Atrial fibrillation and Cognitive impairment

ד"ר רני ברנע

נוירולוגיה ווסקולרית

מרכז רפואי "רבין" - קמפוס בילינסון

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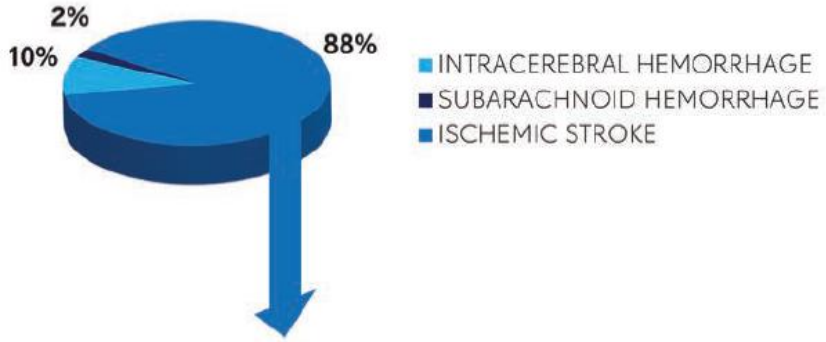
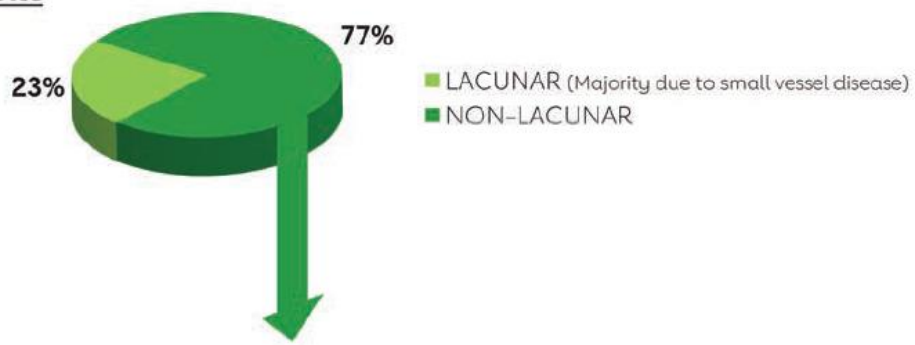
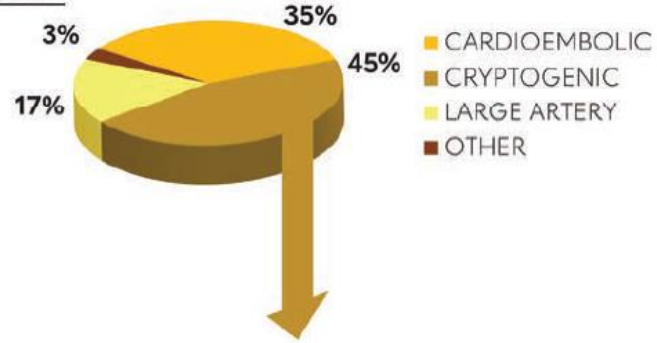
Stroke



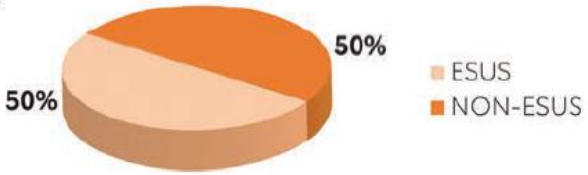
Ischemic Stroke

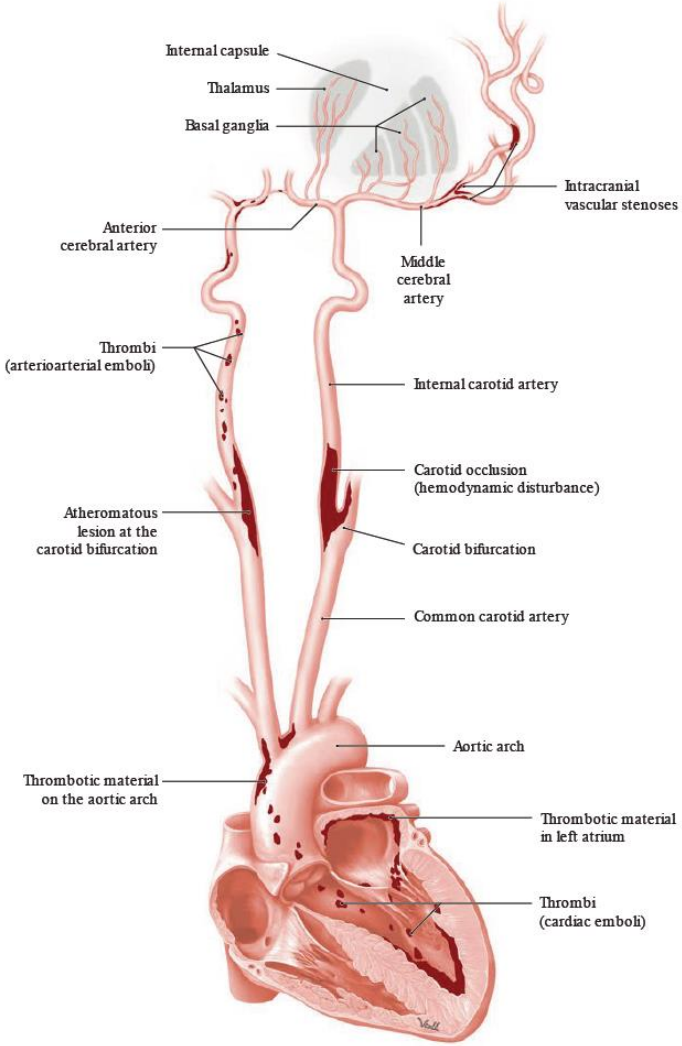


Non-lacunar Stroke

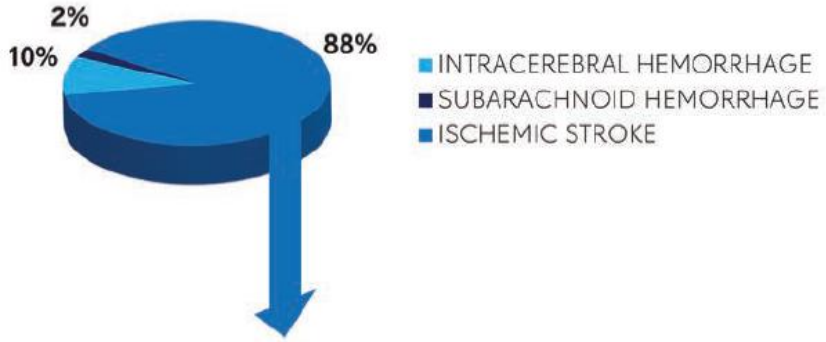


Cryptogenic Stroke

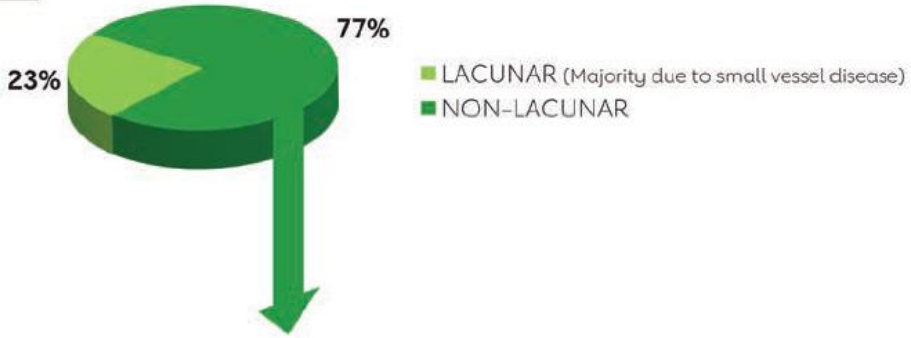




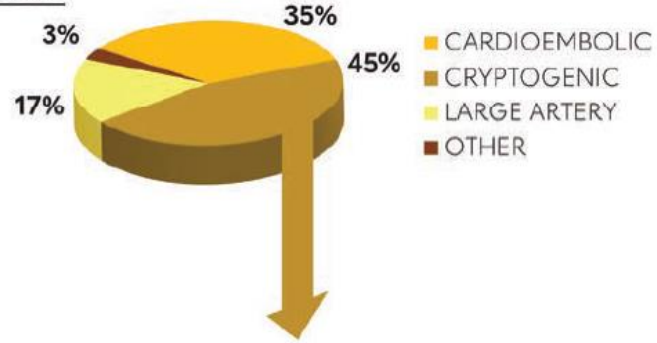
Stroke



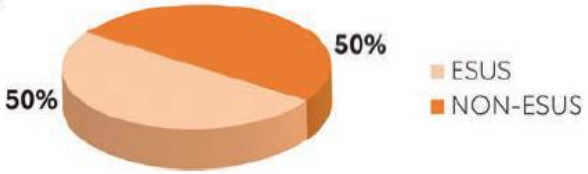
Ischemic Stroke

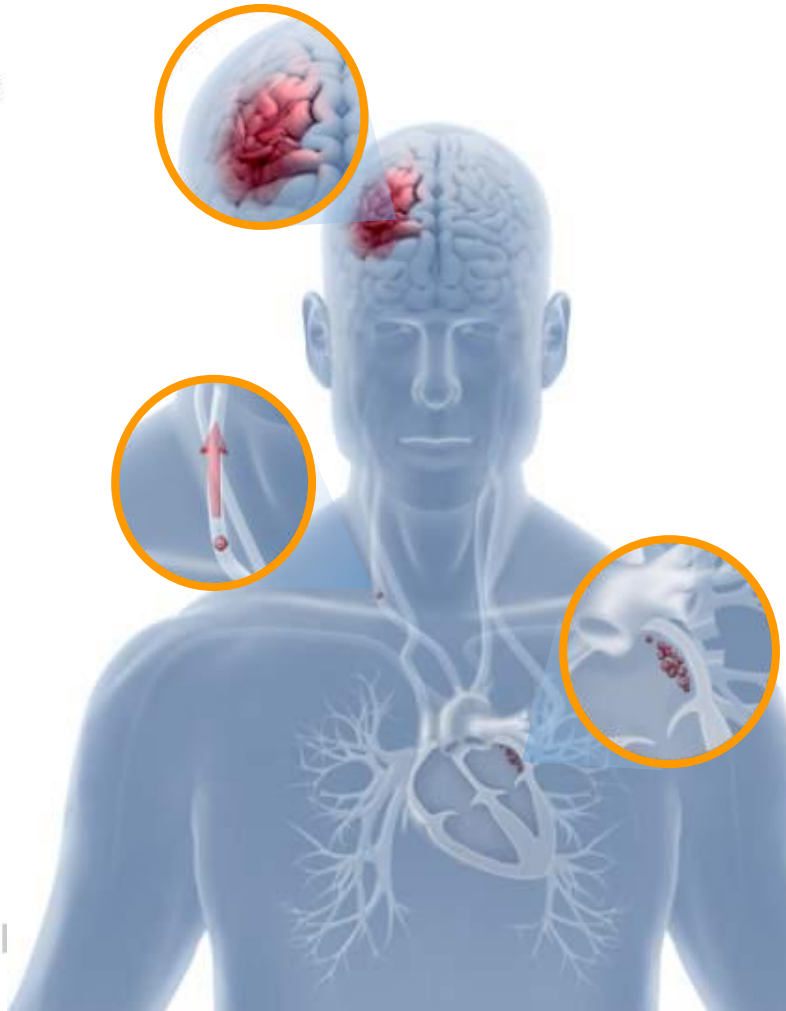


Non-lacunar Stroke



Cryptogenic Stroke





REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Dementia and Atrial Fibrillation: Pathophysiological Mechanisms and Therapeutic Implications

Romain Chopard, MD,[a,b] Gregory Piazza, MD,[a,b] Seth Alan Gale, MD,[c] Umberto Campia, MD,[a,b] Ida Ehlers Albertsen, MD,[a,b,d,e] Jisoo Kim, MD,[a,f] Samuel Z. Goldhaber, MD[a,b]

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ABSTRACT

Atrial fibrillation increases the risk of stroke by a factor of four- to fivefold, and dementia is a common consequence of stroke. However, atrial fibrillation has been associated with cognitive impairment and dementia, even in patients without prior overt stroke. Nonischemic mechanisms include cerebral hypoperfusion, vascular inflammation, brain atrophy, genetic factors, and shared risk factors such as age or hypertension. Critical appraisal of studies evaluating the association between atrial fibrillation and dementia in stroke-free patients reveals that several suffer from methodological issues, such as not including silent stroke or anticoagulation therapy in multivariate analyses. Some studies show a close relationship between atrial fibrillation and dementia due to silent stroke, in the absence of overt stroke. Evidence is accumulating that anticoagulation may be effective to decrease the risk of dementia in atrial fibrillation patients. Overall, the pathogenesis linking atrial fibrillation to dementia is likely multifactorial. Cerebral infarctions, including silent stroke, play a central role. These findings underscore the importance of stroke prevention measures in atrial fibrillation patients.

