AF is strongly associated with a spectrum of cranial injuries including stroke and dementia. Dementia risk is seen in patients with and without a prior stroke and includes idiopathic forms of dementia, such as Alzheimer’s disease. The initiation, use and efficacy of anticoagulation have been shown in multiple observational trials to have an impact on dementia risk. Cerebral hypoperfusion during AF can result in cognitive decline and patients with cranial atherosclerosis may have unique susceptibility. Therapies to carefully control the ventricular rate and catheter ablation have been shown in observational trials to lower dementia risk. There is a need for further research in multiple areas and the observational trials will require prospective trials confirmation. Recent guidelines for AF have advocated the initiation of effective anticoagulation, the treatment of associated disease conditions that may influence the progression of AF and catheter ablation, with long-term management of risk factors to lower risk of dementia.

Keywords
AF, stroke, dementia, ageing, cognition, anticoagulants

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Abstract
AF is strongly associated with a spectrum of cranial injuries including stroke and dementia. Dementia risk is seen in patients with and without a prior stroke and includes idiopathic forms of dementia, such as Alzheimer’s disease. The initiation, use and efficacy of anticoagulation have been shown in multiple observational trials to have an impact on dementia risk. Cerebral hypoperfusion during AF can result in cognitive decline and patients with cranial atherosclerosis may have unique susceptibility. Therapies to carefully control the ventricular rate and catheter ablation have been shown in observational trials to lower dementia risk. There is a need for further research in multiple areas and the observational trials will require prospective trials confirmation. Recent guidelines for AF have advocated the initiation of effective anticoagulation, the treatment of associated disease conditions that may influence the progression of AF and catheter ablation, with long-term management of risk factors to lower risk of dementia.

AF and Dementia Risk With and Without Overt Cerebral Ischaemic Injury
AF is strongly associated with risk of stroke, and patients who experience a stroke have higher rates of progressive cognitive impairment and dementia. Two meta-analyses have shown a composite elevated risk of dementia in patients with AF who have a stroke (RR 2.43–2.70).[6,7] AF patients are also two times more likely to experience silent or subclinical strokes than those without AF.[6] Silent clinical infarcts are common in AF patients, with MRI revealing these injuries in 40% of patients imaged.[7] The premise of a silent infarct is evolving and is likely a misnomer. In AF patients who have subclinical strokes, long-term rates of cognitive dysfunction and dementia are increased compared with those who do not have a stroke.[8,9]

In an analysis of 37,025 patients, we found that patients with AF had higher rates of multiple forms of dementia, including idiopathic or Alzheimer’s disease, than patients who did not have AF.[10] The combined disease state of AF and dementia was significantly associated with mortality (HR 1.38–1.45). Two meta-analyses have evaluated the relationship between AF and incident dementia in patients without clinical stroke or cognitive dysfunction. In this analysis of eight studies, AF was independently associated with increased risk of dementia (HR 1.42; p<0.001).[11]

Although both dementia and AF are diseases of ageing, two large observational studies found a unique and elevated risk in AF patients who were relatively young (<67–70 years of age).[12,13] The association between AF and idiopathic dementia independent of subsequent small or repetitive subclinical strokes is not known. In a subanalysis of the Atherosclerosis Risk in Communities (ARIC) study, cognitive decline was only present in those AF patients who had a subsequent silent cerebral infarct.[13] In a study of Alzheimer’s disease patients, MRI imaging of AF patients showed much higher rates of cerebral infarcts and total gray matter volume loss, compared with those who did not have AF.[14]

The presence of AF in the absence of stroke has also been associated with progressive cognitive dysfunction, without overt dementia. In an analysis from the Cardiovascular Health Study, patients with AF experienced a more rapid decline of cognitive scores – assessed by the Modified Mini Mental State Exam – than those in sinus rhythm (−10.3 versus −6.4 over 5 years for patients with AF and those in sinus rhythm).
AF and Dementia Risk with Anticoagulation

If macro- and micro-cerebral ischaemic events are significant mechanisms underlying the association of AF with both vascular and idiopathic forms of dementia, then the initiation, use and efficacy of anticoagulation is critical. We studied this concept in an analysis of 2,605 AF patients with no history of dementia or cognitive impairment. These patients were enrolled at warfarin therapy start. This analysis showed that as time in therapeutic range (TTR) is decreased among the categories, the associated dementia risk is increased (versus >75% <25% HR 5.34; p<0.0001; 26–50% HR 4.10; p<0.0001; and 51–75% HR 2.57; p=0.001). There was a risk of cognitive decline with both over- and under-anticoagulation, suggesting that not only are cerebral ischaemic events a significant risk factor for dementia, but micro- and macro-bleeds also are.

