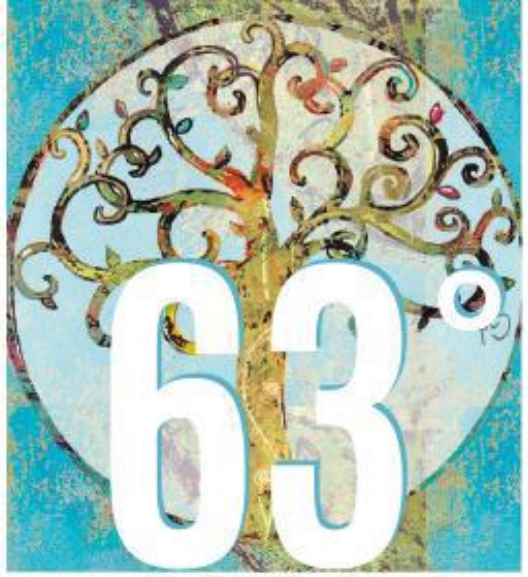


CONGRESSO NAZIONALE SIGG

GLI ANZIANI:
LE RADICI DA PRESERVARE

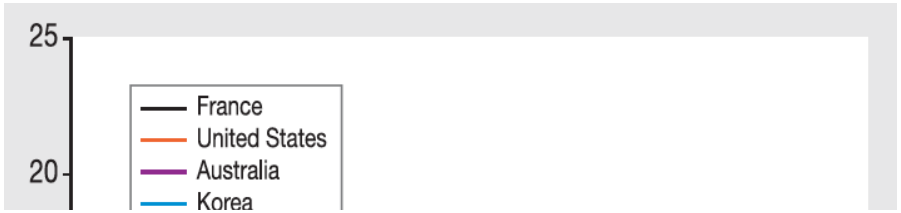
ROMA 28 novembre 01 dicembre 2018 Auditorium della Tecnica, Roma

LA FIBRILLAZIONE ATRIALE NELL'ANZIANO E' UN FATTORE DI RISCHIO SOLO PER LO STROKE?

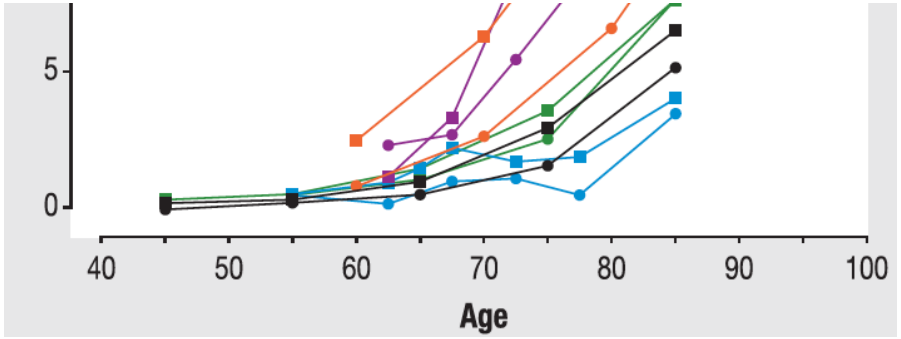
Giuseppe Rengo, MD, PhD

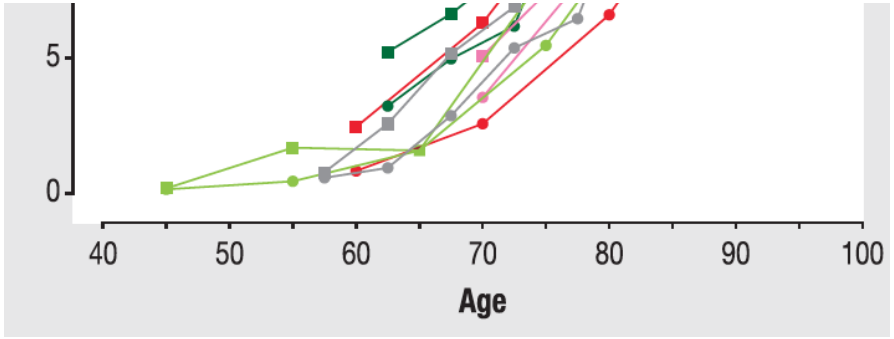
Department of Translational Medical Sciences
University of Naples "Federico II"

Prevalence of atrial fibrillation stratified by age and sex in published studies since 1991



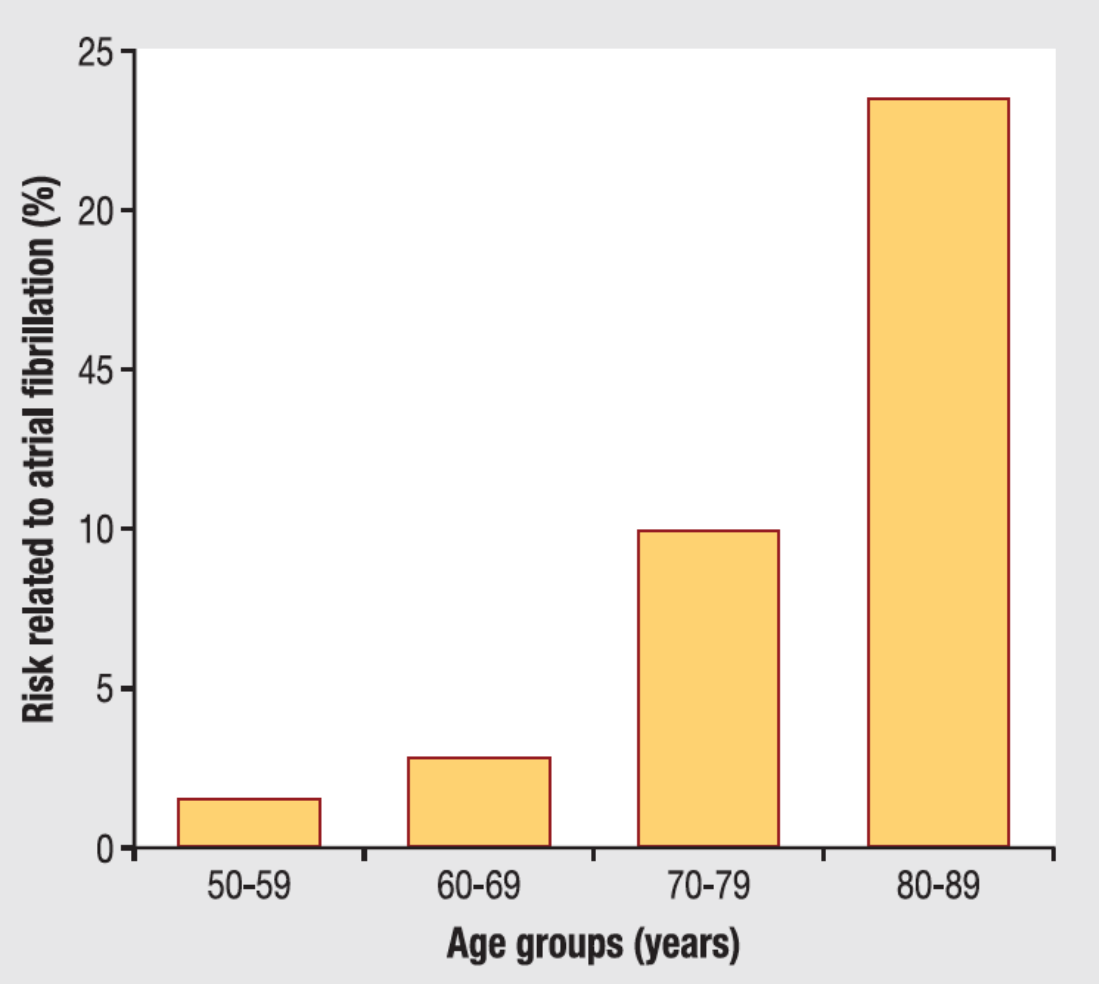
70% of AF patients are aged 75 years or above