 • The American Journal of Medicine (2018) 131:1408–1417

KEYWORDS: Anticoagulation; Atrial fibrillation; Dementia; Stroke

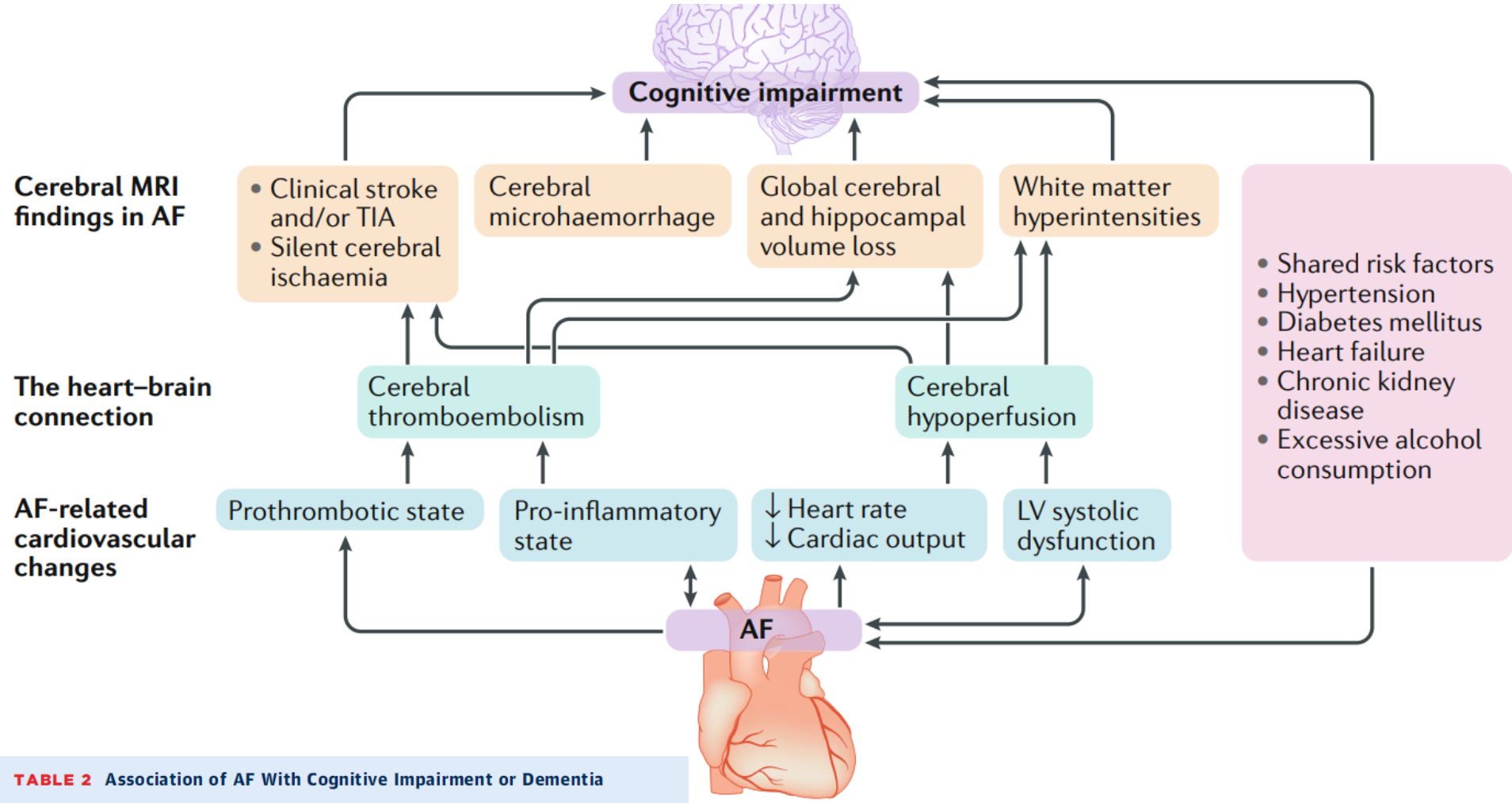

TABLE 2 Association of AF With Cognitive Impairment or Dementia

	Studies (n)	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

Atrial fibrillation and cognitive decline

A longitudinal cohort study

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ABSTRACT

Objective: We sought to determine whether in the absence of clinical stroke, people with atrial fibrillation experience faster cognitive decline than people without atrial fibrillation.

Methods: We conducted a longitudinal analysis in the Cardiovascular Health Study, a community-based study of 5,888 men and women aged 65 years and older, enrolled in 1989/1990 or 1992/1993. Participants did not have atrial fibrillation or a history of stroke at baseline. Participants were censored when they experienced incident clinical stroke. Incident atrial fibrillation was identified by hospital discharge diagnosis codes and annual study ECGs. The main outcome was rate of decline in mean scores on the 100-point Modified Mini-Mental State Examination (3MSE), administered annually up to 9 times.

Results: Analyses included 5,150 participants, of whom 552 (10.7%) developed incident atrial fibrillation during a mean of 7 years of follow-up. Mean 3MSE scores declined faster after incident atrial fibrillation compared with no prior atrial fibrillation. For example, the predicted 5-year decline in mean 3MSE score from age 80 to age 85 was −6.4 points (95% confidence interval [CI]: −7.0, −5.9) for participants without a history of atrial fibrillation, but was −10.3 points (95% CI: −11.8, −8.9) for participants experiencing incident atrial fibrillation at age 80, a 5-year difference of −3.9 points (95% CI: −5.3, −2.5).

Conclusions: In the absence of clinical stroke, people with incident atrial fibrillation are likely to reach thresholds of cognitive impairment or dementia at earlier ages than people with no history of atrial fibrillation. ***Neurology*® 2013;81:119–125**

Atrial fibrillation and the risk of incident dementia: A meta-analysis

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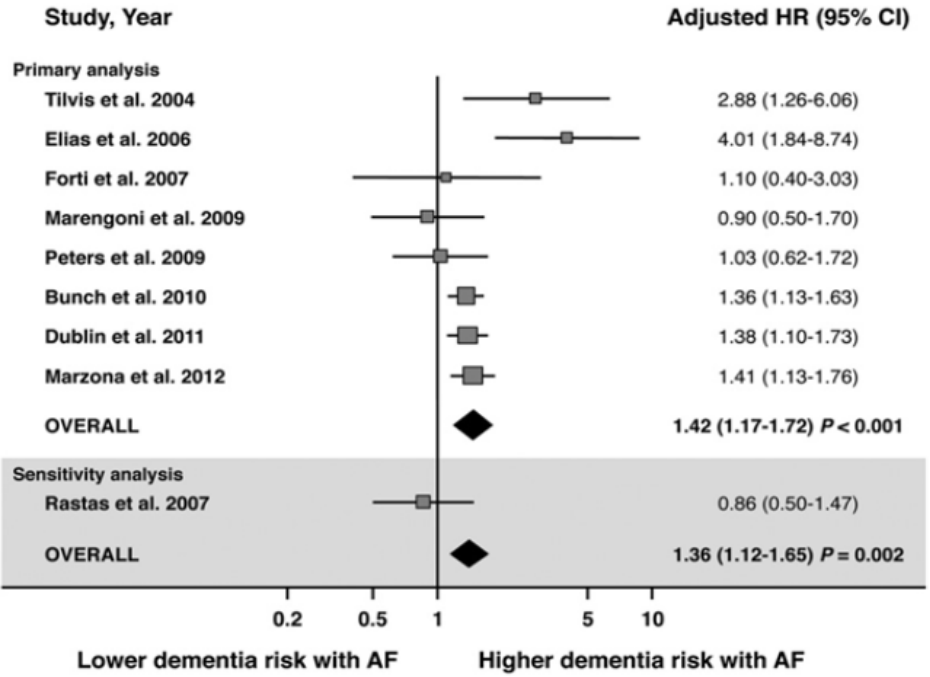

Archives of Gerontology and Geriatrics
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Atrial fibrillation and risk of dementia in non-demented elderly subjects with and without mild cognitive impairment (MCI)

P. Forti, F. Maioli, N. Pisacane, E. Rietti, F. Montesi, G. Ravaglia

https://doi.org/10.1016/j.archger.2007.01.023

Abstract

MCI is regarded as a precursor of dementia, but not all patients with MCI actually develop dementia. As Alzheimer and vascular dementia (AD and VD, respectively) are thought to share many common etiopathogenetic mechanisms, we investigated whether the vascular risk factor atrial fibrillation affect the risk of conversion to dementia for different MCI subtypes diagnosed according to international criteria. One-hundred-eigthy elderly outpatients with MCI and 431 elderly outpatients with a normal cognition were followed-up for a mean of 3 and 4 years, respectively. The risk of conversion to dementia associated with atrial fibrillation was studied in both samples using a Cox proportional-hazards model adjusted for sociodemographic and medical variables. Overall conversion rate to dementia was 10.5 (8.0–13.8) per 100 person-years in the MCI group and 2.2 (1.5–3.1) per 100 person-years in the normal cognition group. Atrial fibrillation was significantly associated with conversion to dementia (hazard ratio = HR = 4.63, 95% confidence interval = CI = 1.72–12.46) in the MCI group, but not in the cognitively normal group (HR = 1.10, 95% CI = 0.40–3.03). Current diagnostic criteria for MCI subtypes define heterogeneous populations, but atrial fibrillation can be useful in identifying people with increased risk of conversion to dementia.

JAMA Neurol. 2015;72(11):1288-1294. doi:10.1001/jamaneurol.2015.2161
Published online September 21, 2015.

Original Investigation

Association Between Atrial Fibrillation and Dementia in the General Population

Renée F. A. G. de Bruijn, MD; Jan Heeringa, MD, PhD; Frank J. Wolters, MD; Oscar H. Franco, MD, PhD; Bruno H. C. Stricker, MD, PhD; Albert Hofman, MD, PhD; Peter J. Koudstaal, MD, PhD; M. Arfan Ikram, MD, PhD

Table 3. Atrial Fibrillation and the Risk of Dementia, Stratified for Age at Median[a]

	Dementia, HR (95% CI)			
Characteristic	No./Total No. (%)[b]	Age, <67 y	No./Total No. (%)[b]	Age, ≥67 y
Atrial fibrillation				
Prevalent	213/3096 (6.9)	1.91 (0.85-4.26)	781/3418 (22.8)	1.28 (0.97-1.70)
Incident	206/3049 (6.8)	1.81 (1.11-2.94)	726/3145 (23.1)	1.12 (0.85-1.46)

Abbreviations: HR, hazard ratio.

[a] Model was adjusted for age, sex, diabetes mellitus, smoking, total cholesterol and high-density lipoprotein cholesterol levels, lipid-lowering medication, systolic and diastolic blood pressure, blood pressure–lowering medication, body mass index, educational level, ever use of oral anticoagulant medication, coronary heart disease, heart failure, and apolipoprotein E ε4 carrier status.

[b] Number of cases/number of participants.

JAMA Neurol. 2015;72(11):1288-1294. doi:10.1001/jamaneurol.2015.2161
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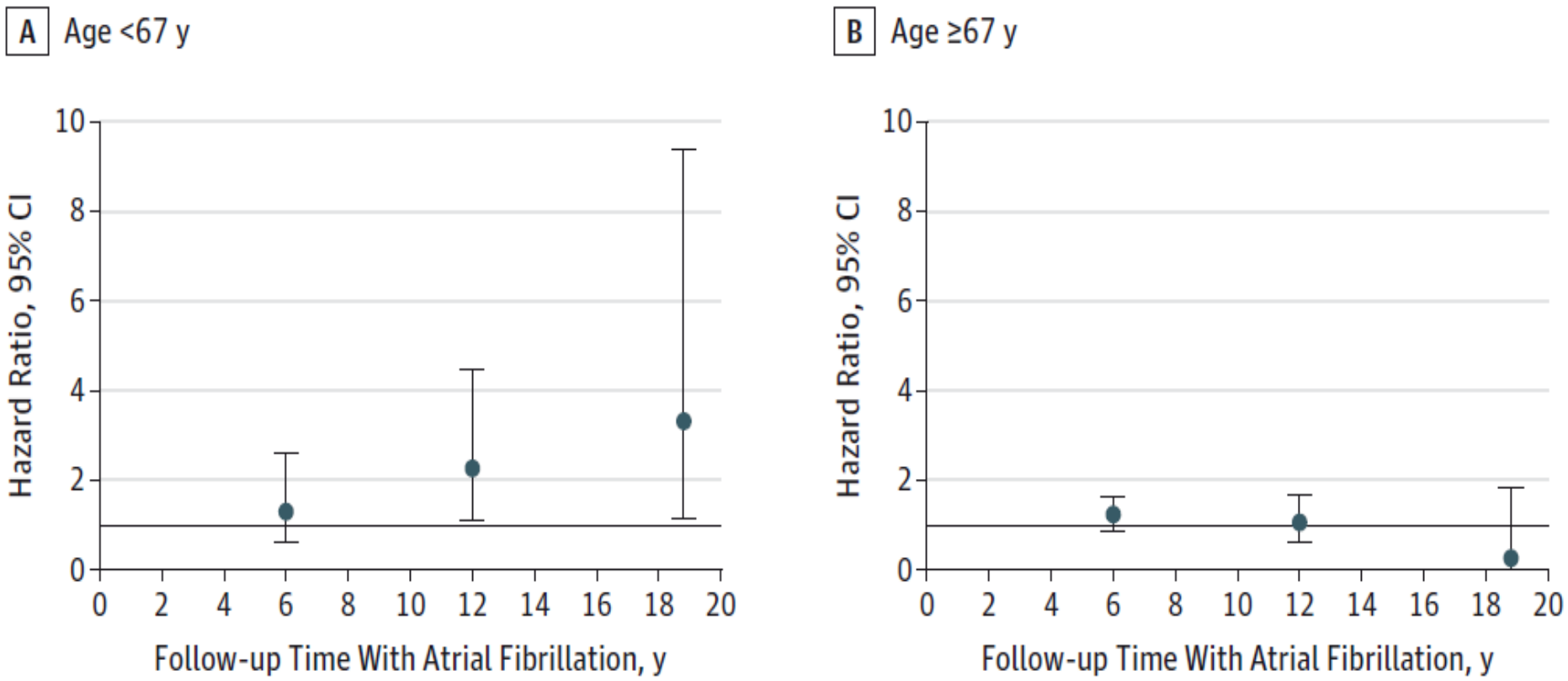

