**Atrial Fibrillation and Cognitive Function: A Review**

**09-08-2018**

Hans-Christoph Diener[1], MD, PhD, Robert G Hart[2], MD, Peter J Koudstaal[3], MD, Deirdre A Lane[4], PhD, Gregory YH Lip[5], MD

From the Department of Neurology, University Hospital Essen and University Duisburg-Essen, Germany (H-CD);
Population Health Research Institute/McMaster University, Vascular and Stroke Research Institute (DBCVSRI), Hamilton, Ontario, Canada (RGH);
Department of Neurology, Erasmus Medical Center, Rotterdam, The Netherlands (PJK);
Institute of Cardiovascular Sciences, University of Birmingham, Birmingham and Liverpool Centre for Cardiovascular Science, Liverpool, United Kingdom (DAL, GYHL).

**Disclosures:**
HCD received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Abbott, Achelios, Allergan, AstraZeneca, Bayer Vital, BMS, Boehringer Ingelheim, CoAxia, Corimmun, Covidien, Daiichi-Sankyo, D-Pharm, Fresenius, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Knoll, Lilly, MSD, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Portola, Sanofi-Aventis, Schering-Plough, Servier, Solvay, St. Jude, Syngis, Talecris, Thrombogenics, WebMD Global and Wyeth. Financial support for research projects was provided by AstraZeneca, GSK, Boehringer Ingelheim, Lundbeck, Novartis, Janssen-Cilag, Sanofi-Aventis, Syngis and Talecris. The Department of Neurology at the University Duisburg-Essen received research grants from the German Research Council (DFG), German Ministry of Education and Research (BMBF), European Union, NIH, Bertelsmann Foundation and Heinz-Nixdorf Foundation. HCD has no ownership interest and does not own stocks of any pharmaceutical company.
Within the past year HCD served as editor of Neurology International Open, Aktuelle Neurologie and Arzneimitteltherapie, as co-editor of Cephalalgia and on the editorial board of Lancet Neurology, Current Neurology and Neuroscience Reports, European Neurology and Cerebrovascular Disorders. HCD chairs the Treatment Guidelines Committee of the German Society of Neurology and contributed to the EHRA and ESC guidelines for the treatment of AF.

RGH receives research support and stipends for research involving rivaroxaban and honoraria for service on advisory boards for Bayer AG.

PJK receives royalties for the textbook of Neurology, Bohn Stafleu & Van Loghum. PJK has not received personal honoraria for participation in clinical trials. As chairman of the European Atrial Fibrillation Trial he has received research grants from the Dutch Heart Foundation, Bayer and Boehringer Ingelheim. The Department of Neurology currently receives research grants from the Dutch Heart Foundation, Dutch Brain Foundation, Dutch Ministry of Health, Stryker Neurovascular, Penumbra, Johnson and Johnson and Covidien for the CONTRAST consortium that coordinates several trials on endovascular treatment of acute stroke. PJK is investigator of the Rotterdam study for over 25 years. This study is supported by several nonpharmaceutical

grants. PJK does not own stocks of any pharmaceutical company.

DL: reports educational grants from Bristol-Myers Squibb and Boehringer Ingelheim, speaker activity for Pfizer, and consultant activity for Bristol-Myers Squibb, Bayer, Boehringer Ingelheim and Daiichi-Sankyo

GYHL: Consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally.

**Correspondence:**
Hans-Christoph Diener
Senior Professor of Clinical Neurosciences
Department of Neurology, University Hospital Essen and University Duisburg-Essen
Hufelandstrasse 55, 45147 Essen, Germany
Telephone: 0012917236540
Fax: 0017236918
E-mail: hans.diener@uk-essen.de

**Abstract:**
A number of vascular risk factors and vascular diseases contribute to cognitive impairment and dementia. Many studies and registries show an association of atrial fibrillation (AF) with cognitive impairment, cognitive decline and dementia. This is true for vascular dementia and Alzheimer's disease. The assumed multifactorial mechanisms include ischemic stroke, both apparent and silent, cerebral micro-infarcts, cerebral hemorrhage and reduced cerebral blood flow. A number of retrospective observational and prospective studies support that anticoagulation in patients with AF may reduce the risk of cognitive decline and dementia. This holds for both vitamin-K antagonists (VKA, e.g. warfarin) and non-vitamin-K antagonist oral anticoagulants (NOACs). However, it still remains unproven, that anticoagulation reduces cognitive decline and dementia in AF patients, based on randomised trials.

**Key words:** atrial fibrillation - cognitive impairment - dementia - anticoagulation

**Condensed Abstract:** Studies and registries show an association of atrial fibrillation (AF) with cognitive impairment, cognitive decline and dementia. The assumed mechanisms include ischemic stroke, both overt and silent, cerebral micro-infarcts and reduced cerebral blood flow. Anticoagulation in patients with AF may reduce the risk of cognitive decline and dementia, however this remains unproven, based on randomised trials.