Hanon O et al. Archives of Cardiovasc Dis 2013;106:303—23

Risk of atrial fibrillation-related stroke according to age



Hanon O et al. Archives of Cardiovasc Dis 2013;106:303—23

Atrial fibrillation in the elderly: beyond stroke prevention

Disability

Cognitive impairment & Dementia

Gait disorders and risk of falls

Pulmonary Embolism

Mood Disorders & Quality of life

Atrial fibrillation in the elderly: beyond stroke prevention

Disability

Cognitive impairment &
Dementia

Gait disorders and risk of falls

Pulmonary Embolism

Mood Disorders &
Quality of life

Atrial fibrillation and Cause-Specific Risk of Pulmonary Embolism

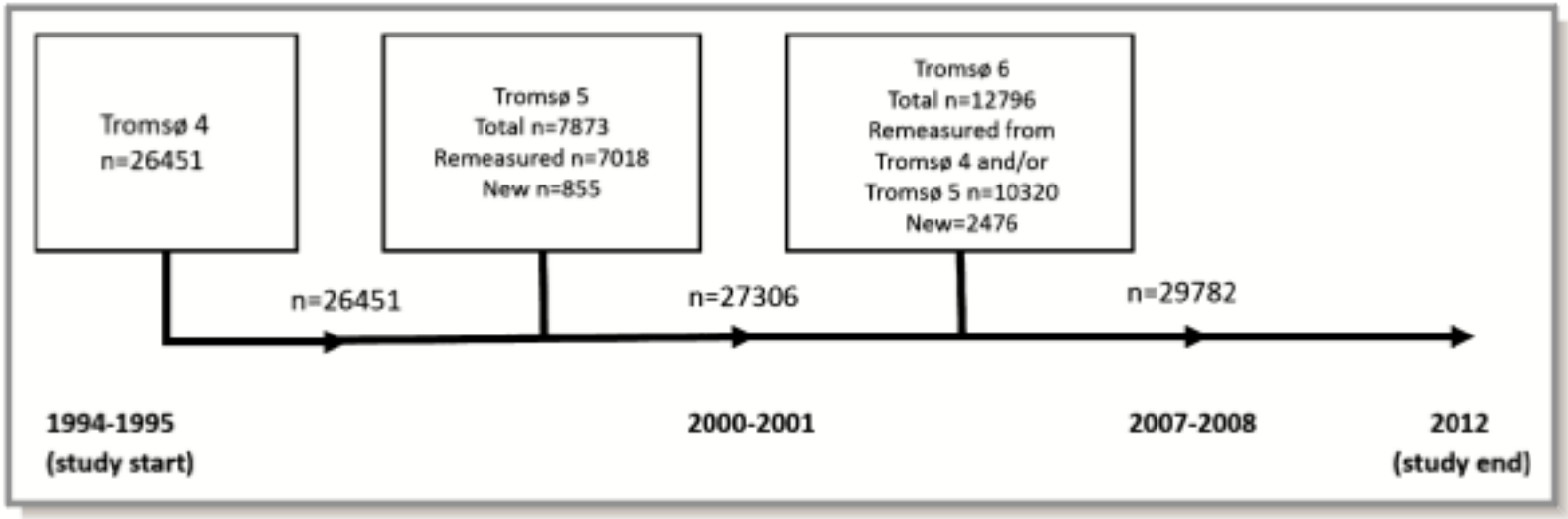


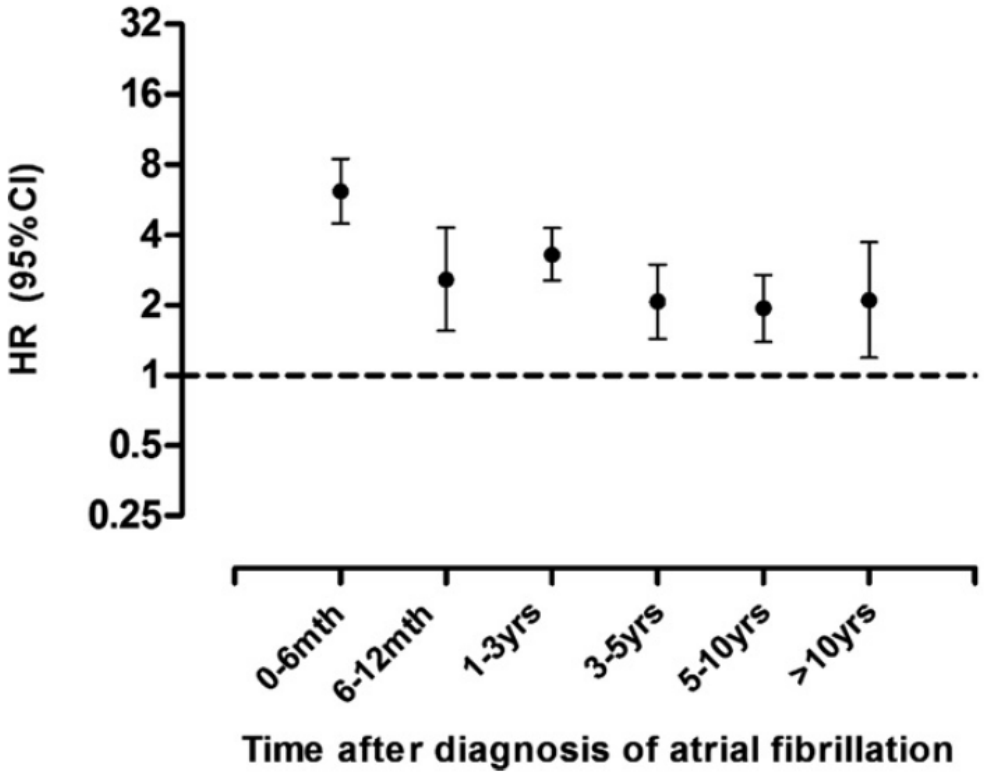
Figure 1. Inclusion of study participants from the fourth (1994–1995), fifth (2001–2002), and sixth (2007–2008) surveys of the Tromsø study.

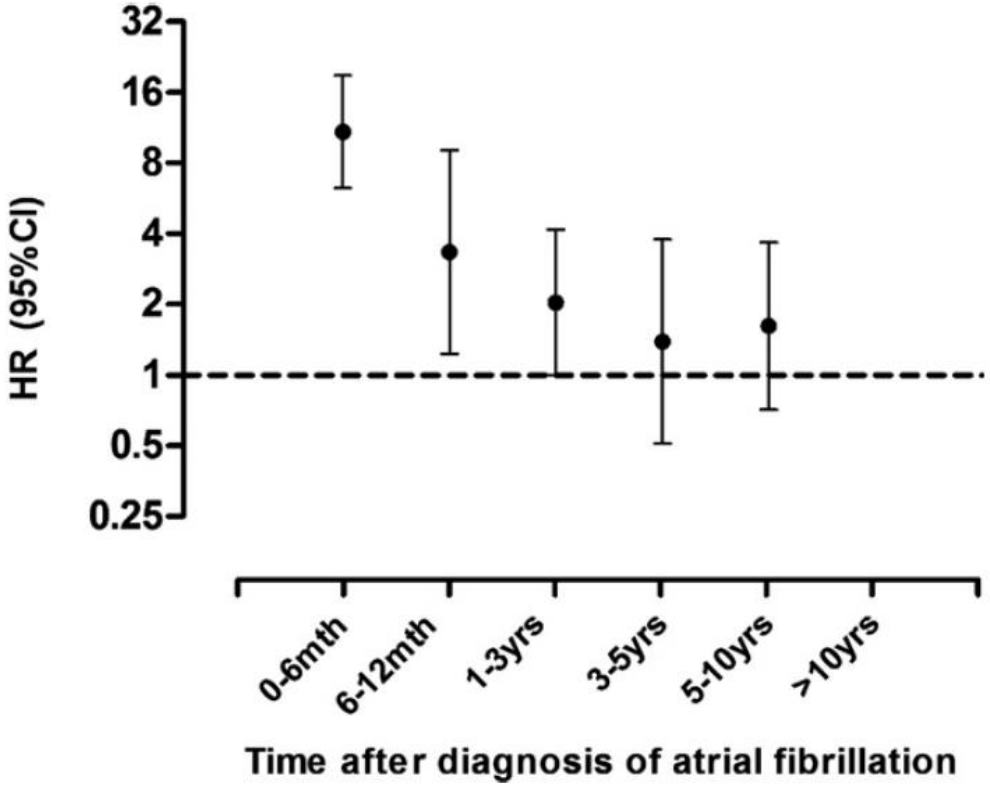
Incident events of AF, IS, and PE during follow-up were recorded

Erin M et al. J Am Heart Assoc 2018;7:e006502

Atrial fibrillation and Cause-Specific Risk of Pulmonary Embolism

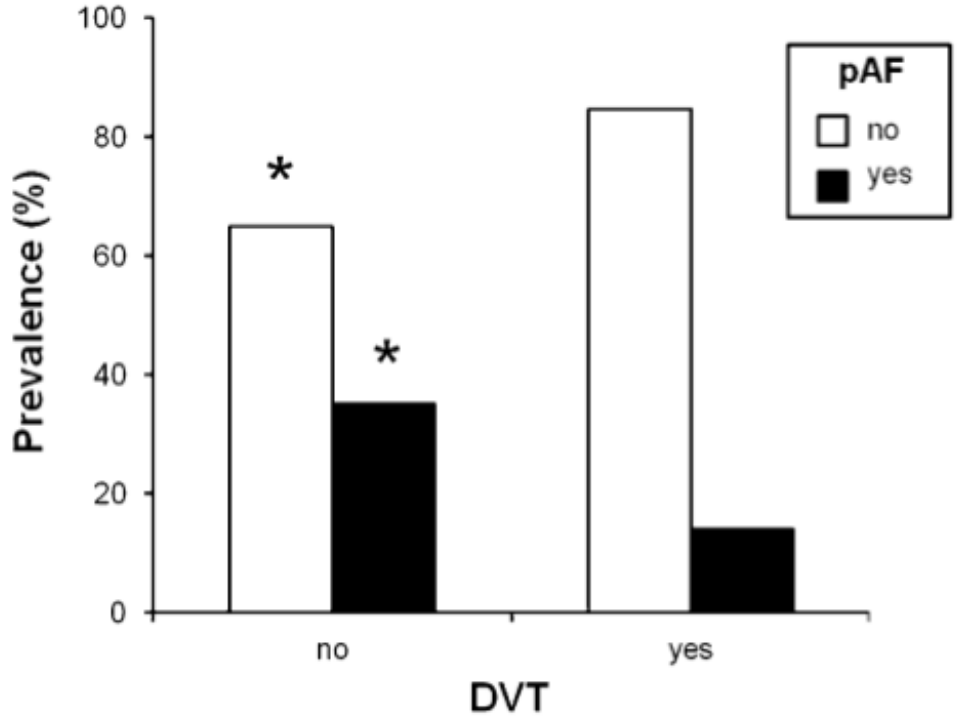
Among 29 782 study participants, 2067 (6.9%) developed AF





Erin M et al. J Am Heart Assoc 2018;7:e006502

In elderly pts with PE, the prevalence of FA was doubled, in the absence of DVT, and it is associated with a more severe PE in the absence than in the presence of DVT.



In the absence of DVT, FA should be considered as cause of PE.