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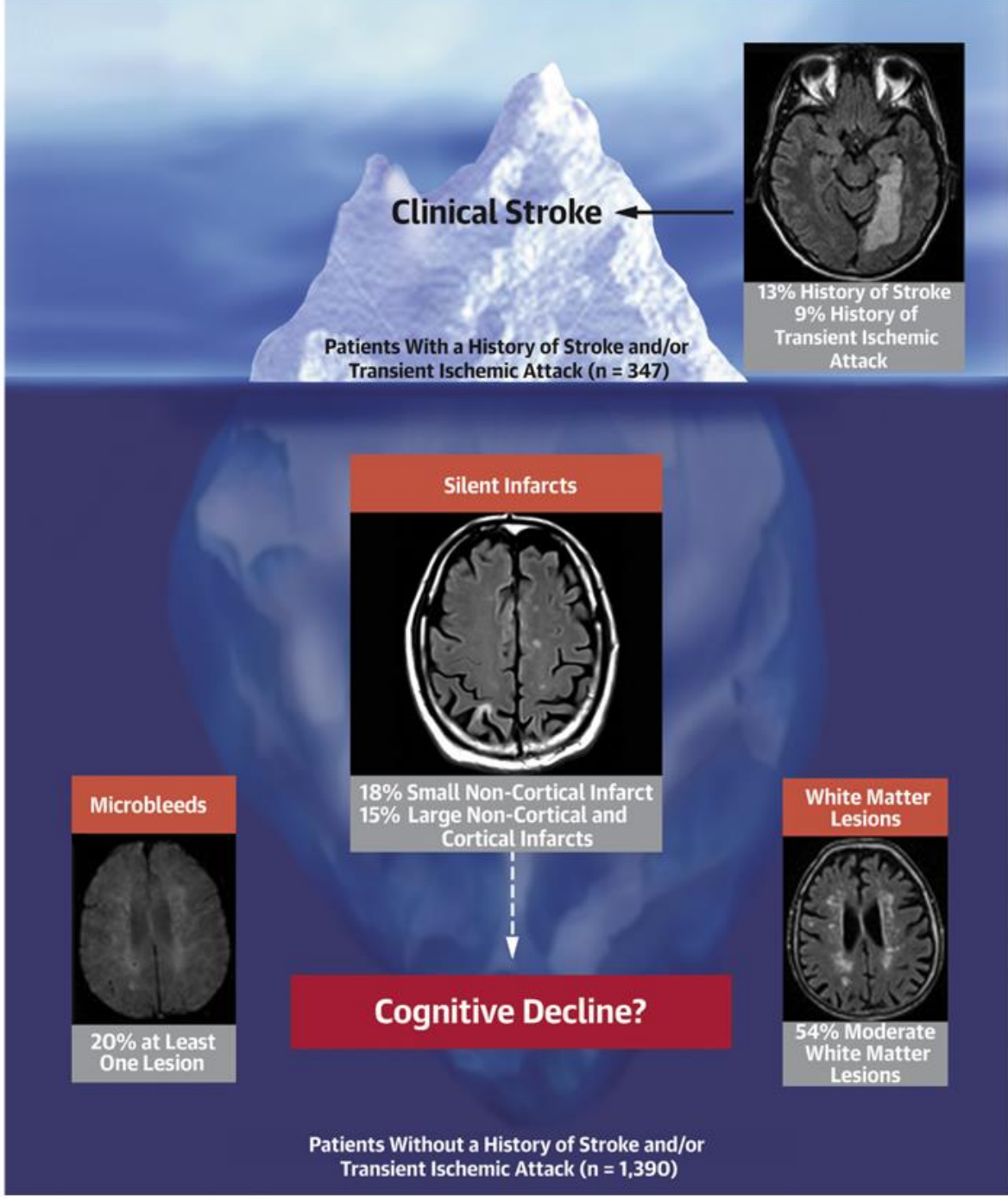
MARCH 12, 2019:989–99

Relationships of Overt and Silent Brain Lesions With Cognitive Function in Patients With Atrial Fibrillation

David Conen, MD, MPH,[a,b,c] Nicolas Rodondi, MD, MAS,[d,e] Andreas Müller, MD,[f] Juerg H. Beer, MD,[g] Peter Ammann, MD,[h] Giorgio Moschovitis, MD,[i] Angelo Auricchio, MD, PhD,[j] Daniel Hayoz, MD,[k] Richard Kobza, MD,[l] Dipen Shah, MD,[m] Jan Novak, MD,[n] Jürg Schläpfer, MD,[o] Marcello Di Valentino, MD,[p] Stefanie Aeschbacher, PhD,[a] Steffen Blum, MD,[a,b] Pascal Meyre, MD,[a,b] Christian Sticherling, MD,[a,b] Leo H. Bonati, MD,[q] Georg Ehret, MD,[m] Elisavet Moutzouri, MD,[d,e] Urs Fischer, MD, MS,[r] Andreas U. Monsch, PhD,[s] Christoph Stippich, MD,[t] Jens Wuerfel, MD,[u] Tim Sinnecker, MD,[q,u] Michael Coslovsky, PhD,[b] Matthias Schwenkglenks, PhD, MPH,[v] Michael Kühne, MD,[a,b,*] Stefan Osswald, MD,[a,b,*] for the Swiss-AF Study Investigators†

TABLE 2 Prevalence of Vascular Brain Lesions Detected on Brain Magnetic Resonance Imaging

	Prevalence	Volume, mm³	Number
All patients (N = 1,737)			
Small noncortical infarcts	368 (21)	63 [30–163]	1 [1–3]
Large noncortical or cortical infarcts	387 (22)	1,623 [255–7,314]	1 [1–2]
Microbleeds	372 (22)	-	1 [1–2]
White matter lesions	1,715 (99)	3,918 [1,439–9783]	23 [11–41]
Fazekas scale ≥2	928 (54)		
Patients without a history of stroke or TIA (n = 1,390)			
Small noncortical infarcts	245 (18)	57 [30–141]	2 [1–3]
Large noncortical or cortical infarcts	201 (15)	525 [162–3,396]	1 [1–2]
Microbleeds	272 (20)	-	1 [1–2]
White matter lesions	1,372 (99)	3,512 [1,323–8,669]	21 [10–40]
Fazekas scale ≥2	694 (50)		



Conen, D. et al. J Am Coll Cardiol. 2019;73(9):989–99.

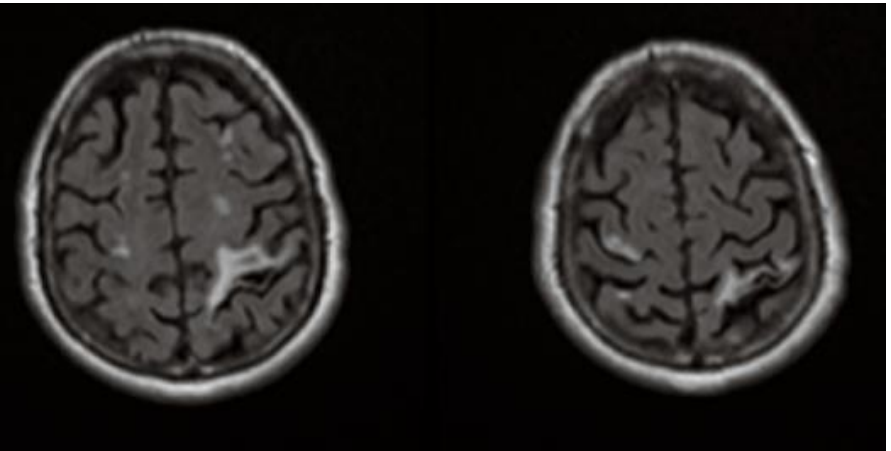
REVIEW | 4 November 2014 | Annals of Internal Medicine | Volume 161 • Number 9 Annals of Internal Medicine

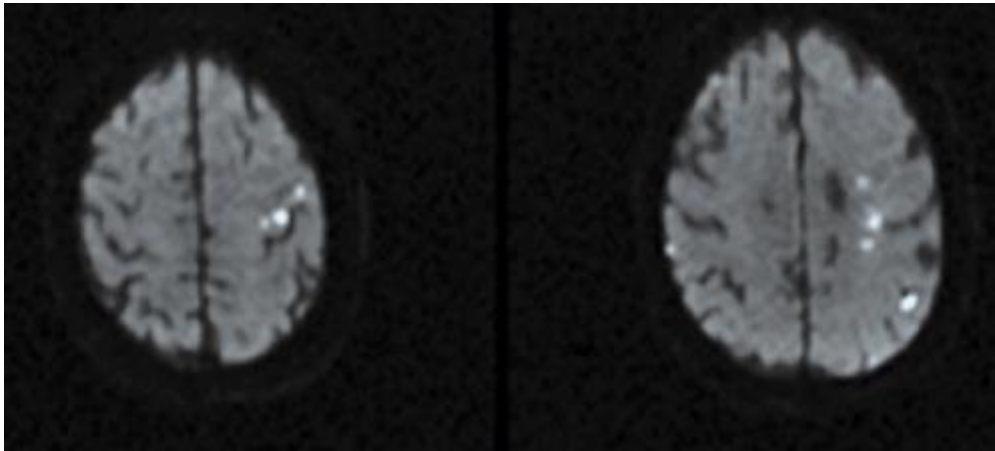
Association Between Atrial Fibrillation and Silent Cerebral Infarctions

A Systematic Review and Meta-analysis

Shadi Kalantarian, MD, MPH; Hakan Ay, MD; Randy L. Gollub, MD, PhD; Hang Lee, PhD; Kallirroi Retzepi, MSc; Moussa Mansour, MD; and Jeremy N. Ruskin, MD

Study, Year (Reference)	Diagnosis Method	Participants, *n*	Events/ Patients With AF, *n/N*	Events/ Patients Without AF, *n/N*	Odds Ratio (95% CI)	Risk of Confounding Bias*
MRI						
Vermeer et al, 2003 (23)	MRI 1.5T	1015	8/32	209/983	1.00 (0.40–2.30)	Moderate
Das et al, 2008 (11)	MRI 1T	2040	11/45	209/1995	2.16 (1.07–4.40)	Moderate
Kim et al, 2011 (13)	MRI 1.5T	406	3/12	61/394	1.34 (0.29–6.38)	Minimal
Kobayashi et al, 2012 (36)	MRI 1.5T	142	35/71	20/71	2.53 (1.21–5.30)†	Minimal
Marfella et al, 2013 (12)	MRI 1.5T	464	107/176	84/288	4.44 (2.42–8.16)	Minimal
Subtotal (I^2 = 39.25%; P = 0.089)					2.30 (1.44–3.68)	





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JACC REVIEW TOPIC OF THE WEEK

Atrial Fibrillation and Cognitive Function

JACC Review Topic of the Week

Hans-Christoph Diener, MD, PhD,[a] Robert G. Hart, MD,[b] Peter J. Koudstaal, MD,[c] Deirdre A. Lane, PhD,[d] Gregory Y.H. Lip, MD[d,e]

TABLE 3 Association of AF and Silent Cerebral Infarctions

	Studies (n)	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	0.29–0.51
Prevalence of silent cerebral infarction in AF patients, CT	6	0.22	0.12–0.32

MAYO CLINIC

ORIGINAL ARTICLE

Efficacy of Warfarin Anticoagulation and Incident Dementia in a Community-Based Cohort of Atrial Fibrillation

Malini Madhavan, MBBS; Tiffany Y. Hu, MD; Bernard J. Gersh, MB, ChB, DPhil; Veronique L. Roger, MD, MPH; Jill Killian, BS; Susan A. Weston, MS; Jonathan Graff-Radford, MD; Samuel J. Asirvatham, MD; and Alanna M. Chamberlain, PhD, MPH

TABLE 3. Associations Between Quartiles of Percentage of Time in Therapeutic Range on Warfarin and Incident Dementia in Patients with Atrial Fibrillation[a]

	HR (95% CI)					
Model	No warfarin	Quartile 1 (0%-36.03%)	Quartile 2 (36.04%-59.50%)	Quartile 3 (59.51%-71.93%)	Quartile 4 (71.94%-100%)	*P* for trend
Unadjusted	1 (referent)	1.12 (0.82-1.53)	1.07 (0.80-1.42)	0.74 (0.55-1.00)	0.34 (0.23-0.51)	<.001
Age- and sex-adjusted	1 (referent)	1.00 (0.73-1.36)	0.99 (0.75-1.32)	0.60 (0.44-0.81)	0.30 (0.20-0.44)	<.001
Adjusted model 1[b]	1 (referent)	0.95 (0.69-1.31)	0.95 (0.71-1.27)	0.54 (0.40-0.73)	0.29 (0.20-0.42)	<.001
Adjusted model 2[c]	1 (referent)	0.94 (0.67-1.31)	0.93 (0.69-1.25)	0.54 (0.39-0.73)	0.28 (0.19-0.42)	<.001

[a]HR = hazard ratio.
[b]Adjusted for age, sex, body mass index, history of smoking, hypertension, hyperlipidemia, diabetes, heart failure, ischemic stroke/transient ischemic attack, hemorrhagic stroke, myocardial infarction, peripheral vascular disease, aortic atherosclerotic disease, chronic pulmonary disease, malignancy, liver disease, and renal disease.
[c]Adjusted for all the variables in model 1 plus ischemic stroke/transient ischemic attack and hemorrhagic stroke modeled as time-dependent variables.

Abstract

Objective: To study the association between time in therapeutic range (TTR) during warfarin therapy and risk of dementia in a population-based cohort of incident atrial fibrillation (AF).

Patients and Methods: We conducted an observational population-based study of 2800 nondemented patients with incident AF from January 1, 2000, through December 31, 2010. The association of incident dementia with warfarin therapy and TTR was examined using Cox proportional hazards regression models.

Results: Mean patient age was 71.2 years; 53% were men (n=1495), and warfarin was prescribed to 50.5% (n=1414) within 90 days of AF diagnosis. Incident dementia diagnosis occurred in 357 patients (12.8%) over a mean ± SD follow-up of 5.0±3.7 years. After adjusting for confounders, warfarin therapy was associated with a reduced incidence of dementia (hazard ratio [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. A 10% increase in TTR with a 10% reduction in time spent in the subtherapeutic (HR, 0.71; 95% CI, 0.64-0.79) and supratherapeutic (HR, 0.67; 95% CI, 0.57-0.79) ranges were associated with decreased risk of dementia.

Conclusion: In the community, warfarin therapy for AF is associated with a 20% reduction in risk of dementia. Increasing TTR on warfarin is associated with reduced risk of dementia. The risk of dementia was reduced with a reduction in time spent in subtherapeutic and supratherapeutic international normalized ratio range. Effective anticoagulation may prevent cognitive impairment in patients with AF.

Thromboprophylaxis in atrial fibrillation and association with cognitive decline: systematic review

Age and Ageing 2016; **45:** 767–775
doi: 10.1093/ageing/afw104
Published electronically 30 June 2016

Peter Moffitt[1], Deirdre A. Lane [2], Helen Park[3], Janice O'Connell[4], Terence J. Quinn[5]

Abstract

Objective: atrial fibrillation (AF) is associated with dementia. If AF-related cognitive decline is driven by cerebral embolic events, thromboprophylaxis may impact on this. This systematic review assessed the association between cognitive impairment and AF thromboprophylaxis.

Methods: two independent reviewers searched CINAHL, EMBASE, MEDLINE, PsycINFO, Web of Science Core Collection and Cochrane Library from inception until 12 November 2014. Eligible studies compared AF thromboprophylaxis to control with an outcome measure of cognition or dementia. Where data allowed, meta-analyses describing between-group differences in cognitive test scores or rates of incident dementia were performed.

Results: nineteen studies were eligible. For two prospective studies (one randomised controlled trial, RCT) comparing anticoagulation against antiplatelet therapy, change in Mini-Mental Score Examination (MMSE) score from baseline to last follow-up (maximal duration: 5.9 years) suggested a difference favouring anticoagulation (mean difference: 0.90, 95% CI: 0.29–1.51), in keeping with a trend seen in the single RCT (mean difference MMSE: 0.80, 95% CI: −0.07 to 1.67). Pooled odds ratio (OR) suggested no association with incident dementia, comparing anticoagulant to antiplatelet therapy (two studies, OR: 1.23, 95% CI: 0.80–1.91) or no treatment (three studies, OR: 0.89, 95% CI: 0.47–1.69).

