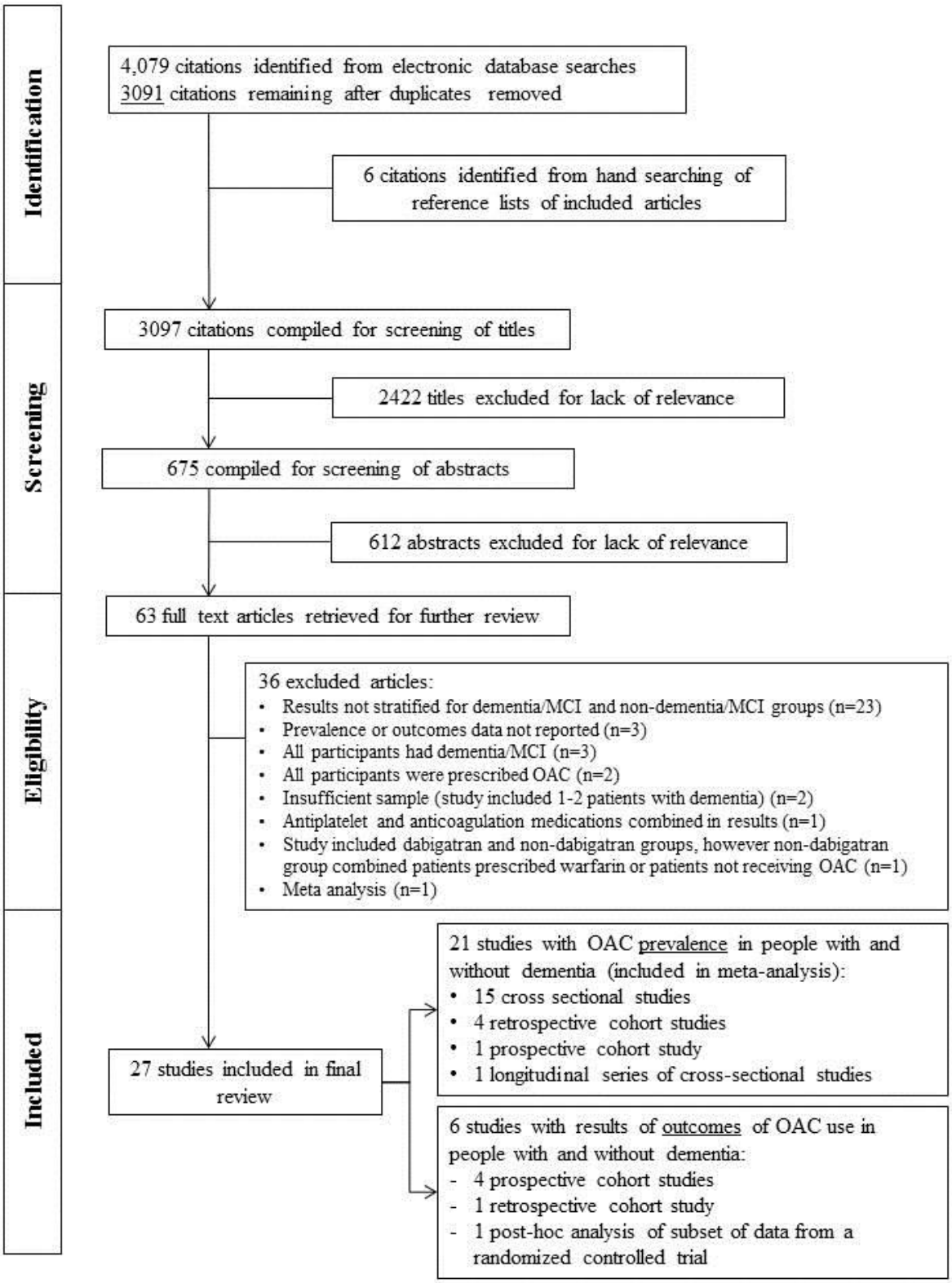

Figure 2. Mean prevalence of OAC use: overall, and stratified by community, hospital and long-term care healthcare settings for dementia/CI and non-dementia/CI groups. *OAC = oral anticoagulation; CI = cognitive impairment.*

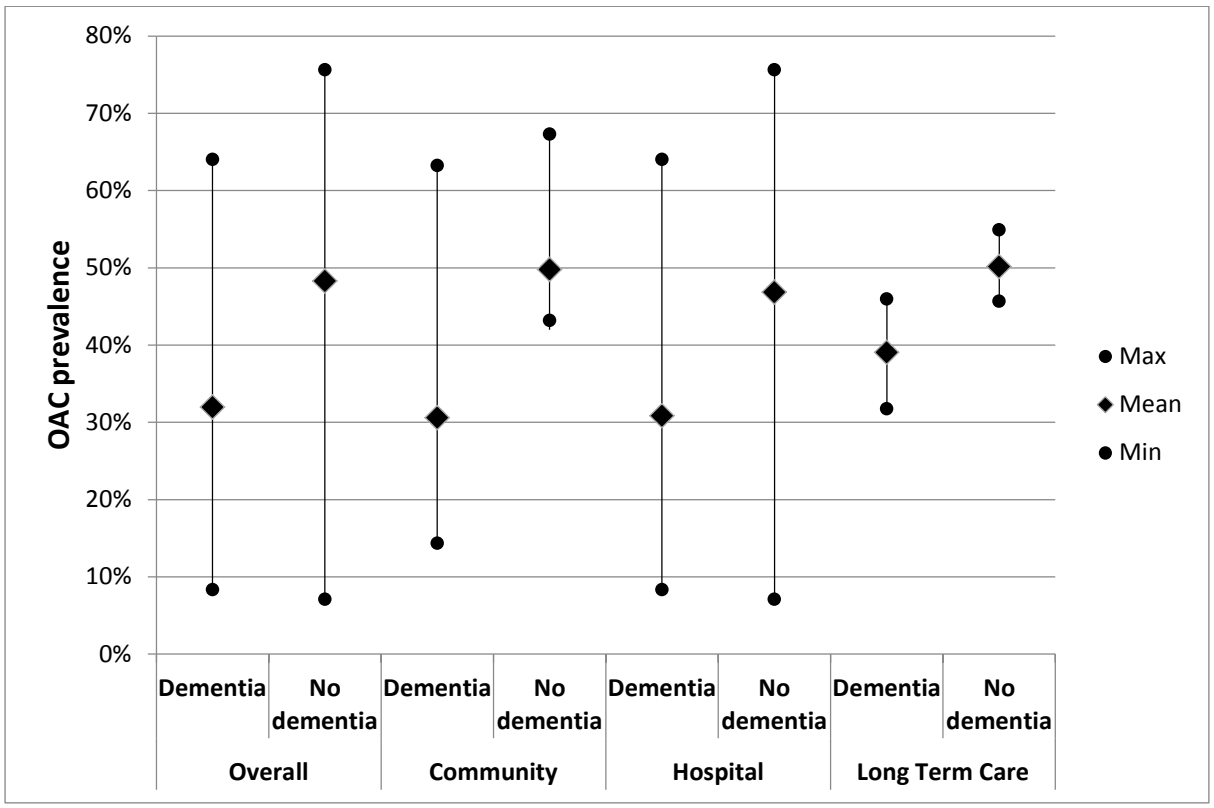

Figure 3. OAC prevalence by mid-year of study observation period: overall and stratified by community, hospital and long-term care healthcare settings for dementia and non-dementia groups, by mid-year of study observation period. *Vertical-axis, prevalence of OAC (%); Horizontal-axis, publication year; Red square and trend line = non-dementia; Blue diamond and trend line = dementia/cognitive impairment; OAC = oral anticoagulation.*