Morella P et al. Aging Clinical and Experimental Research 2018

Atrial fibrillation in the elderly: beyond stroke prevention

Disability

Cognitive impairment & Dementia

Gait disorders and risk of falls

Pulmonary Embolism

Mood Disorders & Quality of life

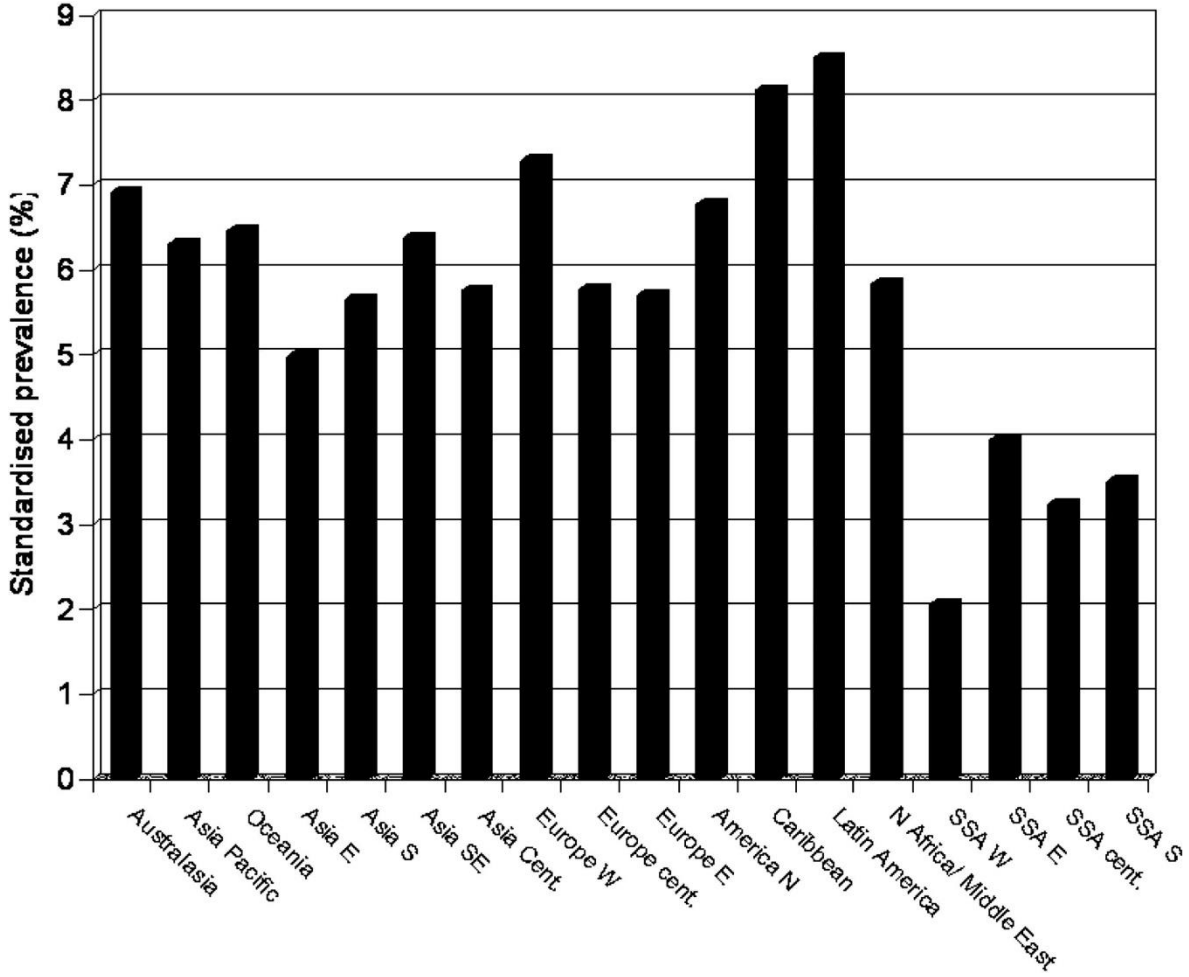
ESC European Society of Cardiology
Europace (2018) **20**, 1399–1400
doi:10.1093/europace/euy046

European Heart Rhythm Association (EHRA)/ Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on arrhythmias and cognitive function: what is the best practice?

Nikolaos Dagres (EHRA Chair)[1]*, Tze-Fan Chao (APHRS Co-Chair)[2], Guilherme Fenelon (LAHRS Co-Chair)[3], Luis Aguinaga[4], Daniel Benhayon[5], Emelia J. Benjamin[6], T. Jared Bunch[7], Lin Yee Chen[8], Shih-Ann Chen[2], Francisco Darrieux[9], Angelo de Paola[10], Laurent Fauchier[11], Andreas Goette[12], Jonathan Kalman[13], Lalit Kalra[14], Young-Hoon Kim[15], Deirdre A. Lane[16,17], Gregory Y.H. Lip[16,17], Steven A. Lubitz[18], Manlio F. Márquez[19], Tatjana Potpara[20,21], Domingo Luis Pozzer[22], Jeremy N. Ruskin[18], Irina Savelieva[23], Wee Siong Teo[24], Hung-Fat Tse[25], Atul Verma[26], Shu Zhang[27], and Mina K. Chung (HRS Co-Chair)[28]

ESC Scientific Document Group: William-Fernando Bautista-Vargas (Colombia), Chern-En Chiang (Taiwan), Alejandro Cuesta (Uruguay), Gheorghe-Andrei Dan (Romania), David S. Frankel (USA), Yutao Guo (People's Republic of China), Robert Hatala (Slovakia), Young Soo Lee (Republic of Korea), Yuji Murakawa (Japan), Cara N. Pellegrini (USA), Claudio Pinho (Brazil), David J. Milan (USA), Daniel P. Morin (USA), Elenir Nadalin (Brazil), George Ntaios (Greece), Mukund A. Prabhu (India, Australia), Marco Proietti (UK, Italy), Lena Rivard (Canada), Mariana Valentino (Argentina), and Alena Shantsila (Reviewer Coordinator) (UK)

The global prevalence of dementia (for those aged ≥60 years): A systematic review and metaanalysis



2010: 35.6 million people lived with dementia worldwide These numbers are expected to almost double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050.

Prince M et al. Alzheimer's & Dementia 2013:9(1):63-75.e2

Risk factors for Dementia

Table 2 **Selected risk factors for dementia**

	Comments
Non-modifiable risk factors	
Demographic factors	
Age	Dementia prevalence increases exponentially with age[8]
Sex	Dementia prevalence greater in women than men[7]
Ethnicity	VaD risk greater in blacks than whites[9]
Genetic factors	Genetic alterations may affect cognitive function, e.g. apolipoprotein E ϵ4 allele and ABCA7 are associated with increased risk of AD; C9ORF72, MAPT, GRN gene mutations associated with frontotemporal dementia; rs12007229 is associated with VaD[10]
Lifestyle factors	
Education	Lower education is associated with higher VaD risk[11]
Physical activity	Increased physical activity is associated with lower risk of general dementia, Alzheimer's dementia, and VaD risk, which was attenuated with further adjustment for baseline cognitive, psychosocial, and vascular factors. Review reported that seven out of eight studies found an association between increased physical activity and lower risk of cognitive decline[12]
Body mass index	U-shaped association between body mass index and dementia, with dementia risk higher in individuals who were obese or underweight[13]
Smoking	Meta-analysis reported that current smokers have higher risk of cognitive decline and dementia over follow-up, than non-smokers or former smokers[14]
Social support and networks	Compared with small social networks, larger social networks were associated with a lower risk of incident dementia over time.[15]
Cardiovascular risk factors	
Blood pressure	Higher mid-life blood pressure was associated with higher dementia risk[16] and cognitive decline[17]
Blood glucose	Diabetes was associated with increased dementia risk[18] and cognitive decline[19]
Lipids	Higher total serum cholesterol was associated with higher VaD and AD risk[20,21]
Clinical cardiovascular or cerebrovascular disease	
Stroke	Stroke is associated with increased dementia risk[22,23]
AF	AF is associated with increased dementia risk[24,25]
Vascular/peripheral arterial disease	Carotid arterial disease is associated with incident dementia risk and cognitive decline[26,27] Lower ankle brachial index is associated with increased dementia risk[28]
Sleep apnoea	Sleep-disordered breathing is associated with an increased risk of cognitive impairment and a small worsening in executive function.[29]

ABCA7, ATP-binding cassette transporter A7; AD, Alzheimer's disease; AF, atrial fibrillation; C9ORF72, *chromosome 9 open reading frame 72;* GRN, *granulin;* MAPT, *microtubule-associated protein tau;* VaD, vascular dementia.

Patients with AF fibrillation are at higher risk for cognitive impairment and dementia

