Title: Thromboprophylaxis in atrial fibrillation and association with cognitive decline: systematic review

Running title: AF thromboprophlaxis and cognitive impairment

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Abstract

Objective:Atrial Fibrillation (AF) is associated with dementia. If AF-related cognitive decline is driven by cerebral embolic events, thromboprophylaxis may impact on this. This systematic review assessed the association between cognitive impairment and AF thromboprophylaxis.

Methods:Two independent reviewers searched CINAHL, EMBASE, MEDLINE, PsycINFO, Web of Science Core Collection, and Cochrane Library from inception until 12th November 2014. Eligible studies compared AF thromboprophylaxis to control with an outcome measure of cognition or dementia. Where data allowed, meta-analyses describing between-group differences in cognitive test scores or rates of incident dementia were performed.

Results:Nineteen studies were eligible. For two prospective studies (one RCT) comparing anticoagulation against antiplatelet therapy, change in Mini-Mental State Examination score from baseline to last follow-up (maximal duration:5.9 years) suggested a difference favouring anticoagulation (mean difference:0.90, 95% CI:0.29 to 1.51), in keeping with a trend seen in the single RCT (mean difference MMSE:0.80. 95% CI:-0.07 to 1.67). Pooled odds ratios suggested no association with incident dementia, comparing anticoagulant to antiplatelet therapy (two studies, OR:1.23, 95% CI:0.80 to 1.91) or no treatment (three studies, OR:0.89, 95%CI:0.47 to 1.69).

Conclusions:Our analyses show no definitive evidence of cognitive benefit or harm from anticoagulation. We demonstrated a potential benefit of anticoagulation in comparison to antiplatelet over time. Larger-scale studies with longer follow-up are needed to determine the true cognitive impact of AF thromboprophylaxis.

Key points

- Atrial fibrillation (AF) is associated with dementia, the mechanism of which is not fully understood.
- Published data do not prove any decrease (or increase) in incident dementia over time in patients anticoagulated versus those treated with antiplatelet or placebo.
- The clinical significance of improvements in cognition comparing those treated with anticoagulation and antiplatelet is uncertain.
- Data are not definitive and future AF studies and registries should collect cognitive outcomes.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting 2% of the European population; rising to between 10%–17% of those aged over 80 years.[1] AF is associated with substantial morbidity and mortality, predominantly driven by cardioembolism.[2] Other adverse health effects of AF have been suggested including an association with dementia.[3]

The pathophysiological mechanisms underlying the cognitive effects of AF remain poorly understood. Clinical stroke alone is not sufficient explanation.[3] A possible mechanism of action is via sub-clinical cerebral infarcts exerting a cumulative effect on cognition. Occult infarcts in a distribution suggesting embolic aetiology are at least twice as common on brain imaging in AF patients as they are in sinus rhythm.[4] Other processes may also play a role, global cerebral hypoperfusion could contribute and there is the possibility of confounding from a shared factor that for example alcohol, smoking and obesity. These concepts are not exclusive and cognitive decline in AF may be related to all of these or other, as yet undetermined, mechanisms.[5,6,7]

There are potent, evidence-based treatments to prevent AF-related cardioembolism, for example vitamin K antagonists (VKAs) or the non-VKA oral anticoagulants (NOACs). It is possible that such treatments could reduce cognitive decline, by reducing (sub-clinical) infarct burden. Cognitive efficacy of AF thromboprophylaxis should not be assumed, anticoagulation is unlikely to impact on non-embolic mechanisms and in the context of amyloid angiopathy and other neuropathological

changes of dementia syndromes, anti-thrombotics could contribute to, or accelerate, cognitive decline by precipitating intracerebral bleeding.

We explored the cognitive effects of AF thromboprophylaxis using systematic review and meta-analysis.

Methods

We followed Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidance in conduct and reporting. We registered our review protocol with the PROSPERO database [CRD42014015073]. All aspects of the review (title searching, data extraction, quality assessment) were carried out by two independent reviewers and results compared and agreed upon through discussion.