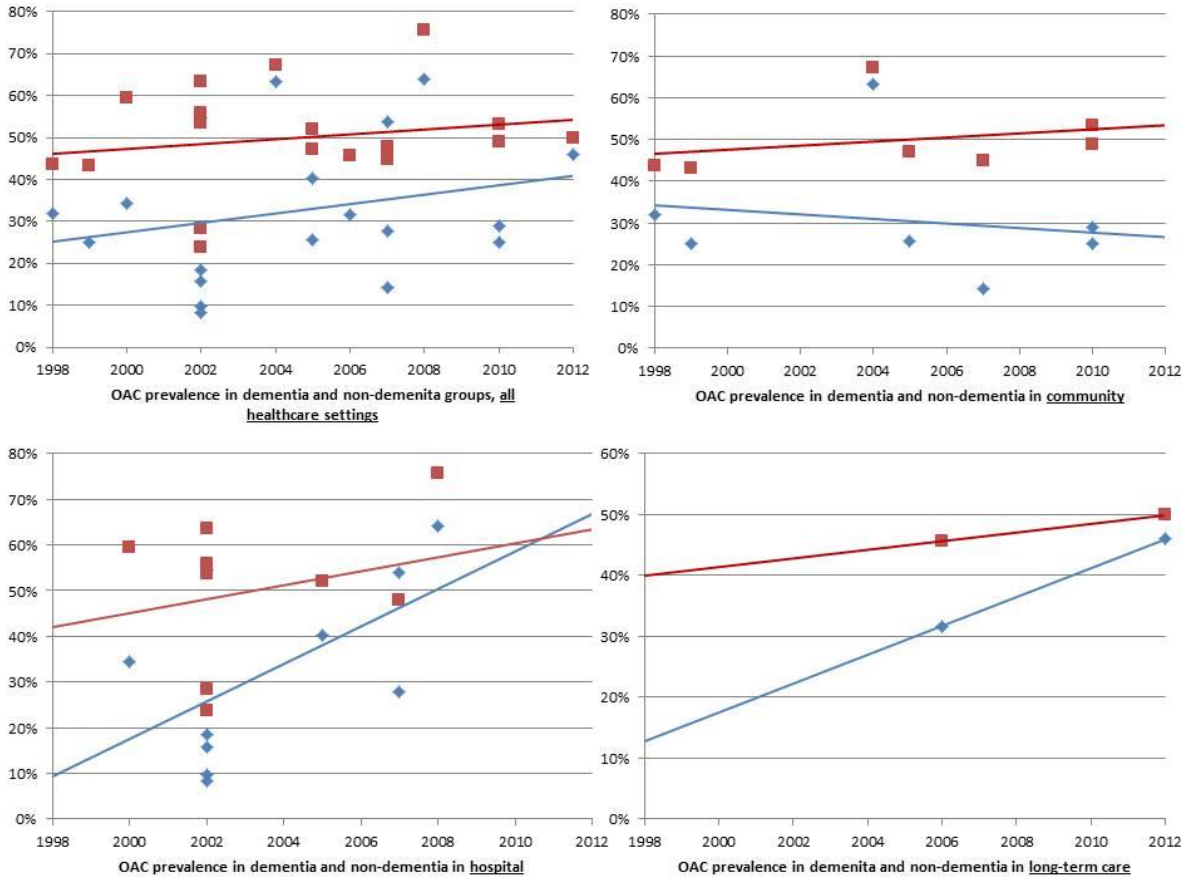

Figure 4. Forest plots of oral anticoagualtion use in people with and without dementia or cognitive impairment for 1.1.1) for all healthcare settings, and then subgroup analysis according to healthcare setting: 1.1.2) studies conducted in the community 1.1.3) studies conducted in hospitals and 1.1.4) studies conducted in long-term care

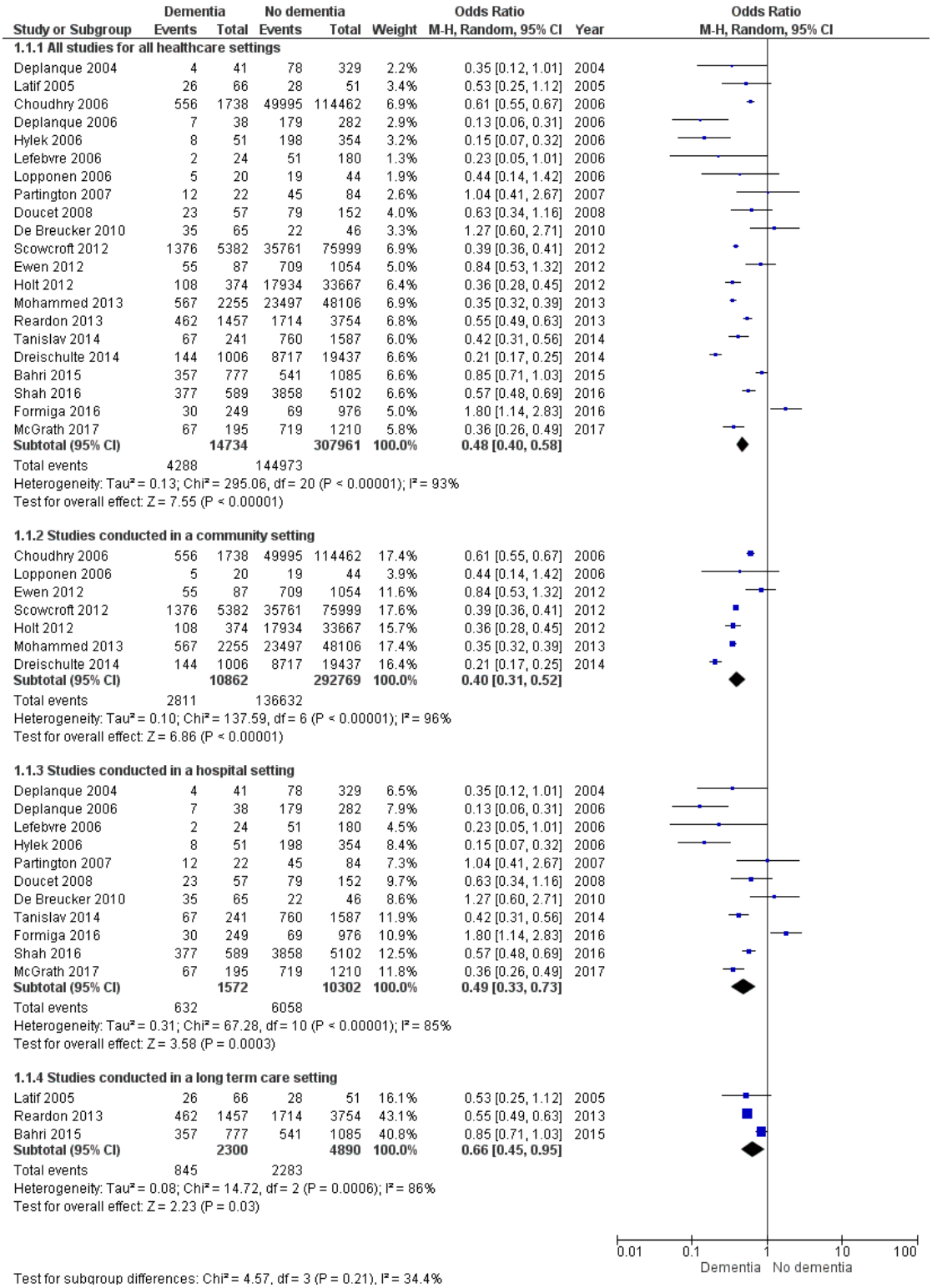

Table 1. Methodological characteristics of included studies of prevalence and outcomes of oral anticoagulant use in people with and without dementia or cognitive impairment (by year of publication)

First author (year)	Study design, country and health care setting	Population (N), description of study sample and study data source(s)	Anticoagulant reviewed and main indication(s)	Dementia type reported, data source and measurement method	Time of data collection
Articles relating to prevalence of oral anticoagulant use (by year of publication)					
Deplanque (2004)[65]	Cross-sectional Five countries: Austria, Belgium, France, Italy and Portugal Hospital	N=370 Patients diagnosed with an acute stroke or TIA with known AF (paroxysmal or permanent) – on admission to hospital Medical histories from a variety of sources: GP, patient interview, family, cardiologist	Warfarin Stroke prevention in AF	Condition reported: Cognitive impairment Data source and measurement method: Ascertainment of documentation of cognitive impairment diagnosis from study data (derived from medical history taking)	September 2001 – June 2002
Latif (2005)[51]	Cross-sectional USA Residential Aged Care Facility	N=117 Nursing home residents with AF Medical charts and administrative data	Warfarin Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Dementia diagnosis within the nursing home medical charts	Not specified
Choudhry (2006)[60]	Cross-sectional Canada Community	N=116200[a] Patients with an identifiable cardiac provider Data sources: 1. Canadian Institutes of Health Information database 2. The Ontario Drug Benefits claims database 3. Ontario Health Insurance Plan 4. Ontario Registered Persons database 5. Corporate Providers Database of the Ontario Ministry of Health 6. Southam Medical database	Warfarin Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Presence of dementia diagnosis coding (hospital ICD-9 codes 290.1 to 290.4, 290.8, 290.9, 294.1, 331.0, 331.1, 331.2 046.1, 046.2) in hospital administrative data	1 January, 1994 – March 31, 2002
Deplanque (2006)[66]	Cross-sectional Five countries: Austria, Belgium, France, Italy and Portugal Hospital	N=320 (subset of Deplanque 2004[65]) Patients with AF who have suffered ischaemic stroke and were being discharged from hospital Medical histories from a variety of sources: GP, patient interview, family, cardiologist	Warfarin Stroke prevention in AF	Condition reported: Cognitive impairment Data source and measurement method: Ascertainment of documentation of cognitive impairment diagnosis from study data (derived from medical history taking)	September 2001 – June 2002
Hylek (2006)[55]	Cross-sectional USA Hospital	N=405 Hospitalized patients with AF Hospital medical records	Warfarin Stroke prevention in AF	Condition reported: Cognitive impairment/dementia Data source and measurement method: Medical diagnosis of dementia within the hospital medical record	January 2001 – June 2003
Lefebvre (2006)[68]	Prospective cohort France and Italy Hospital	N=204 Patients diagnosed with an acute stroke or TIA with known AF (paroxysmal or permanent) Medical histories from a variety of sources:	Warfarin Stroke prevention in AF	Condition reported: Cognitive impairment Data source and measurement method: Ascertainment of documentation of cognitive impairment diagnosis from	September 2001 – June 2002