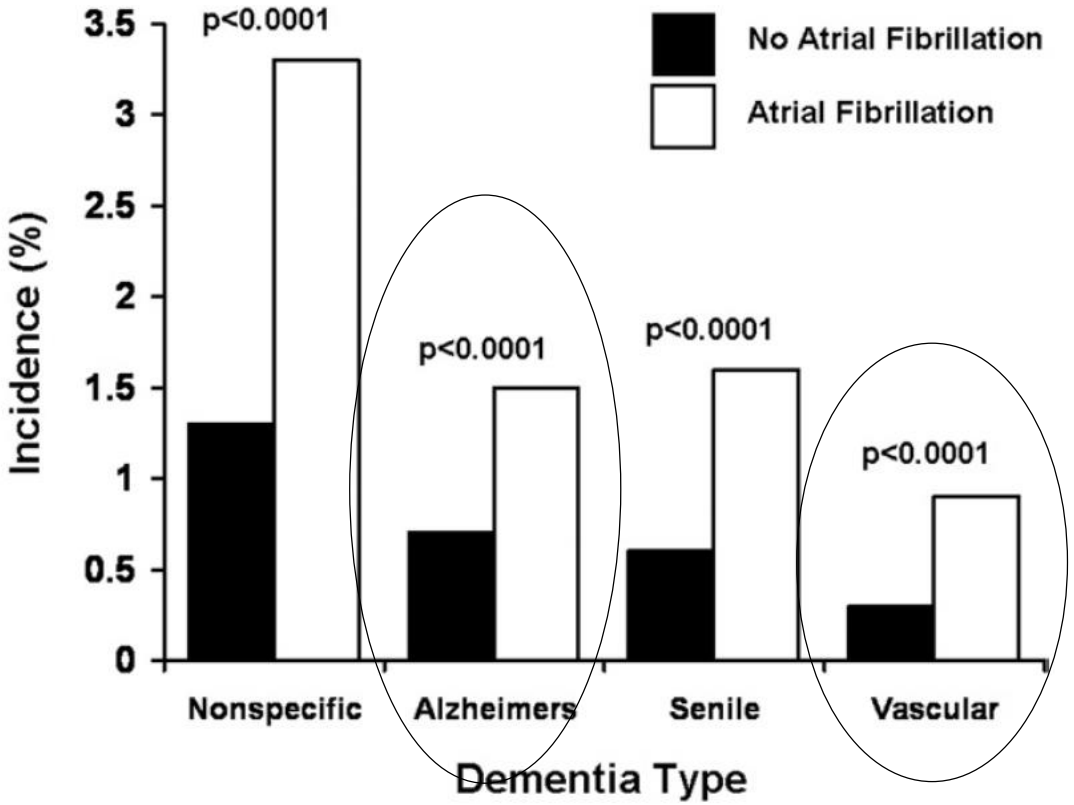
Patients with overt stoke

Patients with silent stroke

Patients without stroke

The incidence of dementia by the patient's AF status

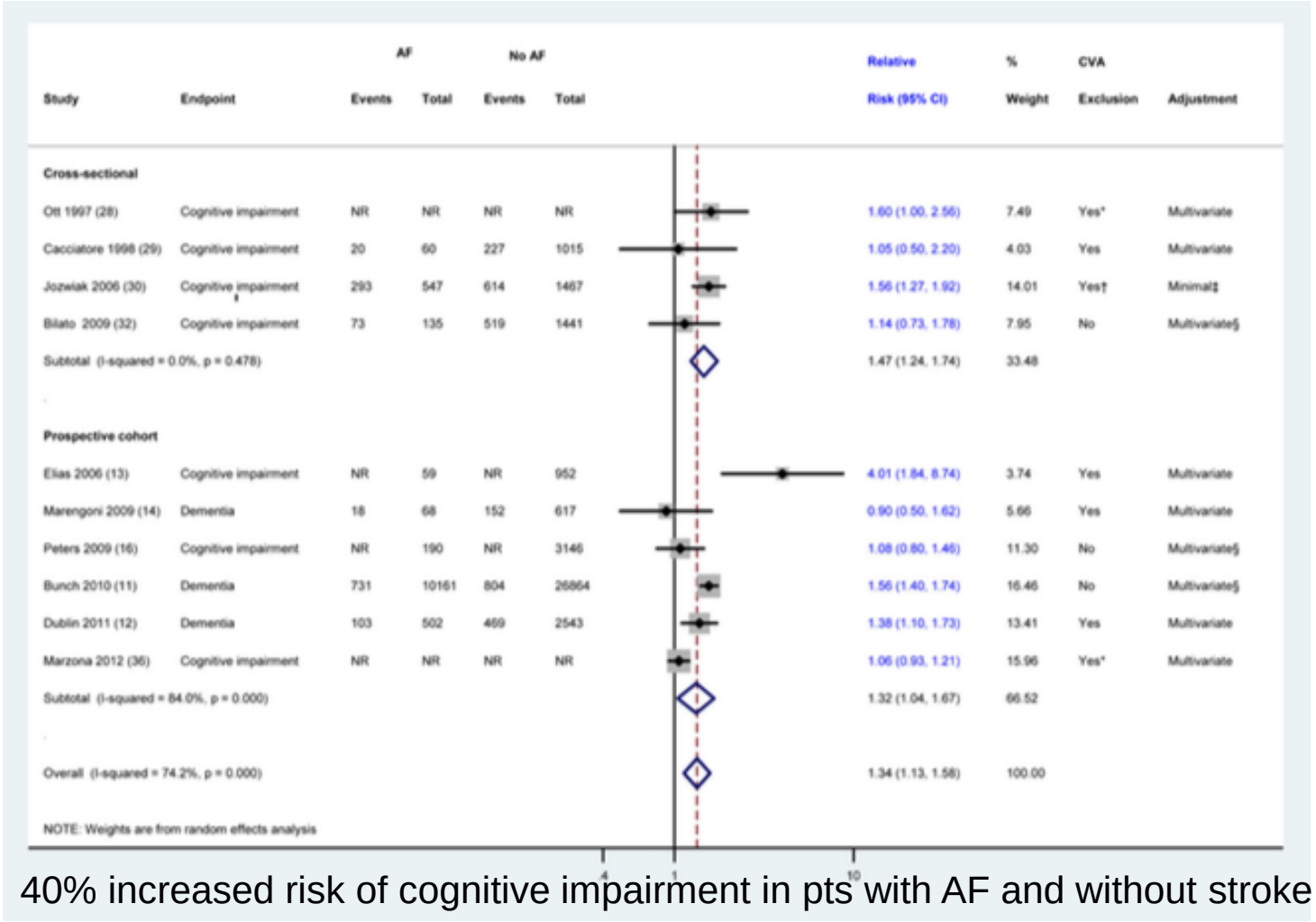
There is a significant increase in dementia in general and in all subtypes in patients with AF



A total of 37,025 consecutive patients from the large ongoing prospective Intermountain Heart Collaborative Study database were prospectively evaluated and followed up for a mean of 5 years for the development of AF and dementia.

Bunch T et al. Heart Rhythm 2010;7:433– 437

Atrial Fibrillation and cognitive impairment <u>independent</u> of stroke

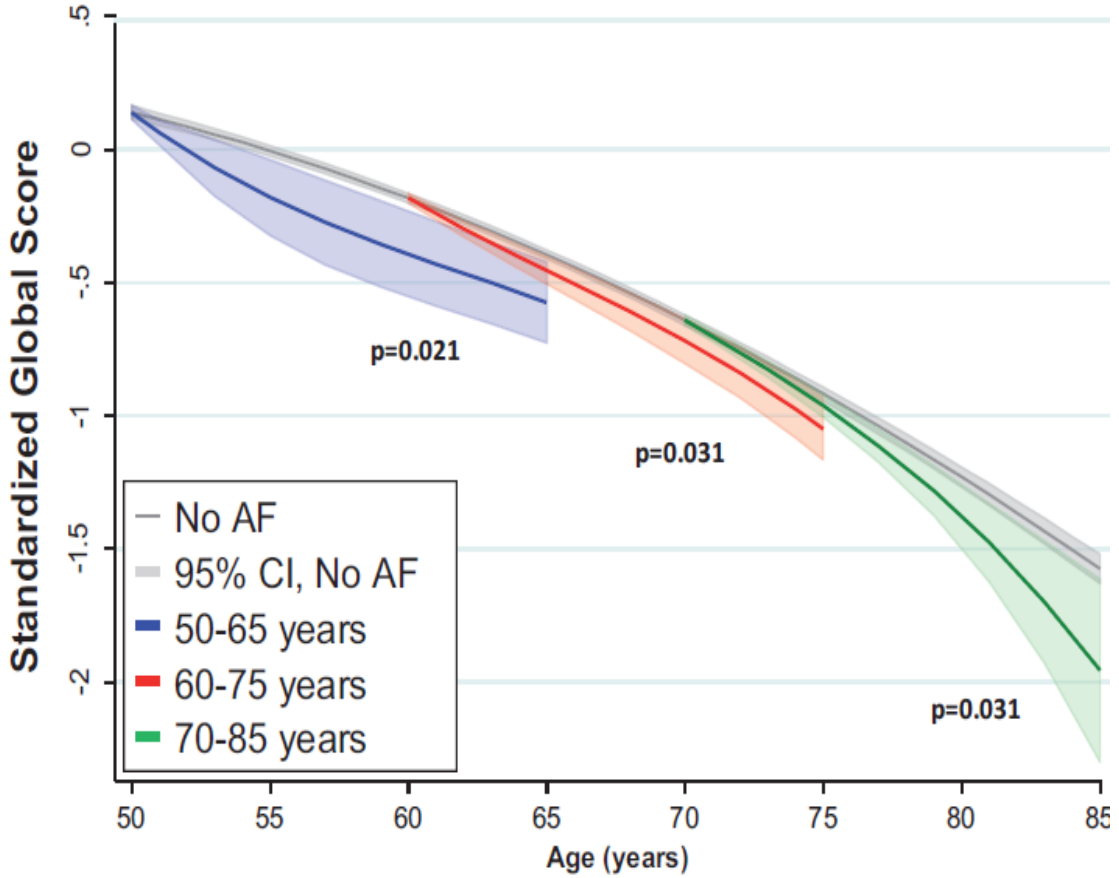


40% increased risk of cognitive impairment in pts with AF and without stroke

Kalantarian S et al. Ann Int Med 2013;158:338– 46

Decline in the global cognitive is accelerated AF pts independently from stroke or CHD

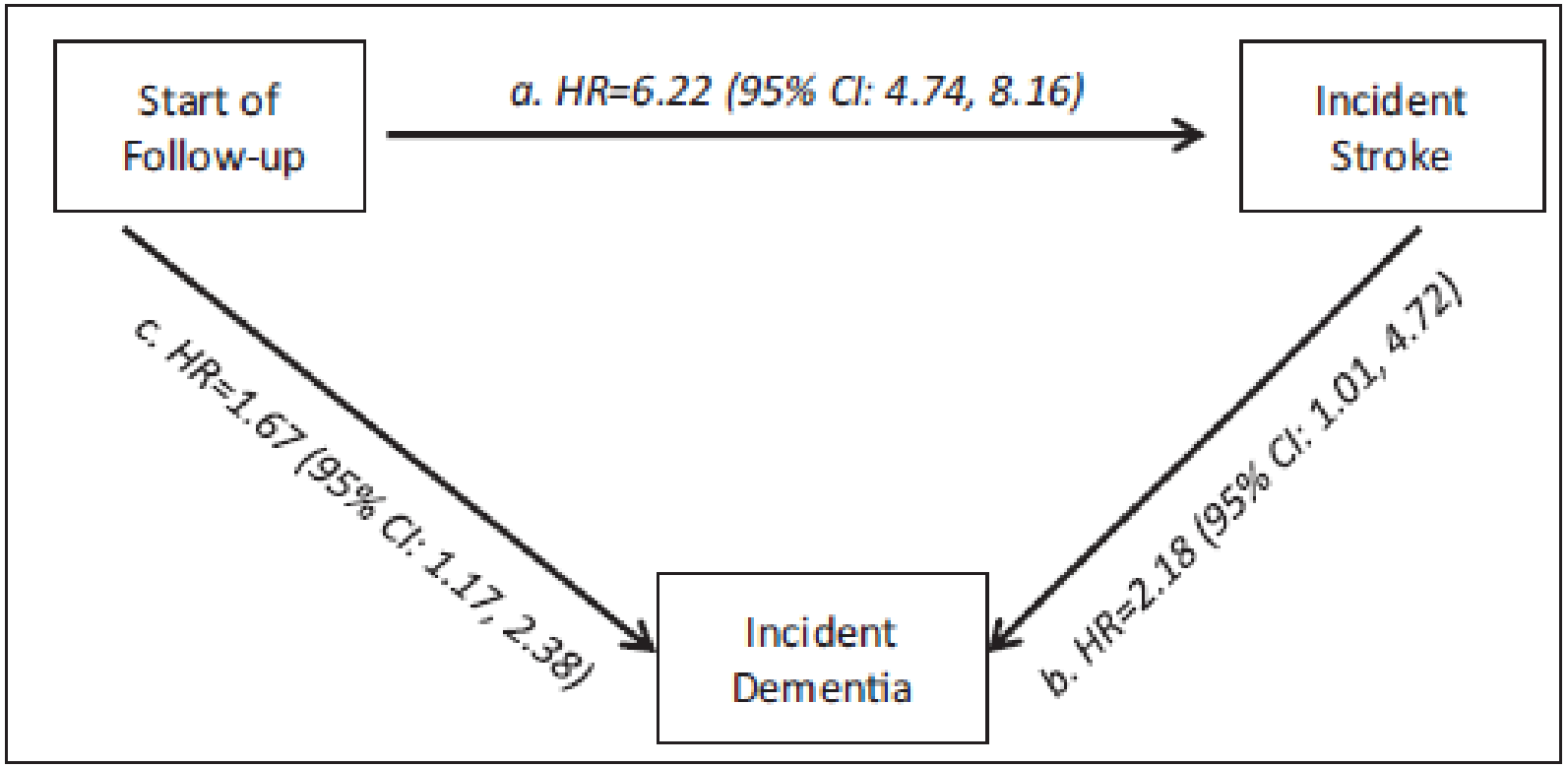
From the Whitehall II study, N= 10 308 at study recruitment in 1985. A battery of cognitive tests was administered four times (1997–2013) to 7428 participants (414 cases of AF).