Conclusion: our analyses show no definitive evidence of cognitive benefit or harm from anticoagulation. We demonstrated a potential benefit of anticoagulation in comparison to antiplatelet over time. Larger scale studies with longer follow-up are needed to determine the true cognitive impact of AF thromboprophylaxis.

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

Victoria Jacobs, NP, Heidi T. May, PhD, Tami L. Bair, RN, Brian G. Crandall, MD, Michael J. Cutler, DO, PhD, John D. Day, MD, Charles Mallender, MD, Jeffrey S. Osborn, MD, Scott M. Stevens, MD, J. Peter Weiss, MD, Scott C. Woller, MD, and T. Jared Bunch, MD*

Direct oral anticoagulants (DOACs) have been used in clinical practice in the United States for the last 4 to 6 years. Although DOACs may be an attractive alternative to warfarin in many patients, long-term outcomes of use of these medications are unknown. We performed a propensity-matched analysis to report patient important outcomes of death, stroke/transient ischemic attack (TIA), bleeding, major bleeding, and dementia in patients taking a DOAC or warfarin. Patients receiving long-term anticoagulation from June 2010 to December 2014 for thromboembolism prevention with either warfarin or a DOAC were matched 1:1 by index date and propensity score. Multivariable Cox hazard regression was performed to determine the risk of death, stroke/TIA, major bleed, and dementia by the anticoagulant therapy received. A total of 5,254 patients were studied (2,627 per group). Average age was 72.4 ± 10.9 years, and 59.0% were men. Most patients were receiving long-term anticoagulation for AF management (warfarin: 96.5% vs DOAC: 92.7%, p <0.0001). Rivaroxaban (55.3%) was the most commonly used DOAC, followed by apixaban (22.5%) and dabigatran (22.2%). The use of DOACs compared with warfarin was associated with a reduced risk of long-term adverse outcomes: death (p = 0.09), stroke/TIA (p <0.0001), major bleed (p <0.0001), and bleed (p = 0.14). No significant outcome variance was noted in DOAC-type comparison. In the AF multivariable model patients taking DOAC were 43% less likely to develop stroke/TIA/dementia (hazard ratio 0.57 [CI 0.17, 1.97], p = 0.38) than those taking warfarin. Our community-based results suggest better long-term efficacy and safety of DOACs compared with warfarin. DOAC use was associated with a lower risk of cerebral ischemic events and new-onset dementia. **(Am J Cardiol 2016;118:210–214)**

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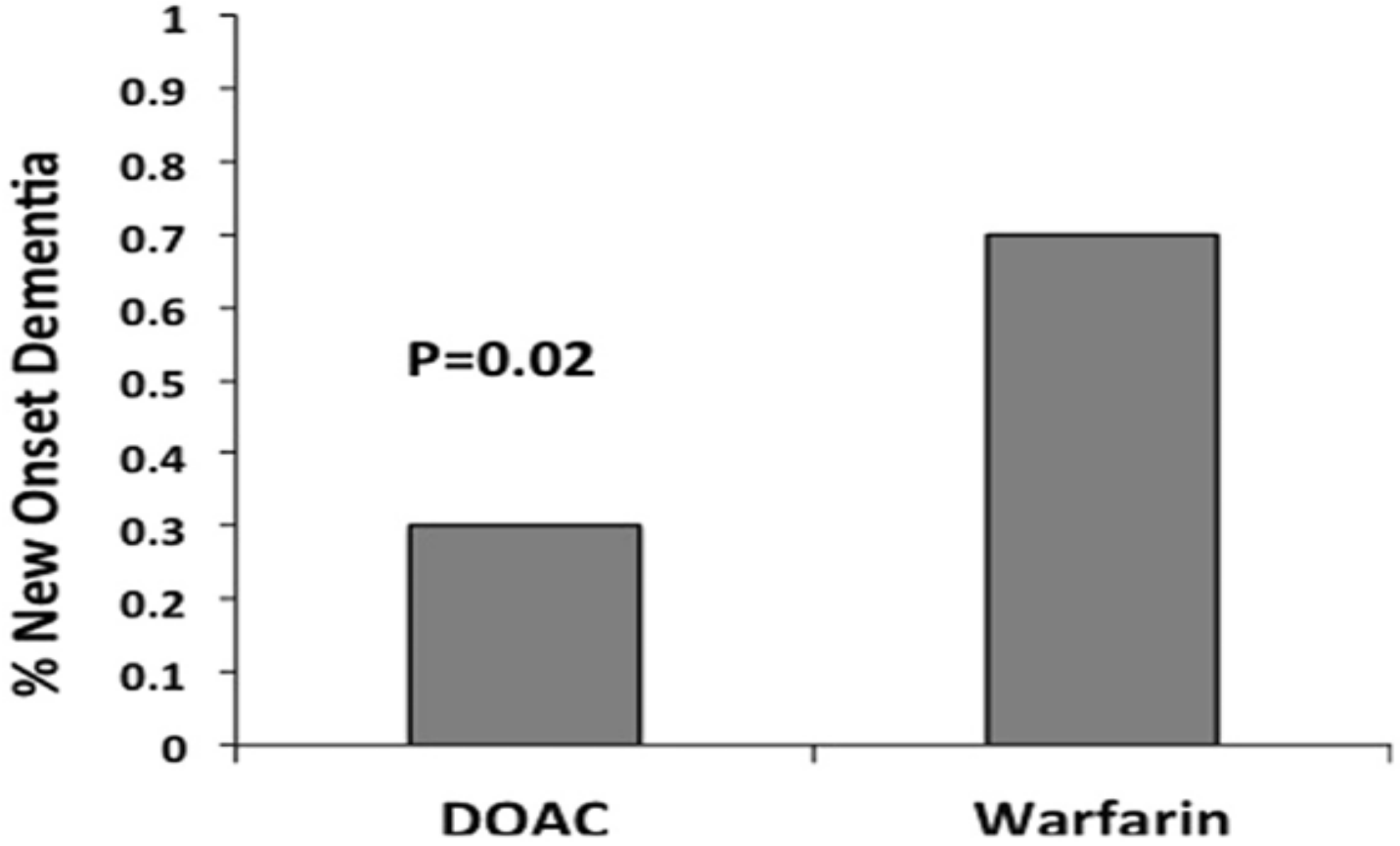

ORIGINAL RESEARCH

American Heart Association | American Stroke Association.

Association of Oral Anticoagulant Type With Risk of Dementia Among Patients With Nonvalvular Atrial Fibrillation

Nemin Chen, MPH; Pamela L. Lutsey, PhD; Richard F. MacLehose, PhD; J'Neka S. Claxton, MPH; Faye L. Norby, MPH, MS; Alanna M. Chamberlain, PhD; Lindsay G. S. Bengtson, PhD; Wesley T. O'Neal, MD, MPH; Lin Y. Chen, MD, MS; Alvaro Alonso, MD, PhD

***Background*—**Oral anticoagulants (OACs) in patients with atrial fibrillation (AF), in addition to reducing stroke risk, could also prevent adverse cognitive outcomes. The purpose of this study was to compare the risk of dementia incidence across patients with AF initiating different OACs.

***Methods and Results*—**We identified patients with nonvalvular AF initiating OACs in 2 US healthcare claim databases, MarketScan (2007–2015) and Optum Clinformatics (2009–2015). Dementia, comorbidities, and use of medications were defined on the basis of inpatient and outpatient claims. We performed head-to-head comparisons of warfarin, dabigatran, rivaroxaban, and apixaban in propensity score–matched cohorts. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia for each propensity score–matched cohort and meta-analyzed database-specific results. We analyzed 307 099 patients with AF from the MarketScan database and 161 346 from the Optum database, of which 6572 and 4391, respectively, had a diagnosis of incident dementia. The mean follow-up of each cohort ranged between 0.7 and 2.2 years. Patients initiating direct OACs experienced lower rates of dementia than those initiating warfarin (dabigatran: HR, 0.85; 95% CI, 0.71–1.01; rivaroxaban: HR, 0.85; 95% CI, 0.76–0.94; apixaban: HR, 0.80; 95% CI, 0.65–0.97). There were no differences in rates of dementia comparing direct OAC user groups (dabigatran versus rivaroxaban: HR, 1.02; 95% CI, 0.79–1.32; dabigatran versus apixaban: HR, 0.92; 95% CI, 0.63–1.36; apixaban versus rivaroxaban: HR, 1.01; 95% CI, 0.86–1.19).

***Conclusions*—**Patients with AF initiating direct OACs experienced lower rates of incident dementia than warfarin users. No obvious benefit was observed for any particular direct OAC in relation to dementia rates. **(*J Am Heart Assoc*. 2018;7:e009561. DOI: 10.1161/JAHA.118.009561.)**

Journal of the American Heart Association

J Am Heart Assoc. 2022;11:e023098. DOI: 10.1161/JAHA.121.023098

ORIGINAL RESEARCH

Oral Anticoagulant Treatment and the Risk of Dementia in Patients With Atrial Fibrillation: A Population-Based Cohort Study

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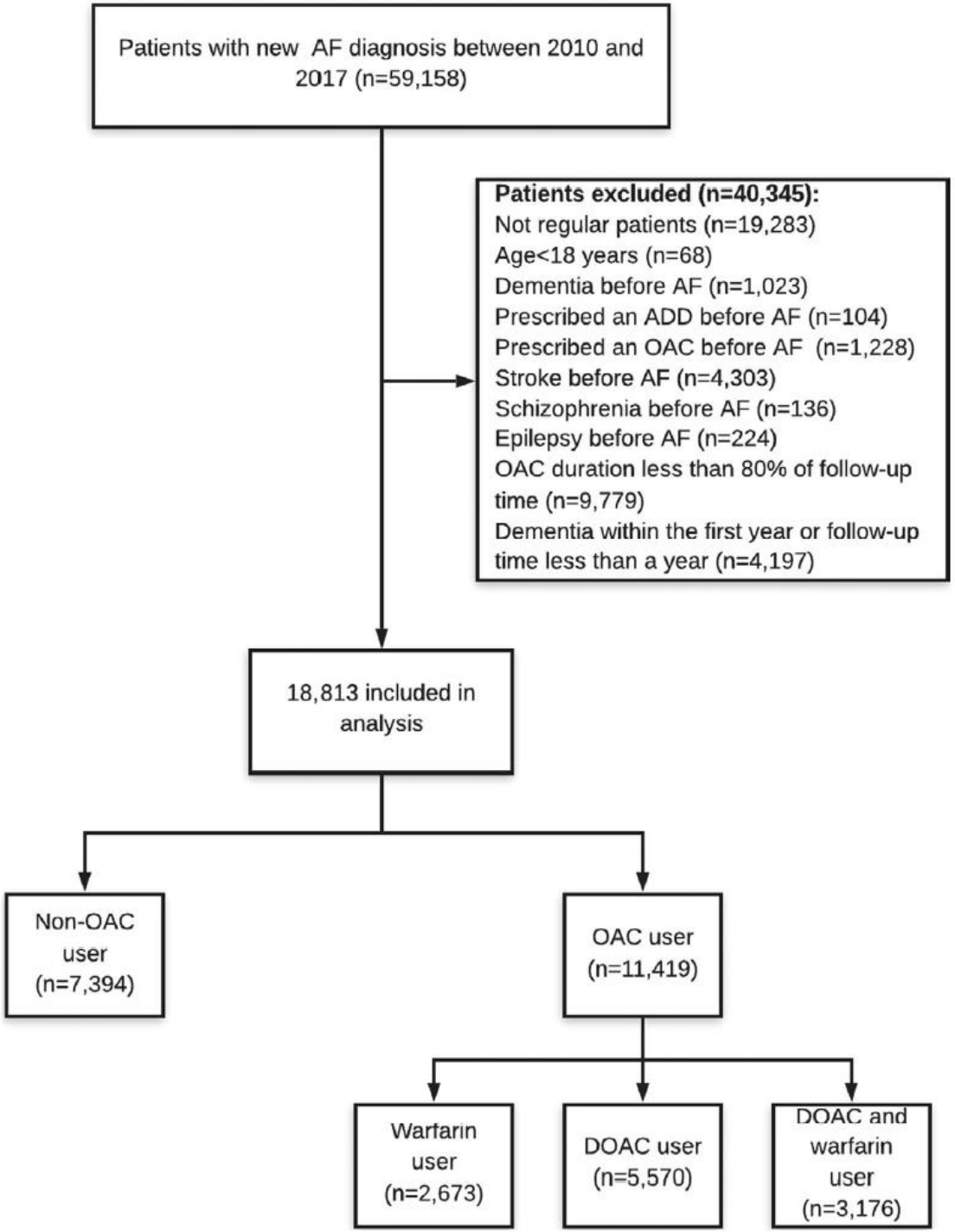
BACKGROUND: We compared the dementia incidence rate between users and nonusers of oral anticoagulants (OACs) in a large cohort of primary care patients with atrial fibrillation.

METHODS AND RESULTS: We performed a retrospective study using an Australia-wide primary care data set, MedicineInsight. Patients aged ≥18 years and newly diagnosed with atrial fibrillation between January 1, 2010, and December 31, 2017, and with no recorded history of dementia or stroke were included and followed until December 31, 2018. We applied a propensity score for 1:1 pair matching of baseline covariates and Cox regression for comparing the dementia incidence rates for OAC users and nonusers. Data were analyzed for 18 813 patients with atrial fibrillation (aged 71.9±12.6 years, 47.1% women); 11 419 had a recorded OAC prescription for at least 80% of their follow-up time. During the mean follow-up time of 3.7±2.0 years, 425 patients (2.3%; 95% CI, 2.1%–2.5%) had a documented diagnosis of dementia. After propensity matching, the incidence of dementia was significantly lower in OAC users (hazard ratio [HR], 0.59; 95% CI, 0.44–0.80; $P<0.001$) compared with nonusers. Direct-acting oral anticoagulant users had a lower incidence of dementia than non-OAC users (HR, 0.49; 95% CI, 0.33–0.73; $P<0.001$) or warfarin users (HR, 0.46; 95% CI, 0.28–0.74; $P=0.002$). No significant difference was seen between warfarin users and non-OAC users (HR, 1.08; 95% CI, 0.70–1.70; $P=0.723$).