In a more recent national study, 444,106 patients were studied over 1.5 million years of risk. Patients treated with anticoagulation at baseline had a 29% lower risk of dementia than patients without anticoagulant treatment (1.14 versus 1.78 per 100 patient years at risk; p<0.001). In this analysis, delays in initiation of anticoagulation had a negative impact on the benefit observed with anticoagulation use (0–1 years HR 0.66; 1–3 years HR 0.80; 3–5 years HR 1.12; >5 years HR 0.80; p<0.001). Unfortunately, underuse and delayed use remain significant issues within our system (Table 1) and worldwide – particularly in women – even in AF patients considered at moderate to high risk.

Direct oral anticoagulants (DOACs) have reduced rates of stroke and intracranial haemorrhage, compared with warfarin. In a propensity-based analysis of 5,254 patients (2,627 in the warfarin and DOAC groups), the use of DOACs was associated with a reduced risk of stroke or transient ischaemic attack (p<0.0001), major bleed (p<0.0001), and bleed (p=0.140). In regard to total cerebral events, patients treated with a DOAC were 43% less likely to develop stroke, transient ischaemic attack or dementia than those taking warfarin.

In a nationwide analysis – limited by the small number of patients who actually received DOAC therapy – use of the newer anticoagulants was associated with a greater relative reduction in dementia risk (HR 0.40) when compared with warfarin. A potential benefit of DOAC therapy versus warfarin for brain health and preservation of cognition in AF patients requires prospective evaluation. The impact of Anticoagulation Therapy on the Cognitive Decline and Dementia in Patients with Non-Valvular Atrial Fibrillation (CAF) trial will evaluate warfarin versus dabigatran over 2 years with serial cognitive testing every 6 months (NCT0361006). As of December 2018, the study was approximately 70% enrolled.

The data regarding anticoagulation use and efficacy are compelling and prompted us to ask if AF contributes to dementia independently in patients treated long term with anticoagulation. In a study of 10,537 patients anticoagulated with warfarin for both AF (n=4,460) and non-AF reasons (thromboembolism n=5,868; valvular heart disease n=209) with no history of dementia, we evaluated the risk of dementia and the potential augmented risk of AF. In both groups there was a higher risk of dementia in patients with a low TTR compared with a high TTR, highlighting the critical role of anticoagulation on outcomes. Additionally, in a propensity-based analysis the presence of AF conveyed additional risk for general dementia (HR 2.42; p<0.0001) and Alzheimer’s disease (HR 2.04; p<0.0001).
Clinical Arrhythmias

Table 1: Delays in Initiation of Antithrombotic Therapies in Patients with Newly Diagnosed AF

| Time to Initiation | Acetylsalicylic acid/clopidogrel (n=21,781) | Warfarin (n=4,408) |
|-------------------|---------------------------------------------|--------------------|
| General population |                                             |                    |
| ≤30 days          | 48.0%                                       | 5.2%               |
| 31 days to 1 year | 10.5%                                       | 12.4%              |
| >1 year to 3 years| 13.1%                                       | 17.1%              |
| >3 years          | 28.4%                                       | 65.3%              |
| CHADS4-VASc 2–4   |                                             |                    |
| ≤30 days          | 50.7%                                       | 4.8%               |
| 31 days to 1 year | 10.2%                                       | 12.5%              |
| 1 year to 3 years | 13.6%                                       | 17.9%              |
| >3 years          | 25.5%                                       | 64.8%              |
| CHADS4-VASc >5    |                                             |                    |
| ≤30 days          | 67.1%                                       | 7.9%               |
| 31 days to 1 year | 8.8%                                        | 18.4%              |
| 1 year to 3 years | 10.9%                                       | 25.4%              |
| >3 years          | 13.2%                                       | 48.3%              |

Figure 2: Mechanisms of Risk of Cognitive Decline and Dementia in Patients with AF

the arteriolar level and hypertensive events at the capillary level.20
The quantitative impact of repetitive microvascular haemodynamic
compromise can be significant in AF patients as another cause of
chronic ischaemic injuries and, as such, is considered one of the
causes of leukoaraiosis or white matter changes.21

Management of rate and rhythm can improve outcomes. In a small
study of patients with persistent AF who were compared with
sinus rhythm controls, atrioventricular node ablation resulted in a
steady and predictable heart rate (R-R interval), improved frontal
and temporal blood flow leading to improved memory and learning
and a flow pattern similar to those in sinus rhythm.22 We have also
found, in an observational analysis, that patients with AF treated
with catheter ablation have lower rates of stroke and dementia than
patients who have AF not treated with ablation. Although this finding
reflects procedural and referral biases, what is interesting is that
patients treated with catheter ablation had stroke and dementia rates
similar to patients without a history of AF. For example, Alzheimer’s
dementia occurred in 0.2% of the AF ablation patients, compared
with 0.9% of the AF no ablation patients and 0.5% of the no AF
patients (p<0.0001).23