Singh-Manoux A et al. Eur Heart J 2017;38:2612–2618

Decline in the global cognitive is accelerated AF pts independently from stroke or CHD

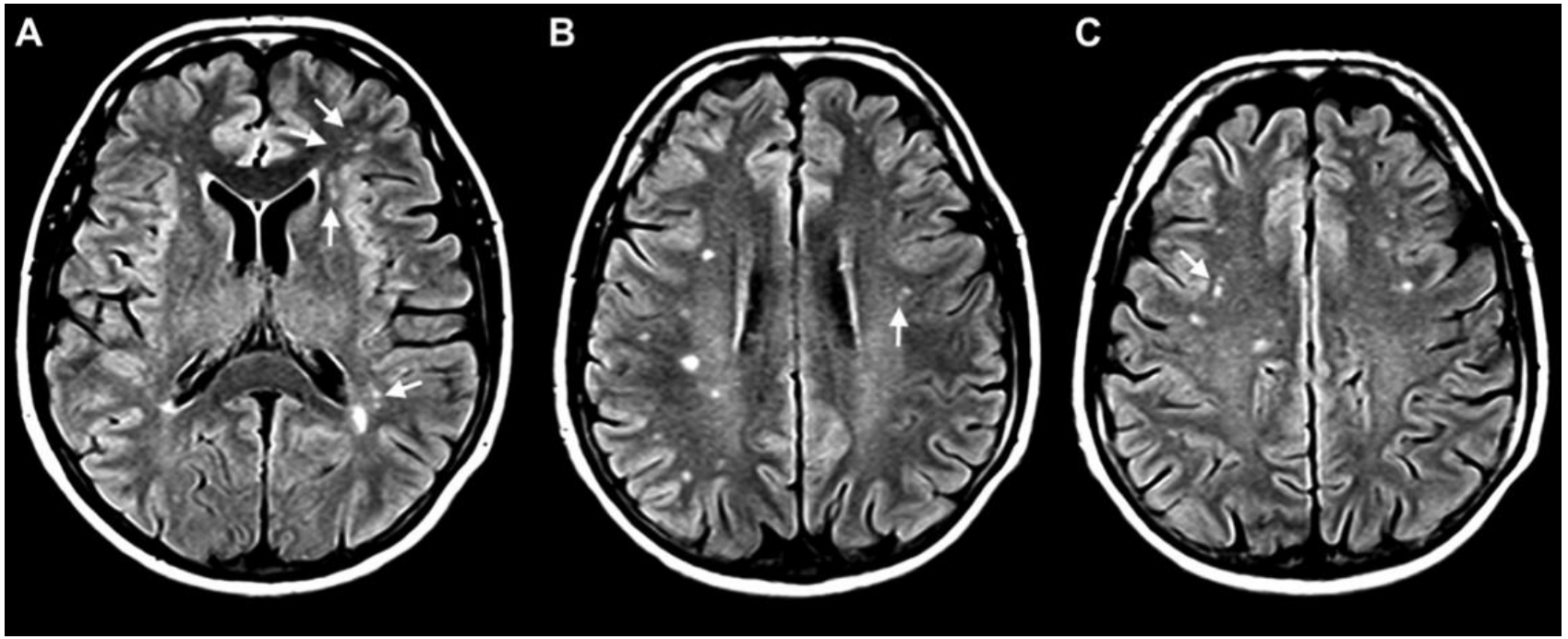
In multistate models, AF was associated with a 6.22 times increased risk of stroke and its association with dementia was not fully explained by stroke as demonstrated by the increased risk of dementia in those free of stroke



Singh-Manoux A et al. Eur Heart J 2017;38:2612–2618

Pathophysiology of AF-induced cognitive impairment

Brain MRIs reveal evidence of silent cerebral infarcts in patients with AF

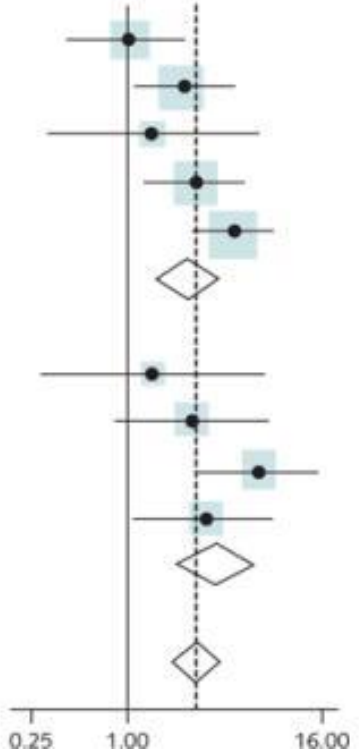


Brain magnetic resonance images of a 55-year-old man with paroxysmal atrial fibrillation without other risk factors: axial fluid-attenuated inversion recovery sequences demonstrate multiple small hyperintense lesions at the subcortical level in both hemispheres. Clusters (arrows) of small lesions are visible in the left frontal and temporo- parietal regions (A), in the left frontal lobe (B), and in the right frontal lobe (C).

Gaita F et al. JACC 2013;62(21):1990-7

Double Risk of Silent Cerebral Infarctions in AF patients: A Systematic Review and Meta-analysis

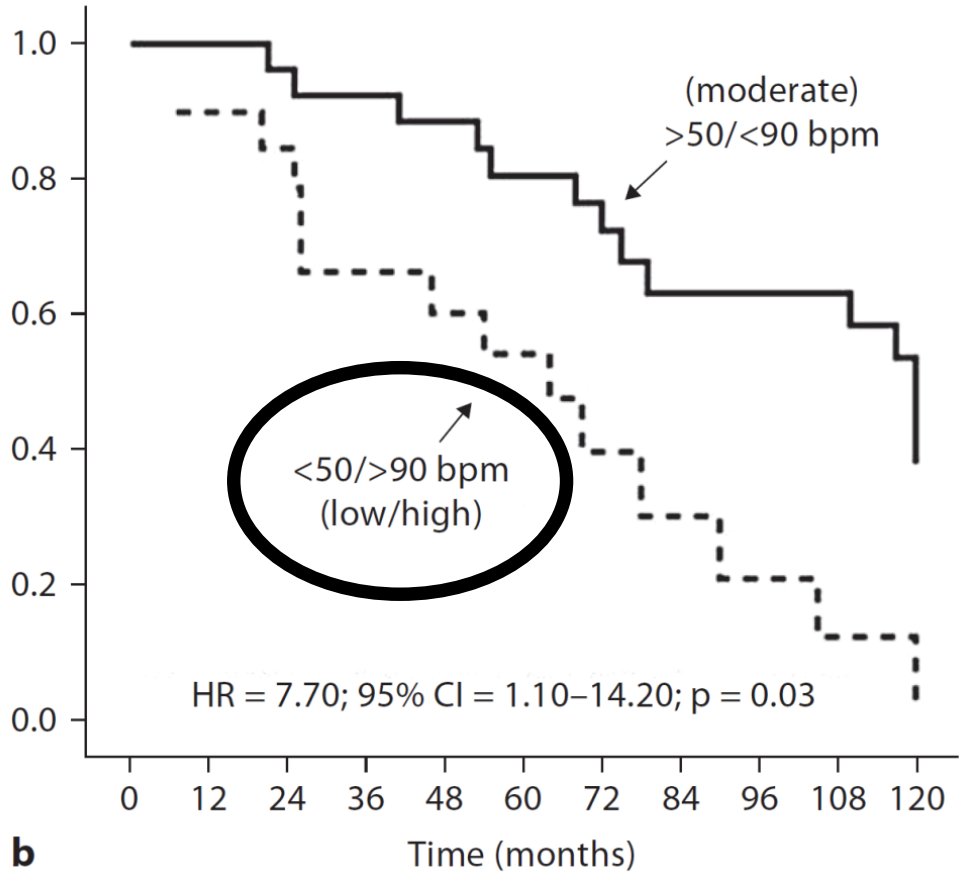
Study, Year (Reference)	Diagnosis Method	Participants, *n*	Events/ Patients With AF, *n/N*	Events/ Patients Without AF, *n/N*	Odds Ratio (95% CI)	Risk of Confounding Bias*
MRI						
Vermeer et al, 2003 (23)	MRI 1.5T	1015	8/32	209/983	1.00 (0.40–2.30)	Moderate
Das et al, 2008 (11)	MRI 1T	2040	11/45	209/1995	2.16 (1.07–4.40)	Moderate
Kim et al, 2011 (13)	MRI 1.5T	406	3/12	61/394	1.34 (0.29–6.38)	Minimal
Kobayashi et al, 2012 (36)	MRI 1.5T	142	35/71	20/71	2.53 (1.21–5.30)†	Minimal
Marfella et al, 2013 (12)	MRI 1.5T	464	107/176	84/288	4.44 (2.42–8.16)	Minimal
Subtotal (I^2 = 39.25%; P = 0.089)					2.30 (1.44–3.68)	
CT						
Petersen et al, 1989 (19)	CT	60	4/30‡	3/30	1.38 (0.28–6.80)	Moderate
Petersen et al, 1989 (32)	CT	58	14/29§	8/29	2.45 (0.82–7.31)	Moderate
Guidotti et al, 1990 (18)	CT	144	32/72	8/72	6.40 (2.68–15.27)	Minimal
Zito et al, 1996 (34)	CT	78	16/38	8/40	2.91 (1.06–7.97)	Minimal
Subtotal (I^2 = 0%; P = 0.297)					3.45 (2.03–5.87)	
Overall (I^2 = 32.12%; P = 0.118)					2.62 (1.81–3.80)	



Atrial fibrillation is associated with more than a 2-fold increase in the odds for SCI.