CONCLUSIONS: In patients with atrial fibrillation, direct-acting oral anticoagulant use may result in a lower incidence of dementia compared with treatment with either warfarin or no anticoagulant.


Patients with new AF diagnosis between 2010 and 2017 (n=59,158)
Patients excluded (n=40,345):
Not regular patients (n=19,283)
Age<18 years (n=68)
Dementia before AF (n=1,023)
Prescribed an ADD before AF (n=104)
Prescribed an OAC before AF (n=1,228)
Stroke before AF (n=4,303)
Schizophrenia before AF (n=136)
Epilepsy before AF (n=224)
OAC duration less than 80% of follow-up time (n=9,779)
Dementia within the first year or follow-up time less than a year (n=4,197)
18,813 included in analysis
Non-OAC user (n=7,394)
OAC user (n=11,419)
Warfarin user (n=2,673)
DOAC user (n=5,570)
DOAC and warfarin user (n=3,176)

Characteristics	Before matching			Propensity-score matched		
	OAC users (n=11 419)	Non-OAC users (n=7394)	Standardized differences*	OAC users (n=4191)	Non-OAC users (n=4191)	Standardized differences*
Female sex	5242 (45.9)	3609 (48.8)	0.06	2017 (48.1)	2017 (48.1)	<0.01
Age, y	73.9±9.8	69.0±15.6	0.38	73.0±10.4	73.2±13.1	0.02
CHA_2DS_2-VA score	2.6±1.3	1.9±1.5	0.47	2.4±1.3	2.4±1.4	<0.01
CHA_2DS_2-VASc score†	3.0±1.4	2.4±1.6		2.9±1.4	2.9±1.5	
Duration of follow-up, y	3.8±2.1	3.6±2.0	0.12	3.6±2.0	3.6±2.0	0.01
Congestive heart failure	1531 (13.4)	628 (8.5)	0.16	465 (11.1)	460 (11.0)	<0.01
Hypertension	7047 (62.3)	3409 (46.5)	0.32	2451 (58.5)	2424 (57.8)	0.01
Diabetes	2377 (20.9)	990 (13.4)	0.20	717 (17.0)	713 (17.0)	<0.01
Vascular disease	3117 (27.4)	1574 (21.3)	0.14	1114 (26.6)	1102 (26.3)	0.01
Venous thromboembolism	700 (6.1)	201 (2.7)	0.17	162 (3.9)	154 (3.7)	0.01
Anxiety	1963 (17.2)	1497 (20.1)	0.08	790 (18.9)	797 (19.0)	<0.01
Arthritis	7325 (64.2)	3860 (52.2)	0.25	2481 (59.2)	2523 (60.2)	0.02
Asthma	2284 (20.0)	1390 (18.8)	0.03	750 (17.9)	799 (19.1)	0.03
Depression	2729 (23.9)	1901 (25.7)	0.04	1083 (25.8)	1029 (24.6)	0.03
Cancer	4824 (42.3)	2818 (38.1)	0.08	1753 (41.8)	1754 (41.9)	
Coronary heart disease	3481 (30.5)	1675 (22.7)	0.18	1175 (28.0)	1188 (28.4)	<0.01
Chronic liver disease	78 (0.7)	96 (1.3)	0.06	34 (0.8)	42 (1.0)	0.02
Chronic obstructive pulmonary disease	2084 (18.3)	1111 (15.0)	0.09	710 (16.9)	739 (17.6)	0.02
Antiplatelets	4138 (36.2)	3129 (42.3)	0.12	1813 (43.3)	1873 (44.7)	0.03
NSAIDs	4747 (41.6)	3045 (41.2)	0.01	1732 (41.3)	1790 (42.7)	0.03
RAAS inhibitors	8996 (78.8)	3883 (52.5)	0.58	2893 (69.0)	2920 (69.7)	0.01
Nitrates	2359 (20.7)	1082 (14.6)	0.16	766 (18.3)	773 (18.4)	<0.01
Statins	7310 (64.0)	3069 (41.5)	0.46	2281 (54.4)	2277 (54.3)	<0.01
β-blockers	8737 (76.5)	3723 (50.4)	0.56	2688 (64.1)	2729 (65.1)	<0.02
Digoxin	3506 (30.7)	1047 (14.2)	0.41	845 (20.2)	819 (19.5)	0.02
Antiarrhythmic drugs, class I or III‡	3692 (32.3)	1499 (20.3)	0.28	1051 (25.1)	1072 (25.6)	0.01

Table 3. HRs for Dementia Diagnosis With 95% CIs for Propensity Score–Matched Groups

Characteristics	OAC users	Non-OAC users	DOAC users	Non-OAC users	Warfarin users	Non-OAC users	DOAC users	Warfarin users
Total	4191	4191	2850	2850	1377	1377	1335	1335
Follow-up, y, mean±SD	3.6±2.0	3.7±2.0	3.0±1.4	3.0±1.7	3.9±2.1	3.9±2.1	3.2±1.4	3.2±1.7
Person-y at risk	15 209	15 242	8663	8637	5404	5423	4408	4288
Dementia diagnosis	67	114	36	74	43	40	24	51
Incidence rate per 1000 person-y (95% CI)	4.4 (3.4–5.6)	7.5 (6.2–9.0)	4.2 (2.9–5.7)	8.6 (6.7–10.7)	8.0 (5.8–10.7)	7.4 (5.3–10.0)	5.4 (3.5–8.1)	11.9 (8.9–15.6)
HRs (95% CI)	0.59 (0.44–0.80)	Reference	0.49 (0.33–0.73)	Reference	1.08 (0.70–1.66)	Reference	0.46 (0.28–0.74)	Reference

DOAC indicates direct-acting oral anticoagulant; HR, hazard ratio; and OAC, oral anticoagulant.

Dementia Incidence HR 0.59 OAC vs. non-OAC

HR 0.49 DOAC vs. non-OAC

HR 0.46 DOAC vs. Warfarin

JACC VOL. 73, NO. 9, 2019
MARCH 12, 2019:989–99

Relationships of Overt and Silent Brain Lesions With Cognitive Function in Patients With Atrial Fibrillation

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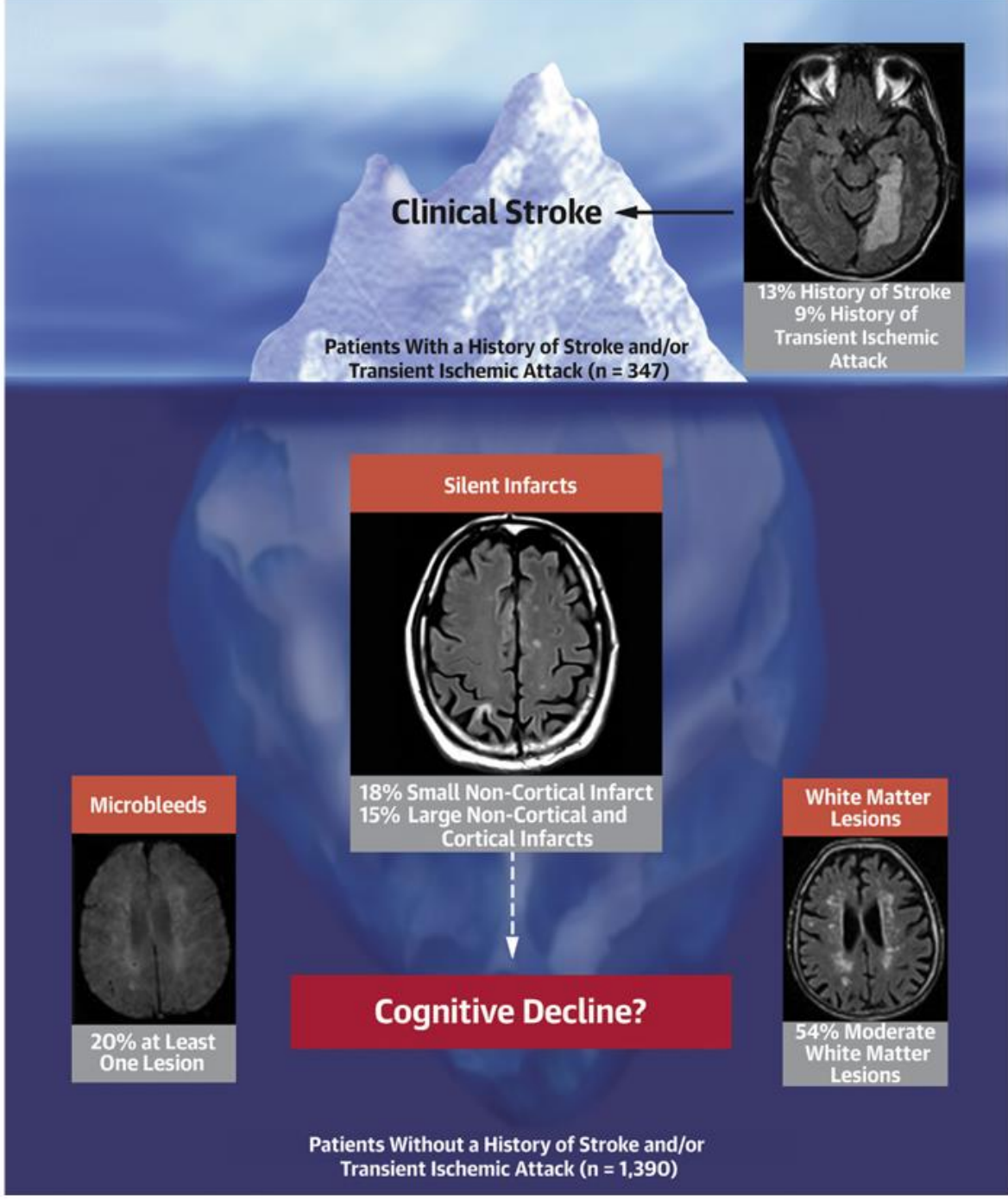
TABLE 2 Prevalence of Vascular Brain Lesions Detected on Brain Magnetic Resonance Imaging

	Prevalence	Volume, mm³	Number
All patients (N = 1,737)			
Small noncortical infarcts	368 (21)	63 [30–163]	1 [1–3]
Large noncortical or cortical infarcts	387 (22)	1,623 [255–7,314]	1 [1–2]
Microbleeds	372 (22)	-	1 [1–2]
White matter lesions	1,715 (99)	3,918 [1,439–9783]	23 [11–41]
Fazekas scale ≥2	928 (54)		
Patients without a history of stroke or TIA (n = 1,390)			
Small noncortical infarcts	245 (18)	57 [30–141]	2 [1–3]
Large noncortical or cortical infarcts	201 (15)	525 [162–3,396]	1 [1–2]
Microbleeds	272 (20)	-	1 [1–2]
White matter lesions	1,372 (99)	3,512 [1,323–8,669]	21 [10–40]
Fazekas scale ≥2	694 (50)		



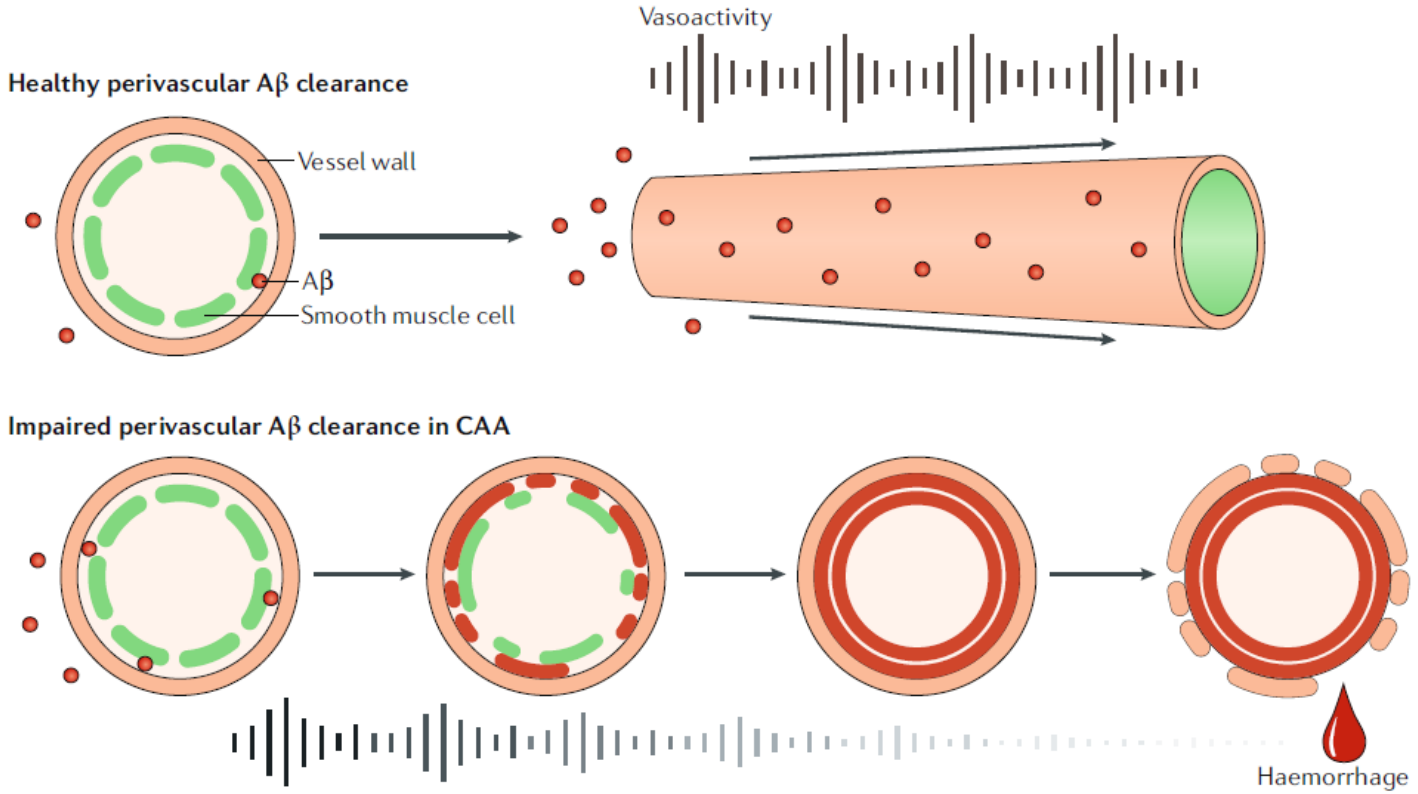
Conen, D. et al. J Am Coll Cardiol. 2019;73(9):989–99.