		GP, patient interview, family, cardiologist		study data (derived from medical history taking)	
Lopponen (2006)[69]	Cross-sectional Finland Community	N=409 Patients aged 75 years and older with CVD Patient interview, laboratory and clinical examinations	Warfarin Stroke prevention in AF	Condition reported: dementia Data source and measurement method: Two stage process: 1) MMSE, 2) Interview covering items of the Hachinski Ischaemic Scale and the Clinical Dementia Rating. Dementia was also assessed in clinical examination according to DSM-IV criteria, diagnosis of possible Alzheimer's disease according to the NINCDS-ADRDA criteria and diagnosis of possible vascular dementia according to the NINDS-AIREN criteria	1998 – 1999
Partington (2007)[59]	Cross-sectional Canada Hospital	N=196 (entire study sample) N=106 (patients eligible for anticoagulation in which dementia stratification presented) Patients with AF and acute ischaemic stroke EMR data	Warfarin Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Dementia documentation in primary diagnoses and comorbid conditions from the hospital's EMR	1999 – 2004
Doucet (2008)[67]	Cross-sectional France Hospital	N=209 Patients ≥ 65 years with chronic AF Medical charts	Warfarin Stroke prevention in AF	Condition reported: dementia (mean MMSE for anticoagulant and aspirin groups provided) Data source: Medical charts	January 2004 – April 2005
De Breucker (2010)[64]	Cross-sectional Belgium Hospital	N=111 Patients admitted to an acute geriatric unit at an academic hospital Computerized medical charts	Vitamin K Antagonist (exact medication not specified) Stroke prevention in AF	Condition reported: Cognitive disorders Data source and measurement method: Documentation of cognitive disorders within comprehensive geriatric assessments	April 2006 – November 2008
Ewen (2012)[54]	Retrospective longitudinal cohort study USA Community	N=1141 Patients with AF EMR data, hospital administrative data	Warfarin Stroke prevention in AF	Condition reported: Cognitive dysfunction Data source and measurement method: EMR problem list, hospital administrative data	January 1, 1998 – June 30, 2010
Holt (2012)[62]	Longitudinal series of cross-sectional surveys United Kingdom Community	N=59804 Patients with AF QResearch database	Specific anticoagulant(s) not specified Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Read code for dementia within the QResearch database	2007-2010 (2010 data only presented in this paper)
Scowcroft (2012)[24]	Retrospective cohort United Kingdom General Practice	N=81381 Patients aged >60 years with a new diagnosis of AF United Kingdom General Practice Research Database	Warfarin Stroke prevention in AF	Condition reported: Alzheimer's disease/dementia Data source and measurement method: Presence of dementia Read Code in the United Kingdom General Practice Research Database	2000 – 2009
Mohammed	Cross-sectional	N=50361	Warfarin	Condition reported: Dementia	1 May 2010

(2013)[19]	United Kingdom General Practice	Patients with a diagnosis of AF (≥ 35 years of age). The Health Improvement Network (THIN) database	Stroke prevention in AF	Data source and measurement method: Dementia Read Code present within patient records of the Health Improvement Network (THIN) database	
Reardon (2013)[57]	Cross-sectional USA Long-term care	N=5211 Long-term care residents with AF National Nursing Home Survey and the AnalytiCare Long-Term Care databases	Warfarin Stroke prevention in AF	Condition reported: Dementia/cognitive impairment Data source and measurement method: Presence of dementia or cognitive impairment diagnosis within the minimum data set of the AnalytiCare Long-Term Care database or from comorbid condition information in the National Nursing Home Survey database	2004 and 1 January 2007 – 30 June 2009
Dreischulte (2014)[61]	Cross-sectional Scotland Community	N=21096 Patients with AF Scottish General Practice data	Warfarin Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Quality and Outcomes defined Read Codes for dementia or prescription for acetylcholinesterase inhibitor) with the population database of Scottish general practices	31 March 2007
Tanislav (2014)[70]	Cross-sectional Germany Hospital	N=1828 Patients >18 years with index event of stroke or TIA; and diagnosed AF and a minimal physical impairment and direct discharge after acute treatment or referral to a rehabilitation facility. Registry data of the Institute of Quality Assurance Hesse and Claims data from a nationwide statutory health insurance company	Phenprocoumaron, warfarin and coumadin Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Presence of dementia ICD-10 codes within the claims data from a nationwide statutory health insurance company (F00, F01, F02, F03, G30)	2004 – 2010
Bahri (2015)[63]	Cross-sectional France Long-term care	N=1085 Nursing home residents over 75 years with a documented history of AF Medical charts	Warfarin Stroke prevention in AF	Condition reported: Cognitive impairment Data source and measurement method: Documentation of dementia/cognitive impairment with or without formal assessment from medical records	March 2012
Formiga (2016)[50]	Cross-sectional Spain Hospital	N=1225 Patients with hip fracture secondary to a high energy impact Hospital medical records	Chronic anticoagulation therapy (CAT) (exact medication not provided) Indication not provided	Condition reported: dementia Data source and measurement method: Short Portable Mental Status questionnaire from the comprehensive geriatric assessment	Not provided
Shah (2016)[17]	Retrospective cohort Canada Hospital	N=5781 Patients ≥ 65 years with AF hospitalized from ischaemic stroke or TIA Databases: Ontario Stroke Registry, Canada	Warfarin, dabigatran, rivaroxaban and apixaban Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Presence of dementia diagnosis within the comorbid condition information in Ontario Stroke Registry	1 July 2003 – 31 December 2011

		Census, Ontario Drug Benefits, Canadian Institute for Health Information Discharge Abstract and the National Ambulatory Reporting System			
McGrath (2017)[20]	Retrospective cohort United States of America Hospital	N=1405 Individuals with AF and acute ischaemic stroke surviving hospitalization Kaiser Permanente database	Warfarin Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Dementia documentation in medical records extracted from structured chart review	July 1996 – September 2003
Articles relating to outcomes from oral anticoagulant use (by year of publication)					
Van Deelen (2005)[72]	Retrospective cohort study The Netherlands Community	N=152 Patients ≥ 70 years with AF treated with acenocoumarol managed by an anticoagulation service	Acenocoumarol (nicoumalone) Stroke prevention in AF	Condition reported: Cognitive impairment Data source and measurement method: MMSE during home visit on index date. Patients with MMSE < 23 were considered cognitively impaired.	March – May 2003
Jacobs (2009)[23]	Retrospective cohort study United State of America Community	N=106 Patients ≥ 65 years with chronic AF receiving warfarin or aspirin Medical records	Warfarin Stroke prevention in AF	Condition reported: Dementia Data source and measurement method: Documentation of dementia in medical records	2003
Flaker (2010)[18]	Post-hoc analysis of a randomized controlled trial 522 centres/31 countries Community	N=2510 Community patients with AF and an additional risk factor for stroke ACTIVE-W study data [73]	Warfarin Stroke prevention in AF	Condition reported: Cognitive impairment Data source and measurement method: Presence of cognitive impairment within clinical trial data which used a modified MMSE	June 2003 and December 2004
Khreizat (2012)[56]	Retrospective cohort study United States of America Community	N=57 Community patients aged ≥ 60 years on warfarin with target INR of 2-3. Medical charts	Warfarin Stroke prevention in AF and treatment of VTE	Condition reported: cognitive impairment Data source and measurement method: Cognitive assessment was part of routine care using the Folstein MMSE. Cognitive impairment was defined as having a MMSE ≤ 26 . A lower cut point of MMSE ≤ 23 was also used to see if it impacted results	2006-2010
Tija (2012)[58]	Prospective cohort study (embedded within a clinical trial) United States of America Long-term care	N=435 Nursing home residents prescribed warfarin Clinical trial data (included medical charts and data abstraction by trained investigators)	Warfarin Stroke prevention in AF Thromboembolic disease Mechanical valve replacement	Condition reported: Dementia Data source and measurement method: Medical record review for dementia diagnosis	1 October 2007 to 31 December 2008
Gorzelak-Pabis (2016)[71]	Retrospective cohort study Poland Community	N=154 Persons with AF and dementia and indications for OAC ($CHA_2DS_2VAS_C \geq 1$ and HASBLED < 3)	Warfarin and acenocoumarol Stroke prevention in AF	Condition reported: Cognitive impairment Data source and measurement method: Cognitive skills were assessed using the Polish version of the correct MMSE.	2013-2015

		Medical charts		MMSE scores were corrected using Mungas adjustments for age and education level. MMSE < 27 was considered cognitive impairment.	

a - study sample was larger, but this group (n-value) were the patients with an identifiable provider in which dementia information was available

Abbreviations: AF = atrial fibrillation; CVD = cardiovascular disease; DOAC = direct oral anticoagulant; TIA = transient ischemic attack; MMSE = Mini-Mental State Examination; VTE = venous thromboembolism; INR = international normalised ratio; GP = general practitioner: ICD-9/ICD-10 = International Classification of Diseases and Health Related Problems, 9th edition or 10 edition; EMR = Electronic Medical Record; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th edition; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NINDS-AIREN = National Institute of Neurological and Communicative Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences.