Our primary objective was to offer a synthesis of the available data describing the cognitive effects of treatments to reduce cardioembolism in AF.

The following subgroup analyses were planned if data allowed:

- Effects of treatment in paroxysmal versus permanent/persistent AF patients.
- Effects of antithrombotic treatment in those with previous stroke compared with no history of stroke.
- Effects of antithrombotic treatment on vascular dementia rates compared to other dementias.

Criteria for considering studies for this review: We created inclusion/exclusion criteria for the review based on the PICOS (participants; interventions; controls; outcomes and study type) method.

Participants:Our population of interest was any adult, human with AF (atrial fibrillation and/or atrial flutter). We included all AF diagnoses including permanent, persistent and paroxysmal. We operated no exclusions based on age, time since diagnosis or treatment received. All other ventricular or supraventricular arrhythmias were excluded.

Interventions:Interventions of interest were any treatment used primarily to prevent cardioembolism in AF. We designed our search to focus on anticoagulation and antiplatelet therapy but included search terms around mechanical interventions, for example, left atrial appendage occlusion devices. We will refer to these as “treatments”, although for observational cohorts “exposed” could be a better term.

Controls:Comparators included "placebo" control arms and also comparison with another active intervention, for example, antiplatelet versus anticoagulation.

Outcomes:Our co-primary outcomes of interest were any quantitative measure of cognition or clinical diagnosis of dementia. For cognitive assessments, we included those studies that described outcomes using a validated cognitive assessment tool. For clinical diagnosis, we included any diagnosis of dementia or related syndromes made using a recognised classification system. We did not include papers reporting only surrogate measures such as neuroimaging.

Study type:We sought to include all relevant Randomised Controlled Trials (RCTs); these were trials with a primary cognitive endpoint or trials that included cognitive data as a secondary endpoint or as a sub-study. We also included observational studies and quasi-randomised trials relevant to the study question. We excluded case reports and case series, which for the purposes of this review we defined as studies having less than 10 participants. We operated no exclusions based on language.

Search strategy: We created a sensitive search strategy based around concepts of AF, cognitive decline/dementia and thromboprophylaxis. Where available we used validated search strings, supplemented with MeSH terms and other controlled vocabulary. We searched various, multidisciplinary electronic databases from inception until 12th November 2014 inclusive: Central (Cochrane Library), CINAHL (EBSCO); EMBASE (OVID); MEDLINE (OVID); PsycINFO (EBSCO); Web of Science Core Collection (Thomson Reuters).(Supplementary materials).

We performed citation searches of relevant papers and reviews in this field, “back” searching the references of papers of interest and also “forward” searching to find other papers citing the paper of interest. We contacted key authors who had published in the field and authors of included studies for relevant unpublished data.

As a test of external validity of our search strategy, two exemplar papers that were known to be relevant to our study question were selected by a team member (TQ)

independent of the search process. We assessed whether our search identified these papers.

Data extraction and synthesis: Titles from all database searches were collated, de-duplicated and screened for relevance (EndNote version X7, Thomson Reuters, Philadelphia, USA). For initial title searching we used a previously validated technique where one reviewer, trained in systematic review (PM), assessed all titles generated while another experienced systematic reviewer (TQ) assessed a random selection of 1,000 of these titles.[8] We compared titles selected, to assess whether the focussed review (TQ) included any titles not included in the long-list review (PM).

Potentially relevant titles had abstracts screened and full papers as required were independently screened by two reviewers (PM, DL [experienced reviewer]). Data was extracted to a study specific proforma, piloted on two relevant papers and refined as necessary.(Supplementary materials)

Two independent assessors (PM, TQ) used the Cochrane Risk of Bias tool for randomised controlled trials and the Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS) to assess those studies providing quantitative data.[9] We modified the anchoring statements to suit our specific research question.(Supplementary materials) Both assessments included seven different categories covering domains of selection bias, confounding, measurement of exposure, blinding, attrition bias, reporting bias and generalizability. Domains were assessed individually and rated, “High risk”, “Low risk” or “Unclear risk”.