**Abbreviations**:
AD = Alzheimer’s disease
AF = atrial fibrillation
CMB = cerebral micro-bleeds
HR = hazard ratio
ICH = intracerebral hemorrhage
INR = international normalized ratio
MMSE = Mini Mental State Examination
NOAC = non-vitamin-K oral anticoagulant
OAC = oral anticoagulant
OR = odds ratio
RR = relative risk
SD = senile dementia
TIA = transient ischemic attack
TTR = time in therapeutic range
VD = vascular dementia

Atrial fibrillation (AF) and dementia are predominantly diseases of elderly people. The incidence of AF and cognitive decline increases with advanced age, and the co-occurrence of these two frequent conditions might be explained by a common factor such as increasing age. A number of studies, however, indicate that vascular risk factors and vascular diseases not only contribute to vascular dementia but also to degenerative dementias such as Alzheimer's disease (1, 2). Importantly, AF increases the risk of stroke five-fold and stroke is an important risk factor and predictor of cognitive decline and dementia (3). Thus, a number of studies have indicated that the presence of AF might accelerate the risk of cognitive decline and dementia, even in patients without prior stroke.

This review article will provide an overview of the current knowledge on the relationship between AF, cognitive impairment and decline, and dementia and the possible role of anticoagulation for the prevention of dementia in patients with AF.

**Is AF associated with cognitive impairment, cognitive decline, and dementia?**

A number of prospective and retrospective studies have investigated the relationship between AF, cognitive decline and dementia (**Table 1**). The prospective Intermountain Heart Collaborative Study database evaluated 37,025 consecutive patients followed up them for a mean of 5 years for the development of AF and dementia (4). In this cohort 10,161 (27%) patients developed AF and 1,535 (4.1%) developed dementia - importantly AF was independently associated with all dementia types, with the highest risk in the younger group (<70 years). A posthoc-analysis of the ONTARGET and TRANSCEND studies showed that AF was associated with an increased risk of cognitive decline (hazard ratio [HR] 1.14, 95% confidence interval [CI] 1.03-1.26), new onset dementia (HR 1.30, 95% CI 1.14-1.49), loss of independence in performing activities of daily living (HR 1.35, 95% CI 1.19-1.54) and admission to long-term

care facilities (HR 1.53, 95% CI 1.31-1.79) (5).

The prospective Rotterdam study followed 6,514 dementia-free participants from 1989 to 2010 (6). and found that Prevalent AF increased the risk of dementia (HR 1.33; 95% CI 1.02-1.73). Among 6,196 participants without prevalent AF during 79,003 person-years of follow-up, 723 participants (11.7%) developed incident AF and 932 individuals (15.0%) developed dementia. As with other studies above, AF was associated with an increased risk of dementia in younger participants (<67 years). The Whitehall II study recruited 10,308 persons aged 33-45 years between 1985 and 1988 and followed them until 2013 (7). In this cohort incident dementia was more frequent in patients with AF compared to persons without AF (HR 1.87, 95% CI 1.37-2.55).

The relationship between AF and dementia is also evident from Asia. For example, a study from Taiwan identified 332,665 AF subjects without dementia from the "National Health Insurance Research Database". Found that patients with AF had a higher risk of dementia (HR 1.42, 95% CI 1.40-1.45) after adjustment for age, gender, baseline differences and medication use (8).

The relationship between AF, cognitive impairment and dementia was also shown in ameta-analysis. Kalantarian et al. (9) identified 21 studies with 89,907 participants and investigated the association of AF with cognitive decline and dementia. AF was significantly associated with a higher risk of cognitive impairment independent of a history of stroke (RR 1.34, 95% CI 1.13-1.58) (**Table 2**).The risk of dementia was also significantly increased (RR 1.38, 95% CI 1.22-1.56) (**Table 2**).

In summary, there is strong evidence from many prospective registries and studies that AF is associated with cognitive impairment, cognitive decline and dementia. This is also true for

patients without prior stroke. Such an association, however, does not necessarily imply a causal relationship, as there is very likely a multifactorial interaction with various cardiovascular risk factors involved, e.g. blood pressure control and renal function changes. The AF patient's risk profile is also dynamic and many risk factors change over time (10, 11); many of the reported associations are based on baseline risk and have not tracked temporal changes in risk.

**Is AF associated with Alzheimer's disease or vascular dementia?**

Alzheimer's disease and vascular dementia are by far the most common subtypes of dementia. Based on postmortem findings in relatively younger patients, Alzheimer's disease is characterized by neurodegenerative changes in the brain like amyloid depositions and neurofibrillary tangles. In the last decades accumulating evidence has established that stroke and cardiovascular disease are important risk factors not only of vascular dementia but also of Alzheimer's disease (4, 12-20).