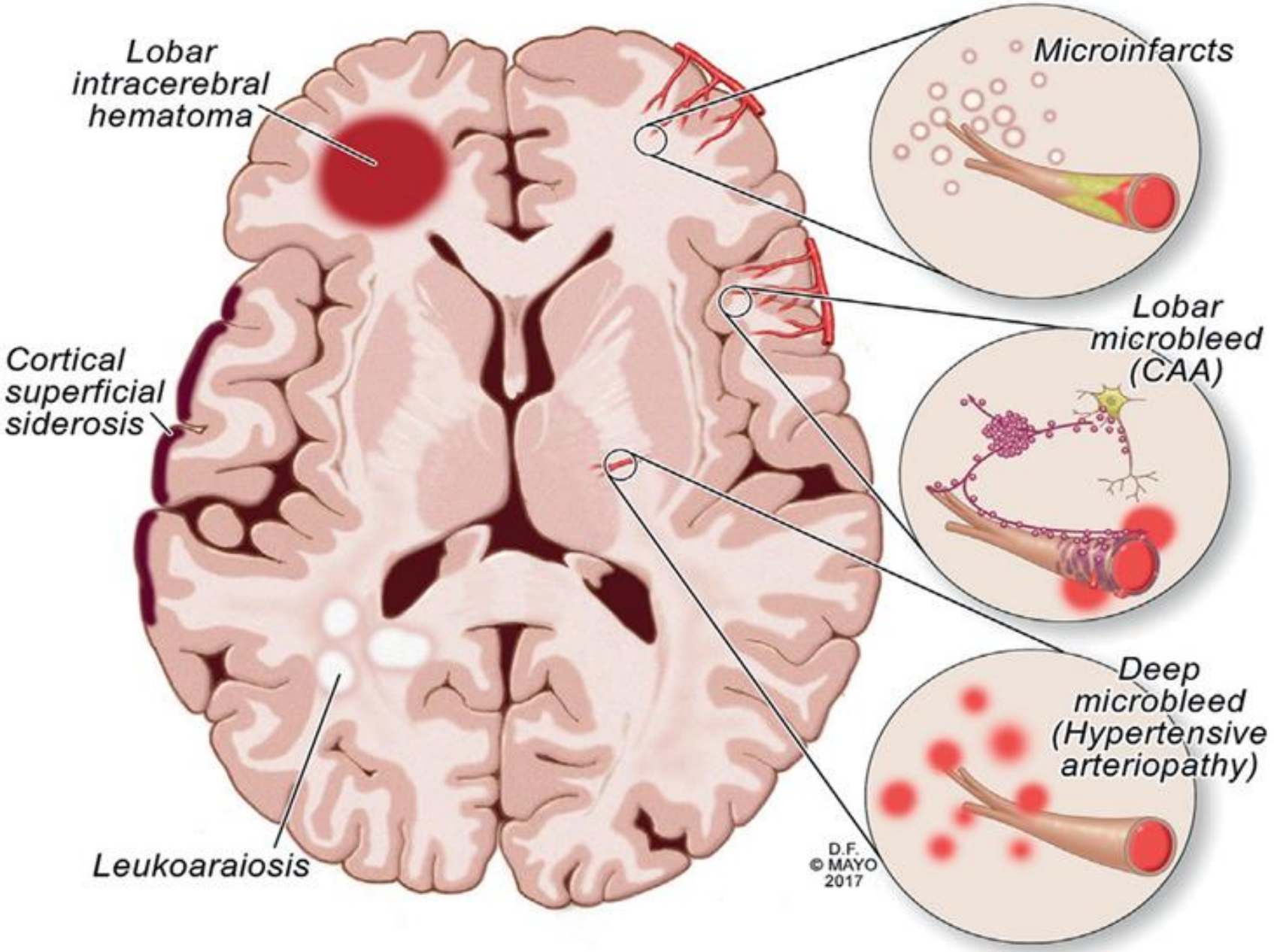
REVIEWS

NATURE REVIEWS | NEUROLOGY

Cerebral amyloid angiopathy and Alzheimer disease — one peptide, two pathways

Steven M. Greenberg[1], Brian J. Bacskai[1], Mar Hernandez-Guillamon[2], Jeremy Pruzin[3], Reisa Sperling[3] and Susanne J. van Veluw[1]*




Lobar intracerebral hematoma
Cortical superficial siderosis
Leukoaraiosis
Microinfarcts
Lobar microbleed (CAA)
Deep microbleed (Hypertensive arteriopathy)
D.F.
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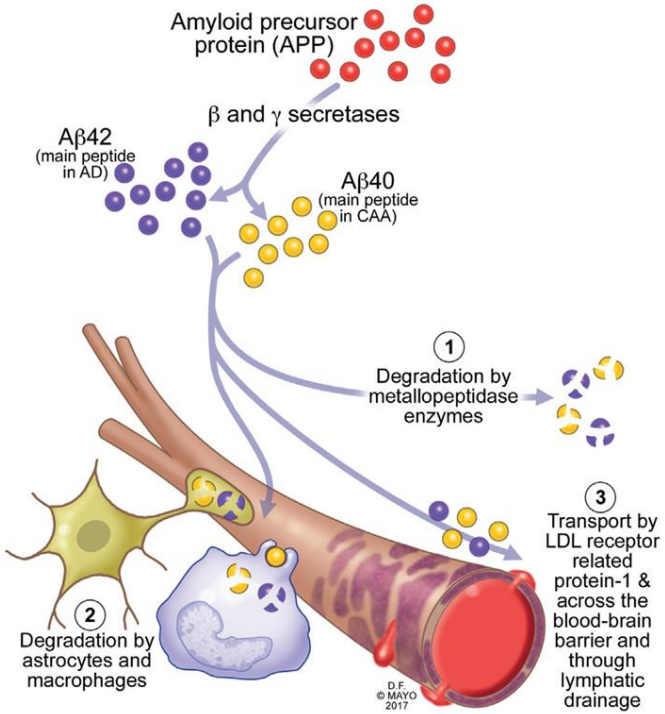
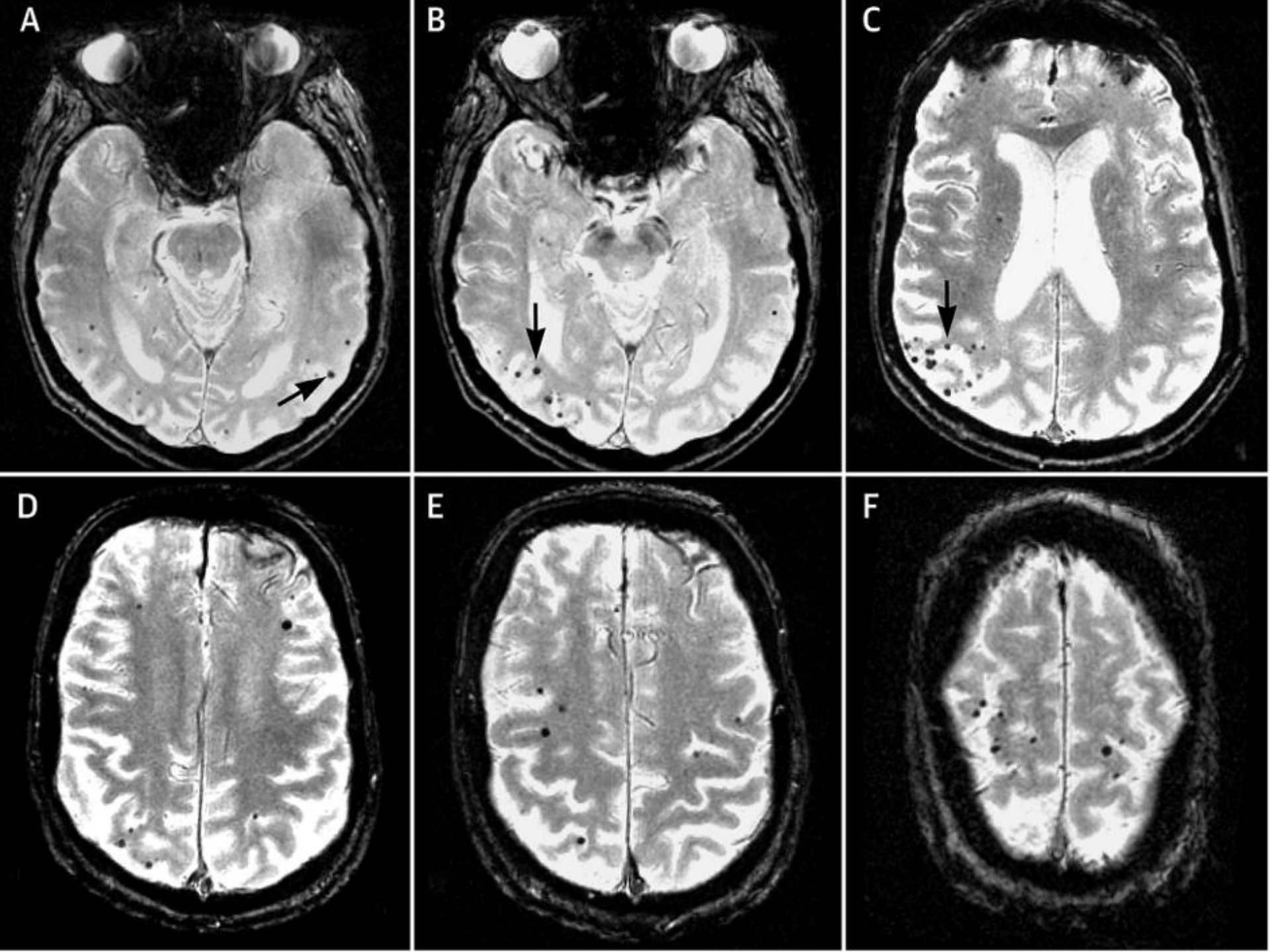
2017



Boston Criteria

Definite CAA	Probable CAA with supporting pathology	Probable CAA†	Possible CAA†
• Full post-mortem pathologic evaluation • Lobar, cortical, or cortico-subcortical hemorrhage • Severe* CAA with vasculopathy	• Clinical data and pathology (biopsy or evacuated hematoma) • Lobar, cortical, or cortico-subcortical hemorrhage • Some degree of CAA in specimen	• Clinical data and MRI/CT: multiple hemorrhages restricted to lobar, cortical, or cortico-subcortical regions • Age ≥ 55	• Clinical data and MRI/CT: single lobar, cortical,or cortico-subcortical hemorrhage • Age ≥ 55
		• Single lobar, cortical, or cortico-subcortical hemorrhage AND focal‡ or disseminated# superficial siderosis • Absence of another cause of superficial siderosis	• Focal‡ or disseminated# superficial siderosis • Absence of another cause of superficial siderosis

Modified Boston Criteria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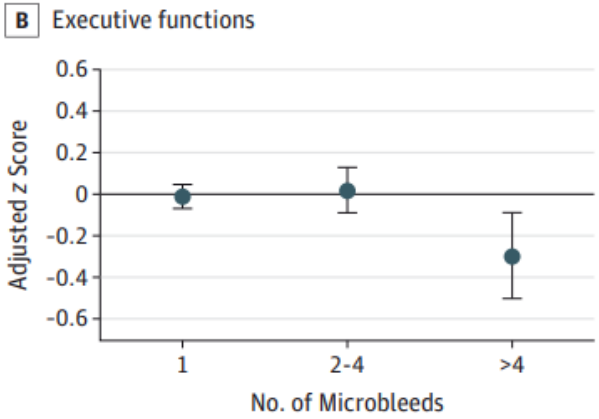
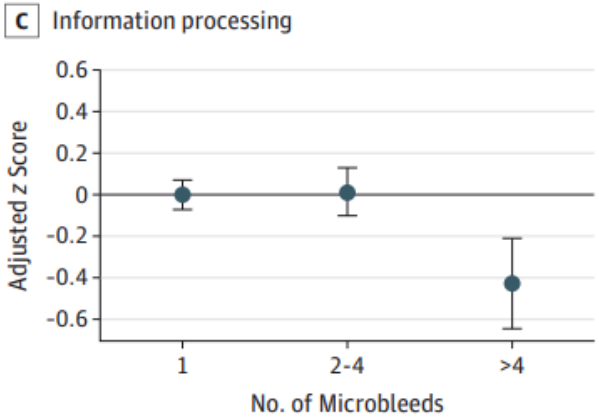
JAMA Neurology | Original Investigation

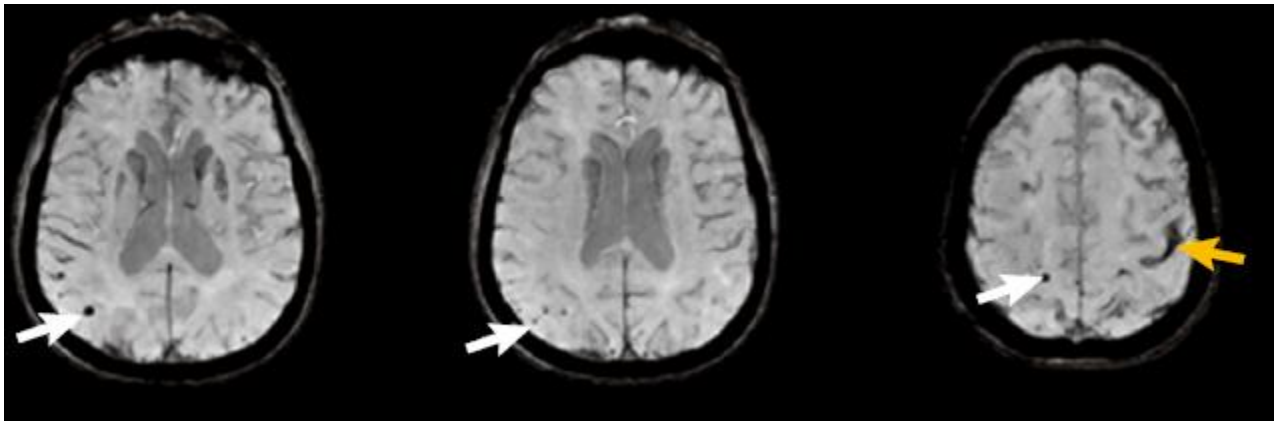
Association of Cerebral Microbleeds With Cognitive Decline and Dementia

JAMA Neurol. 2016;73(8):934-943. doi:10.1001/jamaneurol.2016.1017
Published online June 6, 2016.