Statistical analyses: We anticipated that outcomes of interest would be described as scores on multi-domain cognitive tests or rates of dementia diagnosis. Therefore, we pre-specified two primary analyses:

a)Comparison of temporal change in cognitive score between treatment arms from baseline to point of longest follow-up.

b)Comparison of rates of incident dementia/cognitive impairment between treatment arms.

We described absolute scores on cognitive tests for each treatment arm. For prospective studies we described scores at baseline and follow up(s). We calculated mean differences in scores from baseline to final follow up and then described summary between group change over time.

For prospective studies describing rates of incident diagnoses at a specific time point, we calculated rates of development of a cognitive outcome (including syndromes of cognitive impairment and dementia) comparing treatment arms. We pooled these data to give a summary odds ratio for incident cognitive impairment.

To make greatest use of available data we included mixed study designs in pooled analyses (RCTS and observational cohorts) and performed sensitivity analyses restricted to single study methodologies.

We tested for statistical heterogeneity with the I^2 statistic and qualitatively through visual analysis of forest plots. We present both fixed and random effects summary

data. We assessed publication bias using a “funnel plot” technique. All analyses used Comprehensive Meta-Analysis software (CMA, Version 2, Biostat Inc).

Results

We obtained 8,993 references from the initial electronic database search and reviewed abstracts and/or full text of 234 papers.(Figure 1) Of these, 19 studies (n=15,876 participants) were suitable for inclusion [10-28] (five were extended abstracts, supplemented, where possible, by additional data from authors [23-27]).(Table 1)

The internal validity of title searching process was confirmed as no titles from focused review were missed in the full review. The external validity of the search strategy was confirmed, as both of the pre-identified papers were included in the final selection.[10,14]

Narrative Review of Included Studies: Included studies were heterogeneous in terms of sampling, outcomes assessment and study design. Included data were from RCTs, observational cohorts, with the majority of papers from cross-sectional studies (weaker forms of evidence). Studies were from a range of international centres and year of publication ranged from 1998 to 2015.(Table 1)

Of five RCTs identified, only one had cognitive data suited to our proposed analysis.[11] In this study, the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study, older adults were randomised to warfarin (target International Normalised Ratio:2-3) or aspirin therapy (75mg/d) over a 33-month period in an

open-label, blinded endpoint design. This study found no evidence that anticoagulation was superior to antiplatelet therapy in the prevention of cognitive decline or incident dementia. There was a suggestion of less cognitive decline with anticoagulation in the longer term, but there was substantial attrition.

Three other RCTs collected data on antithrombotic medication and cognition; the cognitive sub-study of the Apixaban Versus Acetylsalicylic acid to Prevent Strokes (AVERROES) trial has not yet released cognitive data [23]; a post-hoc sub-study of the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE-W) study reported association between time in therapeutic range and cognitive scores but did not provide cognitive scores by treatment arm.[13] Similarly, a single-centre study of warfarin versus aspirin provided only aggregate cognitive data.[14]

One RCT compared cognitive outcomes following different methods of left atrial catheter ablation, and showed no significant difference in cognition between differing ablation methods.[12]

We identified seven prospective observational studies.[15,16,20,22,24-6] Across RCT and observational cohorts, timing of assessments varied (Table 1) there was substantial attrition at longer follow-ups. Of the studies not included in meta-analysis, one described participants with AF from two large cardiovascular RCTs (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial [ONTARGET] and Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease [TRANSCEND]) and reported that

antithrombotic medication did not modify the association between AF and a composite outcome of change in cognitive score, incident dementia or admission to institutional care.[15] Analysis of AF in the Atherosclerosis Risk in Communities (ARIC) study reported greater cognitive decline in subjects with AF, particularly where associated with neuroimaging evidence of stroke [16]; similar associations were reported in an Italian study.[17] Both were unsuitable for quantitative analysis as data on medication and cognitive scores were described in aggregate and not by treatment arm.

