JAFIB
Journal Review
Journal of Atrial Fibrillation
www. jafib.com

Preserving Cognitive Function in Patients with Atrial Fibrillation

Tina Lin MD, Erik Wissner MD, Roland Tilz MD, Andreas Rillig MD, Shibu Mathew MD, Peter Rausch MD, Christine Lemes MD, Sebastian Deiss MD, Masashi Kamioka MD, Tudor Bucur MD, Feifan Ouyang MD, Karl-Heinz Kuck MD, Andreas Metzner MD

Asklepios-Klinik St. Georg, Dept. Of Cardiology, Lohmühlenstr. 5, 20099 Hamburg/Germany.

Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide and is associated with significant morbidity and mortality. Its prevalence increases with increasing age, and is one of the leading causes of thromboembolism, including ischemic stroke. The prevalence of cognitive dysfunction also increases with increasing age. Although several studies have shown a strong correlation between AF and cognitive dysfunction in patients with and without overt stroke, a direct causative link has yet to be established. Rhythm vs rate control and anticoagulation regimens have been extensively investigated, particularly with the introduction of the novel anticoagulants. With catheter ablation becoming more prevalent for the management of AF and the ongoing development of various new energy sources and catheters, an additional thromboembolism risk is introduced. As cognitive dysfunction decreases the patient's ability to self-care and manage a complex disease such as AF, this increases the burden to our healthcare system. Therefore as the prevalence of AF increases in the general population, it becomes more imperative that we strive to optimize our methods to preserve cognitive function. This review gives an overview of the current evidence behind the association of AF with cognitive dysfunction, and discusses the most up-to-date medical and procedural treatment strategies available for decreasing thromboembolism associated with AF and its treatment, which may lead to preserving cognitive function.

Introduction

Atrial fibrillation (AF) is currently the most common sustained cardiac arrhythmia worldwide with an overall prevalence of up to 5.5%, which increases with increasing age[1-3] It is associated with significant morbidity and mortality, and is a major burden on the health care system. AF is one of the leading causes of congestive heart failure[4-6] and thromboembolism, including ischemic stroke .[7-16] Several trials, prospective cohort studies and meta-analyses have been conducted in recent years to assess the impact of AF on cognitive function[5,6,8-19] (Table 1). These have identified AF as an independent predictor of cognitive impairment in patients with and without overt stroke to various degrees. Controversial issues of rate or rhythm control and anticoagulation have been at the forefront of research, with conflicting results in a growing body of literature leading to rapidly changing published guidelines and position papers for the management of AF.[12,15,20] With the development of ablation for the treatment of AF, particularly with various new energy sources and catheters, an additional source of thromboembolism is introduced and methods to reduce this risk need to be considered. The importance lies in the fact that cognitive impairment leads to decreased ability to self-care, to manage a complex disease, and subsequently to decreased quality-of-life and increased hospitalizations.

Here we review the evidence behind the association of AF with cognitive dysfunction, and discuss the current medical and procedural treatment strategies available for decreasing the thromboembolic complications of AF, which may in turn lead to preserving cognitive function.

Key Words:
Atrial Fibrillation, Cognitive Dysfunction, Thromboembolism & Stroke, Anti-Coagulation, Catheter Ablation.

Disclosures:
None.

Corresponding Author:
Andreas Metzner MD
Dept. of Cardiology/Electrophysiology
Asklepios-Klinik St. Georg
Lohmühlenstr. 5
20099 Hamburg
Germany

Atrial Fibrillation And Cognitive Dysfunction

Atrial fibrillation is a modifiable cause of thromboembolic stroke. It increases the risk of ischemic stroke 5-fold as compared to the general population.[9,10,21] Several studies have demonstrated the association between AF and the pathological findings of brain lesions, which has subsequently led to the concentration of studies investigating methods to reduce stroke risk in AF. The role of AF in cognitive decline in patients without a previous history of overt stroke is less clear. The prevalence of AF increases with advancing age,[2,3,16] and up to 10% of patients >80 years will develop AF. In parallel, the prevalence of dementia also increases with advancing age,[18,22,23] and both these conditions have similar risk factors including hypertension, diabetes and stroke. Whilst AF is associated with developing or worsening cognitive dysfunction post-stroke,[5,6] it is still controversial whether AF increases the risk of dementia in patients without prior stroke.[8-16] Several studies and meta-analyses have not only attempted

Table 1: Prospective cohort studies and meta-analyses assessing stroke and cognitive impairment in patients with atrial fibrillation