Table 2. Outcomes for oral anticoagulant use in persons with and without dementia (by year of publication)

Author (year)	Age[a] and gender, % female	Prevalence of dementia (study sample)	Outcomes reported that were stratified by dementia/non-dementia	Outcome results
Van Deelen (2005)[72]	Age and gender stratified by %TTR INR 2-3.4 > 70% TT: 78.8 (5.3), 48.5% female INR 2-3.4 > 70% TT: 79.5 (5.3), 50% female	24/152 (15.8%)	Treatment time in therapeutic range	<u>INR with therapeutic range</u> MMSE < 23: 68% of treatment time MMSE ≥23: 76% of treatment time
Jacobs (2009)[23]	65-75 years, n=17 (16%); 75-85, n=51 (48%); >85, n=38 (36%), 75% female	22/106[b] (21%)	Mortality, haemorrhage and stroke (17 people with dementia were receiving warfarin and 73 without dementia or falls were receiving warfarin). *Results are descriptive.*	<u>Mortality</u> Dementia: 8/17 (47.1%) No dementia: 10/73 (13.7%) <u>Haemorrhage</u> Dementia: 1/17 (5.9%) No dementia: 4/73 (5.5%) <u>Stroke</u> Dementia: 0/17 (0%) No dementia: 2/73 (2.7%)
Flaker (2010)[18]	70.9 ± 9.5, 65.5% female	365/2510 (14.5%)	Stroke, non-CNS embolism, vascular events, myocardial infarction, total bleeding (minor and major)	<u>Composite of stroke, vascular death, MI or non-CNS embolism</u> MMSE < 26: 6.7 per 100 person-years MMSE ≥ 26: 3.6 per 100 person-years Unadjusted HR (95% CI) = 0.46 (0.27-0.78), p=0.002 Adjusted HR (95% CI) = 0.72 (0.45-1.14), p=0.155 <u>Total bleeding (includes major and minor)</u> MMSE < 26: 42 per 100 person-years MMSE ≥ 26: 7 per 100 person-years HR (95% CI) = 0.56 (0.37-0.85), p=0.04
Khreizat (2012) [56]	**New warfarin users** MMSE score >26: 79.4 ± 9.5, 92% female MMSE score ≤ 26: 75.6 ± 6.3, 75% female **Long-term warfarin users** MMSE score >26: 81.0 ± 6.9, 68% female	30/57 (53%)	*Outcomes were stratified by new warfarin users and long-term users with and without dementia/cognitive impairment* Visits/days required to achieve therapeutic anticoagulation (new users); TTR/long-term anticoagulation stability; percentage of clinic visits with reported dose mishaps; frequency of in-range INRs following dose	**New warfarin users (n=20; dementia=12, no dementia=8)** <u>Visits to achieve therapeutic anticoagulation</u> MMSE score >26: 5.8 ± 4.3 MMSE score ≤ 26: 4.6 ± 2.4 (p=0.44). <u>Days to reach therapeutic anticoagulation</u> MMSE score >26: 35.8 ± 30.5 MMSE score ≤ 26: 51.6 ± 45.7

	MMSE score ≤ 26: 74.6 ± 9.3, 77% female		mishaps; minor bleeding; major bleeding; thrombosis (long-term users).	(p=0.36). **Long term warfarin users (n=54; dementia=28, no dementia=26)** TTR [mean ± SD] MMSE ≤ 26: 61 ± 16% MMSE > 26: 65 ± 20% (p=0.36) Frequency of dose mishaps MMSE ≤ 26: 86/691 visits MMSE > 26: 74/705 visits (p=0.18) In-range INRs following dose mishaps MMSE ≤ 26: 16% MMSE > 26: 32% (p=0.013) Minor bleeding (per patient-year) MMSE ≤ 26: 0.20±0.42 MMSE > 26: 0.28±0.54 (p=0.51) Major bleeding (per patient-year) MMSE ≤ 26: 0.02±0.10 MMSE > 26: 0.07±0.25 (p=0.29) Thrombosis (per patient-year) MMSE ≤ 26: 0 MMSE > 26: 0.01±0.06 (p=N/A)
Tija (2012)[58]	**Dementia** 83.6 ± 9.3, 74% female **No dementia** 80.4 ± 11.6, 61% female	218/435 (50%)	Number of INR tests; percentage of days with subtherapeutic, therapeutic and supratherapeutic INRs; incidence of AWEs (injuries from warfarin), incidence of preventable and potential AWEs (INRs >	Number of INR tests, mean (SD) Dementia: 24.2 (13.9) No dementia: 26.0 (14.5) (p=0.017)

			4.5), adjusted association of dementia with AWEs and preventable and potential AWEs	<u>INR < 2, % (SD)</u> Dementia: 37.8 (23.2) No dementia: 37.7 (20.4) (p=0.95) <u>INR < 2-3, % (SD)</u> Dementia: 49.5 (22.2) No dementia: 48.6 (19.9) (p=0.72) <u>INR < 3-4.5, % (SD)</u> Dementia: 10.7 (9.8) No dementia: 11.7 (12.2) (p=0.34) <u>INR >4.5, % (SD)</u> Dementia: 2.1 (6.7) No dementia: 2.0 (7.1) (p=0.82) <u>Incidence rates of AWEs (injuries from warfarin, events per 100 resident-months)</u> Dementia: 12.8 No dementia: 9.99 IRR (95% CI) = 1.40 (1.14-1.72) – after adjustment for resident characteristics IRR (95% CI) = 1.48 (1.20-1.82) – after adjustment for nursing home characteristics and case mix <u>Incidence of preventable and potential AWEs (INR >4.5, events per 100 resident-months)</u> Dementia:8.09 No dementia: 6.50 IRR (95% CI) = 1.35 (1.04-1.74) – after adjustment for resident characteristics IRR (95% CI) = 1.36 (1.06-1.76) – after adjustment for nursing home characteristics and case mix
Gorzelak-Pabis (2016)[71]	MMSE score ≥ 27: 73 ± 9, 61% female MMSE score < 27: 77 ± 11, 69% female	42/104 (40%)	Mean TTR and INR values	<u>Mean TTR, % (mean ± SD):</u> MMSE < 27: 38±26 MMSE ≥ 27: 61±27 (p<0.0001)

				TTR > 60, n (%): MMSE < 27: 12/42 (28%) MMSE ≥ 27: 38/62 (61%) (p<0.0001) *INR < 2*, n (%): MMSE < 27: 19/42 (46%) MMSE ≥ 27: 37/62 (59%) (p<0.05) *INR 2-3*, n (%): MMSE < 27: 11/42 (26%) MMSE ≥ 27: 37/62 (60%) (p<0.05) *INR > 3*, n (%): MMSE < 27: 12/42 (28%) MMSE ≥ 27: 14/62 (22%) (p<0.05)

a – presented as mean (years) ± standard deviation unless otherwise indicated

b – 112 patients in study sample, but 106 undergoing antithrombotic treatment

Abbreviations: TTR = time in therapeutic range; INR = international normalized ratio; OR = odds ratio; HR = Hazard Ratio; CI = confidence interval; N/A=not applicable; AWEs = adverse warfarin-associated events; IRR = incident rate ratio; TT = treatment time; CNS = central nervous system

Table 3. Outcomes for oral anticoagulant use in persons with and without dementia (by year of publication)