We found seven cross-sectional studies describing association between cognition and thromboprophylaxis.[10,17,18,19,21,27,28] Two studies [19,27] were combined with baseline data from prospective studies to offer a “snapshot” of the cross-sectional association between anticoagulation and cognition.(Supplementary materials).

Quantitative analysis: Ten studies had suitable quantitative data, comprising one RCT [11] and four prospective, observational studies [20,24-26] (total participants:7,063). Studies were comparisons of antithrombotic or anticoagulant therapy versus antiplatelet therapy or no treatment. No studies looked at surgical procedures. The outcome measures were dementia/cognitive impairment or scores on Folstein’s Mini Mental State Examination (MMSE). Funnel plot suggested no major publication bias.(Supplementary materials)

Where studies offered prospective follow-up, temporal decline in MMSE was less for those anticoagulated compared to those receiving antiplatelet therapy (mean

difference MMSE:0.90, 95%CI:0.29 to 1.51). This result is in keeping with the trend seen in the single RCT (mean difference MMSE:0.80. 95%CI:-0.07 to 1.67).

There was no between-group difference in incident dementia/cognitive impairment across studies comparing anti-thrombotic/anticoagulant to control (overall summary odds ratio:1.11 (95%CI:0.77-1.60). In subgroup analyses there was no difference in incident cognitive syndromes comparing anticoagulant and antiplatelet (two studies, summary odds ratio:1.23 (95%CI:0.79-1.92 [odds ratio:1.46 (0.83-2.58) on sensitivity analysis, removing the RCT]) or anticoagulant versus no treatment/placebo (three studies, summary odds ratio:0.89 (95%CI:0.47-1.69)).(Figure 2)

Included studies did not contain sufficient information to allow for any of our pre-specified subgroup analyses.(Supplementary materials)

Risk of Bias and Generalisability Assessment for Included Studies: Using our assessment tools, all included studies had potential risk of bias. The main methodological issues were around blinding; only one study had sufficient blinding [20], and robustness of measures of exposure and outcomes, four studies[11,,20,24,25] had unclear or poor measures of dementia and/or AF diagnosis, such as self-reporting.[11,20,24,25](Table 2)

Discussion

We found few studies evaluating the cognitive consequences of AF thromboprophylaxis and where data were available, there was substantial risk of bias. Prospective data were suggestive of a modest protective cognitive effect from

anticoagulation in AF in the longer term but we found no decrease in rates of incident dementia.

We can speculate on the reasons for these results. Detecting change in incident dementia rates probably requires larger sample sizes and longer follow-up than studies describing change in a surrogate cognitive measure. Thus even with meta-analysis, sample sizes may be too small to detect modest effects. It may also be that the cognitive decline associated with AF is not solely a result of cardioembolism (various other mechanistic explanations have been postulated).[5-7] A degree of cognitive harm, for example from cerebral amyloid angiopathy related bleeding, remains possible.

The data that informed our analyses are liable to a variety of biases. Populations were not matched, with those prescribed anticoagulants having higher baseline cognitive scores. A degree of selection bias, wherein those with better cognition, or at greater risk of stroke, are more likely to be prescribed warfarin, seems possible and the resulting cognitive trajectories may differ independent of antithrombotic agent used. The ideal study design would be a RCT in a cohort with AF, free from dementia at baseline. We found only one full published paper that used this method.[11] This study reported no significant difference in incident dementia comparing warfarin and aspirin but was probably underpowered for this secondary outcome.