Risk of Dementia Related to Inflammation,
Oxidative Stress and Genetic Components in AF
From a histologic evaluation, Alzheimer’s disease is associated
with the accumulation of abnormally folded beta-amyloid and tau
proteins that form cerebral plaques. These plaques are associated
with cerebral atrophy and cellular death. Amyloid deposits and
misfolded proteins are also seen in degenerative atrial myopathy
in AF patients.24 Whether the same predisposition of atrial changes
associated with amyloid deposits is seen in the brain of patients
with AF-related cognitive decline is unknown. From a genetic
standpoint the apolipoprotein E epsilon4 allele is associated with
risk of dementia and amyloid deposits. However, this allele did not
act as a second hit or contributor of accelerated cognitive decline
in patients with AF.25

Oxidative stress, inflammation and endothelial dysfunction have been
shown to increase the risk of Alzheimer’s disease.26–28 In patients
with AF, biomarkers of oxidative stress, inflammation and endothelial
dysfunction are elevated.29–31 These markers associated with both
disease states suggest both organs that manifest end organ disease –
brain (dementia) and heart (AF) – reflect symptoms of a systemic and
inflammatory vascular disease that has early roots in hypertension,
obesity, low physical activity and metabolic syndrome.27

Figure 2 highlights pathways of cranial injury with common mediators
that are likely to drive incidence and progression.

Improving Risk Prediction of Cognitive Decline
in Patients with AF
Preservation of cognition must be a critical goal in the long-term
management of patients with AF. If we consider the concept that
chronic cognitive changes reflect repetitive cranial injuries from
macro- or micro-clots and bleeds, then traditional risk scores should
predict dementia. As discussed previously, the timing, use and efficacy
of anticoagulation does influence dementia risk in AF patients. The
CHADS2 and CHA2DS2-VASC scores are risk scores used to minimise risk
of macro events or clinical events.32 These scores are largely comprised
of static baseline risk factors and only augment with time. These scores
also do not have the ability to discriminate between the seventies
of individual diseases, such as a patient with poorly controlled
hypertension versus well controlled hypertension. As a consequence,
the predictive values of each score are relatively poor, with c-statistics
ranging from 0.50–0.70 across multiple cohorts of the study.33 Although
these scores also predict dementia risk, there remains broad variability
in risk across all CHADS2 and CHA2DS2-VASC strata.27

Risk scores that can be used dynamically and judge severity of disease
will likely perform better, so can potentially have an impact on clinical
care. For example, a dynamic score can assist in understanding
current brain health and risk when transitioning from warfarin with a
low TTR to a DOAC therapy, or after lifestyle modifications including
increasing activity, lowering weight and improving blood pressure and
glycemic control. Risk factor management is complex and multiple
factors related to lifestyle drive both AF incidence, progression and
adverse outcomes.34

When lifestyle modification is advocated in patients – with the
assistance of a multidisciplinary team – arrhythmia-related outcomes
can be improved, and some diseases can be reversed. This concept
has many potential positive inroads towards cognitive health and
In conclusion, recent guidelines were provided to raise awareness of the critical association between cognitive decline, dementia and cardiovascular disease, to identify key areas of additional research needed and to provide recommendations on how to lower risk. In regard to risk in patients with AF, a recommendation for appropriate anticoagulation was made to prevent stroke and cognitive dysfunction. Other areas that may be useful for recommendations include when to consider a DOAC rather than warfarin, optimising TTR to >70%, managing lifestyle changes such as prevention of smoking, hypertension, obesity, diabetes, sleep apnoea, etc., to lower risk of both disorders, and rhythm control – particularly in younger patients (<65 years of age) – which may include ablation in highly-trained centres with long-term follow-up to optimise post-ablation care.

Clinical Perspective

- **AF** is associated with long-term risk of cognitive decline and dementia.
- Dementia rates are higher in women and those who have AF.
- Chronic cerebral ischaemic injuries from macro- and micro-clots and bleeds is a mechanism supported by trials of anticoagulation use and cranial imaging.
- Unmasked cerebral vascular dysfunction, through haemodynamic, oxidative and inflammatory mechanisms, is also a probable mechanism that can explain abrupt cognitive changes with onset of AF.
- Several mechanisms of risk can be targeted with current pharmacological and nonpharmacological therapies that may lower dementia risk and, as such, require prospective study.