Pre-clinical markers of cerebrovascular disease, which can be visualized with various imaging techniques, such as intima media thickness of the carotid artery and white matter lesions and lacunar infarcts in the brain, have likewise been related to Alzheimer's disease (17, 20-22). Besides cardiovascular disease, conventional vascular risk factors, such as hypertension, diabetes mellitus and smoking, have also been associated with an increased risk of Alzheimer's disease (23, 24). The similarity of the presumed underlying pathophysiology of vascular dementia and Alzheimer's disease is clinically relevant, as treatment of cardiovascular disease and vascular risk factors may potentially prevent a significant proportion of dementia cases, a disease for which no treatment is currently available (25).

The population-based Rotterdam Study previously showed that AF was more prevalent in participants with dementia (26) and a stronger association for Alzheimer's disease compared to

vascular dementia; however, the cross-sectional design of this study does not allow conclusions regarding a possible causal relationship. More recently, the Rotterdam Study explored the longitudinal relationship between AF and the risk of dementia, separately for prevalent and incident AF, and for all-cause dementia and Alzheimer's disease (6). In this cohort. Alzheimer's disease occurred in 787 of 994 (79%) participants with prevalent AF and in 741 of 932 (79%) with incident AF. For both prevalent and incident AF, associations were only slightly attenuated when Alzheimer's disease was separately investigated - in persons with prevalent AF, the HRs for all-cause dementia was 1.33 (95% CI 1.02-1.73) versus a non-significant 1.29 (95% CI 0.95-1.75) for Alzheimer's disease, and in those with incident AF, the HRs were non-significant for all-cause dementia 1.23 (95% CI 0.98-1.56) versus 1.18 (95% CI 0.91-1.54) for Alzheimer's disease.

Since dementia gradually develops over many years, AF probably needs to develop at a younger age to contribute to the neuropathology of underlying dementia, i.e. the typical Alzheimer changes or vascular lesions or both. Associations of other vascular risk factors of dementia, such as hypertension, hypercholesterolemia, and obesity also appear to differ with age; these elements are risk factors for dementia only when diagnosed earlier in life (27-29).

Similarly, if AF is a causal factor in the etiology of dementia, one would expect that the longer a person suffers from this condition, the higher the risk of dementia would be. Indeed, the Rotterdam Study demonstrated that the risk of either all-cause dementia or Alzheimer's disease was highest for people who suffered the longest duration of AF, although this dose-response relationship was only present in younger participants. In contrast, a Finnish study concluded that the presence of AF in mid-life was not a risk factor of subsequent dementia, whereas late-life AF was (30); however, survival bias might have influenced these results, because only persons who

survived until a late re-examination were included in the study.

In summary, AF probably increases the risk of both vascular dementia and Alzheimer's disease, however the relationship to dementia is most probably stronger when AF starts at middle age and with a longer-duration of AF.

**What are the mechanisms leading to cognitive decline and dementia in patients with AF?**

AF-associated cognitive decline occurs even in the absence of clinical strokes. Clinically recognized strokes are only the tip of the iceberg of AF-induced brain ischemia. Covert (i.e. silent) brain infarcts detected by neuroimaging in AF patients are more frequent than clinical strokes (31) and are associated with cognitive dysfunction (32) (Table 3). In addition to macroscopic covert brain infarcts, smaller cerebral micro-infarcts (beyond the resolution of conventional neuroimaging) are linked to cognitive impairment (33) and AF is an independent risk factor for such cerebral micro-infarcts (34). Indeed, the Atherosclerosis Risk in Communities Study observed that cognitive decline in patients with AF was only observed in those who had subclinical cerebral infarcts (35). Hence, unrecognized embolism is a plausible mechanism underlying AF-associated cognitive impairment and dementia.

Reduced cardiac output in the absence of clinical heart failure is associated with reduced cerebral blood flow in the elderly, particularly blood flow to the temporal lobes (36) and this has been associated with incident dementia, including Alzheimer's disease (37). AF is associated with reduced cardiac output and cerebral blood flow (38, 39), and chronic cerebral hypoperfusion could play a role (which is unresponsive to anticoagulation) in AF-associated cognitive decline. If so, then efforts to re-establish sinus rhythm could have a beneficial effect on cognition – at least theoretically. In the largest randomized trial so far, assignment to rhythm control had no benefit on cognition, but this was potentially confounded by unequal use of

anticoagulation (39). This is being further assessed in a large ongoing randomized controlled trial (EAST) (40). Other potential mechanisms also warrant consideration (**Table 4**).