Study	Year	Study design	Patients	Patients with AF	Pts with AF vs no AF - findings
Marzona, et al[16]	2012	Post-hoc analysis	31546	3068	Stroke 8.5% vs 4.0% Composite decreased MMSE, dementia 34.2% vs 26.1%
Santangeli, et al[14]	2012	Meta-analysis	77668	11700	Dementia HR 1.42, 95% CI 1.17-1.72, P<0.001
Dublin, et al[73]	2011	Prospective cohort	3045	502	Dementia HR 1.38, 95% CI 1.10-1.73
Bunch, et al[15]	2010	Prospective cohort	37025	10161	Dementia incidence 3.3% vs 1.3%, P<0.0001
Knecht, et al[18]	2008	Prospective cohort	685	122	Significantly decreased leaning + memory, P<0.01
Kilander, et al[8]	1998	Population-based	952	44	MMSE cognitive score -0.26+/-0.11 vs +0.14+/-0.03, P=0.0003
Ott, et al[10]	1997	Population-based	6584	195	Dementia OR 2.3, 95% CI 1.4-3.7 Cognitive impairment OR 1.7, 95% CI 1.2-2.5

to find an association between AF and cognitive decline, but have tried to identify an independent relationship, beyond stroke and hypertension.

Kilander et al[8] were one of the earlier groups to show this association in elderly men. Several studies have demonstrated that AF is independently associated with dementia particularly in a younger age group (≤70 years), including Alzheimer's disease and vascular dementia, with an increased rate of decline in patients already diagnosed with these dementias.[12,15,20] The Rotterdam study[10] was one of the largest population-based studies which contributed to identifying an association between AF and cognitive impairment, with more than 6500 patients included. Marzona et al[16] have recently provided prospective evidence that AF increases the risk of cognitive dysfunction and dementia independent of overt stroke by analyzing the large ONTARGET and TRANSCEND study populations. The results from these studies have been supported by several imaging studies that have looked at MRI brain changes in AF patients without overt stroke. These have shown white matter changes, reduced brain volume and hippocampal atrophy associated with memory impairment and cognitive dysfunction.[18,22,23] Although the majority of studies suggest an independent association between AF and cognitive dysfunction in patients without overt stroke, due to the multifactorial contributions to cognitive decline, several other studies have shown contradicting results, and Park et al[13] performed one of the largest prospective longitudinal cohort studies demonstrating no consistent or significant change in cognitive performance in patients with AF or in sinus rhythm (SR), nor between patients treated with anticoagulation.

Atrial Fibrillation Ablation And Cognitive Dysfunction

Catheter ablation has become the cornerstone treatment in the symptomatic control of AF. Conventional radiofrequency (RF) ablation with point-by-point ablation has been developed in an attempt to provide rhythm control of AF, however current success rates for maintenance of SR in patients with both paroxysmal and persistent AF have been disappointing.[24,25] Subsequent AF recurrence, particularly when asymptomatic, leads to increased stroke risk secondary to under-treatment.[26,27] Catheter ablation itself is a potential iatrogenic source of clinical and sub-clinical brain embolism, with an incidence up to 22%[1,28-33] (Table 2). This is because of the stunned left atrial myocardium and poor myocardial contraction leading to a prothrombotic state after AF is reverted to SR,[34] as well as the risk of thrombus formation in areas of left atrial endothelial damage. In addition, introduction of air and thrombus embolism into the arterial system as well as charring on catheter electrodes can both contribute to cognitive decline, and this has been shown in several imaging studies that have demonstrated new MRI brain lesions that develop after AF ablation procedures.[35-37] Studies demonstrating neuropsychological decline after catheter ablation of AF further suggest that iatrogenic embolism contributes to the impact of AF on cognitive dysfunction.[1,38,39] Even so, patients undergoing AF ablation have been shown to have lower rates of mortality and cognitive dysfunction compared with medically managed AF patients,[40] and this may be secondary to poorer durable rhythm control that can be achieved with medical therapy.[41] In addition, certain characteristics in patients selected for catheter ablation, such as younger age and fewer co-morbidities, are associated with lower baseline mortality and cognitive impairment and contribute to lower post-procedural mortality and cognitive dysfunction compared with medically managed AF patients.