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Jacobs (2009)[23]	65-75 years, n=17 (16%); 75-85, n=51 (48%); >85, n=38 (36%), 75% female	22/106[b] (21%)	Mortality, haemorrhage and stroke (17 people with dementia were receiving warfarin and 73 without dementia or falls were receiving warfarin). *Results are descriptive.*	<u>Mortality</u> Dementia: 8/17 (47.1%) No dementia: 10/73 (13.7%) <u>Haemorrhage</u> Dementia: 1/17 (5.9%) No dementia: 4/73 (5.5%) <u>Stroke</u> Dementia: 0/17 (0%) No dementia: 2/73 (2.7%)
Flaker (2010)[18]	70.9 ± 9.5, 65.5% female	365/2510 (14.5%)	Stroke, non-CNS embolism, vascular events, myocardial infarction, total bleeding (minor and major)	<u>Composite of stroke, vascular death, MI or non-CNS embolism</u> MMSE < 26: 6.7 per 100 person-years MMSE ≥ 26: 3.6 per 100 person-years Unadjusted HR (95% CI) = 0.46 (0.27-0.78), p=0.002 Adjusted HR (95% CI) = 0.72 (0.45-1.14), p=0.155 <u>Total bleeding (includes major and minor)</u> MMSE < 26: 42 per 100 person-years MMSE ≥ 26: 7 per 100 person-years HR (95% CI) = 0.56 (0.37-0.85), p=0.04
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	MMSE score ≤ 26: 74.6 ± 9.3, 77% female		mishaps; minor bleeding; major bleeding; thrombosis (long-term users).	(p=0.36). **Long term warfarin users (n=54; dementia=28, no dementia=26)** TTR [mean ± SD] MMSE ≤ 26: 61 ± 16% MMSE > 26: 65 ± 20% (p=0.36) Frequency of dose mishaps MMSE ≤ 26: 86/691 visits MMSE > 26: 74/705 visits (p=0.18) In-range INRs following dose mishaps MMSE ≤ 26: 16% MMSE > 26: 32% (p=0.013) Minor bleeding (per patient-year) MMSE ≤ 26: 0.20±0.42 MMSE > 26: 0.28±0.54 (p=0.51) Major bleeding (per patient-year) MMSE ≤ 26: 0.02±0.10 MMSE > 26: 0.07±0.25 (p=0.29) Thrombosis (per patient-year) MMSE ≤ 26: 0 MMSE > 26: 0.01±0.06 (p=N/A)
Tija (2012)[58]	**Dementia** 83.6 ± 9.3, 74% female **No dementia** 80.4 ± 11.6, 61% female	218/435 (50%)	Number of INR tests; percentage of days with subtherapeutic, therapeutic and supratherapeutic INRs; incidence of AWEs (injuries from warfarin), incidence of preventable and potential AWEs (INRs >	Number of INR tests, mean (SD) Dementia: 24.2 (13.9) No dementia: 26.0 (14.5) (p=0.017)

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				TTR > 60, n (%): MMSE < 27: 12/42 (28%) MMSE ≥ 27: 38/62 (61%) (p<0.0001) *INR < 2*, n (%): MMSE < 27: 19/42 (46%) MMSE ≥ 27: 37/62 (59%) (p<0.05) *INR 2-3*, n (%): MMSE < 27: 11/42 (26%) MMSE ≥ 27: 37/62 (60%) (p<0.05) *INR > 3*, n (%): MMSE < 27: 12/42 (28%) MMSE ≥ 27: 14/62 (22%) (p<0.05)

a – presented as mean (years) ± standard deviation unless otherwise indicated

b – 112 patients in study sample, but 106 undergoing antithrombotic treatment

Abbreviations: TTR = time in therapeutic range; INR = international normalized ratio; OR = odds ratio; HR = Hazard Ratio; CI = confidence interval; N/A=not applicable; AWEs = adverse warfarin-associated events; IRR = incident rate ratio; TT = treatment time; CNS = central nervous system

SUPPLEMENTAL MATERIAL

Appendix 1. Database search strategies (EMBASE, Medline, and CINAHL)

Appendix 2a. Methodological quality of studies checklist for prevalence studies

Appendix 2b. Methodological quality of studies checklist for outcomes studies

Appendix 3a. Results of quality assessment for prevalence studies

Appendix 3b. Results of quality assessment for outcomes studies

Appendix 4. Sensitivity analyses investigating sources of heterogeneity in meta-analyses of oral anticoagulant use in people with and without dementia or mild cognitive impairment for all healthcare settings

Appendix 1. Database search strategies (EMBASE, Medline and CINAHL)

EMBASE

1. Dementia/ **2.** dementia.mp. **3.** Alzheimer Disease/ **4.** alzheimer*.mp. **5.** Cognition Disorders/ **6.** cognition disorder*.mp. **7.** Cognitive Aging/ **8.** cognitive aging.mp. **9.** Memory Disorders/ **10.** memory disorder*.mp. **11.** Mild Cognitive Impairment/ **12.** mild cognitive impairment.mp.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. Anticoagulants/ **15.** anticoag*.mp. **16.** NOAC.mp. **17.** DOAC.mp. **18.** Antithrombins/ **19.** direct thrombin inhibitor.mp. **20.** Warfarin/ **21.** warfarin.mp. **22.** Dabigatran/ **23.** dabigatran.mp. **24.** apixaban.mp. **25.** Rivaroxaban/ **26.** rivaroxaban.mp. **27.** edoxaban.mp. **28.** VKA.mp. **29.** vitamin k antagonist.mp. **30.** novel oral anticoagulant.mp. **31.** direct oral anticoagulant.mp. **32.** Factor Xa Inhibitors/ **33.** factor Xa inhibitor*.mp.
34. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. 13 and 34

MEDLINE

1. dementia/ **2.** dementia.mp. **3.** Alzheimer disease/ **4.** alzheimer.mp. **5.** alzheimer*.mp. **6.** cognitive defect/ **7.** cognitive defect.mp. **8.** memory disorder/ **9.** memory disorder.mp. **10.** cognitive aging/ **11.** cognitive aging.mp. **12.** mild cognitive impairment/ **13.** mild cognitive impairment.mp.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. anticoagulant agent/ **16.** anticoagulant.mp. **17.** anticoag*.mp. **18.** NOAC.mp. **19.** DOAC.mp. **20.** direct thrombin inhibitor.mp. **21.** thrombin inhibitor/ **22.** warfarin/ **23.** warfarin.mp. **24.** dabigatran/ **25.** dabigatran etexilate/ **26.** dabigatran.mp. **27.** apixaban/ **28.** apixaban.mp. **29.** rivaroxaban/ **30.** rivaroxaban.mp. **31.** edoxaban/ **32.** edoxaban.mp. **33.** VKA.mp.**34.** antivitamin K/ **35.** vitamin k antagonist.mp. **36.** novel oral anticoagulant.mp. **37.** direct oral anticoagulant.mp. **38.** blood clotting factor 10a inhibitor/ **39.** factor Xa inhibitor.mp.
40. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41. 14 and 40

CINAHL

1. (MH "Dementia+") OR "dementia" **2.** (MH "Alzheimer's Disease") OR "alzheimer" **3.** alzheimer* **4.** (MH "Cognition Disorders") **5.** (MH "Memory Disorders") **6.** "memory disorder" **7.** "cognition disorder*" **8.** "cognitive aging" **9.** "cognitive impairment"
10. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
11. (MH "Anticoagulants") **12.** "anticoag*" **13.** "NOAC" **14.** "DOAC" **15.** "direct thrombin inhibitor" **16.** "antithrombin" **17.** (MH "Warfarin") **18.** "warfarin" **19.** (MH "Dabigatran Etexilate") **20.** "dabigatran" **21.** "apixaban" **22.** (MH "Rivaroxaban") **23.** "rivaroxaban" **24.** "edoxaban" **25.** "VKA" **26.** "vitamin k antagonist" **27.** "antivitamin k" **28.** "novel oral anticoagulant" **29.** "direct oral anticoagulant" **30.** "factor Xa inhibitor" **31.** "blood clotting factor 10a inhibitor" **32.** "blood clotting factor 10a inhibitor" (SmartText Searching)
33. S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32
34. S10 AND S33

Appendix 2. Risk of bias assessment tools

<u>Appendix 2a.</u> Adapted Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross Sectional Studies

*This tool was used to assess the quality of **<u>prevalence studies</u>**. One point was awarded if the criterion was satisfied. A maximum of 5 points could be awarded for each study that provided oral anticoagulation prevalence estimates as sub-group analyses in results - as criteria 5, 6 and 8 are not applicable to sub-group results. A maximum of 8 points could be awarded for each study that assessed oral anticoagulation prevalence as the primary research question (ie: criteria 5, 6 and 8 become applicable). This checklist has been adapted from the original version and provides a description for how each criterion were applied and assessed.*