We set no time limits on our study inclusion and we note that clinical guidance for AF has changed over time. In older studies, the majority of patients with AF received no

thromboprophlaxis or were prescribed antiplatelets; the latter treatment (as monotherapy) is no longer recommended for stroke thromboprophylaxis in AF due to limited efficacy.[29] Collating these older datasets with large numbers on no treatment or aspirin offered the potential to describe the “natural history” of cognitive decline in AF patients free from treatment that could be compared with VKA data. Unfortunately, across the relevant studies, sample sizes were modest or data were not available in a format that allowed such an analysis. The anticoagulant studied was predominantly warfarin. We recognise the increasing use of NOACs and these agents may have a differing cognitive profile. As the NOACs have lower incidence of intracerebral haemorrhage, plausibly they may have greater net cognitive benefit.

It could be argued that our research question is redundant, as in contemporary practice, the majority with AF will require anticoagulation for stroke prevention regardless of any potential added cognitive benefit. However, had we demonstrated beneficial cognitive effects of thromboprophlaxis this could have expanded the population who may benefit from anticoagulation and may have increased anticoagulant prescriptions. We recognise that, despite compelling evidence of efficacy, anticoagulation remains under-prescribed particularly in older adults.[30] There were plausible reasons to think that intracerebral bleeding due to anticoagulation may worsen cognitive decline, and indeed one paper in our review demonstrated such an effect.[24] However, we found no evidence of worsening cognitive decline with anticoagulation in the pooled analysis. This is an important finding and supports the use of anticoagulation in older adults.

The major limitation of our included studies was in their study design, with only one RCT included. Methodological limitations were highlighted by our quality assessment tool. Generalisability was variable and participants included in studies may not be equivalent to patients seen in practice, several studies did not employ blinded outcome assessments and there was substantial attrition in longitudinal studies. This is of particular relevance, as participants with cognitive issues may be more likely to be lost to follow-up. We included a variety of cognitive diagnoses and tests as our outcomes of interest, this was necessary to allow for pooled analyses. We recognise that cognitive test scores alone are not synonymous with clinical dementia and that within a label of clinical cognitive impairment there can be substantial variation in severity.

We used a comprehensive search strategy. In designing our search, we limited to drugs and procedures that directly reduce cardioembolism. Maintenance of sinus rhythm may prevent cardioembolism but to keep our review focussed we did not specifically search for cardioversion interventions. We followed best practice in conduct and reporting. All papers were quality assessed using a robust method tailored to our specific study question. We recognise the substantial heterogeneity in the included studies and need to be cautious in our interpretation of pooled data.

Our review does not suggest a need for change in practice, those with AF at risk of stroke should continue to be anticoagulated. However, our review highlights an important evidence gap. There is sufficient signal of a beneficial cognitive effect from anticoagulation to justify further study. Our assessment of risk of bias and reporting of important features such as incident stroke and AF risk stratification

highlight limitations in previous studies and may be helpful in the design, conduct and reporting of future studies. Future studies of AF patients should include serial measures of cognition to provide data on the impact of thromboprophylaxis on cognitive function; studies should also include data on stroke and stroke risk stratification. We recognise that a patient who warrants anticoagulation should not be randomised to placebo or antiplatelet. Studies could look at “low risk” groups or compare NOACs which still have a portfolio of research and development. This is particularly important as a potential reduction in dementia risk may influence clinical decision-making regarding initiation of these agents in older, frailer people with AF.

In summary, we were unable to provide definitive evidence of a beneficial cognitive effect of thromboprophylaxis for AF patients. Available data suggest that anticoagulant therapy may be associated with reduced cognitive decline over time, although the clinical significance is uncertain. Our findings need to be interpreted in the context of the included studies, as these had substantial risk of bias and even pooled results may have been underpowered.

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PM: No relevant COI

DAL: Investigator-initiated educational grants from Bayer Healthcare, Boehringer Ingelheim and Bristol-Myers-Squibb. Speaker's bureau for Boehringer Ingelheim, Bayer, and Bristol Myers Squibb/Pfizer. DAL is a Steering Committee member of a Bristol-Myers-Squibb Phase IV trial.