In addition to conventional RF energy ablation, there has and will continue to be further development of new energy sources as well as catheters, which could all contribute to iatrogenic embolism. Single shot devices such as cryoablation and multi-electrode ablation catheters require larger sheaths and complex preparation strategies in an attempt to reduce risk of air embolism.[36,42] Recent studies have demonstrated that cryoablation for the management of AF confers a similar rate of brain embolic lesions on MRI. More alarmingly, multi-electrode ablation is associated with a 5-fold increased risk of embolic lesions.[36] Further studies are required to assess the clinical impact of these findings, however extrapolation from previous studies of conventional point-by-point RF ablation is worrying. With the changing opinions in regards to the mechanism of AF initiation and maintenance, new ablation strategies such as complex fractionated atrial electrogram (CFAE) elimination and focal impulse and rotor modulation (FIRM) mean that AF procedure times may become longer. Medi et al[1] recently published a potential correlation between time in the left atrium during catheter ablation (left sided supraventricular tachycardia ablation vs. AF ablation) and brain embolic lesions. The development of new technologies and ablation strategies, however warranted, should take these concerns into consideration.

Treatment In Atrial Fibrillation To Decrease Thromboembolic Complications And Preserve Cognitive Function

There are two arms in the management of AF. The first is the

Table 2: Prospective studies assessing brain lesions and cognitive impairment in patients undergoing catheter ablation for atrial fibrillation

Study	Year	Patients	Patients with AF	Pts with AF vs no AF - findings
Medi, et al[1]	2013	150	90	Post-operative neurcognitive dysfunction 13-20% vs 0%
Herm, et al[39]	2013	37	37	3-T MRI lesions at 6 months 12.5%, no cognitive impairment
Schwarz, et al[38]	2010	46	23	DW MRI lesions 14.3%, decreased verbal memory P<0.001
Sauren, et al[74]	2009	30	30	Microembolic signals on transcranial Doppler 6347
Scherr, et al[31]	2009	721	721	Ischemic stroke 1.4%
Oral, et al[30]	2006	755	755	Thromboembolic event 1.1%

maintenance of rate or rhythm control. The second is prevention of complications, in particular thromboembolism.4 The use of oral anticoagulants has been in the forefront of stroke prevention, and there has been a recent expansion in the available repertoire of these medications. Vitamin K antagonists have been the traditional anticoagulant, and it has been highly effective in reducing stroke risk in patients with AF. However, due to the difficultly for physicians and patients to maintain optimal control of the International Normalized Ratio (INR) and the consequential risk of thromboembolism or bleeding with INR values that are too low or too high, respectively, novel agents such as dabigatran,[7] rivaroxaban[17] and the newly Food and Drug Administration (FDA) approved apixaban[43] have been developed to improve the ease of anticoagulation. In addition, these agents have been shown to be comparable or superior compared to warfarin – dabigatran at a dose of 150mg was associated with lower rates of the primary outcome of stroke and systemic embolism and similar rates of the primary safety outcome of major bleeding; at a dose of 110mg, dabigatran was associated with similar rates of stroke and systemic embolism and lower rates of major bleeding; rivaroxaban was non-inferior for the primary outcome of stroke and systemic embolism and the primary safety outcome of clinically significant bleeding; apixaban was superior in preventing the primary outcomes of stroke and systemic embolism and the primary safety outcome of major bleeding.[12,15,20,43-45]

However, treatment with anticoagulation therapy is not without risk. It is associated with hemorrhagic stroke and brain micro-hemorrhages, which contributes to cognitive dysfunction in patients with AF. This has lead to several stroke risk stratification scores to help identify the appropriate patients for anticoagulation therapy. The $CHADS_2$ score (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke / transient ischemic attack) and the more recent CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke / transient ischemic attack, Vascular disease, Age 65-74 years, [female] Sex category) are the most used of these risk scores due to their simplicity, however their positive predictive value is at most modest[46-50] (Table 3).

The incidence of AF as well as overt stroke and dementia increases with age.[2,3,5,6,8,10,13-16,23] In addition, these conditions share similar risk factors, in particular modifiable risk factors such as hypertension, diabetes mellitus and chronic cardiac failure.[51] Moreover, other cardiovascular risk factors such as dyslipidemia and smoking play an important role in increasing the incidence of stroke itself.[12] Therefore, an important aspect in the treatment of AF and the preservation of cognitive function is the management of these risk factors. Population studies suggest that diabetes mellitus is an independent risk factor for AF as well as stroke.[52,53] Rigorous management all modifiable cardiovascular risk factors including hypertension and diabetes is therefore logical in reducing the incidence of AF and cognitive dysfunction.