1. Were the criteria for inclusion in the sample clearly defined? *To score a 'yes,' authors should have provided clear and comprehensive inclusion and exclusion criteria for study sample selection and which were developed prior to recruitment of the study participants.*	□ Yes (1 point) □ No (0 points) □ Unclear (0 points) □ Not Applicable
2. Were the study subjects and the setting described in detail? *To score a 'yes,' authors should have described the study sample in sufficient detail including a clear description of the population from which the study participants were selected or recruited, including demographics, location and healthcare setting, and time period.*	□ Yes (1 point) □ No (0 points) □ Unclear (0 points) □ Not Applicable
3. Was the exposure measured in a valid and reliable way? *Authors should have clearly described the method of measurement of exposure. Note: for prevalence studies - exposure is dementia or mild cognitive impairment. To score a 'yes,' a standard criterion for identifying the presence of dementia should have been reported.* *Standard criteria include:* • *Dementia codes available in administrative data (e.g: International Classification of Diseases and Health Related Problems codes (ICD))* • *Validated diagnostic criteria (e.g: Diagnostic and Statistical Manual of Mental Disorders, Mini-Mental State Exam)* • *Medical diagnosis* • *Medical record review or structured interview* *Standard criteria do not include:* • *self-report / patient-report / family or carer-report* • *no description of a standard criteria*	□ Yes (1 point) □ No (0 points) □ Unclear (0 points) □ Not Applicable
4. Were objective, standard criteria used for measurement of the condition? *This criterion is useful to determine if patients were included in the study based on either a specified diagnosis or definition. This is more likely to decrease the risk of bias. To score a 'yes,' the authors should have provided the method or criteria for which specific inclusion and exclusion criteria relating to disease/conditions were measured.*	□ Yes (1 point) □ No (0 points) □ Unclear (0 points) □ Not Applicable
5. Were confounding factors identified? *To score a "yes," confounding factors for oral anticoagulant use or contraindications to oral anticoagulant use should be identified and provided by the authors.* *Answer "<u>not applicable</u>" if oral anticoagulant use estimates were derived from sub-group analyses of results.*	□ Yes (1 point) □ No (0 points) □ Unclear (0 points) □ Not Applicable
6. Were strategies to deal with confounding factors stated? *To score a "yes," confounding factors should be controlled for by multivariate*	□ Yes (1 point) □ No (0 points)

analysis, including logistic regression, stratification, restricting or matching methods. *Answer "not applicable" if oral anticoagulant use estimates were derived from sub-group analyses of results.*	□ Unclear (0 points) □ Not Applicable
7. Were the outcomes measured in a valid and reliable way? *Note: outcome measure is oral anticoagulant use.* *To score a 'yes,' a standard criterion for identifying oral anticoagulant use should have been reported. In addition, oral anticoagulant use should have been measured in the same way for dementia and non-dementia groups.* *Standard criteria include:* • *Medication charts (paper or electronic)* • *Linkage of medication records (prescribing or dispensing data)* • *Structured interview* *Standard criteria do not include:* • *self-report / patient-report / family or carer-report* • *no description of a standard criteria*	□ Yes (1 point) □ No (0 points) □ Unclear (0 points) □ Not Applicable
8. Was appropriate statistical analysis used? *To score a "yes," the methods section should have been detailed enough to identify analytical techniques used, for example logistic regression or stratification and how specific confounders were identified, measured and controlled for. In studies using logistic regression, explanation of how variables were included in the logistic regression model and their relation to the outcome should have been provided.* *Answer "not applicable" if oral anticoagulant use estimates were derived from sub-group analyses of results.*	□ Yes (1 point) □ No (0 points) □ Unclear (0 points) □ Not Applicable

Appendix 2b. Adapted Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies

*This tool was used to assess the quality of **outcomes studies**. One point was awarded if the criterion was satisfied. A maximum of 11 points could be awarded for each study. This checklist has been adapted from the original version and provides a description for how each criterion were applied and assessed.*

1. Were the two groups similar and recruited from the same population? *To score a 'yes,' the dementia and non-dementia groups should have been selected from the same study population and be as similar as possible in all characteristics except for the presence of dementia. The authors should have provided clear inclusion and exclusion criteria that were developed prior to recruitment of the study participants.*	□ Yes (1 point) □ No (0 points) □ Unclear (0 points) □ Not Applicable
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups? *Note: exposure is oral anticoagulant use. Description of how the exposure was measured should have been described in sufficient detail.* *To score a 'yes' – both a standard criteria should have been used and oral anticoagulation use should have been measured in the same way for dementia and non-dementia groups.* *Standard criteria include:* • *Medication charts (paper or electronic)* • *Linkage of medication records (prescribing or dispensing data)* • *Structured interview* *Standard criteria do not include:* • *self-report / patient-report / family or carer-report* • *no description of a standard criteria*	□ Yes (1 point) □ No (0 points) □ Unclear (0 points) □ Not Applicable
3. Was the exposure measured in a valid and reliable way?	□ Yes (1 point)

Note: exposure is oral anticoagulant use. *To score a 'yes,' the study should have clearly described the method of measurement of exposure (above) and in addition provided evidence of the validity and reliability of the measurement method.* *Validity refers to the percentage of cases in which the exposure is true (correctly identified) when verified with an independent, 'gold standard' data source (reference standard).* *Reliability refers to the processes included in an epidemiological study to check repeatability of measurements of the exposures.* *Evidence of validity could include:* • *Validation studies* • *Systematic reviews of validation studies* *Evidence of reliability could include (relevant for medication chart and structured interviews only):* • *Intra-observer reliability* • *Inter-observer reliability*	□ No (0 points) □ Unclear (0 points) □ Not Applicable
4. Were confounding factors identified? *Confounding occurs when the estimated intervention exposure effect is biased by the presence of some difference between the comparison groups (apart from the exposure investigated/of interest). Typical confounders include baseline characteristics, prognostic factors, or concomitant exposures (e.g. smoking).* *To score a "yes," confounding factors should have been identified and reported by the authors.*	□ Yes (1 point) □ No (0 points) □ Unclear (0 points) □ Not Applicable
5. Were strategies to deal with confounding factors stated? *To score a "yes," confounding factors should have been controlled for by statistical analysis using validated methods, including: logistic regression, stratification, restricting or matching methods. Sufficient description of statistical methods employed should have been provided by the authors.*	□ Yes (1 point) □ No (0 points) □ Unclear (0 points) □ Not Applicable
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? *To score a 'yes,' authors should report whether the participants were free of the outcomes of interest at the start of the study. The methods section of research papers should include: descriptions of participant/sample recruitment, definitions of variables, and inclusion/exclusion criteria.*	□ Yes (1 point) □ No (0 points) □ Unclear (0 points) □ Not Applicable
7. Were the outcomes measured in a valid and reliable way? *Note: outcomes are events from oral anticoagulant use (embolic events, bleeding events or anticoagulation control)* *To score a 'yes,' a standard criterion for identifying outcomes should be specified by the authors and some evidence of validity and reliability of the measurement method reported (half a point for each).* *Standard criteria include:* • *Disease codes available in administrative data (e.g: International Classification of Diseases and Health Related Problems codes (ICD))* • *Validated diagnostic criteria or algorithms* • *Medical diagnosis* • *Medical record review or structured interview* *Standard criteria do not include:* • *self-report / patient-report / family or carer-report* • *no description of a standard criteria* *Evidence of validity and reliability for all included standard criteria should also be described.* *Evidence of validity could include:* • *Validation studies* • *Systematic reviews of validation studies*	□ Yes (1 point) □ No (0 points) □ Unclear (0 points) □ Not Applicable

Evidence of reliability could include (relevant for medical record review or structured interview): • *Intra-observer reliability* • *Inter-observer reliability* • *Evidence of specific training of those involved in collecting data* • *Evidence of more than one data collector*	
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur? *To score a 'yes,' follow up time should be reported and ⩾ 1 month for all outcomes.*	□ Yes (1 point) □ No (0 points) □ Unclear (0 points) □ Not Applicable
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored? *To score a 'yes,' the proportion of patients followed up should be reported and be greater than 80%. If follow up was less than 80% but the follow-up period was long (greater than 2 years) and sufficient details regarding efforts for follow up are described, then a score of 'yes' can also be awarded.*	□ Yes (1 point) □ No (0 points) □ Unclear (0 points) □ Not Applicable
10. Were strategies to address incomplete follow up utilized? *To score a 'yes,' appropriate strategies to deal with incomplete follow-up should have been described and employed by the authors. For example, rates calculated as person-years at risk and intention to treat analysis.*	□ Yes (1 point) □ No (0 points) □ Unclear (0 points) □ Not Applicable
11. Was appropriate statistical analysis used? *To score a "yes," the methods section should have been detailed enough to identify analytical techniques used, for example logistic regression or stratification and how specific confounders were identified, measured and controlled for. In studies using logistic regression, explanation of how variables were included in the logistic regression model and their relation to the outcome should have been provided.*	□ Yes (1 point) □ No (0 points) □ Unclear (0 points) □ Not Applicable

Appendix 3a. Results of quality assessment for prevalence studies (n=21)