On balance, subclinical embolic brain ischemia (covert brain infarcts, cerebral micro-infarcts) is likely to account for most of the cognitive deterioration associated with AF, but until further established by response to anticoagulants based on randomized trials, (for example, BRAIN-AF NCT02387229) this remains unproven.

**How might treatment of AF decrease the risk of cognitive decline and dementia?**

If we assume that dementia and AF are associated we can perhaps assume that anticoagulation might reduce the risk of cognitive decline and incident dementia in patients with AF.

There is some suggestive evidence from observational studies that anticoagulation of AF patients (and good time in therapeutic range (TTR) with warfarin anticoagulation) is associated with reduced cognitive decline (41), supporting the contribution of embolism to cognitive impairment. However, potential confounding in these observational studies limits confidence in a cause-effect relationship.

One randomized trial did not report a difference in cognition between AF patients treated with warfarin versus aspirin during 2.7 years of follow-up, but assessment of cognition was insensitive for decline (42). Another small prospective longitudinal cohort study in the UK did not find an effect of antithrombotic therapy in patients with AF on cognitive function (43).

A systematic review of 19 studies assessed the association between cognitive impairment and AF thromboprophylaxis (44). One randomized controlled trial, comparing anticoagulation against antiplatelet therapy and change in MMSE score from baseline to last follow-up (maximal duration: 5.9 years) suggested a nonsignificant difference perhaps favoring anticoagulation

(mean difference: 0.90, 95% CI: 0.29-1.51). Another randomized controlled trial found a mean difference in MMSE score of 0.80 (95% CI: -0.07 to 1.67) in favor of anticoagulation. The pooled odds ratio (OR) suggested no association with incident dementia, when comparing anticoagulant to antiplatelet therapy (two studies, Odds Ratio (OR): 1.23, 95% CI: 0.80-1.91) or no treatment (three studies, OR: 0.89, 95% CI: 0.47-1.69). Thus, there was no definitive evidence of cognitive benefit or harm from anticoagulation.

When VKAs are used as thromboprophylaxis, the efficacy and safety are closely related to the quality of anticoagulation control, as reflected by the average TTR(45). This is relevant to the impact on dementia. For example, decreasing categories of percentage TTR were associated with increased dementia risk (vs TTR>75%) as follows: <25%: HR 5.34, P < .0001; 26%-50%: HR 4.10, P < .0001; and 51%-75%: HR 2.57, P = .001(46).

The Olmsted County population-based study also investigated the association of TTR during warfarin therapy and risk of dementia in 2800 non-demented AF patients (41). Incident dementia diagnosis occurred in 357 patients (12.8%) over a mean follow-up of five years. After adjusting for confounders, warfarin therapy was associated with a reduced incidence of dementia ( HR 0.80; 95% CI, 0.64-0.99); however, only those in the 2 highest quartiles of TTR were associated with lower risk of dementia. Overall, better quality of anticoagulation management represented as percentage TTR among AF patients without dementia seems to be associated with lower dementia incidence.

In recent years, the NOACs have changed the landscape of stroke prevention in AF, with their increasing use in many countries compared to warfarin (47). The question arises as to whether NOAC use may be associated with a lower risk of new-onset dementia compared to warfarin. In a propensity-matched analysis, patients taking NOAC were 43% less likely to develop

stroke/TIA/dementia than those taking warfarin but this difference was non-significant (HR 0.57; 95% CI 0.17 - 1.97; p = 0.38)(48).

Further, a retrospective registry study of all patients with hospital diagnosis of AF and no previous diagnosis of dementia in Sweden between 2006 and 2014 investigated the possible impact of anticoagulation on the incidence of dementia in patients with AF (49). Propensity score matching, falsification endpoints, and analyses according to intention-to-treat as well as on-treatment principles were used, and the study included 444,106 patients and over 1.5 million person years at risk. Patients without prior stroke on anticoagulant treatment at *baseline* had a 29% lower risk of dementia than patients without anticoagulant treatment (HR 0.71, 95% CI 0.68-0.74) with a 48% lower risk when analyzed on treatment (HR 0.52, 95% CI 0.50-055). Direct comparisons between NOACs and warfarin showed no significant difference.

A possible mechanism underlying the observed benefit of anticoagulation could be the prevention of cerebral micro-emboli and silent brain infarcts. The benefit of OAC treatment was more pronounced among patients in whom treatment had been initiated early after the first diagnosed AF episode suggesting that there could be a dose-response relationship between unprotected time in AF and development of dementia. There was also a trend towards more benefit from treatment in patients with higher $CHA_2DS_2$-VASc scores supporting the notion that micro-embolization might be a cause of dementia in AF patients.

In summary, we have only indirect evidence that effective anticoagulation in AF reduces the risk of cognitive impairment and dementia. Nevertheless, these observational results are supportive in arguing for the initiation of prospective clinical trials on the possible benefit of anticoagulation in AF for the prevention of cognitive decline and dementia.