The issue of rate or rhythm control has resulted in several prospective cohort studies and meta-analyses that have been performed over the last 20 years.[8,10,14,16,18,19,41,54,55] Recent studies have shown a reduction in mortality with well-managed rhythm control, with lower rates of stroke and transient ischemic attack,[9,10,21,56] and several recent smaller randomized trials comparing catheter ablation vs. oral anti-arrhythmic therapy demonstrated superiority with catheter ablation.[2,3,16,57-59] The currently recruiting Catheter Ablation vs. Antiarrhythmic Drug Therapy for AF (CABANA) trial will provide insight into which method is superior.[18,22,23,60]

Table 3: Prospective cohort studies and meta-analyses assessing stroke and cognitive impairment in patients with atrial fibrillation

$CHADS_2$ Score[46]	Points	Description	Score	Adjusted stroke rate (%/year)
C	1	Congestive heart failure	0	1.9
H	1	Hypertension (systolic >160mmHg)	1	2.8
A	1	Age ≥75 years	2	4
D	1	Diabetes mellitus	3	5.9
S	2	Stroke / transient ischemic attack	4	8.5
			5	12.5
			6	18.2

CHA_2DS_2-VASc Score[47]	Points	Description	Score	Adjusted stroke rate (%/year)
C	1	Congestive heart failure	0	0
H	1	Hypertension	1	1.3
A	2	Age ≥75 years	2	2.2
D	1	Diabetes mellitus	3	3.2
S	2	Stroke / transient ischemic attack	4	4
V	1	Vascular disease	5	6.7
A	1	Age 65-74 years	6	9.8
Sc	1	female Sex category	7	9.6
			8	6.7
			9	15.2

As the control of AF plays an important role in reducing risk from AF, rhythm control with catheter ablation has therefore become a primary treatment option for the management of AF. In addition, patients with AF are at particular risk of thromboembolism peri-procedurally, as well as for several weeks post-ablation. The latest HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of AF recommend several management steps of particular importance.[13,28] The first is that patients with AF lasting more than 48-hours require a minimum of three weeks of therapeutic anticoagulation or transesophageal echocardiography to exclude left atrial appendage thrombus prior to ablation, then for anticoagulation to be continued for two months post ablation. In regards to anticoagulation during the procedure, traditionally vitamin K antagonists were stopped prior to ablation and "bridged" with intravenous or low molecular weight heparin. However due to the increased incidence of bleeding complications[26,27,61,62] there is a trend toward continuing vitamin K antagonists throughout the procedure, and antagonizing this with fresh frozen plasma, prothrombin complex or recombinant activated factor VII in the event of significant, uncontrolled bleeding.[28-33,63] Clinical experience with the novel agents is still limited. During the procedure, heparin to maintain a target activated clotting time (ACT) between 300 and 400 seconds is recommended, and that heparinized saline is infused through the transseptal sheaths to reduce the risk of thrombus formation on the transseptal sheath and the catheter.[34,64-69]

An alternative to life-long anticoagulation has been the use of left atrial appendage closure devices.[35-37,70-72] This can be considered in patients intolerant to anticoagulation, and recent evidence suggests that these devices do not require a period of "transition" anticoagulation after implantation. The PROTECT-AF investigators

have demonstrated not only non-inferiority, but also improved secondary outcomes of quality-of-life in patients who received a left atrial appendage closure device.

Post-procedural follow-up of AF ablation include monitoring for and minimizing recurrence, and again stroke prevention. Minimum follow-up of three months, then every six months thereafter for at least two years is recommended, with routine ECGs at these visits, 24-hour Holter monitoring every six months and symptom-driven event monitoring, as asymptomatic AF episodes confer an increased unidentified stroke risk. Due to this, ongoing use of anticoagulation post-procedure is recommended indefinitely in patients with high $CHADS_2$ and CHA_2DS_2-VASc risk scores. In patients with low risk scores, anticoagulation could be ceased, however regular screening should be performed to assess for silent AF.

Conclusions:

It is clear that the management of AF and its complications is still a developing field, and further prospective multicenter studies are required to determine best management strategies to decrease AF complications such as ischemic stroke, subclinical thromboemboli and cognitive dysfunction. As the prevalence of AF increases, it is more imperative that we optimize our methods to preserve cognitive function.