Author (Year)	Clearly defined inclusion criteria	Study subjects and setting well described	Exposure measured in a valid and reliable way	Objective, standard criteria used for condition measurement	Confounding factors identified	Strategies used to deal with confounding factors	Outcomes measured in a valid and reliable way	Appropriate statistical analysis used	TOTAL SCORE*
Bahri (2015)[63]	Yes	Yes	Yes	Yes	N/A	N/A	Yes	N/A	5/5
Choudhry (2006)[60]	Yes	Yes	Yes	Yes	N/A	N/A	Yes	N/A	5/5
De Breucker (2010)[64]	Yes	Yes	Yes	Yes	N/A	N/A	No	N/A	4/5
Deplanque (2004)[65]	Yes	Yes	Yes	Yes	N/A	N/A	Yes	N/A	5/5
Deplanque (2006)[66]	Yes	Yes	Yes	Yes	N/A	N/A	Yes	N/A	5/5
Doucet (2008)[67]	Yes	Yes	Yes	Yes	N/A	N/A	No	N/A	4/5
Dreischulte (2014)[61]	Yes	Yes	Yes	Yes	N/A	N/A	Yes	N/A	5/5
Ewen (2012)[54]	Yes	Yes	Yes	Yes	N/A	N/A	Yes	N/A	5/5
Formiga (2016)[50]	Unclear	Yes	Yes	Unclear	N/A	N/A	Unclear	N/A	2/5
Holt (2012)[62]	Yes	Yes	Unclear	Yes	N/A	N/A	No	N/A	3/5
Hylek (2006)[55]	Yes	Yes	Yes	Yes	N/A	N/A	Yes	N/A	5/5
Latif (2005)[51]	Yes	Yes	Yes	Yes	N/A	N/A	Yes	N/A	5/5
Lefebvre (2006)[68]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	5/5
Lopponen (2006)[69]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	5/5
McGrath (2016)[20]	Yes	Yes	Yes	Yes	N/A	N/A	Yes	N/A	5/5
Mohammed (2013)[19]	Yes	Yes	Yes	Yes	N/A	N/A	Yes	N/A	5/5
Partington (2007)[59]	Yes	No (3/4 criteria met)	Yes	Yes	N/A	N/A	Yes	N/A	4/5
Reardon (2013)[57]	Yes	Yes	Yes	Yes	N/A	N/A	Yes	N/A	5/5
Scowcroft (2012)[24]	Yes	Yes	Yes	Yes	N/A	N/A	Yes	N/A	5/5
Shah (2016)[17]	Yes	Yes	Yes	Yes	N/A	N/A	Yes	N/A	5/5
Tanislav (2014)[70]	Yes	No	Yes	No	N/A	N/A	No	N/A	3/5

**A maximum of 5 points could be awarded for each study that provided oral anticoagulation prevalence estimates as sub-group analyses in results - as criteria 5, 6 and 8 are not applicable to sub-group results. A maximum of 8 points could be awarded for each study that assessed oral anticoagulation prevalence as the primary research question (ie: criteria 5, 6 and 8 become applicable).*

Appendix 3b. Results of quality assessment for outcomes studies (n=6)

Author (Year)	Similar study groups recruited from same population	Exposures measured similarly in assignment of exposed and unexposed groups	Exposure measured in a valid and reliable way	Confounding factors identified	Strategies to deal with confounding factors used	Groups/participants free of the outcome at the start of the study	Outcomes measured in a valid and reliable way	Follow-up time reported and sufficient to measure outcomes	Complete follow up. If not, reasons for incomplete follow up discussed	Strategies to address incomplete follow up used	Statistical analysis appropriate	TOTAL SCORE
Flaker (2010)[18]	Yes	Yes[a]	Yes[a]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	10/11
Gorzelak-Pabis (2016)[71]	Yes	No	No	No	No	Unclear	Yes	Yes	Yes	Yes	No	5/11
Jacobs (2009)[23]	Yes	Unclear	Unclear	No	No	Unclear	Yes	Yes	Yes	Yes	No	4/11
Khreizat (2012)[56]	Yes	Yes	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	No	7/11
Tija (2012)[58]	Yes	Yes[b]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	10/11
Van Deelen (2005)[72]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	10/11

a – study protocol details published elsewhere[73]; b – study protocol details published elsewhere[95]

Appendix 4. Sensitivity analyses investigating sources of heterogeneity in meta-analyses of oral anticoagulant use in people with and without dementia or mild cognitive impairment for all healthcare settings. Types of studies included or excluded are indicated above each forest plot.

Figure 1. Studies with less than 100 people with dementia *were excluded*

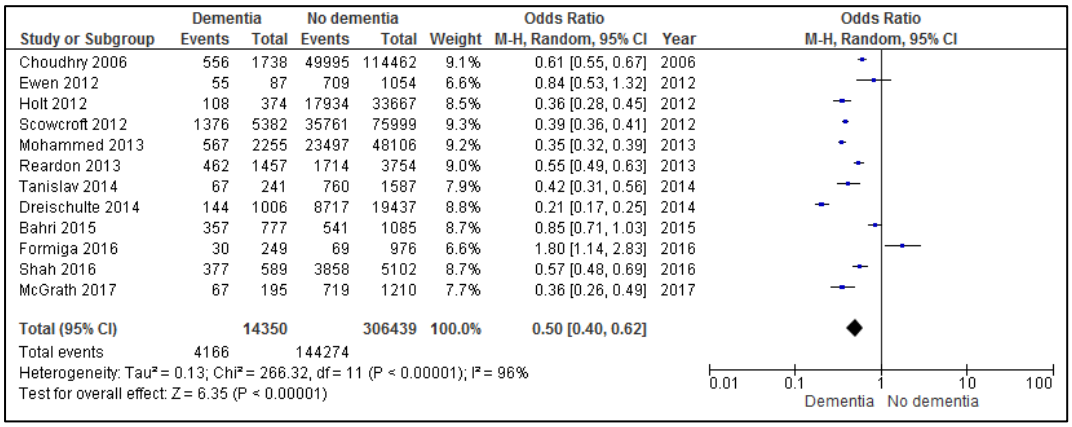

Figure 2. Studies published before 2010 *were excluded*

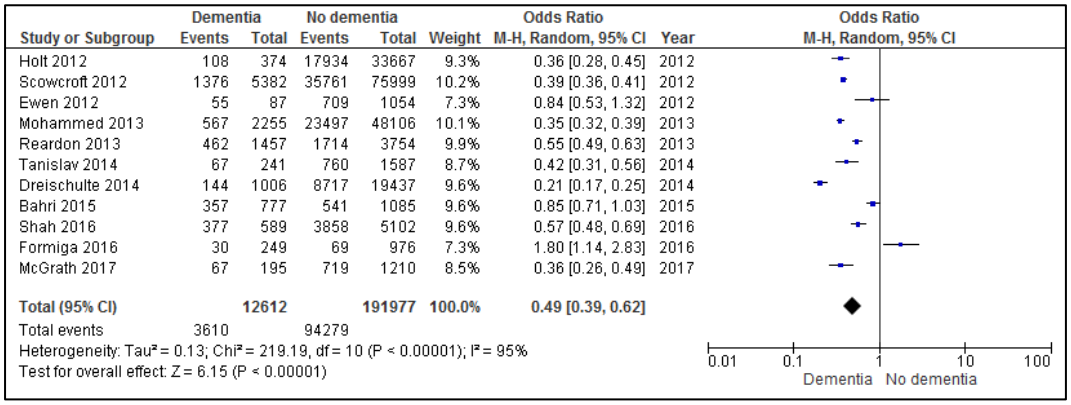

Figure 3. Studies reporting less than 50% of the study sample as female *were excluded*

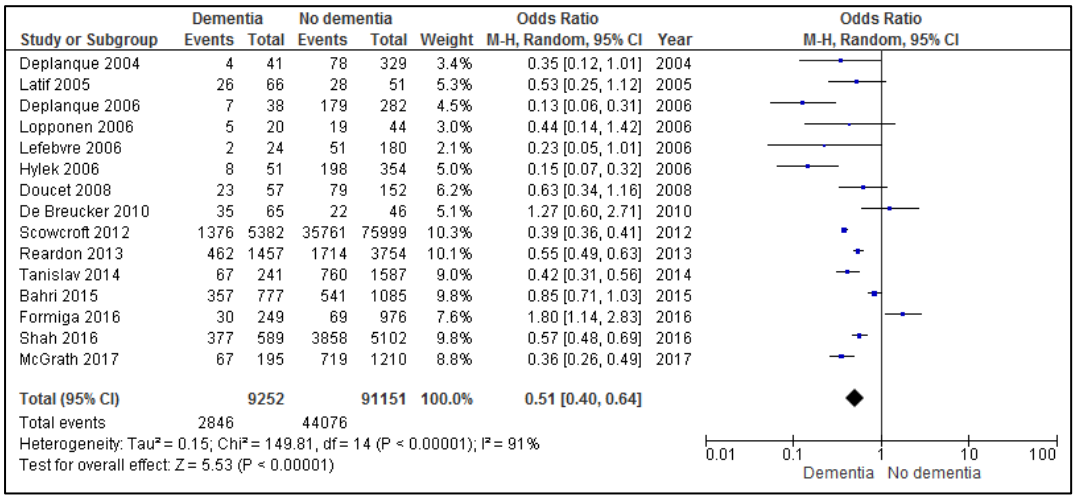

Figure 4. Studies reporting less than 40% prevalence of oral anticoagulation use overall (dementia and non-dementia groups combined) *were excluded*