*Impact of rhythm control*

Cardioversion or AF ablation may result in sinus rhythm and improve cardiac output and cerebral perfusion. In the Intermountain AF study, for example, Bunch et al (50) compared 4,212 consecutive patients who underwent AF ablation to 16,848 age/gender matched controls with AF (no ablation) and 16,848 age/gender matched controls without AF, who were followed up for at least 3 years. Of the 37,908 patients, Alzheimer's dementia occurred in 0.2% of the AF ablation patients compared to 0.9% of the AF non-ablation patients and 0.5% of the non-AF patients ($P < 0.0001$). Other forms of dementia were also reduced significantly in AF patients treated with ablation.

Prospective randomized trials investigating the potential benefit of rhythm control or cardioversion in AF would need to run for at least 10 years to show an impact on cognitive decline and dementia, and would require many thousands of patients. Therefore, it is unlikely that such trials will ever be funded.

**Practical considerations**

Elderly patients with AF and cognitive impairment can be difficult to treat with oral anti-coagulation. Anticoagulation should only be initiated and maintained if a family member/carer or nurse supervises drug intake. In the case of VKAs, adequate INR control and continued adherence with therapy is required to avoid adverse outcomes (51, 52). With the NOACs, drug adherence is crucial given the relatively short half-life of these drugs (53).

Another unresolved practical issue is the question of whether anticoagulation should be introduced in AF patients with $CHA_2DS_2$-VASc score of 0-1 in males or 1-2 in females who have covert (i.e. silent) brain infarcts detected by neuroimaging performed due to various clinical indications or in patients with mild cognitive decline (no previous stroke or transient ischemic attack) or not. If silent infarcts show an “embolic” pattern (e.g. multiple infarcts in different vas-

cular territories) this appearance might justify anticoagulation use (35). Considering the relatively weak evidence that anticoagulation in AF prevents the progression from cognitive impairment to dementia, we would not recommend anticoagulation in these patients simply for the prevention of dementia at the present time.

Patients with cognitive impairment and dementia also have a higher risk of falls (54). While a very high risk of falls might constitute a contraindication for anticoagulation, it has been estimated that a patient would need to fall 295 times per year for the benefits of ischemic stroke reduction with anticoagulation to be outweighed by serious bleeding risks (55). The present availability of a specific reversal agent for dabigatran (Idaruzicumab) (54) and andexanet alfa for antiXa inhibitors (56) where available, makes the management of NOAC-induced major hemorrhage or injury much easier (57).

**Conclusions**

A number of recent epidemiological studies have reported an association of AF with cognitive impairment, cognitive decline, and dementia. The risk of dementia was increased both for total dementia and Alzheimer's disease with HRs ranging from 1.03 to 2.9, with the association between AF and dementia being strongest for patients aged <65 years. The increased risk of dementia was seen for vascular as well as Alzheimer's disease, but this is perhaps unsurprising since dementia and AF share a number of common vascular risk factors such as hypertension, heart failure, diabetes and lipid disorders. Other common risk factors include age, obesity and physical inactivity. Also, silent strokes and micro-bleeds are more common in patients with AF than in patients in sinus rhythm.

In our view, the data are sufficient to regard AF as an independent cardiovascular risk

factor for accelerated cognitive impairment and dementia. Clinical stroke is only part of the story of AF-associated brain ischemia; the most likely mechanism linking AF and cognitive impairment is covert embolism to the brain causing silent (macro) brain infarcts and cerebral micro-infarcts. Chronic cerebral hypoperfusion is also plausible. While it is tempting to justify initiation of anticoagulation, it remains unproven thus far that anticoagulation (which is so effective for reducing clinical stroke) also reduces cognitive decline and dementia in AF patients. This is currently being investigated in a number of ongoing clinical trials.

