Terapia anticoagulante e decadimento cognitivo in pazienti con fibrillazione atriale

Background

Atrial fibrillation (AF) is a common cardiac arrhythmia, especially in the elderly.

Growing evidence supports a role for AF as a risk factor for **cognitive decline** and **dementia**.

Background

Selected prospective studies reporting the association of atrial fibrillation with cognitive decline

Reference	Setting	Study population	Follow-up length	Cognitive assessment	Main findings
Marzona et al, 2012	Multi-country	31,506 men and women (30% women, mean age 67)	Mean 4.7 years	Repeated MMSE	AF associated with increased risk of cognitive decline (HR 1.14, 95%CI 1.03–1.26)
Thacker et al, 2013	United States	5,150 men and women (59% women, mean age 73)	Mean 7 years	100-point modified MMSE	Faster decline in individuals with incident AF, with stronger impact at older age
Chen et al, 2014	United States	935 men and women (62% women, mean age 62)	Median 10.6 years	DWR, DSS, WF tests	Incident AF associated with faster decline in DSS and WF tests

CI: Confidence interval; DSS: Digit Symbol Substitution; DWR: Delayed Word Recall; HR: Hazard ratio; MMSE: Mini-Mental State Examination; WF: Word Fluency

Background

Selected prospective studies reporting the association of atrial fibrillation with incident dementia

Reference	Setting	Study population	Follow-up length	Dementia ascertainment	Main findings
Dublin et al, 2011	Seattle area, United States	3,045 men and women (60% women, median age 74)	Mean 6.8 years	Cognitive screening followed by detailed neuropsychological and clinical assessment	AF associated with increased risk of all-cause dementia (HR 1.38, 95% 1.10–1.73) and Alzheimer's disease (HR 1.50, 95%CI 1.16–1.94)
Marzona et al, 2012	Multi-country	31,506 men and women (30% men, mean age 67)	Mean 4.7 years	"New diagnosis of dementia, reported severe cognitive impairment, MMSE<23"	AF associated with increased risk of dementia (HR 1.30, 95%CI 1.14–1.49)

CI: Confidence Interval; HR: Hazard Ratio; MMSE: Mini-Mental State Examination

Background

Selected prospective studies reporting the association of atrial fibrillation with incident dementia

Reference	Setting	Study population	Follow-up length	Dementia ascertainment	Main findings
Rusanen et al, 2014	Eastern Finland	1,510 men and women (62% women, mean age 65)	Mean 7.8 years	Cognitive screening followed by detailed neuropsychological and clinical assessment	AF in late life independently associated with dementia (HR 2.61, 95%CI 1.05–6.47) and Alzheimer's disease (HR 2.54, 95%CI 1.04–6.16)
De Bruijn et al, 2015	Rotterdam, the Netherlands	6,196 men and women without prevalent AF (59% women, mean age 68)	Mean 12.8 years	Cognitive screening followed by detailed examination, plus review of medical records	Incident AF associated with increased risk of dementia in younger participants (<67 years, HR 1.81, 95%CI 1.11–2.95) but not in older (≥67, HR 1.12: 95%CI 0.85–1.46)
Liao et al, 2015	Taiwan	665,330 men and women (44% women, mean age 70)	Mean 4.9 years	Diagnosis codes from medical claims	AF associated with increased risk of dementia (HR 1.42, 95%CI 1.39–1.45)