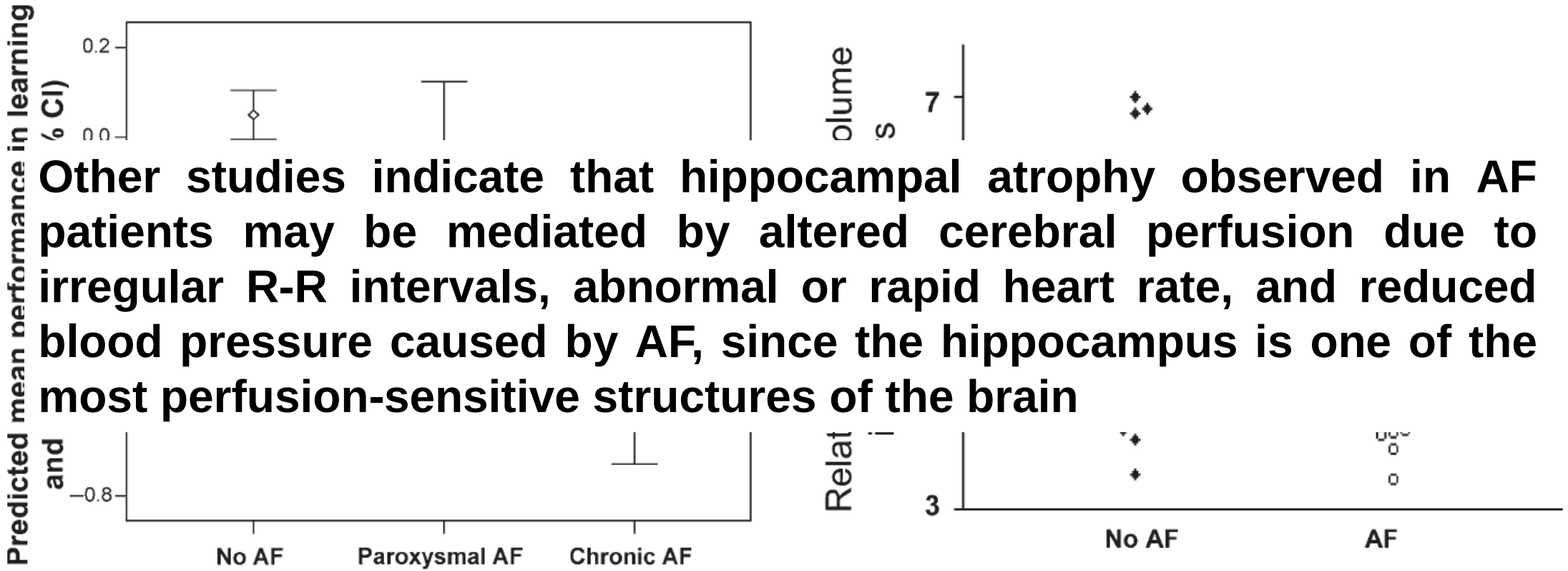
Kalantarian Set al. Ann Intern Med. 2014;161(9):650–8

Low/high (<50/>90 bpm) predicts dementia in cognitively impaired elderly subjects with AF: role of ventricular rate response



Cacciatore F et al., Dement Geriatr Cogn Disord 2012

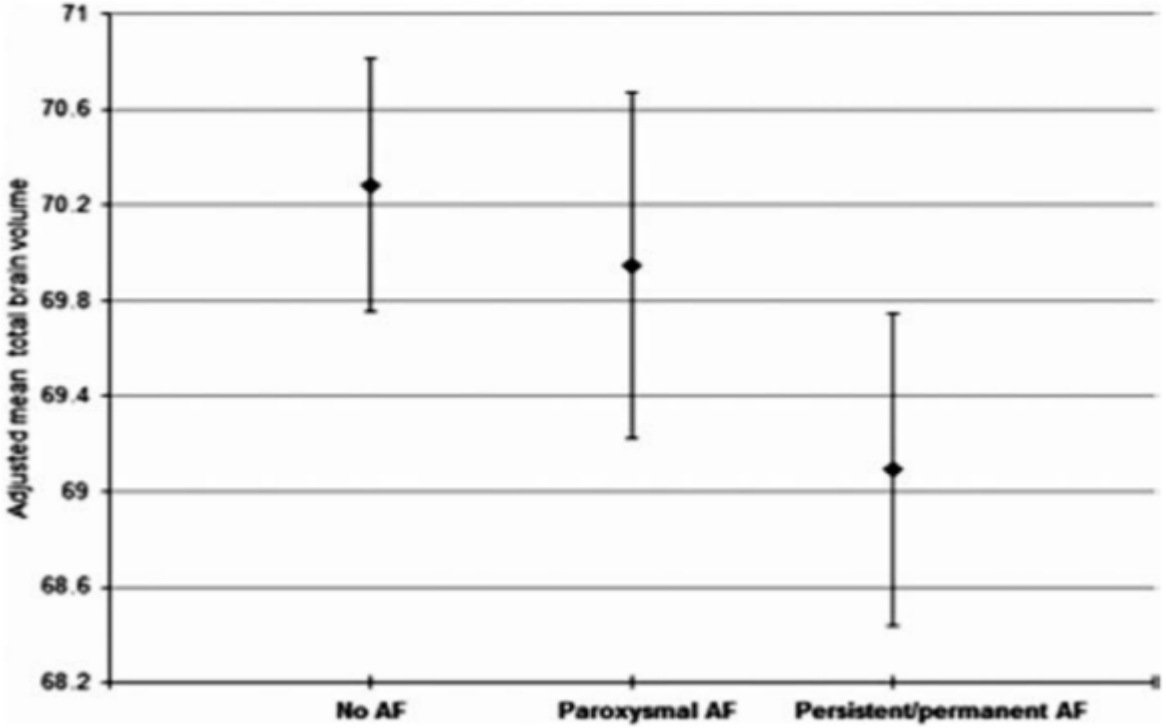
Atrial fibrillation in stroke-free and dementia-free patients is associated with memory impairment and hippocampal atrophy



Other studies indicate that hippocampal atrophy observed in AF patients may be mediated by altered cerebral perfusion due to irregular R-R intervals, abnormal or rapid heart rate, and reduced blood pressure caused by AF, since the hippocampus is one of the most perfusion-sensitive structures of the brain

Knecht S et al. Eur Heart J 2008;29:2125-32

Atrial fibrillation is associated with reduced brain volume and cognitive function independent of cerebral infarcts

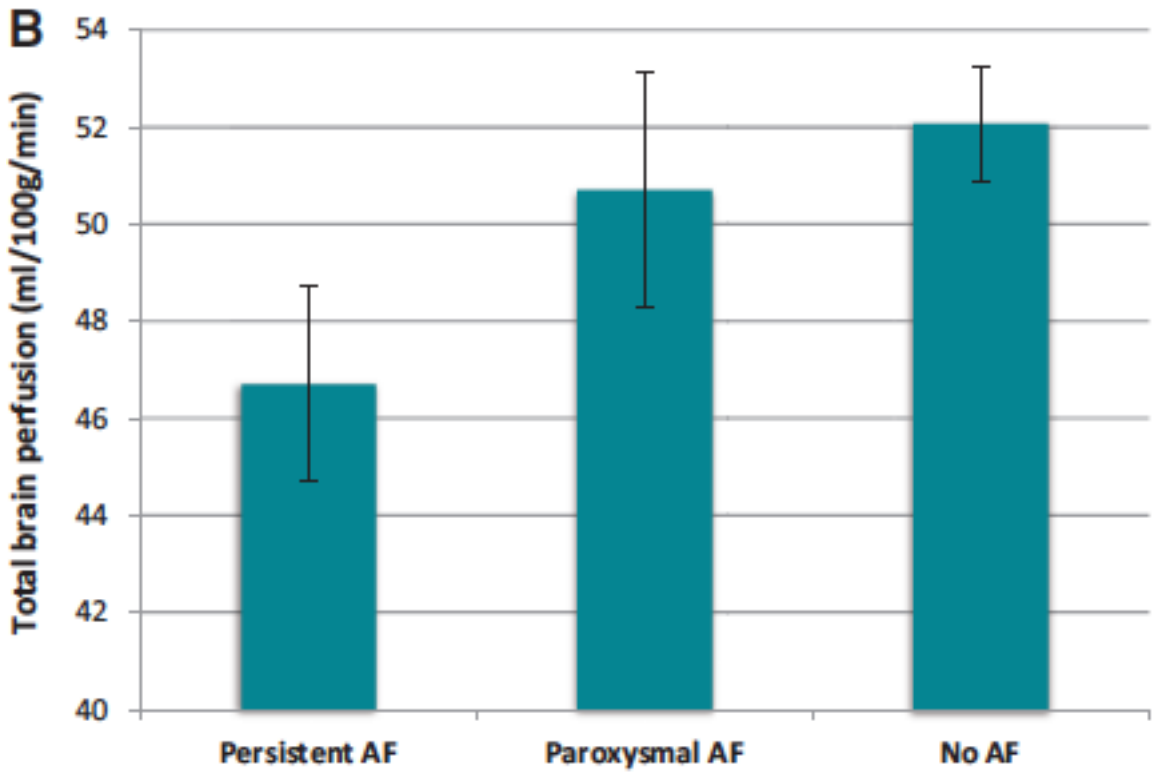


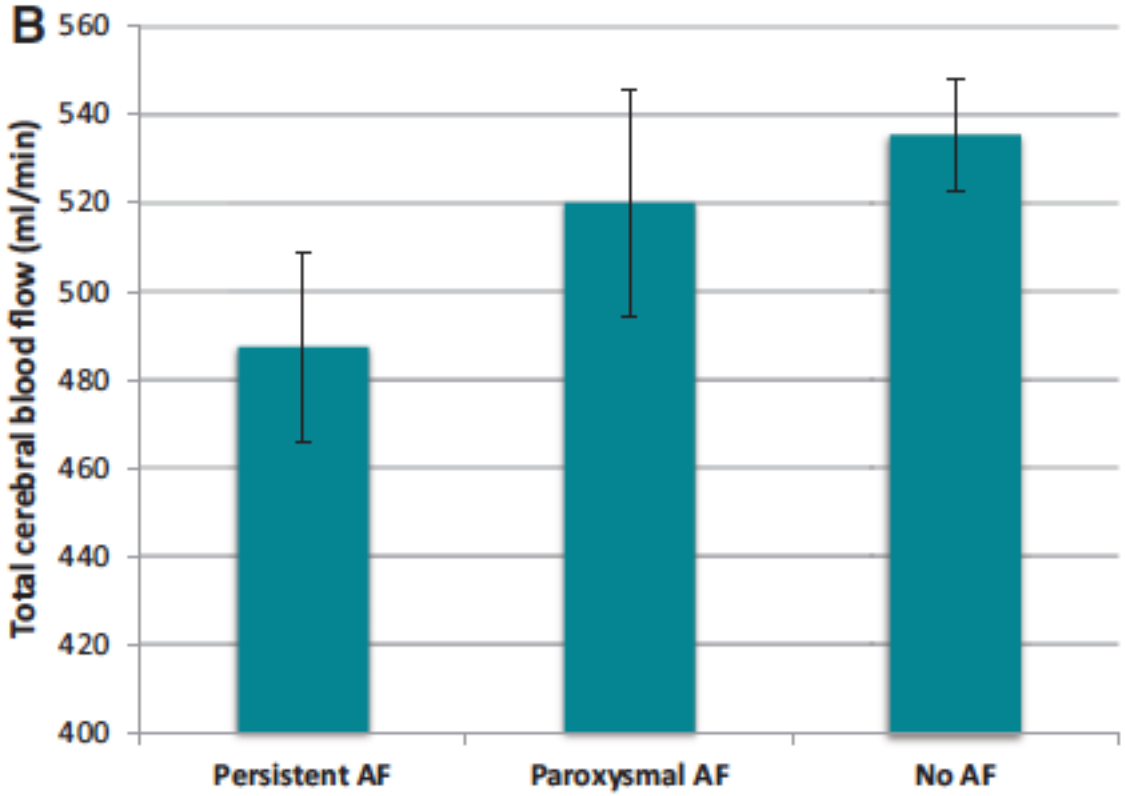
Cross-sectional analysis on 4251 non-demented participants (mean age 76 ± 5 years) in the population-based AGES-Reykjavik Study. 330 participants had AF.