Saloua Akoudad, MD, PhD; Frank J. Wolters, MD; Anand Viswanathan, MD, PhD; Renée F. de Bruijn, MD, PhD; Aad van der Lugt, MD, PhD; Albert Hofman, MD, PhD; Peter J. Koudstaal, MD, PhD; M. Arfan Ikram, MD, PhD; Meike W. Vernooij, MD, PhD







Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): a multicentre observational cohort study

Lancet Neurol 2018; 17: 539–47

*Duncan Wilson, Gareth Ambler, Clare Shakeshaft, Martin M Brown, Andreas Charidimou, Rustam Al-Shahi Salman, Gregory Y H Lip, Hannah Cohen, Gargi Banerjee, Henry Houlden, Mark J White, Tarek A Yousry, Kirsty Harkness, Enrico Flossmann, Nigel Smyth, Louise J Shaw, Elizabeth Warburton, Keith W Muir, Hans Rolf Jäger, David J Werring, on behalf of the CROMIS-2 collaborators**

Findings Between Aug 4, 2011, and July 31, 2015, we recruited 1490 participants of whom follow-up data were available for 1447 (97%), over a mean period of 850 days (SD 373; 3366 patient-years). The symptomatic intracranial haemorrhage rate in patients with cerebral microbleeds was 9·8 per 1000 patient-years (95% CI 4·0–20·3) compared with 2·6 per 1000 patient-years (95% CI 1·1–5·4) in those without cerebral microbleeds (adjusted hazard ratio 3·67, 95% CI 1·27–10·60). Compared with the HAS-BLED score alone (C-index 0·41, 95% CI 0·29–0·53), models including cerebral microbleeds and HAS-BLED (0·66, 0·53–0·80) and cerebral microbleeds, diabetes, anticoagulant type, and HAS-BLED (0·74, 0·60–0·88) predicted symptomatic intracranial haemorrhage significantly better (difference in C-index 0·25, 95% CI 0·07–0·43, p=0·0065; and 0·33, 0·14–0·51, p=0·00059, respectively).

Interpretation In patients with atrial fibrillation anticoagulated after recent ischaemic stroke or transient ischaemic attack, cerebral microbleed presence is independently associated with symptomatic intracranial haemorrhage risk and could be used to inform anticoagulation decisions. Large-scale collaborative observational cohort analyses are needed to refine and validate intracranial haemorrhage risk scores incorporating cerebral microbleeds to identify patients at risk of net harm from oral anticoagulation.

Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): a multicentre observational cohort study

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	Absolute event rate*	Rate per 1000 patient-years (95% CI)	Absolute rate increase per 1000 patient-years (95% CI)	Univariable hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)†
Symptomatic intracranial haemorrhage					
No cerebral microbleeds	7/2654	2·6 (1·1 to 5·4)	1 (ref)	1 (ref)	1 (ref)
Cerebral microbleeds present	7/712	9·8 (4·0 to 20·3)	7·2 (2·9 to 14·9)	3·73 (1·31 to 10·64)	3·67 (1·27 to 10·60)
1 cerebral microbleed	2/367	5·4 (0·7 to 19·7)	2·8 (–0·4 to 14·3)	2·04 (0·42 to 9·84)	2·03 (0·42 to 9·83)
≥2 cerebral microbleeds	5/345	14·4 (4·7 to 33·8)	11·8 (3·6 to 28·4)	5·58 (1·77 to 17·58)	5·46 (1·70 to 17·51)
Recurrent ischaemic stroke					
No cerebral microbleeds	39/2608	15·0 (10·6 to 20·4)	1 (ref)	1 (ref)	1 (ref)
Cerebral microbleeds present	17/704	24·1 (14·1 to 38·7)	9·1 (3·5 to 18·3)	1·62 (0·92 to 2·87)	1·53 (0·85 to 2·76)
1 cerebral microbleed	9/362	24·9 (11·4 to 47·2)	9·9 (0·8 to 32·2)	1·68 (0·82 to 3·47)	1·75 (0·84 to 3·65)
≥2 cerebral microbleeds	8/341	23·4 (10·1 to 46·2)	8·4 (–0·5 to 25·8)	1·56 (0·73 to 3·35)	1·32 (0·60 to 2·93)

Data are calculated on the 1447 participants with follow-up data available. *Calculated as number of events/patient-years. †Adjusted for age and hypertension for symptomatic intracranial haemorrhage, and adjusted for age, sex, hypertension, diabetes, previous ischaemic stroke, and age-related white matter hyperintensities score for recurrent ischaemic stroke.

Table 3: Absolute event rates, absolute risks, and univariable and multivariable hazard ratios for symptomatic intracranial haemorrhage and recurrent ischaemic stroke during follow-up, according to baseline presence and burden of cerebral microbleeds

frontiers in NEUROLOGY

MINI REVIEW ARTICLE
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MRI screening for chronic anticoagulation in atrial fibrillation

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Anticoagulation is highly effective in preventing stroke due to atrial fibrillation, but numerous studies have demonstrated low utilization of anticoagulation for these patients. Assessment of clinicians' attitudes on this topic indicate that fear of intracerebral hemorrhage (ICH), rather than appreciation of anticoagulation benefits, largely drives clinical decision-making for treatment with anticoagulation in atrial fibrillation. Risk stratification strategies have been used for anticoagulation benefits and hemorrhage risk, but ICH is not specifically addressed in the commonly used hemorrhage risk stratification systems. Cerebral microbleeds are cerebral microscopic hemorrhages demonstrable by brain MRI, indicative of prior microhemorrhages, and predictive of future risk of ICH. Prevalence of cerebral microbleeds increases with age; and cross-sectional and limited prospective studies generally indicate that microbleeds confer substantial risk of ICH in patients treated with chronic anticoagulation. MRI thus is a readily available and appealing modality that can directly assess risk of future ICH in patients receiving anticoagulants for atrial fibrillation. Incorporation of MRI into routine practice is, however, fraught with difficulties, including the uncertain relationship between number and location of microbleeds and ICH risk, as well as cost-effectiveness of MRI. A proposed algorithm is provided, and relevant advantages and disadvantages are discussed. At present, MRI screening appears most appropriate for a subset of atrial fibrillation patients, such as those with intermediate stroke risk, and may provide reassurance for clinicians whose concerns for ICH tend to outweigh benefits of anticoagulation.

Keywords: atrial fibrillation, stroke, microbleeds, anticoagulation, MRI, hemorrhage

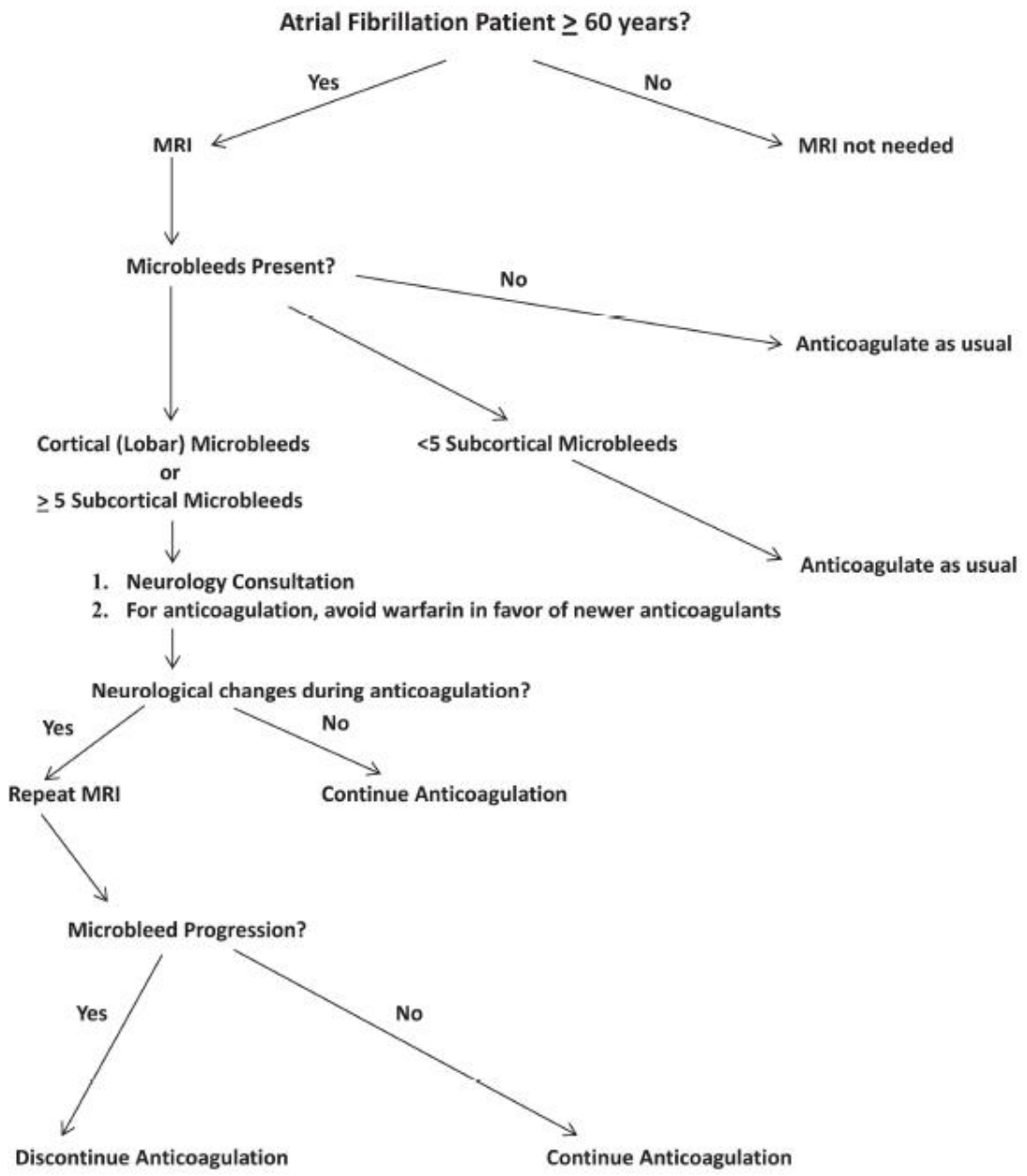


FIGURE 1 | Proposed algorithm for incorporation of MRI screening into decision-making for anticoagulation for atrial fibrillation patients. "Newer anticoagulants" refers to agents such as dabigatran and rivaroxaban.

Incidence of Symptomatic Hemorrhage in Patients With Lobar Microbleeds

Ellis S. van Etten, MD; Eitan Auriel, MD, MSc; Kellen E. Haley, BA; Alison M. Ayres, BA; Anastasia Vashkevich, BA; Kristin M. Schwab, BA; Jonathan Rosand, MD, MSc; Anand Viswanathan, MD, PhD; Steven M. Greenberg, MD, PhD; M. Edip Gurol, MD, MSc

Background and Purpose—Lobar microbleeds suggestive of cerebral amyloid angiopathy (CAA) are often identified on MRI in the absence of lobar intracerebral hemorrhage (ICH). We compared the baseline characteristics and risk of subsequent ICH among such patients to those presenting with CAA-related lobar ICH.

Methods—Clinical data (demographics, risk factors), apolipoprotein E genotype, neuroimaging markers of CAA severity (microbleed counts, leukoaraiosis volume), and clinical outcomes (incidence rates of ICH and death during a mean follow-up of 5.3±3.8 years) were compared between 63 patients enrolled because of incidentally found microbleeds and 316 with CAA-related ICH, in our prospectively enrolled cohort. Predictors of incident ICH were explored in the microbleed-only patients using multivariable Cox regression models.

Results—Microbleed-only patients shared similar demographic, apolipoprotein E, and vascular risk profiles with lobar ICH patients, but had more lobar microbleeds (median, 10 versus 2; $P<0.001$) and higher leukoaraiosis volumes (median, 31 versus 23 mL; $P=0.02$). Microbleed-only patients had a nontrivial incidence rate of ICH, not different from patients presenting with ICH (5 versus 8.9 per 100 person-years; adjusted hazard ratio, 0.58; 95% confidence interval, 0.31–1.06; $P=0.08$). Microbleed-only patients had a higher mortality rate (hazard ratio, 1.67; 95% confidence interval, 1.1–2.6) compared with ICH survivors. Warfarin use and increasing age were independent predictors of future ICH among microbleed-only patients after correction for other covariates.

Conclusions—Patients presenting with isolated lobar microbleeds on MRI have a genetic, neuroimaging, and hemorrhagic risk profile suggestive of severe CAA pathology. They have a substantial risk of incident ICH, potentially affecting decisions regarding anticoagulation in clinical situations. **(*Stroke*. 2014;45:2280-2285.)**

Key Words: cerebral amyloid angiopathy ■ cerebral hemorrhage ■ cerebral microbleeds ■ magnetic resonance imaging

Brain microbleeds, anticoagulation, and hemorrhage risk

Meta-analysis in stroke patients with AF

Andreas Charidimou, MD, PhD
Christopher Karayiannis, MD
Tae-Jin Song
Dilek Necioglu Orken, MD
Vincent Thijs, MD
Robin Lemmens, MD, PhD
Jinkwon Kim
Su Mei Goh
Thanh G. Phan
Cathy Soufan
Ronil V. Chandra
Lee-Anne Slater
Shamir Haji
Vincent Mok, MD, PhD
Solveig Horstmann, MD
Kam Tat Leung, BSc
Yuichiro Kawamura
Nobuyuki Sato
Naoyuki Hasebe, MD, PhD

ABSTRACT

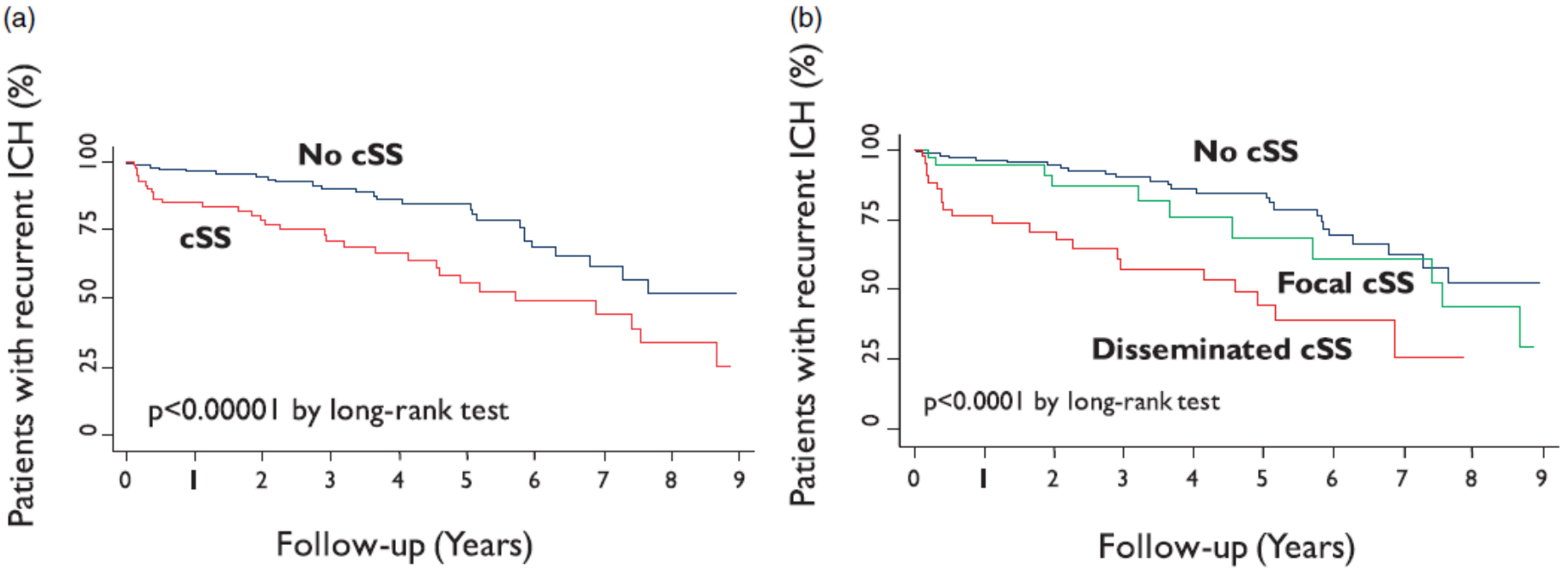
Objectives: To assess the association between cerebral microbleeds (CMBs) and future spontaneous intracerebral hemorrhage (ICH) risk in ischemic stroke patients with nonvalvular atrial fibrillation (AF) taking oral anticoagulants.