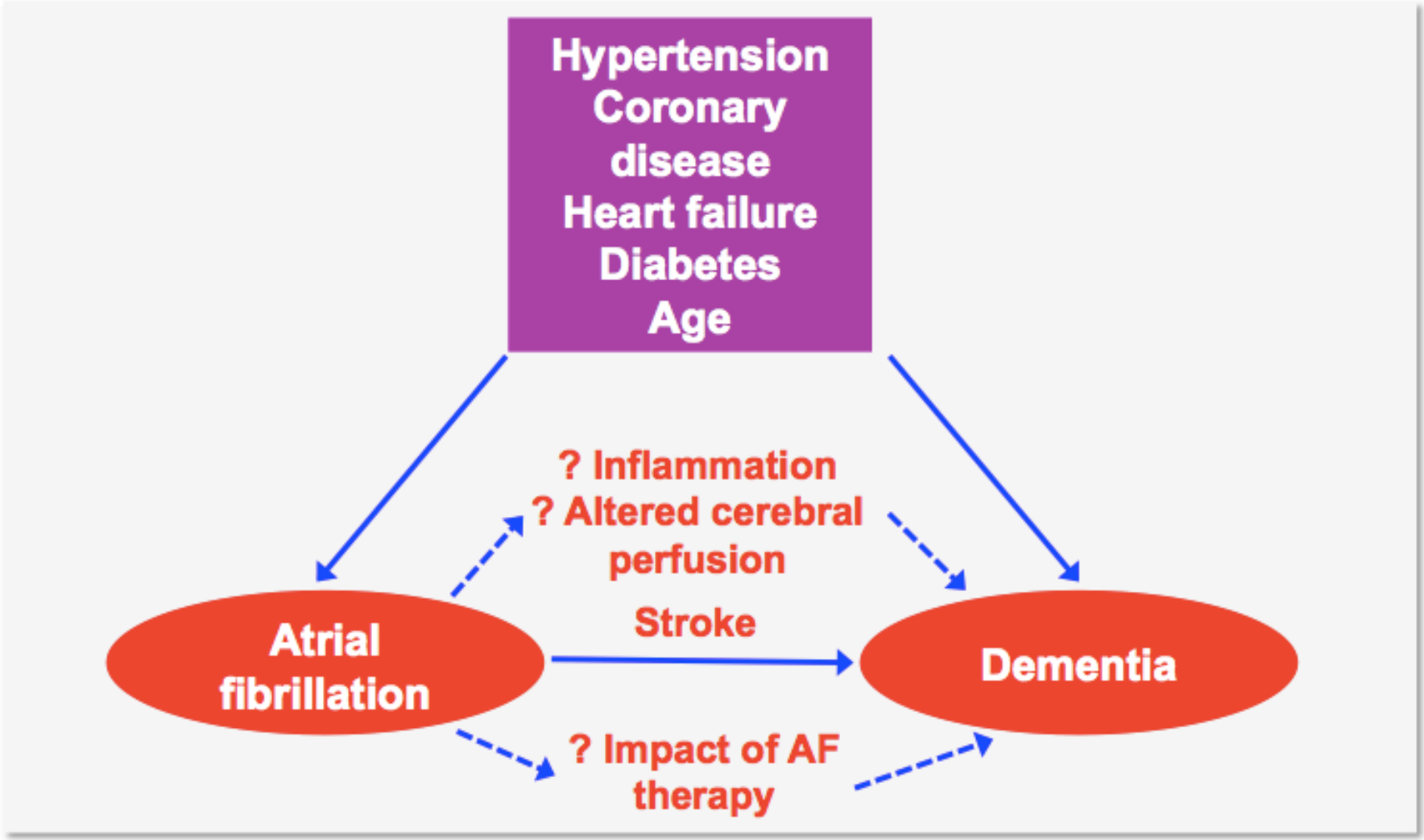
CI: Confidence Interval; HR: Hazard Ratio;

Background

While a majority of risk can be attributed to cardioembolic stroke secondary to AF, additional risk is apparent, and may be driven by vascular inflammation and changes in cerebral perfusion.

Atrial fibrillation and dementia:

common risk factors and additional mechanisms possibly explaining their association