Of the brain tissue volumes, AF was associated with lower volume of gray and white matter ($p<0.001$ and $p=0.008$ respectively) but not of white matter hyperintesities ($p=0.49$)

Stefansdottir H et al.Stroke 2013;44:1020-25

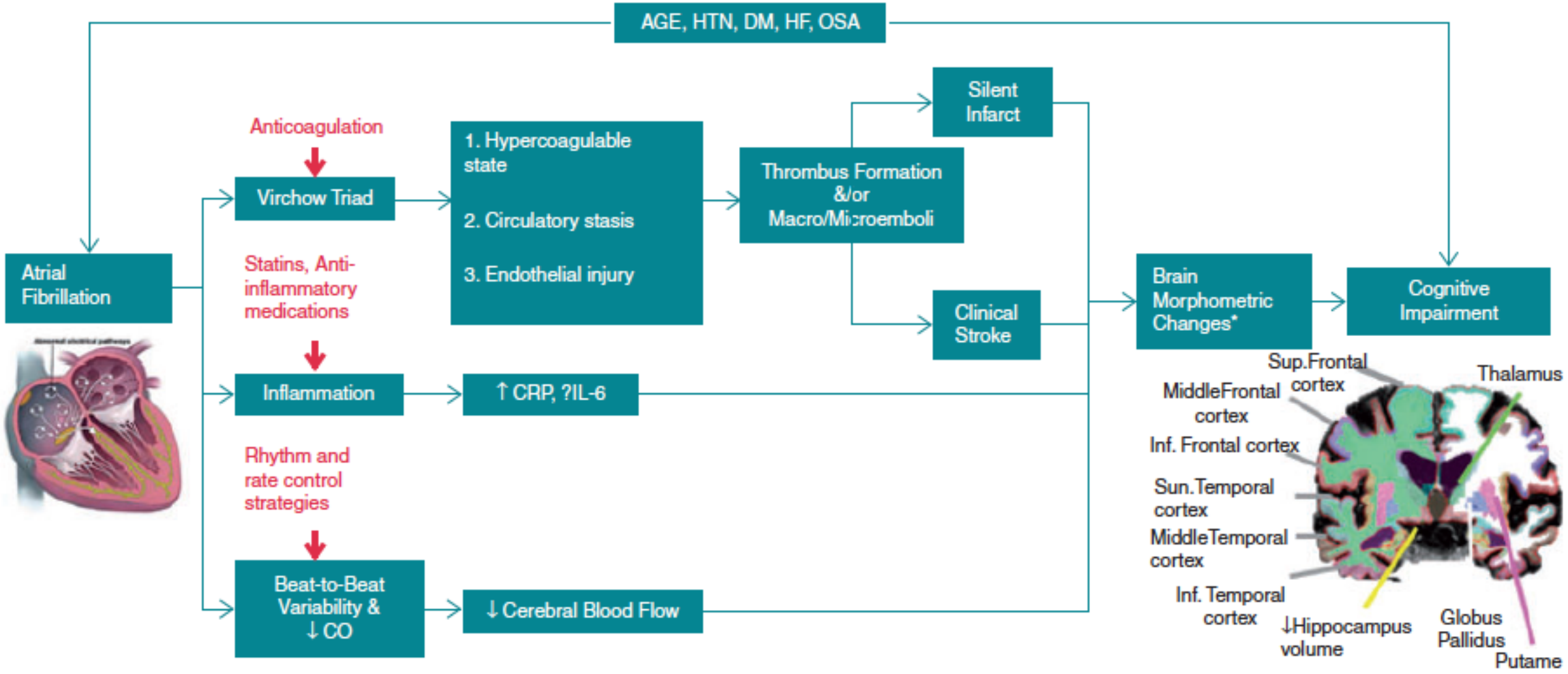
Atrial fibrillation is associated with decreased total cerebral blood flow and brain perfusion detected by phase contrast MRI





Gardarsdottir M et al. Europace 2018;20:1252-58

Different mechanisms through which atrial fibrillation may contribute to cognitive impairment



Dagres et al. Europace 2018;20:1399–1400

Physician who takes care of AF patients should be able to detect cognitive impairment

Cardiologists and arrhythmia specialists are frequently not familiar with these issues

Table 3 Assessment of cognitive impairment

Suspect	Patient history, appearance, changes in behaviour
Confirm	Collateral history from family
Examine	Full medical examination, brief screening assessment
Investigate	Renal/liver/respiratory/thyroid compromise, B_{12}, folate; syphilis serology (in high-risk patients)
Exclude	Depression, neurological/psychiatric disease, medication/drug use
Measure	Psychometric testing using validated battery
Image	Multimodal MRI (T1, T2, T2*, DWI) for brain changes
Establish	Diagnosis based on clinical + psychometric + imaging

DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging.

Cognitive assessment should be performed in AF patients where there is suspicion of cognitive impairment.

204

Dagres et al. Europace 2018;20:1399–1400

THERAPY

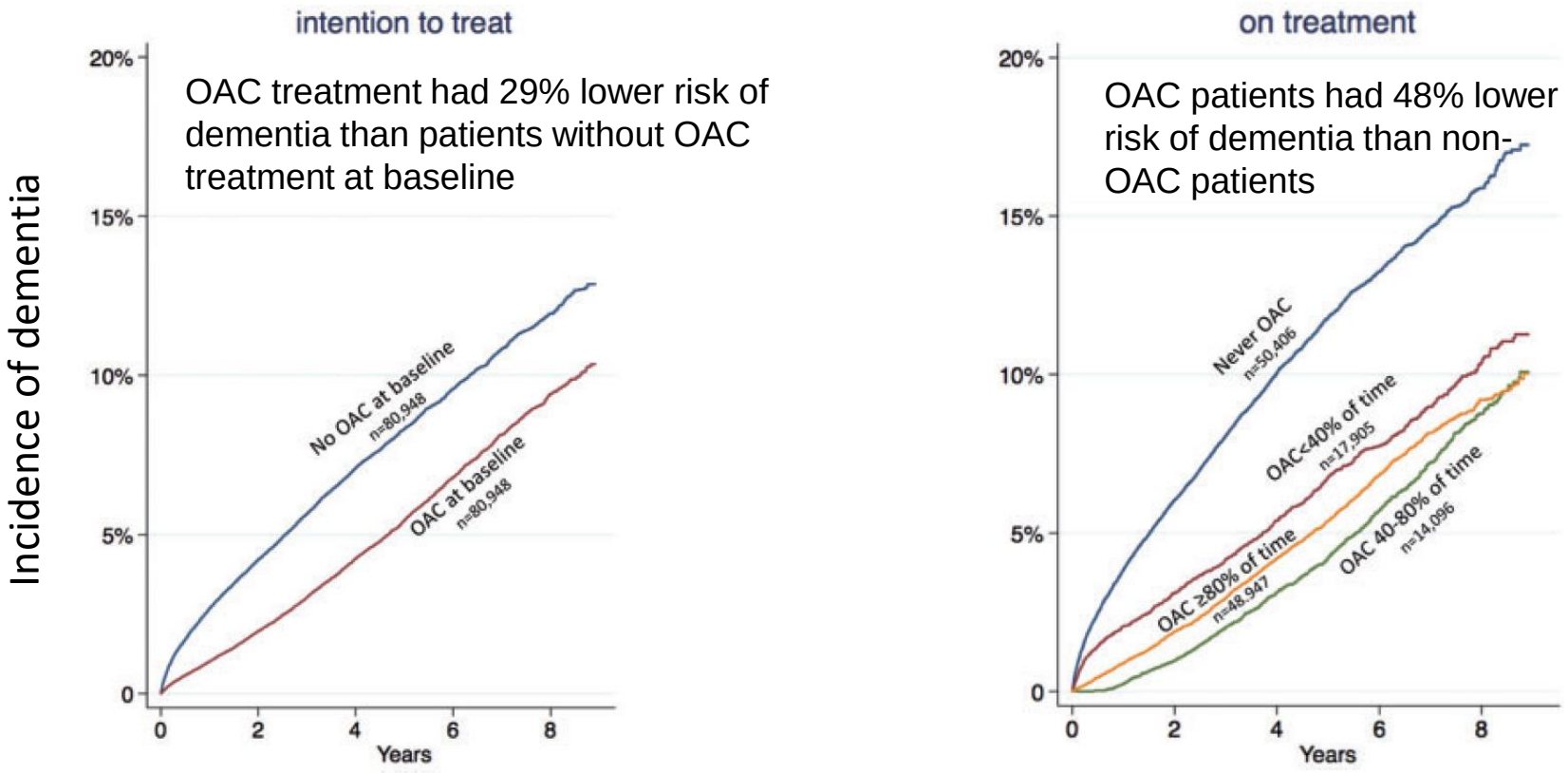
Recommendations – Colored Hearts Scheme

Definitions related to a treatment or procedure	Consensus statement instruction	Symbol
Scientific evidence that a treatment or procedure is beneficial and effective. Requires at least one randomized trial, or is supported by strong observational evidence and authors' consensus (as indicated by an asterisk).	'Should do this'	
General agreement and/or scientific evidence favour the usefulness/efficacy of a treatment or procedure. May be supported by randomized trials based on a small number of patients or which is not widely applicable.	'May do this'	
Scientific evidence or general agreement not to use or recommend a treatment or procedure.	'Do not do this'	

Dagres et al. Europace 2018;20:1399–1400

Oral Anticoagulation and dementia

Retrospective registry study of 444 106 patients with hospital diagnosis of AF and no dementia in Sweden between 2006-2014.