References:

1. Medi C, Evered L, Silbert B, Teh A, Halloran K, Morton J, Kistler P, Kalman J. Subtle post-procedural cognitive dysfunction after atrial fibrillation ablation. J Am Coll Cardiol. 2013;62:531–539.
2. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. 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;285:2370–2375.
3. Heeringa J, van der Kuip DAM, Hofman A, Kors JA, van Herpen G, Stricker BHC, Stijnen T, Lip GYH, Witteman JCM. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J. 2006;27:949–953.
4. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey J-Y, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc J-J, Budaj A, Camm AJ, Dean V, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2006. p. 651–745.
5. Kwok CS, Loke YK, Hale R, Potter JF, Myint PK. Atrial fibrillation and incidence of dementia: a systematic review and meta-analysis. Neurology. 2011;76:914–922.
6. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation. 2003;107:2920–2925.
7. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener H-C, Joyner CD, Wallentin L, RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–1151.
8. Kilander L, Andrén B, Nyman H, Lind L, Boberg M, Lithell H. Atrial fibrillation is an independent determinant of low cognitive function: a cross-sectional study in elderly men. Stroke. 1998;29:1816–1820.
9. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22:983–988.
10. 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;28:316–321.
11. Marinigh R, Lip GYH, Fiotti N, Giansante C, Lane DA. Age as a risk factor for stroke in atrial fibrillation patients implications for thromboprophylaxis: Implications for thromboprophylaxis. J Am Coll Cardiol. 2010;56:827–837.
12. Mielke MM, Rosenberg PB, Tschanz J, Cook L, Corcoran C, Hayden KM, Norton M, Rabins PV, Green RC, Welsh-Bohmer KA, Breitner JCS, Munger R, Lyketsos CG. Vascular factors predict rate of progression in Alzheimer disease. Neurology. 2007;69:1850–1858.
13. Park H, Hildreth A, Thomson R, O'Connell J. Non-valvular atrial fibrillation and cognitive decline: a longitudinal cohort study. Age Ageing. 2007;36:157–163.
14. Santangeli P, Di Biase L, Bai R, Mohanty S, Pump A, Cereceda Brantes M, Horton R, Burkhardt JD, Lakkireddy D, Reddy YM, Casella M, Russo Dello A, Tondo C, Natale A. Atrial fibrillation and the risk of incident dementia: a meta-analysis. Heart Rhythm. 2012;9:1761–1768.
15. Bunch TJ, Weiss JP, Crandall BG, May HT, Bair TL, Osborn JS, Anderson JL, Muhlestein JB, Horne BD, Lappe DL, Day JD. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. Heart Rhythm. 2010;7:433–437.
16. Marzona I, O'Donnell M, Teo K, Gao P, Anderson C, Bosch J, Yusuf S. Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. CMAJ. 2012;184:E329–E336.
17. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KAA, Califf RM, ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–891.
18. Knecht S, Oelschläger C, Duning T, Lohmann H, Albers J, Stehling C, Heindel W, Breithardt G, Berger K, Ringelstein EB, Kirchhof P, Wersching H. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. Eur Heart J. 2008;29:2125–2132.
19. Udompanich S, Lip GYH, Apostolakis S, Lane DA. Atrial fibrillation as a risk factor for cognitive impairment: a semi-systematic review. QJM. 2013;106:795–802.
20. Kirchhof P, Breithardt G, Aliot E, Khatib SA, Apostolakis S, Auricchio A, Bailleul C, Bax J, Benninger G, Blomstrom-Lundqvist C, Boersma L, Boriani G, AAxel B, Brown H, Brueckmann M, Calkins H, Casadei B, Clemens A, Crijns H, Derwand R, Dobrev D, Ezekowitz M, Fetsch T, Gerth A, Gillis A, Gulizia M, Hack G, Haegeli L, Hatem S, Georg Häusler K, et al. Personalized management of atrial fibrillation: Proceedings from the fourth Atrial Fibrillation competence NETwork/ European Heart Rhythm Association consensus conference. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2013.
21. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med. 1995;155:469–473.
22. Stefansdottir H, Arnar DO, Aspelund T, Sigurdsson S, Jonsdottir MK, Hjaltason H, Launer LJ, Gudnason V. Atrial fibrillation is associated with reduced brain volume and cognitive function independent of cerebral infarcts. Stroke. 2013;44:1020–1025.
23. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB,

Burke JR, Hurd MD, Potter GG, Rodgers WL, Steffens DC, Willis RJ, Wallace RB. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. 2007;29:125–132.