Shah AD, Journal of Atrial Fibrillation, 2016

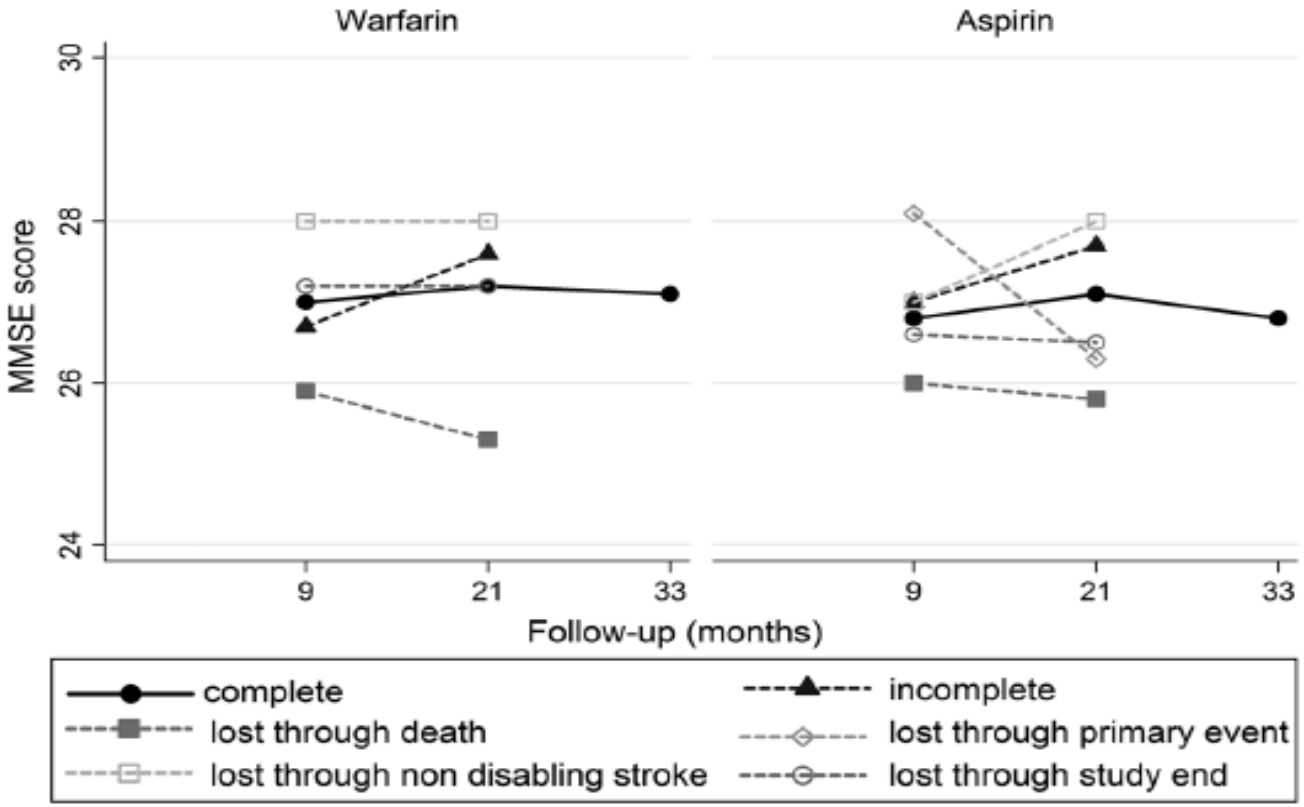
Background

However, there are numerous controversies over whether anticoagulants can reduce the occurrence of dementia in patients with AF.

Warfarin Versus Aspirin for Prevention of Cognitive Decline in Atrial Fibrillation

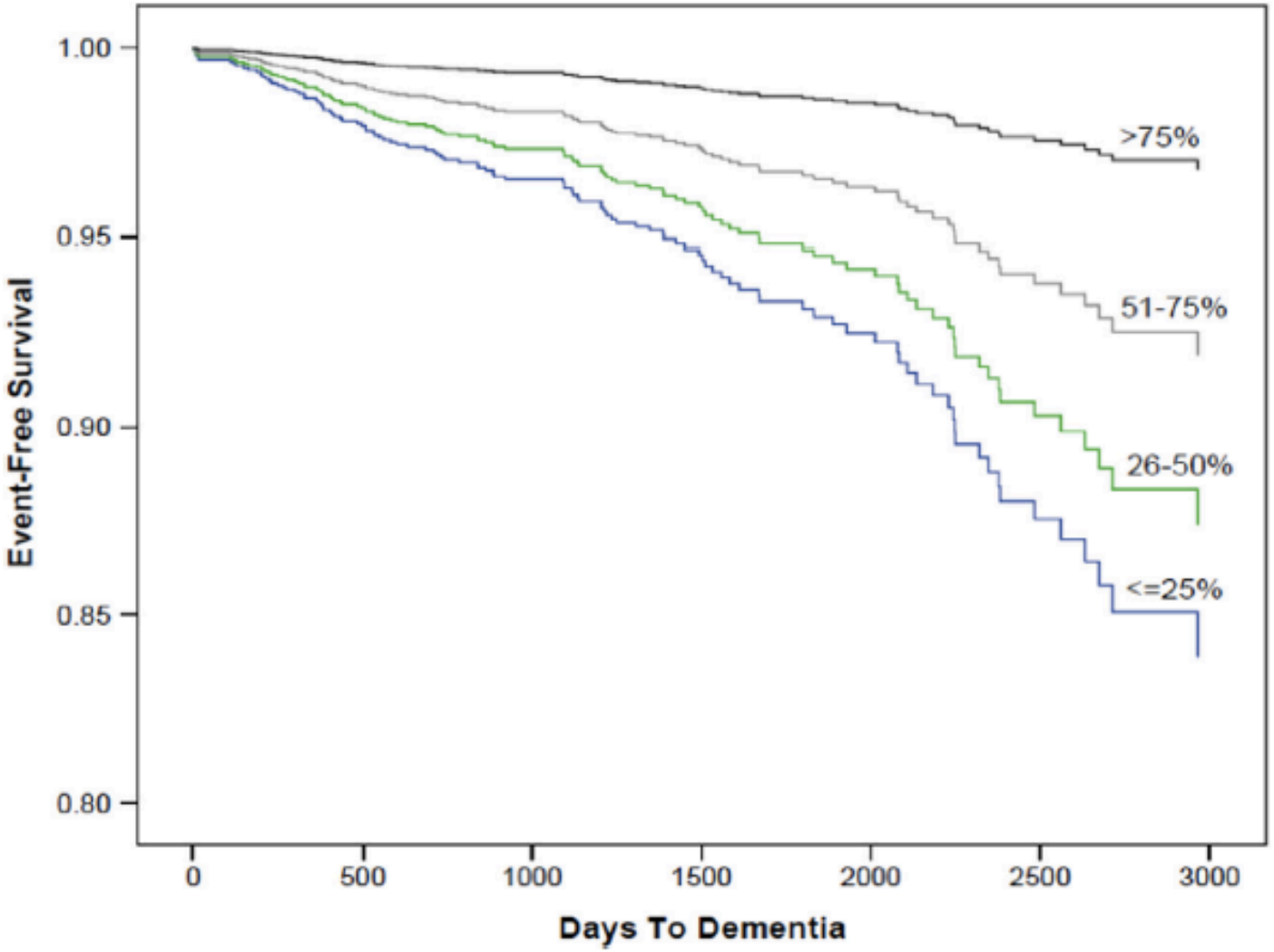
Randomized Controlled Trial (Birmingham Atrial Fibrillation Treatment of the Aged Study)

No evidence that anticoagulation confers clinically important protection over aspirin against cognitive decline as measured by the Mini-Mental State Examination in AF in the first 33 months of treatment other than that provided by preventing clinical stroke.