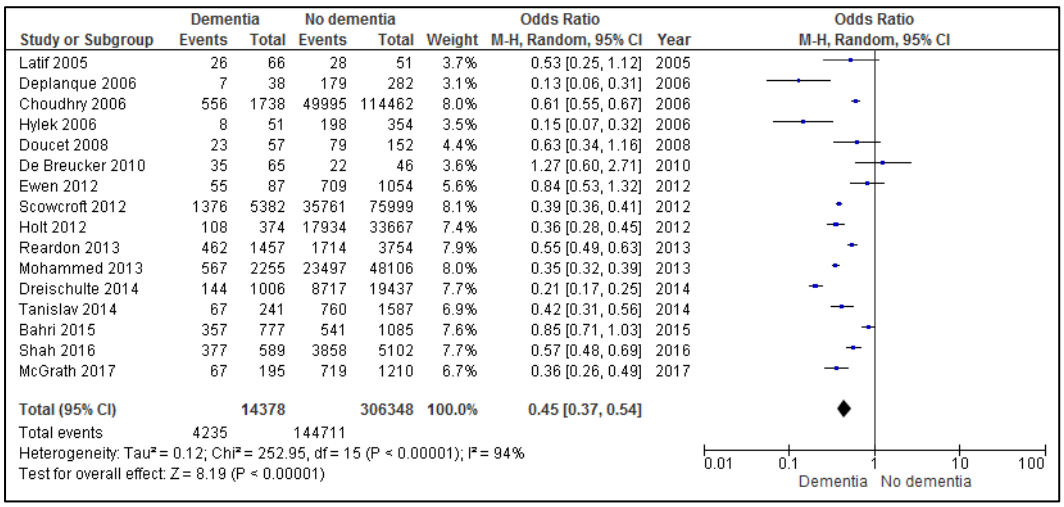

Figure 5. Studies reporting less than 20% prevalence of dementia *were excluded*

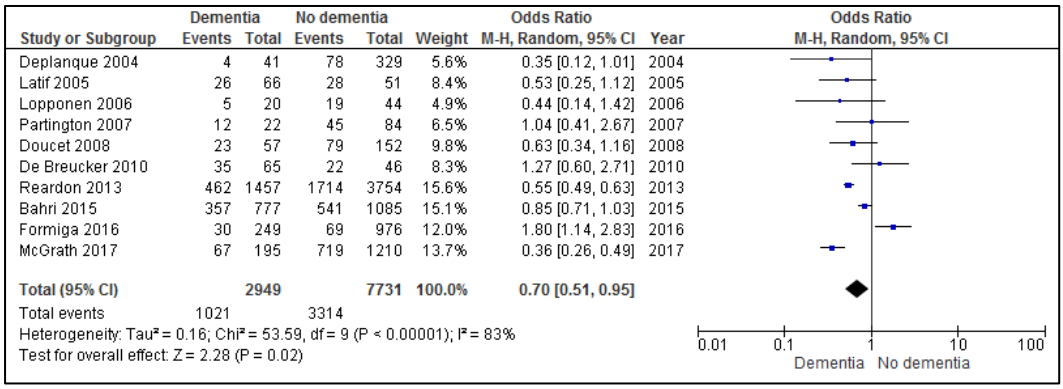

Figure 6. Studies reporting ≥ 30% of study participants with a prior history of stroke or transient ischaemic attack *were included*

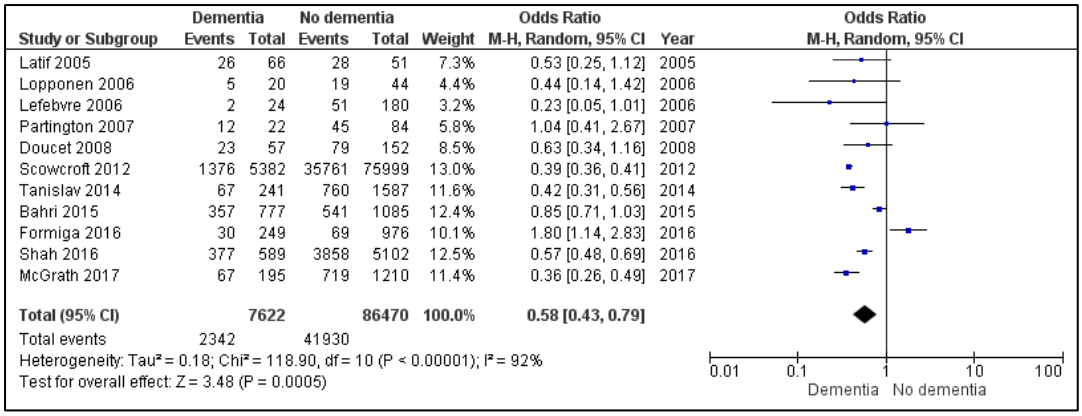

Figure 7. Studies reporting < 30% of study participants with a prior history of stroke or transient ischaemic attack *were included*

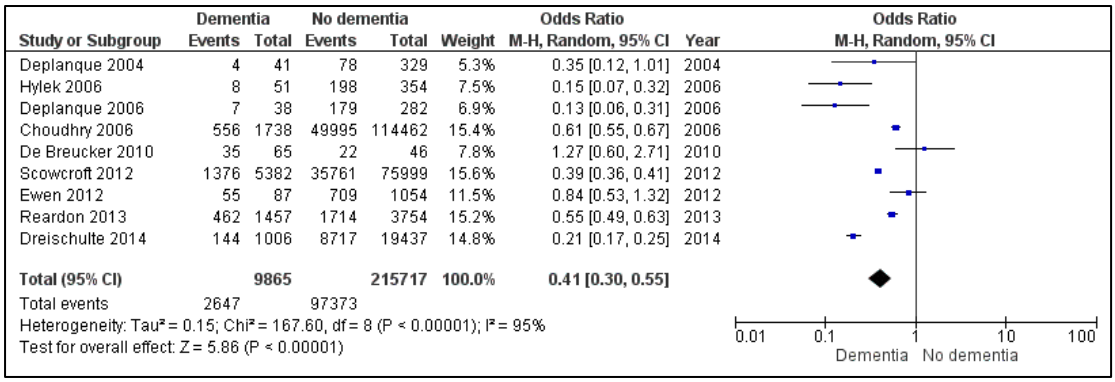

Figure 8. Studies reporting dementia *were included* (studies reporting cognitive impairment *were excluded*)

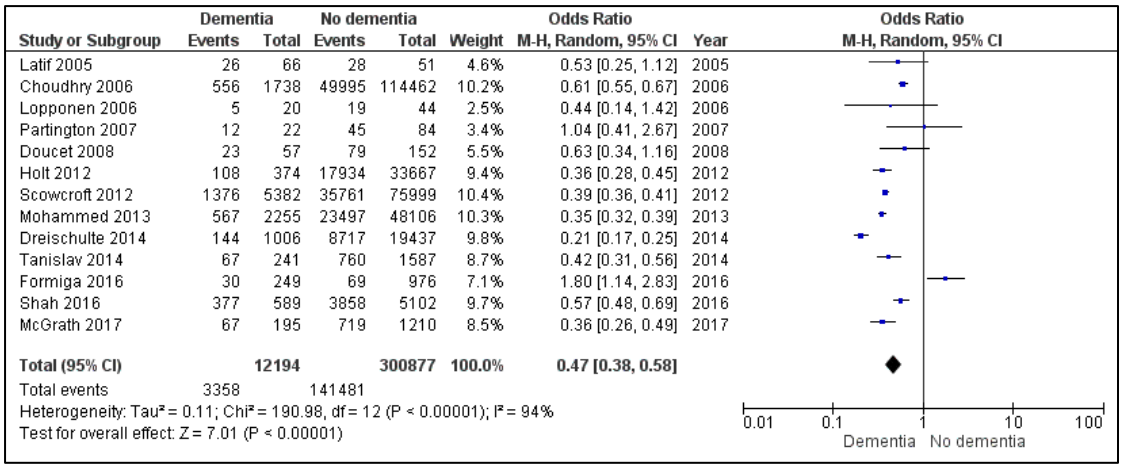

Figure 9. Studies reporting cognitive impairment were included (studies reporting dementia *were excluded*)