HP: No relevant COI

JOC: No relevant COI

TQ: Has received investigator initiated grants and honoraria from Bristol Myers Squibb/Pfizer Alliance and Boehringer Ingelheim.

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Table 1: Characteristics of included studies

Author/ Year	Setting	Recruitment	N included	Cognitive Measure	Assessment timing	Intervention	Control
Randomised Controlled Trials							
Mavaddat 2014 [11]	England/ Wales	C	973	MMSE, Dementia	9/12, 21/12, 33/12	Anticoagulant	Antiplatelet
Haeusler 2013 [12]	Germany	H	37	NPB	9/12	Left atrial catheter ablation	Left atrial catheter ablation
O'Donnell 2011 [23]	International	C	1184	m-MoCA, DSS	unclear	Anticoagulant	Antiplatelet
Flaker 2010 [13]	Global	C	2510	MMSE	16/12	Anticoagulant	Antiplatelet
Rash 2007 [14]	England	H	75	MMSE	12/12	Anticoagulant	Antiplatelet
Cross-Sectional Comparisons							
Ball 2013 [21]	Australia	H	260	Cognitive impairment	N/A	Anticoagulant	Antiplatelet
Cannon 2015 [27]	Scotland	H	61	MMSE	N/A	Anticoagulant	Antiplatelet
Formiga 2009 [19]	Spain	H	84	MMSE	N/A	Anticoagulant	Antiplatelet

Gaita 2013 [17]	Italy	H	270	NPB	N/A	Anticoagulant	Antiplatelet
Maes 2014 [18]	Belgium	H	773	Cognitive Disorders	N/A	Anticoagulant	No Treatment
O'Connell 1998 [10]	England	C	81	MMSE	N/A	Antiplatelet	No Treatment
Puccio 2009 [28]	Italy	H	42	NPB, MMSE	N/A	Anticoagulant	Antiplatelet
Prospective Observational Cohorts							
Chen 2014 [16]	USA	C	48	NPB	12/12	Anticoagulant	Antiplatelet
Liao 2013 [25]	Taiwan	C	5,221	Dementia	71/12	Anticoagulant	Antiplatelet
						Antithrombotic*	No Treatment
Meranus 2013 [24]	USA	H	420	Dementia	42/12	Anticoagulant	No Treatment
						Antithrombotic*	
Marzona 2012 [15]	Global	C	3,068	MMSE	56/12	Antithrombotic	No Treatment
Franco 2012 [26]	Italy	H	191	MMSE	48/12	Anticoagulant	Antiplatelet
Park 2007 [22]	England	C	119	MMSE	12/12, 36/12	Anticoagulant	Antiplatelet
Barber 2004 [20]	Scotland	C	258	Dementia	36/12	Anticoagulant	No Treatment

**The use of both anticoagulant and antiplatelet therapy*

CDR=Clinical Dementia Rating; dementia=clinical diagnosis of dementia; DSS=Digit Symbol Substitution; MMSE=Mini Mental State Exam; m-MoCA=modified Montreal Cognitive Assessment; NPB=neuropsychological battery; RCT=Randomised Controlled Trial

H= Hospital-based

C= Community-based

Table 2: Risk of Bias Assessment Table

Papers	**Selection Bias**	**Confounding variables**	**Measurement of exposure**	**Blinding**	**Attrition Bias**	**Reporting Bias**	**Generalizability**
Liao 2013	Low risk	Low risk	High risk	Unclear	Low risk	Unclear	Low risk
Meranus 2013	Low risk	Low risk	High risk	High risk	Low risk	Unclear	High risk
Franco 2012	Low risk	Low risk	Low risk	Unclear	High risk	Unclear	High risk
Barber 2004	Low risk	Low risk	Unclear	Low risk	High risk	High risk	Low risk
Randomised controlled trials							
Papers	**Random Sequence Generation**	**Allocation Concealment**	**Blinding of Participants**	**Blinding of Outcome**	**Reporting Bias**	**Selective Reporting**	**Generalizability**
Mavaddat 2014	Low risk	High risk	High risk	High risk	High risk	Low risk	High risk