24. Tilz RR, Rillig A, Thum A-M, Arya A, Wohlmuth P, Metzner A, Mathew S, Yoshiga Y, Wissner E, Kuck K-H, Ouyang F. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. J Am Coll Cardiol. 2012;60:1921–1929.
25. Ouyang F, Tilz R, Chun J, Schmidt B, Wissner E, Zerm T, NEVEN K, Köktürk B, KONSTANTINIDOU M, Metzner A, Fuernkranz A, Kuck K-H. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. Circulation. 2010;122:2368–2377.
26. Botto GL, Padeletti L, Santini M, Capucci A, Gulizia M, Zolezzi F, Favale S, Molon G, Ricci R, Biffi M, Russo G, Vimercati M, Corbucci G, Boriani G. Presence and duration of atrial fibrillation detected by continuous monitoring: crucial implications for the risk of thromboembolic events. J Cardiovasc Electrophysiol. 2009;20:241–248.
27. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH, ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012;366:120–129.
28. Calkins H, Kuck K-H, Cappato R, Brugada J, Camm AJ, Chen S-A, Crijns HJG, Damiano RJ, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jaïs P, Kalman J, Keane D, Kim Y-H, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Heart Rhythm. 2012. p. 632–696.e21.
29. Pappone C, Rosanio S, Augello G, Gallus G, Vicedomini G, Mazzone P, Gulletta S, Gugliotta F, Pappone A, Santinelli V, Tortoriello V, Sala S, Zangrillo A, Crescenzi G, Benussi S, Alfieri O. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. J Am Coll Cardiol. 2003;42:185–197.
30. Oral H, Chugh A, Ozaydin M, Good E, Fortino J, Sankaran S, Reich S, Igic P, Elmouchi D, Tschopp D, Wimmer A, Dey S, Crawford T, Pelosi F, Jongnarangsin K, Bogun F, Morady F. Risk of thromboembolic events after percutaneous left atrial radiofrequency ablation of atrial fibrillation. Circulation. 2006;114:759–765.
31. Scherr D, Sharma K, Dalal D, Spragg D, Chilukuri K, Cheng A, Dong J, Henrikson CA, Nazarian S, Berger RD, Calkins H, Marine JE. Incidence and predictors of periprocedural cerebrovascular accident in patients undergoing catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2009;20:1357–1363.
32. Wissner E, Metzner A, Neuzil P, Petru J, Skoda J, Sediva L, Kivelitz D, Wohlmuth P, Weichet J, Schoonderwoerd B, Rausch P, Bardyszewski A, TILZ RR, Ouyang F, Reddy VY, Kuck K-H. Asymptomatic brain lesions following laserballoon-based pulmonary vein isolation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2013.
33. Schmidt B, Gunawardene M, Krieg D, Bordignon S, Fürnkranz A, Kulikoglu M, Herrmann W, Chun KRJ. A prospective randomized single-center study on the risk of asymptomatic cerebral lesions comparing irrigated radiofrequency current ablation with the cryoballoon and the laser balloon. J Cardiovasc Electrophysiol. 2013;24:869–874.
34. Sparks PB, Jayaprakash S, Vohra JK, Mond HG, Yapanis AG, Grigg LE, Kalman JM. Left atrial 'stunning' following radiofrequency catheter ablation of chronic atrial flutter. J Am Coll Cardiol. 1998;32:468–475.
35. Gaïta F, Caponi D, Pianelli M, Scaglione M, Toso E, Cesarani F, Boffano C, Gandini G, Valentini MC, De Ponti R, Halimi F, Leclercq JF. Radiofrequency catheter ablation of atrial fibrillation: a cause of silent thromboembolism? Magnetic resonance imaging assessment of cerebral thromboembolism in patients undergoing ablation of atrial fibrillation. Circulation. 2010;122:1667–1673.
36. Herrera Siklódy C, Deneke T, Hocini M, Lehrmann H, Shin D-I, Miyazaki S, Henschke S, Fluegel P, Schiebeling-Römer J, Bansmann PM, Bourdias T, Dousset V, Haissaguerre M, Arentz T. Incidence of asymptomatic intracranial embolic events after pulmonary vein isolation: comparison of different atrial fibrillation ablation technologies in a multicenter study. J Am Coll Cardiol. 2011;58:681–688.
37. Haeusler KG, Koch L, Herm J, Kopp UA, Heuschmann PU, Endres M, Schultheiss H-P, Schirdewan A, Fiebach JB. 3 Tesla MRI-detected brain lesions after pulmonary vein isolation for atrial fibrillation: results of the MACPAF study. J Cardiovasc Electrophysiol. 2013;24:14–21.
38. Schwarz N, Kuniss M, Nedelmann M, Kaps M, Bachmann G, Neumann T, Pitschner H-F, Gerriets T. Neuropsychological decline after catheter ablation of atrial fibrillation. Heart Rhythm. 2010;7:1761–1767.
39. Herm J, Fiebach JB, Koch L, Kopp UA, Kunze C, Wollboldt C, Brunecker P, Schultheiss H-P, Schirdewan A, Endres M, Haeusler KG. Neuropsychological Effects of MRI-Detected Brain Lesions after Left Atrial Catheter Ablation for Atrial Fibrillation: Long Term Results of the MACPAF Study. Circ Arrhythm Electrophysiol. 2013.
40. Bunch TJ, Crandall BG, Weiss JP, May HT, Bair TL, Osborn JS, Anderson JL, Muhlestein JB, Horne BD, Lappe DL, Day JD. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. J Cardiovasc Electrophysiol. 2011;22:839–845.
41. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD, Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002;347:1825–1833.
42. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, Dubuc M, Reddy V, Nelson L, Holcomb RG, Lehmann JW, RUSKIN JN, STOP AF Cryoablation Investigators. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. J Am Coll Cardiol. 2013;61:1713–1723.
43. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FWA, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–992.
44. Hohnloser SH, Shestakovska O, Eikelboom J, Franzosi MG, Tan RS, Zhu J, Yusuf S, Connolly SJ. The effects of apixaban on hospitalizations in patients with different types of atrial fibrillation: insights from the AVERROES trial. Eur Heart J. 2013;34:2752–2759.
45. Al-Khatib SM, Thomas L, Wallentin L, Lopes RD, Gersh B, Garcia D, Ezekowitz J, Alings M, Yang H, Alexander JH, Flaker G, Hanna M, Granger CB. Outcomes