Friberg et al. Eur Heart J 2018;39:453–60

Anticoagulation

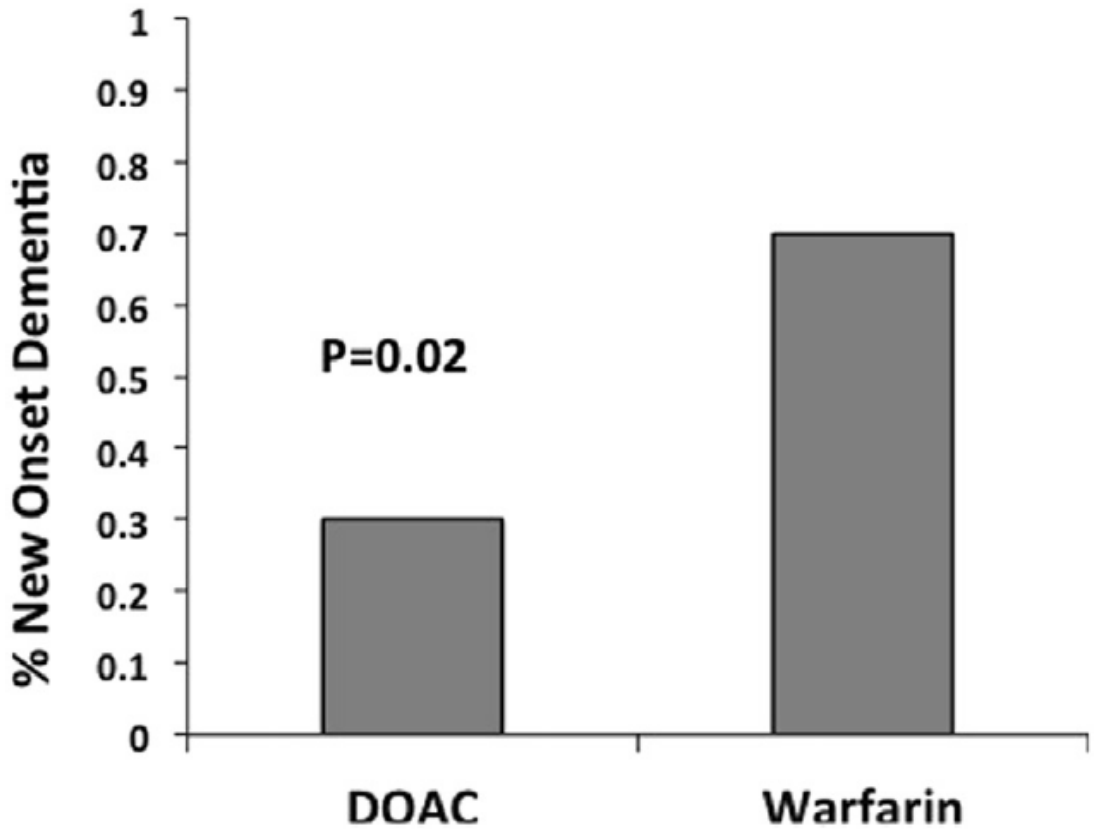
Appropriate anticoagulation in patients with AF and stroke risk factors should be applied for the prevention of cognitive dysfunction.

107,111

Anticoagulation for prevention of cognitive decline

- Why not “green heart”?
- Not proven in large randomized clinical trials (yet)

Long-term incident dementia events in 5254 patients with AF compared by DOACs and warfarin treatment



Dementia occurred more frequently in patients taking Warfarin (mean follow-up 243 days), although statistical significance was noticed, the importance of such an association is unclear (0.7% vs 0.3% of the patients taking DOAC [p . 0.03].

Only prospective studies can produce conclusive evidence. No difference in rate of dementia was observed comparing one DOAC with another (apixaban 0.2%, rivaroxaban 0.4%, dabigatran 0%, p . 0.36).

Jacobs V et al. Am J Cardiol 2016;118:210–14

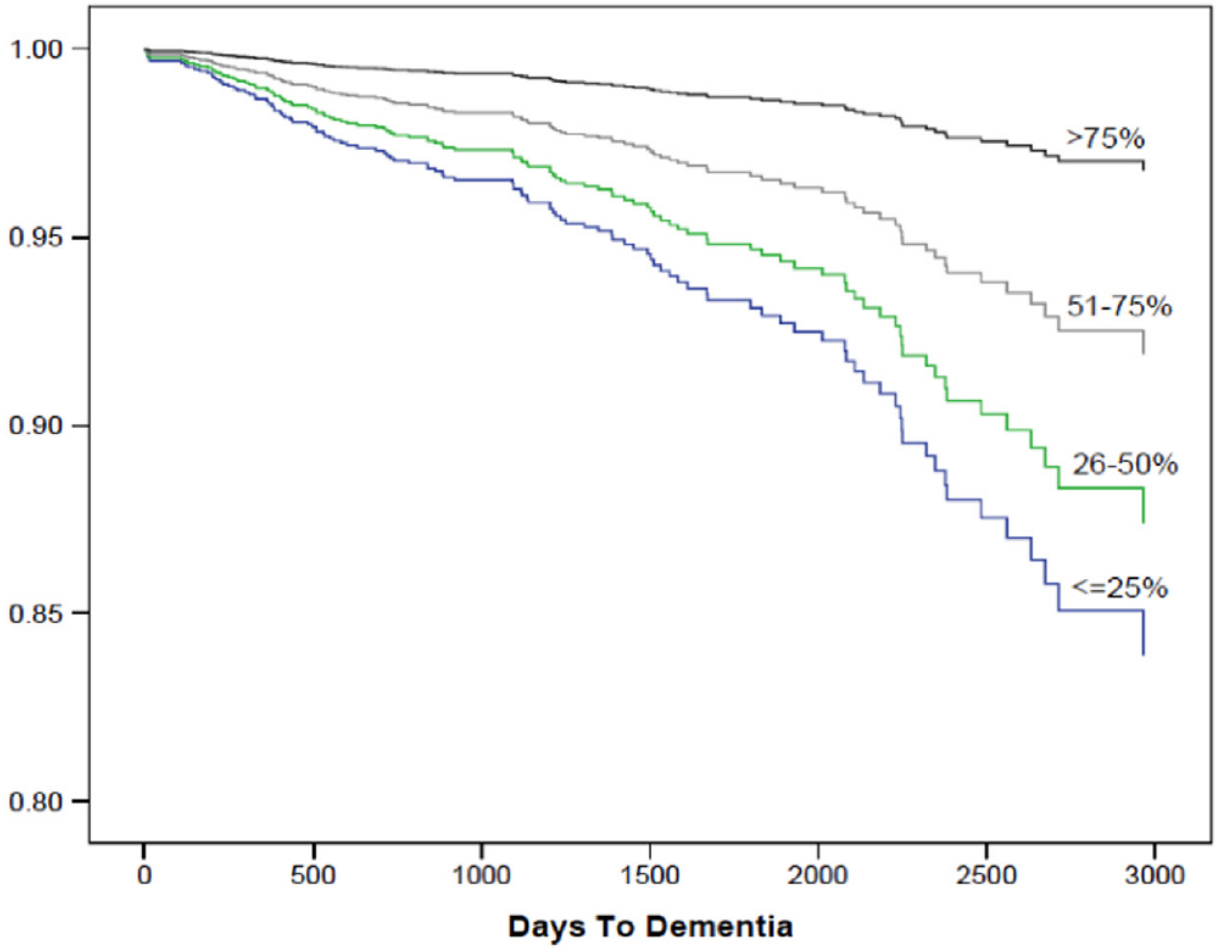
Novel oral anticoagulants vs. Vitamin K antagonists

Consider NOAC instead of VKA when using oral anticoagulation for the prevention of stroke in AF, which may have a beneficial effect on subsequent cognitive disorders

107,114

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

Event-free survival estimates for dementia incidence among categories of percent time in the therapeutic range.



2605 pts age: 73.7±10.8 years, median follow-up: 4.0 years (maximum 9.9 years)

Jacobs V et al. Heart Rhythm 2014;11:2206–13

Quality of anticoagulation with Vitamin K inhibitors

In patients with AF managed with long-term VKA, a high anticoagulation time in therapeutic range may be beneficial for optimal prevention of new-onset dementia

75,107

Ongoing Trials

Table 8 **Studies that are currently examining the effect of different therapies and interventions on cognitive function in patients with AF or atrial tachyarrhythmias**

Study name	Target population	Intervention	Cognitive function as outcome
Impact of Anticoagulation Therapy on the Cognitive Decline and Dementia in Patients With Non-Valvular Atrial Fibrillation (CAF), NCT03061006	Non-valvular AF	Randomization to dabigatran or warfarin	Primary outcome: incident dementia and moderate decline in cognitive function
Comparison of Brain Perfusion in Rhythm Control and Rate Control of Persistent Atrial Fibrillation, NCT02633774	Persistent AF	Randomization to rhythm or rate control	Primary outcome: cognitive assessment
Cognitive Impairment Related to Atrial Fibrillation Prevention Trial (GIRAF), NCT01994265	AF patients >65 years old and CHA_2DS_2-VASc >1	Randomization to dabigatran or warfarin	Primary outcome: cognitive impairment
Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST), NCT01288352	AF patients	Randomization to early standardized rhythm control or usual care	Secondary outcome: cognitive function
Apixaban During Atrial Fibrillation Catheter Ablation: Comparison to Vitamin K Antagonist Therapy (AXAFA), NCT02227550	Patients undergoing catheter ablation of non-valvular AF	Randomization to vitamin K antagonists or apixaban	Secondary outcome: cognitive function change
NOACs for Stroke Prevention in Patients With Atrial Fibrillation and Previous ICH (NASPAF-ICH), NCT02998905	Patients with a high-risk of AF and previous intracerebral haemorrhage	Randomization to non-vitamin K antagonist oral anticoagulant or acetylsalicylic acid	Secondary outcome: cognitive function
Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes (NOAH), NCT02618577	patients with atrial high rate episodes and at least two stroke risk factors but without AF	Randomization to edoxaban or acetylsalicylic acid or placebo	Secondary outcome: cognitive function
Optimal Anticoagulation for Higher Risk Patients Post-Catheter Ablation for Atrial Fibrillation Trial (OCEAN), NCT02168829	Patients having undergone a successful AF catheter ablation	Randomization to rivaroxaban or acetylsalicylic acid	Secondary outcome: neuropsychological testing
Blinded Randomized Trial of Anticoagulation to Prevent Ischaemic Stroke and Neurocognitive Impairment in AF (BRAIN-AF), NCT02387229	Patients with non-valvular AF and with low risk of stroke	Randomization to rivaroxaban or acetylsalicylic acid	Primary outcome: composite endpoint of stroke, TIA and neurocognitive decline Secondary outcomes: neurocognitive decline, new onset of cognitive impairment