## References


1. Santos CY, Snyder PJ, Wu WC, Zhang M, Echeverria A, Alber J. Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: A review and synthesis. Alzheimers Dement (Amst). 2017;7:69-87.
2. Dietzel J, Haeusler KG, Endres M. Does atrial fibrillation cause cognitive decline and dementia? Europace. 2018;20(3):408-19.
3. Lip G, Freedman B, De Caterina R, Potpara TS. Stroke prevention in atrial fibrillation: Past, present and future. Comparing the guidelines and practical decision-making. Thrombosis and haemostasis. 2017;117(7):1230-9.
4. Bunch TJ, Weiss JP, Crandall BG, May HT, Bair TL, Osborn JS, et al. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. Heart rhythm : the official journal of the Heart Rhythm Society. 2010;7(4):433-7.
5. Marzona I, O'Donnell M, Teo K, Gao P, Anderson C, Bosch J, et al. Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. CMAJ. 2012;184(6):E329-36.
6. de Bruijn RF, Heeringa J, Wolters FJ, Franco OH, Stricker BH, Hofman A, et al. Association between atrial fibrillation and dementia in the general population. JAMA neurology. 2015;72(11):1288-94.
7. Singh-Manoux A, Fayosse A, Sabia S, Canonico M, Bobak M, Elbaz A, et al. Atrial fibrillation as a risk factor for cognitive decline and dementia. Eur Heart J. 2017;38(34):2612-8.
8. Liao JN, Chao TF, Liu CJ, Wang KL, Chen SJ, Tuan TC, et al. Risk and prediction of dementia in patients with atrial fibrillation--a nationwide population-based cohort study. Int J Cardiol. 2015;199:25-30.
9. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. Ann Intern Med. 2013;158(5 Pt 1):338-46.
10. Chao TF, Lip GYH, Liu CJ, Lin YJ, Chang SL, Lo LW, et al. Relationship of Aging and Incident Comorbidities to Stroke Risk in Patients With Atrial Fibrillation. Journal of the American College of Cardiology. 2018;71(2):122-32.
11. Yoon M, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. Dynamic Changes of CHA2DS2-VASc Score and the Risk of Ischaemic Stroke in Asian Patients with Atrial Fibrillation: A Nationwide Cohort Study. Thrombosis and haemostasis. 2018.
12. de la Torre JC. Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. Lancet Neurol. 2004;3(3):184-90.
13. Hachinski V, Munoz DG. Cerebrovascular pathology in Alzheimer's disease: cause, effect or epiphenomenon? Ann N Y Acad Sci. 1997;826:1-6.
14. Kelleher RJ, Soiza RL. Evidence of endothelial dysfunction in the development of Alzheimer's disease: Is Alzheimer's a vascular disorder? Am J Cardiovasc Dis. 2013;3(4):197-226.
15. Vermeer S, Prins N, den Heijer T, Hofman A, Koudstaal P, Breteler M. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med. 2003;348:1215-22.
16. Troncoso JC, Zonderman AB, Resnick SM, Crain B, Pletnikova O, O'Brien RJ. Effect of infarcts on dementia in the Baltimore longitudinal study of aging. Ann Neurol. 2008;64(2):168-76.

17. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA. 1997;277(10):813-7.
18. Ikram MA, van Oijen M, de Jong FJ, Kors JA, Koudstaal PJ, Hofman A, et al. Unrecognized myocardial infarction in relation to risk of dementia and cerebral small vessel disease. Stroke. 2008;39(5):1421-6.
19. Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L. Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. Arch Intern Med. 2006;166(9):1003-8.
20. Newman AB, Fitzpatrick AL, Lopez O, Jackson S, Lyketsos C, Jagust W, et al. Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort. J Am Geriatr Soc. 2005;53(7):1101-7.
21. Wendell CR, Waldstein SR, Ferrucci L, O'Brien RJ, Strait JB, Zonderman AB. Carotid atherosclerosis and prospective risk of dementia. Stroke. 2012;43(12):3319-24.
22. Prins ND, van Dijk EJ, den Heijer T, Vermeer SE, Koudstaal PJ, Oudkerk M, et al. Cerebral white matter lesions and the risk of dementia. Arch Neurol. 2004;61(10):1531-4.
23. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol. 2006;5(1):64-74.
24. Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. Am J Epidemiol. 2007;166(4):367-78.
25. de Bruijn RF, Bos MJ, Portegies ML, Hofman A, Franco OH, Koudstaal PJ, et al. The potential for prevention of dementia across two decades: the prospective, population-based Rotterdam Study. BMC medicine. 2015;13:132.
26. Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. Stroke. 1997;28(2):316-21.
27. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol. 2005;4(8):487-99.
28. Anstey KJ, Lipnicki DM, Low LF. Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. Am J Geriatr Psychiatry. 2008;16(5):343-54.
29. Tolppanen AM, Ngandu T, Kareholt I, Laatikainen T, Rusanen M, Soininen H, et al. Midlife and late-life body mass index and late-life dementia: results from a prospective population-based cohort. J Alzheimers Dis. 2014;38(1):201-9.
30. Rusanen M, Kivipelto M, Levalahti E, Laatikainen T, Tuomilehto J, Soininen H, et al. Heart diseases and long-term risk of dementia and Alzheimer's disease: a population-based CAIDE study. J Alzheimers Dis. 2014;42(1):183-91.
31. Bernhardt P, Schmidt H, Hammerstingl C, Luderitz B, Omran H. Patients at high risk with atrial fibrillation: a prospective and serial follow-up during 12 months with transesophageal echocardiography and cerebral magnetic resonance imaging. J Am Soc Echocardiogr. 2005;18(9):919-24.
32. Gaita F, Corsinovi L, Anselmino M, Raimondo C, Pianelli M, Toso E, et al. Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function. J Am Coll Cardiol. 2013;62(21):1990-7.