of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial. Eur Heart J. 2013;34:2464–2471.
46. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285:2864–2870.
47. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. 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;137:263–272.
48. Coppens M, Eikelboom JW, Hart RG, Yusuf S, Lip GYH, Dorian P, Shestakovska O, Connolly SJ. The CHA2DS2-VASc score identifies those patients with atrial fibrillation and a CHADS2 score of 1 who are unlikely to benefit from oral anticoagulant therapy. Eur Heart J. 2013;34:170–176.
49. Mason PK, Lake DE, DiMarco JP, Ferguson JD, Mangrum JM, Bilchick K, Moorman LP, Moorman JR. Impact of the CHA2DS2-VASc score on anticoagulation recommendations for atrial fibrillation. Am J Med. 2012;125:603.e1–.e6.
50. Taillandier S, Olesen JB, Clémenty N, Lagrenade I, Babuty D, Lip GYH, Fauchier L. Prognosis in patients with atrial fibrillation and CHA2DS2-VASc Score = 0 in a community-based cohort study. J Cardiovasc Electrophysiol. 2012;23:708–713.
51. Abraham JM, Connolly SJ. Atrial fibrillation in heart failure: stroke risk stratification and anticoagulation. Heart Fail Rev. 2014;19:305–313.
52. Huxley RR, Filion KB, Konety S, Alonso A. Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. Am J Cardiol. 2011;108:56–62.
53. Nichols GA, Reinier K, Chugh SS. Independent contribution of diabetes to increased prevalence and incidence of atrial fibrillation. Diabetes Care. 2009;32:1851–1856.
54. Carlsson J, Miketic S, Windeler J, Cuneo A, Haun S, Micus S, Walter S, Tebbe U, STAF Investigators. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. J Am Coll Cardiol. 2003;41:1690–1696.
55. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJM, Tijssen JGP, Crijns HJGM, Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med. 2002;347:1834–1840.
56. Tsadok MA, Jackevicius CA, Essebag V, Eisenberg MJ, Rahme E, Humphries KH, Tu JV, Behlouli H, Pilote L. Rhythm versus rate control therapy and subsequent stroke or transient ischemic attack in patients with atrial fibrillation. Circulation. 2012;126:2680–2687.
57. Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, Paglino G, Mazzone P, Sora N, Greiss I, Santagostino A, LiVolsi L, Pappone N, Radinovic A, Manguso F, Santinelli V. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. J Am Coll Cardiol. 2006;48:2340–2347.
58. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert R, Brandes A, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R, Raviele A, Themistoclakis S, Rossillo A, Bonso A, Natale A. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. JAMA. 2005;293:2634–2640.
59. 59. Jaïs P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, Hocini M, Extramiana F, Sacher F, Bordachar P, Klein G, Weerasooriya R, Clementy J, Haissaguerre M. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. Circulation. 2008;118:2498–2505.
60. Cleland JGF, Coletta AP, Buga L, Ahmed D, Clark AL. Clinical trials update from the American College of Cardiology meeting 2010: DOSE, ASPIRE, CONNECT, STICH, STOP-AF, CABANA, RACE II, EVEREST II, ACCORD, and NAVIGATOR. Eur J Heart Fail. 2010;12:623–629.
61. Hoyt H, Bhonsale A, Chilukuri K, Alhumaid F, Needleman M, Edwards D, Govil A, Nazarian S, Cheng A, Henrikson CA, Sinha S, Marine JE, Berger R, Calkins H, Spragg DD. Complications arising from catheter ablation of atrial fibrillation: temporal trends and predictors. Heart Rhythm. 2011;8:1869–1874.