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370–5. https://doi.org/10.1001/jama.285.18.2370.
2. Chugh SS, Havmoeller R, Narayan S, et al. Worldwide epidemiology of atrial fibrillation: A Global Burden of Disease 2010 Study. Circulation 2012;125:888–900. https://doi.org/10.1161/CIRCULATIONAHA.110.151591.
3. Asbach S, Olschewski M, Faber TS, et al. Mortality in patients with atrial fibrillation has significantly decreased during the last three decades: 35 years of follow-up in 627261 patient. Europace 2008;10:391–4. https://doi.org/10.1093/europace/eun014; PMID: 18326852.
4. Schnabel RB, Yin X, Gona P, et al. 50 year trends in cardiovascular disease, to identify key areas of additional research needed and to provide recommendations on how to lower risk. In regard to risk in patients with AF, a recommendation for appropriate anticoagulation was made to prevent stroke and cognitive dysfunction. In 2014:1762–8. https://doi.org/10.1161/CIRCULATIONAHA.110.151591.
5. Kwok CS, Loke YK, Hale R, et al. Atrial fibrillation and cognitive decline: a longitudinal cohort study. Neurology 2013;81:386–92. https://doi.org/10.1212/WNL.0b013e31829a33d1; PMID: 23739229.
6. Coma M, Gonzalez-Moneo MJ, Enjuanes C, et al. Effect of Permanent Ablation on Cognitive Function in Patients With Chronic Heart Failure. Am J Cardiol 2016;117:233–9. https://doi.org/10.1016/j.amjcard.2015.10.038; PMID: 2686573.
7. Licher S, Danweeck SKL, Wolters FJ, et al. Lifetime risk of common morbidities and mortality in the population. Heart Rhythm 2019;16:144–5. https://doi.org/10.1016/j.hrthm.2018.11.014; https://doi.org/10.1016/j.hrthm.2018.11.014; https://doi.org/10.1016/j.hrthm.2018.11.014.
8. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370–5. https://doi.org/10.1001/jama.285.18.2370.
9. Kwok CS, Loke YK, Hale R, et al. Atrial fibrillation and cognitive decline: a longitudinal cohort study. Neurology 2013;81:386–92. https://doi.org/10.1212/WNL.0b013e31829a33d1; PMID: 23739229.
10. Bunch TJ, Weiss JP, Crandall BG, et al. Atrial fibrillation and cardiovascular disease, to identify key areas of additional research needed and to provide recommendations on how to lower risk. In regard to risk in patients with AF, a recommendation for appropriate anticoagulation was made to prevent stroke and cognitive dysfunction. Other areas that may be useful for recommendations include when to consider a DOAC rather than warfarin, optimising TTR to >70%, managing lifestyle changes such as prevention of smoking, hypertension, obesity, diabetes, sleep apnoea, etc., to lower risk of both disorders, and rhythm control – particularly in younger patients (<65 years of age) – which may include ablation in highly-trained centres with long-term follow-up to optimise post-ablation care.

11. ARRHYTHMIA & ELECTROPHYSIOLOGY REVIEW
38. Goette A, Ittenson A, Hoffmanns P, et al. Increased expression of P-selectin in patients with chronic atrial fibrillation. *Pacing Clin Electrophysiol* 2000;23:1872–3. https://doi.org/10.1111/j.1540-8159.2000.tb07041.x; PMID: 1139946.

39. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;137:118–72. https://doi.org/10.1378/chest.09-1584; PMID: 20972536.

40. Van Staa TE, Setakis E, Di Tanna G, et al. A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. /Thromb Haemost 2011;9:39–48. https://doi.org/10.1111/j.1538-7836.2010.04685.x; PMID: 21029959.

41. Brandes A, Smid MD, Nguyen BQ, et al. Risk Factor Management in Atrial Fibrillation. *Arrhythm Electrophysiol Rev* 2018;7:118–27. https://doi.org/10.15420/yer.2018.18.2; PMID: 29967684.

42. Graves KG, May HT, Jacobs V, et al. CHA2DS2-VASc scores and Intermountain Mortality Risk Scores for the joint risk stratification of dementia among patients with atrial fibrillation. *Heart Rhythm* 2019;16:3–9. https://doi.org/10.1016/j.hrthm.2018.10.018; PMID: 30611392.

43. Graves KG, May HT, Knowlton KJ, et al. Improving CHA2DS2-VASc stratification of non-fatal stroke and mortality risk using the Intermountain Mortality Risk Score among patients with atrial fibrillation. *Open Heart* 2018;5:e000907. https://doi.org/10.1136/openhrt-2018-000907; PMID: 30564375.

44. Dagres N, Chao TF, Feneion G, et al. 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? *Heart Rhythm* 2018;15:e37–60. https://doi.org/10.1016/j.hrthm.2018.03.005; PMID: 29563049.