Figure 1: PRISMA flow diagram detailing search

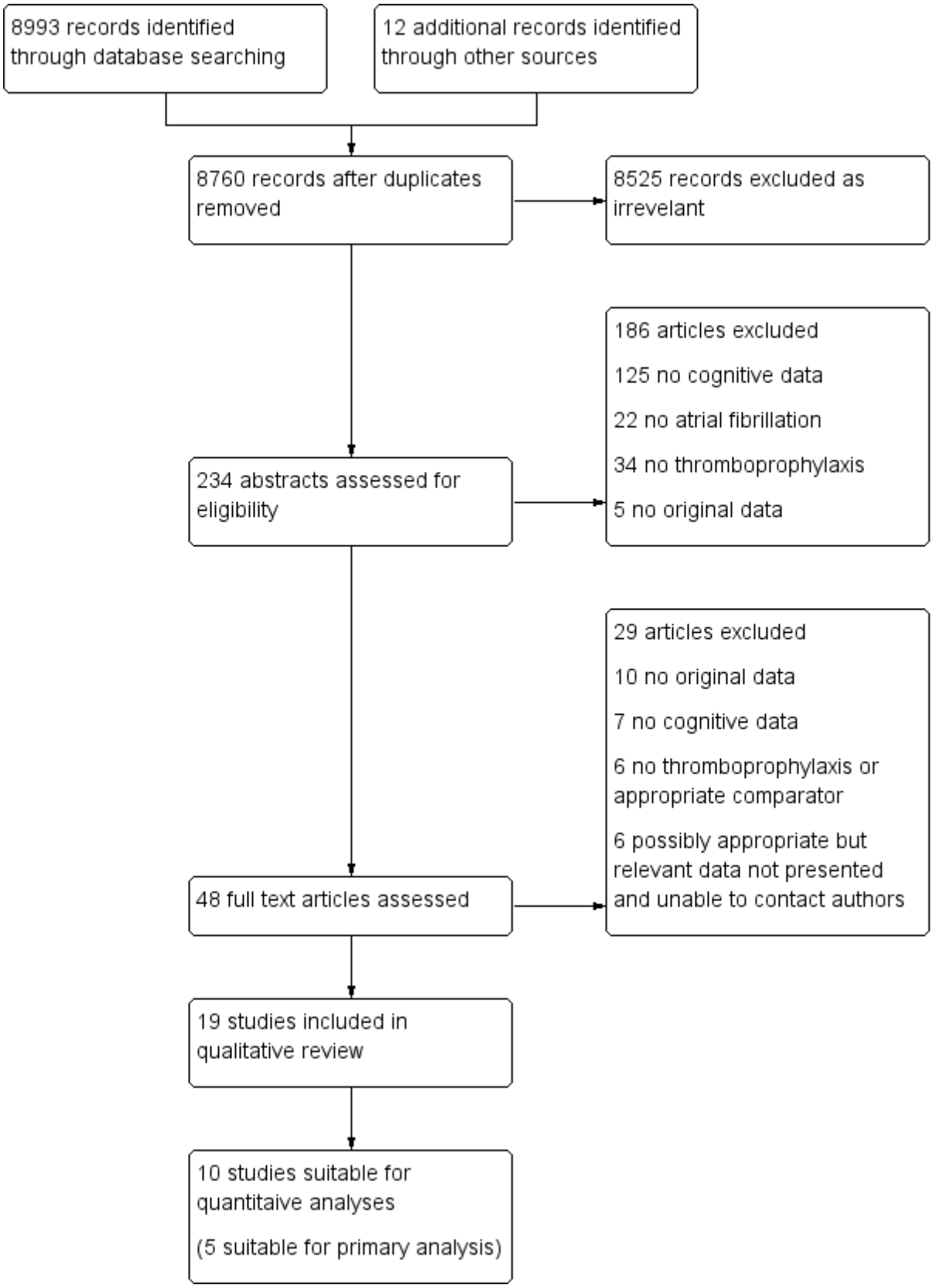
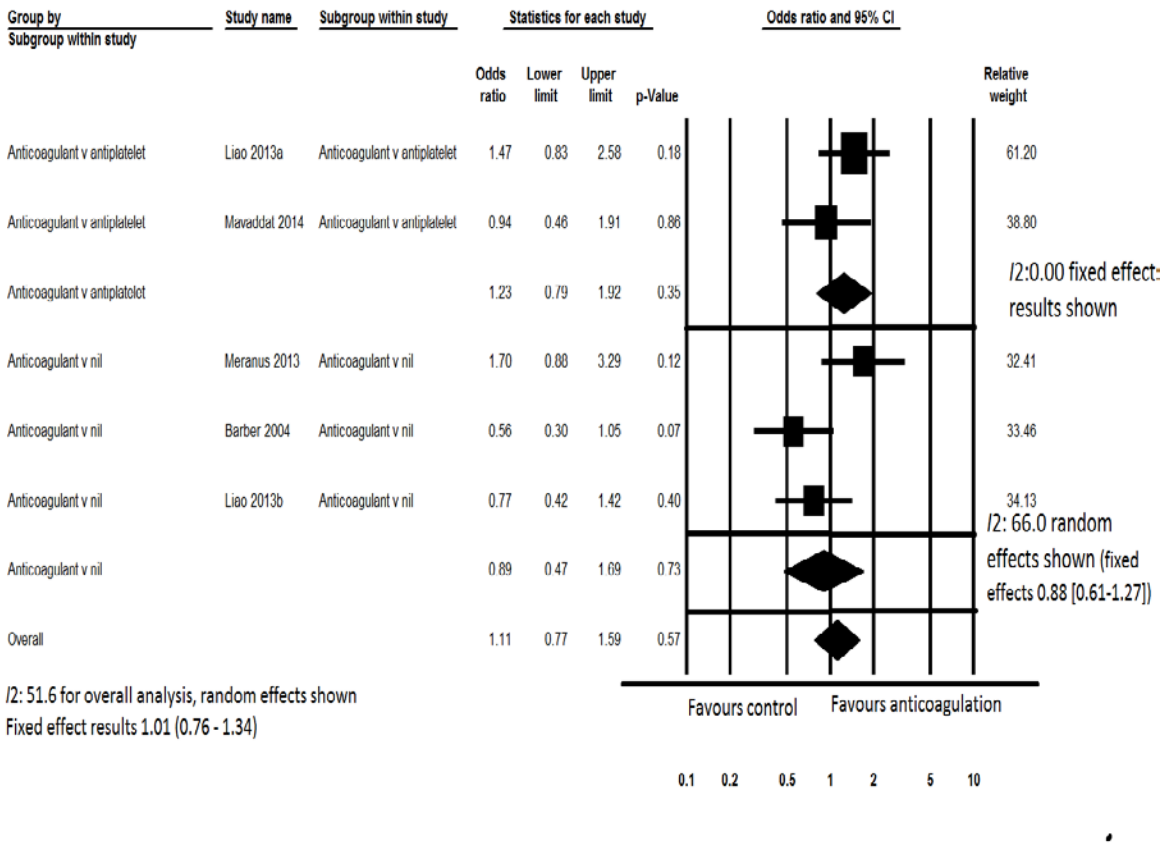


Figure 2: Forest plot of odds ratio for developing dementia/cognitive impairment comparing anticoagulants and other therapy



Included data are from prospective cohorts, other than Mavaddat which is a RCT.

Sensitivity anlayses removing the RCT are presented in the text.