Mavaddat N, Stroke 2014

Time outside of therapeutic range in atrial fibrillation patients is associated with long-term risk of dementia

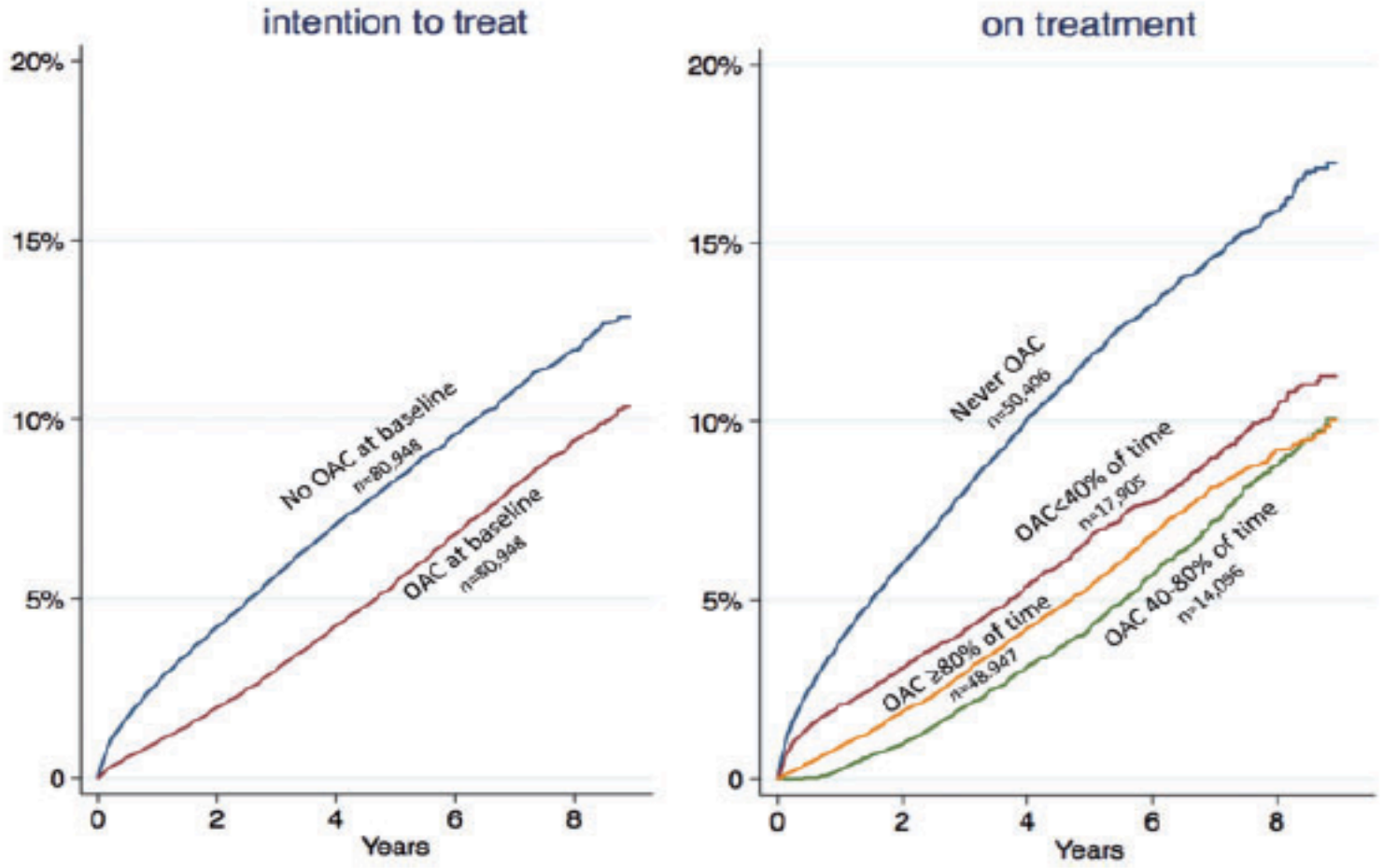


Jacobs V, Heart Rhythm 2014

Less dementia with oral anticoagulation in atrial fibrillation

Unadjusted incidence of dementia in relation to oral anticoagulant treatment among 161.896 patients with AF:

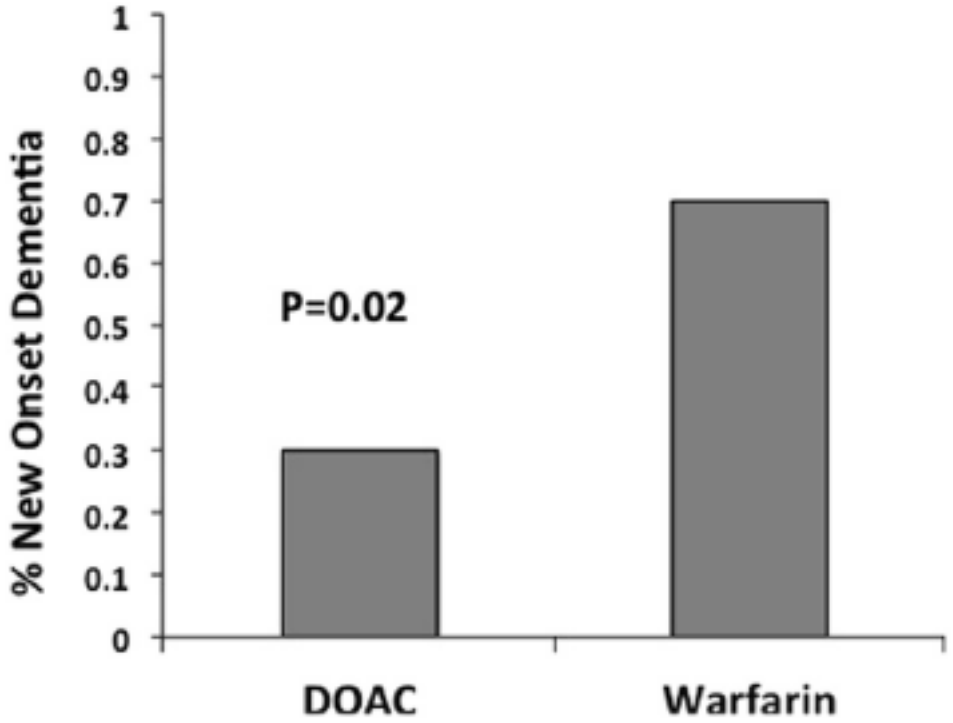
The risk of dementia is higher without oral anticoagulant treatment in patients with AF.



Friberg L, Eur Heart J 2017

Long-Term Population-Based Cerebral Ischemic Event and Cognitive Outcomes of Direct Oral Anticoagulants Compared With Warfarin Among Long-term Anticoagulated Patients for Atrial Fibrillation

Long-term incident dementia events in patients with AF compared by DOACs and warfarin treatment.



Jacobs V, Am J Cardiol 2016

Relationship of Anticoagulant Therapy With Cognitive Impairment Among Patients With Atrial Fibrillation: A Meta-Analysis and Systematic Review