62. Lip GYH, Andreotti F, Fauchier L, Huber K, Hylek E, Knight E, Lane DA, Levi M, Marin F, Palareti G, Kirchhof P, Document Reviewers, Collet J-P, Rubboli A, Poli D, Camm J. Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis. Europace. 2011. p. 723–746.
63. Majeed A, Eelde A, Agren A, Schulman S, Holmström M. Thromboembolic safety and efficacy of prothrombin complex concentrates in the emergency reversal of warfarin coagulopathy. Thromb Res. 2012;129:146–151.
64. 64. Wazni OM, Rossillo A, Marrouche NF, Saad EB, Martin DO, Bhargava M, Bash D, Beheiry S, Wexman M, Potenza D, Pisano E, Fanelli R, Bonso A, Themistoclakis S, Erciyes D, Saliba WI, Schweikert RA, Brandes A, Raviele A, Natale A. Embolic events and char formation during pulmonary vein isolation in patients with atrial fibrillation: impact of different anticoagulation regimens and importance of intracardiac echo imaging. J Cardiovasc Electrophysiol. 2005;16:576–581.
65. Maleki K, Mohammadi R, Hart D, Cotiga D, Farhat N, Steinberg JS. Intracardiac ultrasound detection of thrombus on transseptal sheath: incidence, treatment, and prevention. J Cardiovasc Electrophysiol. 2005;16:561–565.
66. Shah D. Filamentous thrombi during left-sided sheath-assisted catheter ablations. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2010;12:1657–1658.
67. Asbach S, Biermann J, Bode C, Faber TS. Early Heparin Administration Reduces Risk for Left Atrial Thrombus Formation during Atrial Fibrillation Ablation Procedures. Cardiol Res Pract. 2011;2011:615087.
68. Bruce CJ, Friedman PA, Narayan O, Munger TM, Hammill SC, Packer DL, Asirvatham SJ. Early heparinization decreases the incidence of left atrial thrombi detected by intracardiac echocardiography during radiofrequency ablation for atrial fibrillation. J Interv Card Electrophysiol. 2008;22:211–219.
69. Ren J-F, Marchlinski FE, callans DJ, Gerstenfeld EP, Dixit S, Lin D, Nayak HM, Hsia HH. Increased intensity of anticoagulation may reduce risk of thrombus during atrial fibrillation ablation procedures in patients with spontaneous echo contrast. J Cardiovasc Electrophysiol. 2005;16:474–477.
70. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. Circulation. 2011;123:417–424.
71. Reddy VY, Möbius-Winkler S, Miller MA, Neuzil P, Schuler G, Wiebe J, Sick P, Sievert H. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). J Am Coll Cardiol. 2013;61:2551–2556.
72. Alli O, Doshi S, Kar S, Reddy V, Sievert H, Mullin C, Swarup V, Whisenant B, Holmes D. Quality of life assessment in the randomized PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) trial of patients at risk for stroke with nonvalvular atrial fibrillation. J Am Coll Cardiol. 2013;61:1790–1798.
73. Dublin S, Anderson ML, Haneuse SJ, Heckbert SR, Crane PK, Breitner JCS, McCormick W, Bowen JD, Teri L, McCurry SM, Larson EB. Atrial fibrillation and risk of dementia: a prospective cohort study. J Am Geriatr Soc. 2011;59:1369–1375.

74. Sauren LD, van Belle Y, DE Roy L, Pison L, LA Meir M, van der Veen FH, Crijns HJ, Jordaens L, Mess WH, Maessen JG. Transcranial measurement of cerebral microembolic signals during endocardial pulmonary vein isolation: comparison of three different ablation techniques. J Cardiovasc Electrophysiol. 2009;20:1102–1107.