33. van Veluw SJ, Shih AY, Smith EE, Chen C, Schneider JA, Wardlaw JM, et al. Detection, risk factors, and functional consequences of cerebral microinfarcts. Lancet Neurol. 2017;16(9):730-40.
34. Wang Z, van Veluw SJ, Wong A, Liu W, Shi L, Yang J, et al. Risk Factors and Cognitive Relevance of Cortical Cerebral Microinfarcts in Patients With Ischemic Stroke or Transient Ischemic Attack. Stroke. 2016;47(10):2450-5.
35. Chen LY, Lopez FL, Gottesman RF, Huxley RR, Agarwal SK, Loehr L, et al. Atrial fibrillation and cognitive decline-the role of subclinical cerebral infarcts: the atherosclerosis risk in communities study. Stroke. 2014;45(9):2568-74.
36. Jefferson AL, Liu D, Gupta DK, Pechman KR, Watchmaker JM, Gordon EA, et al. Lower cardiac index levels relate to lower cerebral blood flow in older adults. Neurology. 2017;89(23):2327-34.
37. Jefferson AL, Beiser AS, Himali JJ, Seshadri S, O'Donnell CJ, Manning WJ, et al. Low cardiac index is associated with incident dementia and Alzheimer disease: the Framingham Heart Study. Circulation. 2015;131(15):1333-9.
38. Wyse DG. Therapeutic considerations in applying rate control therapy for atrial fibrillation. J Cardiovasc Pharmacol. 2008;52(1):11-7.
39. Lavy S, Stern S, Melamed E, Cooper G, Keren A, Levy P. Effect of chronic atrial fibrillation on regional cerebral blood flow. Stroke. 1980;11(1):35-8.
40. Kirchhof P, Breithardt G, Camm AJ, Crijns HJ, Kuck KH, Vardas P, et al. Improving outcomes in patients with atrial fibrillation: rationale and design of the Early treatment of Atrial fibrillation for Stroke prevention Trial. Am Heart J. 2013;166(3):442-8.
41. Madhavan M, Hu TY, Gersh BJ, Roger VL, Killian J, Weston SA, et al. Efficacy of Warfarin Anticoagulation and Incident Dementia in a Community-Based Cohort of Atrial Fibrillation. Mayo Clin Proc. 2018;93(2):145-54.
42. Mavaddat N, Roalfe A, Fletcher K, Lip GY, Hobbs FD, Fitzmaurice D, et al. Warfarin versus aspirin for prevention of cognitive decline in atrial fibrillation: randomized controlled trial (Birmingham Atrial Fibrillation Treatment of the Aged Study). Stroke. 2014;45(5):1381-6.
43. Park H, Hildreth A, Thomson R, O'Connell J. Non-valvular atrial fibrillation and cognitive decline: a longitudinal cohort study. Age Ageing. 2007;36(2):157-63.
44. Moffitt P, Lane DA, Park H, O'Connell J, Quinn TJ. Thromboprophylaxis in atrial fibrillation and association with cognitive decline: systematic review. Age Ageing. 2016;45(6):767-75.
45. Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. Circ Cardiovasc Qual Outcomes. 2008;1(2):84-91.
46. Jacobs V, Woller SC, Stevens S, May HT, Bair TL, Anderson JL, et al. Time outside of therapeutic range in atrial fibrillation patients is associated with long-term risk of dementia. Heart rhythm : the official journal of the Heart Rhythm Society. 2014;11(12):2206-13.
47. Mazurek M, Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, et al. Regional Differences in Antithrombotic Treatment for Atrial Fibrillation: Insights from the GLORIA-AF Phase II Registry. Thrombosis and haemostasis. 2017;117(12):2376-88.
48. Jacobs V, May HT, Bair TL, Crandall BG, Cutler MJ, Day JD, et al. 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. Am J Cardiol. 2016;118(2):210-4.
49. Friberg L, Rosenqvist M. Less dementia with oral anticoagulation in atrial fibrillation. Eur Heart J. 2017.
50. Selim M, Diener HC. Atrial Fibrillation and Microbleeds. Stroke. 2017;48(10):2660-4.
51. Rivera-Caravaca JM, Roldan V, Esteve-Pastor MA, Valdes M, Vicente V, Lip GYH, et al. Cessation of oral anticoagulation is an important risk factor for stroke and mortality in atrial fibrillation patients. Thrombosis and haemostasis. 2017;117(7):1448-54.
52. Rivera-Caravaca JM, Roldan V, Esteve-Pastor MA, Valdes M, Vicente V, Marin F, et al. Reduced Time in Therapeutic Range and Higher Mortality in Atrial Fibrillation Patients Taking Acenocoumarol. Clinical therapeutics. 2018;40(1):114-22.
53. Raparelli V, Proietti M, Cangemi R, Lip GY, Lane DA, Basili S. Adherence to oral anticoagulant therapy in patients with atrial fibrillation. Focus on non-vitamin K antagonist oral anticoagulants. Thrombosis and haemostasis. 2017;117(2):209-18.
54. Pollack CV, Jr., Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med. 2017;377(5):431-41.
55. Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. Archives of internal medicine. 1999;159(7):677-85.
56. Connolly SJ, Milling TJ, Jr., Eikelboom JW, Gibson CM, Curnutte JT, Gold A, et al. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. 2016;375(12):1131-41.
57. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. Europace. 2018.
58. Kalantarian S, Ruskin JN. Atrial Fibrillation and Cognitive Decline: Phenomenon or Epiphenomenon? Cardiol Clin. 2016;34(2):279-85.
59. Kalantarian S, Ay H, Gollub RL, Lee H, Retzepi K, Mansour M, et al. Association between atrial fibrillation and silent cerebral infarctions: a systematic review and meta-analysis. Ann Intern Med. 2014;161(9):650-8.