Wenke Cheng, MD, Weijun Liu, PhD,* Bin Li, MD,† and Dongfang Li, MD**

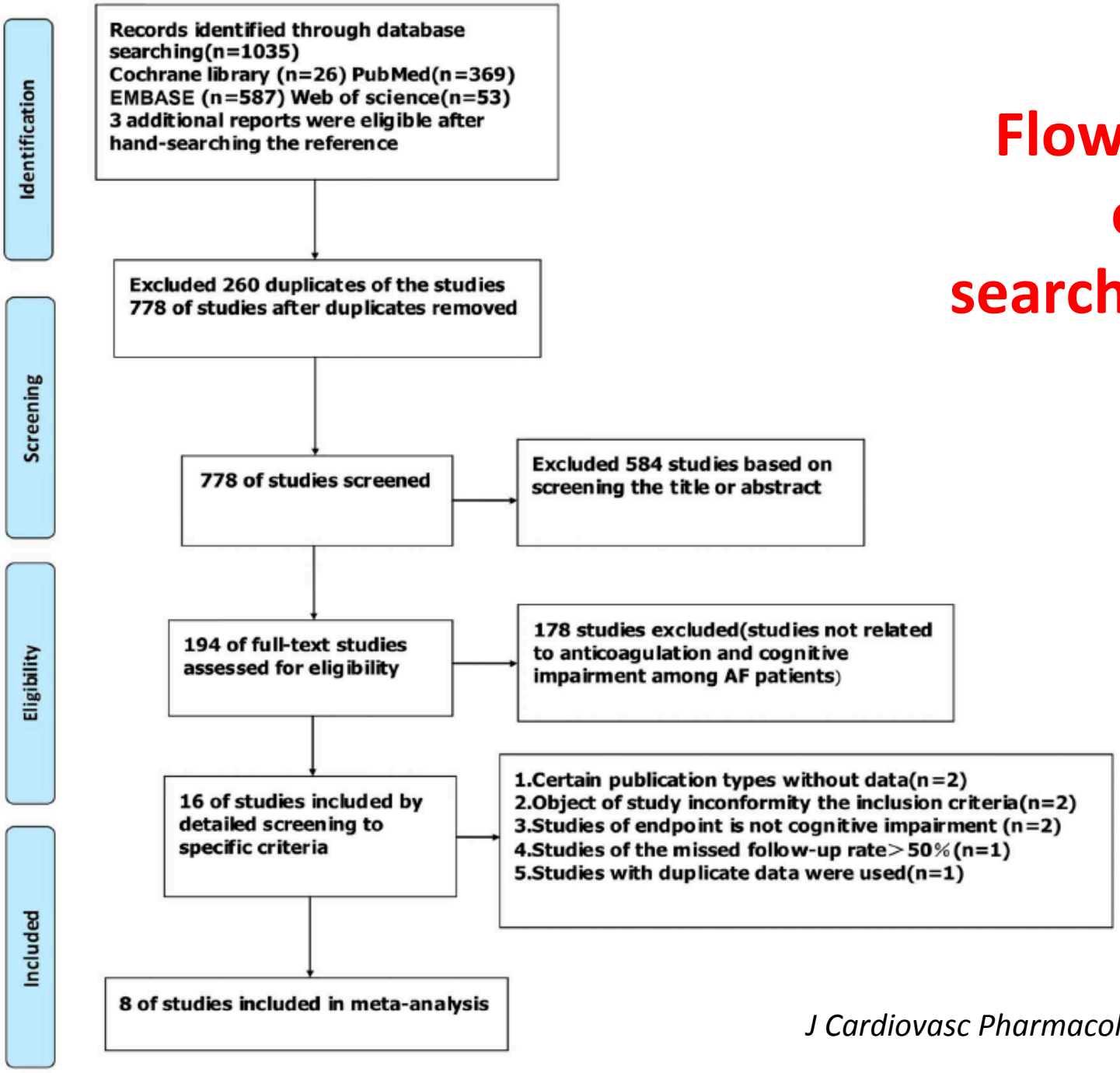
J Cardiovasc Pharmacol 2018;71:380–387

Objective

To complete a meta-analysis of studies and investigate the association between anticoagulant therapy and cognitive impairment in patients with AF.

J Cardiovasc Pharmacol 2018;71:380–387

Flow chart of search results



J Cardiovasc Pharmacol 2018;71:380–387

Characteristics of studies evaluating the association between anticoagulation and cognitive impairment and dementia among patients with AF

Author	Year	Country	Study Design	Follow-Up, y*	Patients, n	Female, %	Age, y*	Stroke Exclusion	Maximum Adjusted Covariate
Bunch et al[11]	2016	America	Re cohort	2021 d†	10,537	49.8%	63.5 (13.8)	NO	Age, sex, hypertension, diabetes, hyperlipidemia, renal failure, smoking history, previous myocardial infarction cerebrovascular accident, heart failure, previous TIA, CHADS2, and CHADS2VASC
Friberg L and Rosenqvist[12]	2017	Sweden	Re cohort	9 y†	444,106	44.7%	74.8‡	NO	Age, female, years since first AF diagnosis, CHA2DS2VASc, heart failure, hypertension, diabetes, stroke/systemic emboli/TIA, vascular disease, renal disease, liver disease, peripheral artery disease, and hypothyroidism
Jacobs et al[13]	2016	Australia	Re cohort	243 d†	5254	41%	72.4 (10.9)	NO	Age, sex, hypertension, diabetes mellitus, heart failure, hyperlipidemia, coronary artery disease, coronary bypass, previous bleeding, previous major bleeding, history of vascular disease, CCHADS2, previous thromboembolism, and CHADS2-VASC

J Cardiovasc Pharmacol 2018;71:380–387

Characteristics of studies evaluating the association between anticoagulation and cognitive impairment and dementia among patients with AF

Author	Year	Country	Study Design	Follow-Up, y*	Patients, n	Female, %	Age, y*	Stroke Exclusion	Maximum Adjusted Covariate
Jacobs et al[14]	2014	Australia	Re cohort	4.0 y†	2605	46%	73.7 (10.8)	YES	Age, sex, hypertension, diabetes, hyperlipidemia, smoking, heart failure, coronary artery disease, valve disease, previous maligancy, previous myocardial infarction, renal failure, previous bleeding, previous major bleeding, history of vascular disease, CHADS2, thromboembolism, and left atrial area
Hu et al[15]	2016	USA	Re cohort	5.0 (3.7) y	2800	47%	71 (15)	NC	Age, sex, TTR, CHADS2-VASC, and TTR
Viscogliosi et al[16]	2017	Italy	Re cohort	1 y†	316	55.7%	74.7 (7.0)	NO	Age, sex, hypertension, diabetes, education <8 year. hyperlipidemia, renal failure, smoking history, previous myocardial infarction cerebrovascular accident, heart failure, previous TIA, Barthel Index Score, CHADS2VASC, and paroxysmal atrial fibrillation

J Cardiovasc Pharmacol 2018;71:380–387

Characteristics of studies evaluating the association between anticoagulation and cognitive impairment and dementia among patients with AF

Author	Year	Country	Study Design	Follow-Up, y*	Patients, n	Female, %	Age, y*	Stroke Exclusion	Maximum Adjusted Covariate
Liao et al[17]	2013	Taiwan	Re cohort	5.90 (3.39) y	5221	NC	NC	NO	Age, sex, hyperlipidemia, heart failure, history of myocardial infarction, peripheral artery disease, coronary artery disease, chronic kidney disease, vulvular heart disease, and CHADS2
Barber et al[6]	2004	England	Pro cohort	3 y†	258	54%	72†	NO	Age, sex, duration of AF, paroxysmal AF, valvular heart disease, prosthetic valve, LV dysfunction, ischemic heart disease, previous stroke, hypertension, diabetes, and smoking history

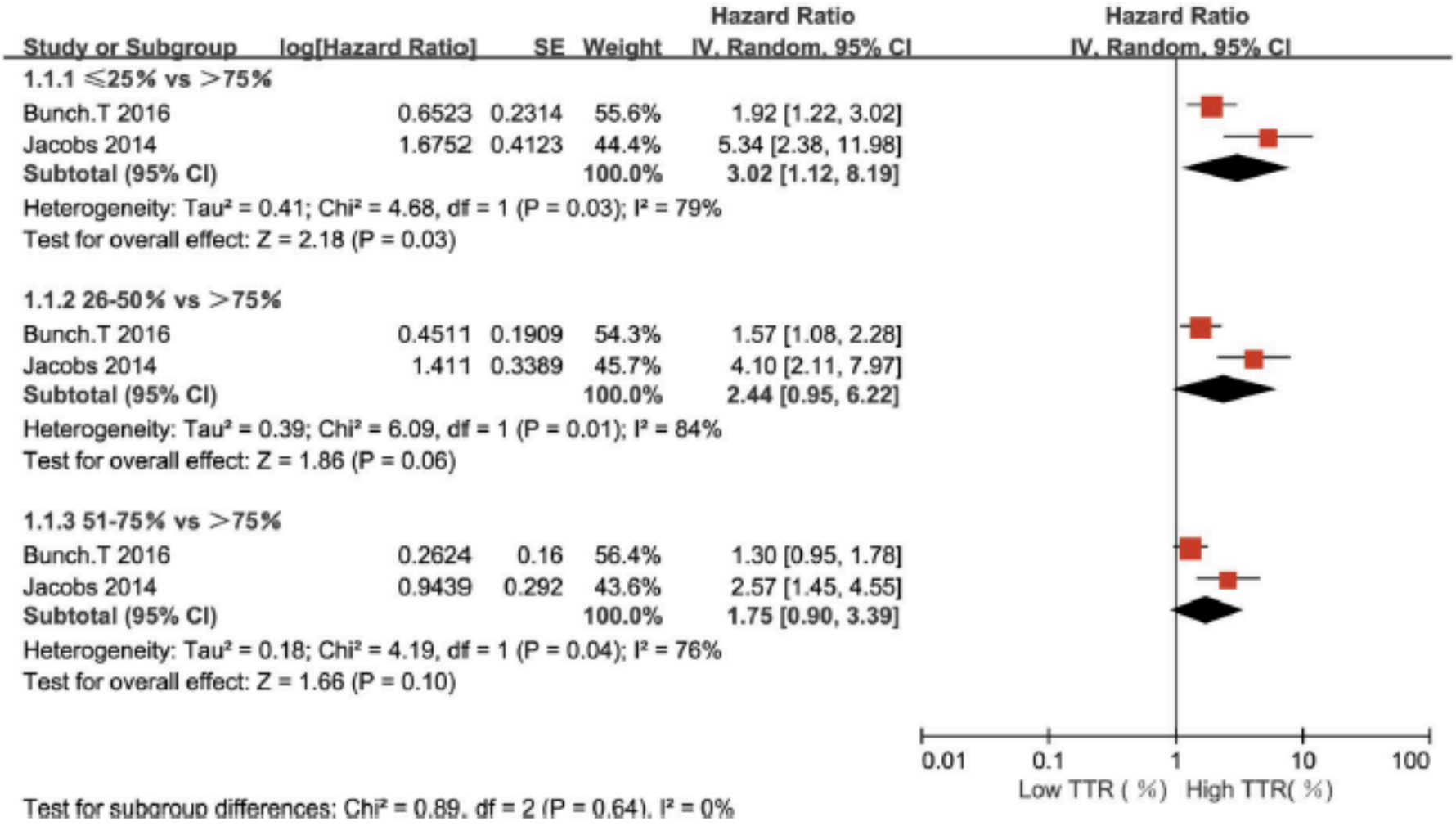
J Cardiovasc Pharmacol 2018;71:380–387

Characteristics of studies evaluating the association between anticoagulation and cognitive impairment and dementia among patients with AF

Author, year	AF Ascertainment	Cognitive Impairment Ascertainment	Intervention	Control	Outcome
Bunch et al[11]	*ICD-9* *ICD-10* ECG	*ICD-9* *ICD-10*	OAC with AF (INR 2–3) TTR ≤25%, TTR 26%–50%, TTR 50%–75%, TTR >75%	OAC Without AF	Dementia
Friberg and Rosenqvist[12]	*IDC-10*	*ICD-10*	OAC with AF NOAC	No OAC with AF Warfarin	Dementia NOAC versus warfarin
Jacobs et al[13]	ECG	*ICD-9*	Warfarin, INR 2–3	NOAC	Dementia
Jacobs et al[14]	*ICD-9*	*ICD-9*	OAC, INR 2–3 TTR ≤25%, TTR 26%–50%, TTR 50%–75%, TTR >75%	No	Dementia
Hu et al[15]	H&P	ICD-9	OAC with AF	No OAC with AF	Dementia
Viscoglios et al[16]	ECG	CDR	OAC With AF	No OAC with AF	Dementia
Liao et al[17]	H&P	H&P	OAC With AF Anti With AF	No OAC with AF No Anti with AF	Dementia
Barber et al[6]	H&P	TICSm/IQCODE	OAC with AF	No OAC With AF	Dementia