**Figure Legends**

**Figure 1: Relationship between atrial fibrillation, cognitive decline and dementia via different mechanisms.** (adapted from Kalantarian & Ruskin, Cardiol Clin 2016)(58). Atrial fibrillation can lead by a number of mechanisms to thrombus formation in the left atrial appendage and cause clinical stroke or silent stroke. Both lead to morphological changes in the brain promoting cognitive decline or dementia. Genetic factors can contribute to both, dementia and atrial fibrillation. A number of vascular diseases and vascular risk factors have been associated with cognitive decline and dementia.

**Table 1**

**Association of AF with cognitive impairment or dementia.** Results from 5 prospective registries. Odds ratios and (95% confidence intervals)

| Study | N | Follow-up (Years) | Cognitive Decline | Dementia |
|---|---|---|---|---|
| Bunch et al (4) | 37025 | 5 | | 1.06-1.73* |
| Marzona et al. (5) | 31506 | 5 | 1.14 (1.03-1.26) | 1.30 (1.14-1.54) |
| De Bruijn et al. (6) | 6514 | 21 | | 1.33 (1.02-1.73) |
| Sing-Manoux et al. (7) | 10308 | 15 | 1.87 (1.37-2.55) | |
| Liao et al (8) | 332665 | 15 | | 1.42 (1.40-1.45) |

*Odds ratios across 4 subgroups of dementia; 95% CI not provided

**Table 2**

**Association of AF with cognitive impairment or dementia.** Results from a meta-analysis of 14 studies with 31506 AF patients and controls (9). RR = relative risk

| Parameter | N studies | RR | (95% CI) |
|---|---|---|---|
| Association between AF and cognitive impairment with or without stroke | 14 | 1.40 | 1.19-1.64 |
| Association between AF and dementia | 8 | 1.38 | 1.22-1.56 |
| Association between AF and cognitive impairment | 9 | 1.50 | 1.18-1.91 |
| AF and cognitive impairment independent of stroke | 10 | 1.34 | 1.13-1.58 |
| AF and cognitive impairment after stroke | 7 | 2.70 | 1.82-4.00 |

**Table 3. Association of AF and silent cerebral infarctions.** Results from a meta-analysis of 11 studies with 5317 AF patients and controls (59) OR = Odds ratio

| **Parameter** | **N studies** | **OR** | **(95% CI)** |
|---|---|---|---|
| Association of AF and silent cerebral infarction, MRI | 5 | 2.30 | 1.44-3.68 |
| Association of AF and silent cerebral infarction, CT | 4 | 3.45 | 2.03-5.87 |
| Prevalence of silent cerebral infarction in AF patients, MRI | 9 | 0.40 (40%) | 0.29-0.51 |
| Prevalence of silent cerebral infarction in AF patients, CT | 6 | 0.22 (22%) | 0.12-0.32 |

**Table 4. Potential mechanisms underlying atrial fibrillation (AF)-associated cognitive impairment**

| | | |
|---|---|---|
| **Association** | Genetic predisposition common to both dementia and AF | |
| | Shared risk factors (e.g. age, hypertension, diabetes) | |
| **Causation** | Clinical stroke | |
| | Covert/silent (macro) brain infarcts detected by neuroimaging | |
| | Cerebral microinfarcts caused by: | Microembolism |
| | | AF-associated prothrombotic state |
| | | AF-induced neuroendocrine perturbations (e.g. BNP) |
| | | Hypoperfusion |
| | | Inflammation |
| | Reduced cerebral blood flow | |
| **Epiphenomenon** | Treatment for AF causes cognitive impairment (e.g. beta-blockers) | |