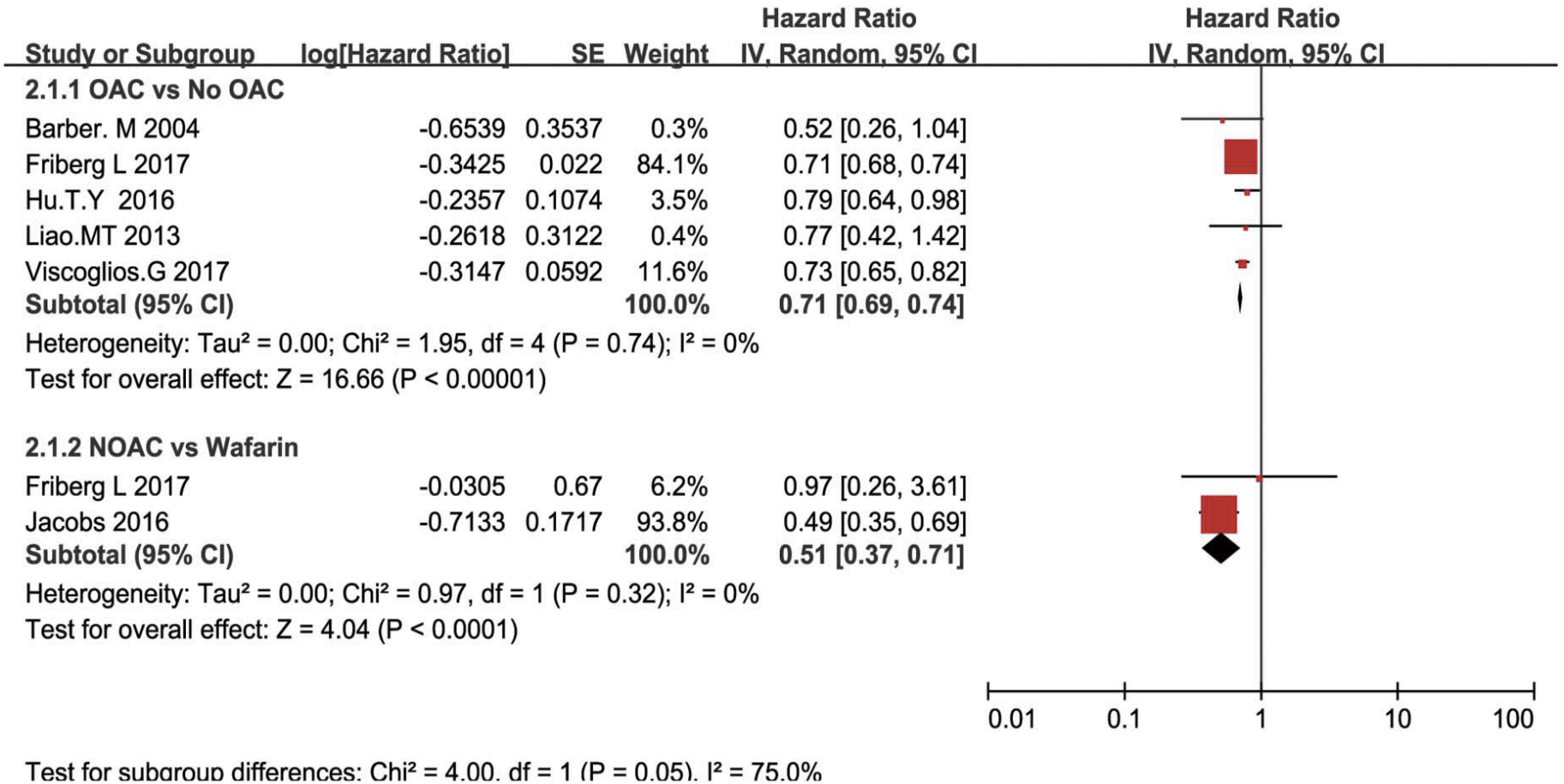
J Cardiovasc Pharmacol 2018;71:380–387

Comparison of the indexes between the low TTR group and the high TTR group



J Cardiovasc Pharmacol 2018;71:380–387

Comparison of the OAC group and no OAC group and NOAC group and warfarin group



J Cardiovasc Pharmacol 2018;71:380–387

Conclusions

OACs significantly reduce the occurrence of cognitive impairment in patients with AF.

In the range of INR 2–3, with the increase of TTR, the incidence of cognitive impairment is lower.

Compared with warfarin, new oral anticoagulants have an efficiently protective effect on cognition.

J Cardiovasc Pharmacol 2018;71:380–387