Methods: This was a meta-analysis of cohort studies with >50 patients with recent ischemic stroke and documented AF, brain MRI at baseline, long-term oral anticoagulation treatment, and ≥6 months of follow-up. Authors provided summary-level data on stroke outcomes stratified by CMB status. We estimated pooled annualized ICH and ischemic stroke rates from Poisson regression. We calculated odds ratios (ORs) of ICH by CMB presence/absence, ≥5 CMBs, and CMB topography (strictly lobar, mixed, and strictly deep) using random-effects models.

Results: We established an international collaboration and pooled data from 8 centers including 1,552 patients. The crude CMB prevalence was 30% and 7% for ≥5 CMBs. Baseline CMB presence (vs no CMB) was associated with ICH during follow-up (OR 2.68, 95% confidence interval [CI] 1.19–6.01, $p = 0.017$). Presence of ≥5 CMB was related to higher future ICH risk (OR 5.50, 95% CI 2.07–14.66, $p = 0.001$). The pooled annual ICH incidence increased from 0.30% (95% CI 0.04–0.55) among CMB-negative patients to 0.81% (95% CI 0.17–1.45) in CMB-positive patients ($p = 0.01$) and 2.48% (95% CI 1.2–6.2) in patients with ≥5 CMBs ($p = 0.001$). There was no association between CMBs and recurrent ischemic stroke.

Conclusions: The presence of CMB on MRI and the dichotomized cutoff of ≥5 CMBs might identify subgroups of ischemic stroke patients with AF with high ICH risk and after further validation could help in risk stratification, in anticoagulation decisions, and in guiding randomized trials and ongoing large observational studies. *Neurology*® 2017;89:2317–2326

Figure 1. Time to recurrent symptomatic lobar intracerebral hemorrhage (ICH) during follow-up in our cohort. Kaplan–Meier estimate curves of progression to recurrent ICH (a) in CAA patients with vs. without any cSS and (b) according to cSS burden (i.e. none, focal, disseminated). Testing of significance is by the log-rank test.



Research

International Journal of Stroke WSO

Cortical superficial siderosis and recurrent intracerebral hemorrhage risk in cerebral amyloid angiopathy: Large prospective cohort and preliminary meta-analysis

Andreas Charidimou[1], Gregoire Boulouis[1], Duangnapa Roongpiboonsopit[1,2], Li Xiong[1], Marco Pasi[1], Kristin M Schwab[1], Jonathan Rosand[1,3], M Edip Gurol[1], Steven M Greenberg[1] and Anand Viswanathan[1]

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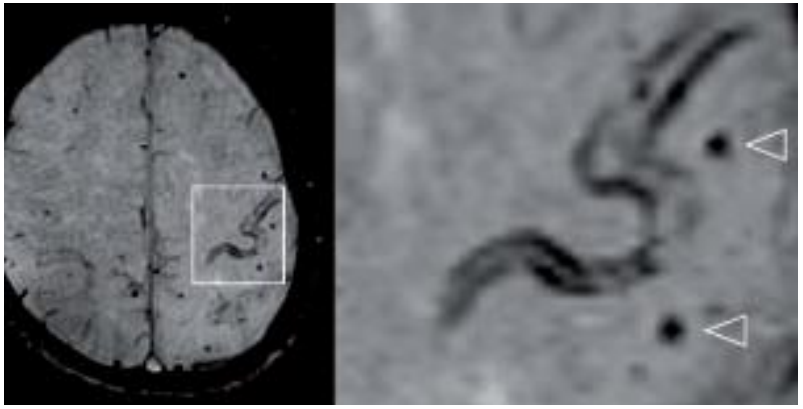


GUIDELINES

A European Academy of Neurology guideline on medical management issues in dementia

K. S. Frederiksen[a], C. Cooper[b], G. B. Frisoni[c], L. Frölich[d], J. Georges[e], M. G. Kramberger[f], C. Nilsson[g,h], P. Passmore[i], L. Mantoan Ritter[j], D. Religa[k,l], R. Schmidt[m], E. Stefanova[n], A. Verdelho[o], M. Vandenbulcke[p], B. Winblad[q,l] and G. Waldemar[a]

- To address important medical management issues including systematic medical follow-up, vascular risk factors in dementia, pain in dementia, use of antipsychotics in dementia and epilepsy in dementia.

Frederiksen KS, et al. Eur J Neurol. 2020 Oct;27(10):1805-1820. doi: 10.1111/ene.14412

Journal of Alzheimer's Disease 61 (2018) 1119–1128
DOI 10.3233/JAD-170575
IOS Press

Treatment of Atrial Fibrillation in Patients with Dementia: A Cohort Study from the Swedish Dementia Registry

Ana Subic[a,b,c,*], Pavla Cermakova[a,d], Dorota Religa[a,f,g], Shuang Han[e,h], Mia von Euler[i,j,k], Ingemar Kåreholt[l,m], Kristina Johnell[m], Johan Fastbom[m], Liselia Bognandi[e], Bengt Winblad[a,f], Milica G. Kramberger[a,b,c], Maria Eriksdotter[e,f] and Sara Garcia-Ptacek[e,f,n,*]

Hazard ratios (HR) of ischemic stroke, nontraumatic intracranial hemorrhage, any hemorrhage and death compared to no treatment

	HR for ischemic stroke (95% CI)	HR for nontraumatic intracranial hemorrhage (95% CI)	HR for any hemorrhage (95% CI)	HR for death (95% CI)
No treatment	Ref.	Ref.	Ref.	Ref.
Warfarin	0.76 (0.59–0.98)*	1.47 (0.91–2.37)	1.08 (0.87–1.35)	0.84 (0.59–0.98)**
Antiplatelets	1.25 (1.01–1.54)*	1.29 (0.81–2.04)	0.84 (0.68–1.04)	0.91 (0.83–0.99)*

Hazard ratios (HR) and 95% confidence intervals (CI) for the association of treatment with warfarin or antiplatelets (aspirin or clopidogrel) and risk of ischemic or nontraumatic intracranial hemorrhage and death after dementia diagnosis, as obtained from Cox Hazards regression models. Adjusted for age, sex, number of drugs, Mini-Mental State Examination, dementia type (Alzheimer's dementia versus other), nursing home placement, previous diabetes, hypertension, heart failure, ischemic stroke, any-cause hemorrhage, liver and kidney disease.

Management of Vascular Risk Factors in Dementia

Research question 2.1

Should patients with atrial fibrillation (without previous stroke, but where there is indication for anticoagulants), and dementia be treated with anticoagulants?

Recommendation

The authors conclude that there should be a weak recommendation for treatment with anticoagulants in patients with dementia (without previous stroke) and atrial fibrillation.

Frederiksen KS, et al. Eur J Neurol. 2020 Oct;27(10):1805-1820. doi: 10.1111/ene.14412

Justification for recommendations

It is the opinion of the authors that the recommendation may be extended to include non-vitamin K oral anticoagulants, as these offer a better protection against ischemic stroke and a comparable safety profile [37]. There is a trend in the directions of the point estimates towards a beneficial profile, which importantly is in line with many other studies clearly demonstrating a beneficial effect of anticoagulation in patients with atrial fibrillation but no dementia [38]. In the opinion of the authors there is no reason to believe that some patients with dementia would not have a similar benefit from anticoagulation. Atrial fibrillation remains the commonest cause of ischemic stroke in the older population [39], and a study showed that elderly persons would accept a higher risk of a hemorrhagic event for a smaller reduction in the risk of an ischemic stroke [40]. There is no reason to believe that patients with dementia differ in this regard.

Frederiksen KS, et al. Eur J Neurol. 2020 Oct;27(10):1805-1820. doi: 10.1111/ene.14412

ESC
European Society of Cardiology

2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

Stroke as well as intracerebral haemorrhage are significant events for patients with dementia with a greater risk of cognitive and functional decline, loss of independence and institutionalization compared to non-dementia patients.[360,361] AF in patients with dementia therefore requires similarly rigorous assessment for stroke prevention.

Steffel J, et al. Europace. 2021 Oct 9;23(10):1612-1676. doi: 10.1093/europace/euab065.

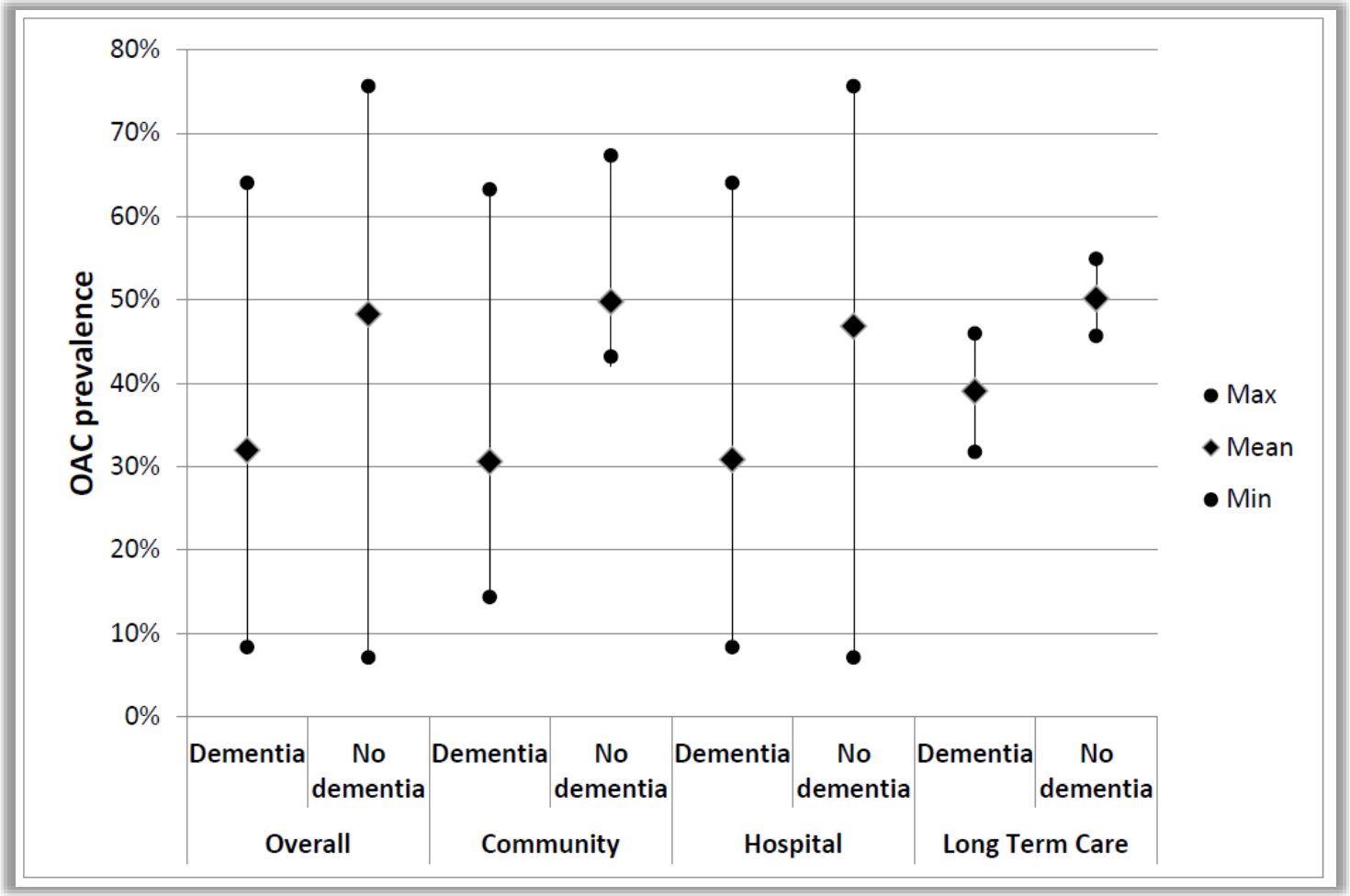
Dementia does pose unique considerations of adherence and safety when considering OAC. All patients with dementia should have a careful assessment of their ability to understand and make a treatment decision regarding OAC in AF, with indicative risks of stroke and bleeding provided. Where capacity is lacking, it may be reasonable for the physician to recommend treatment on the basis of the 'best medical interest' principle. This should be documented and explanation given to both patient and next of kin/legal attorney with assent/consent sought as relevant.

tions for initiation and follow-up' section). Paradoxically, the fact that others may be supervising medication with dementia patients may guarantee higher adherence.[363] Telemedicine to enhance treatment adherence in dementia and other assistive technologies may be useful in this population.[364] It is advisable to re-assess cognitive function in older AF patients on a regular basis particularly considering and assessing their ability to adhere to the prescribed anticoagulation regimen.

Steffel J, et al. Europace. 2021 Oct 9;23(10):1612-1676. doi: 10.1093/europace/euab065.

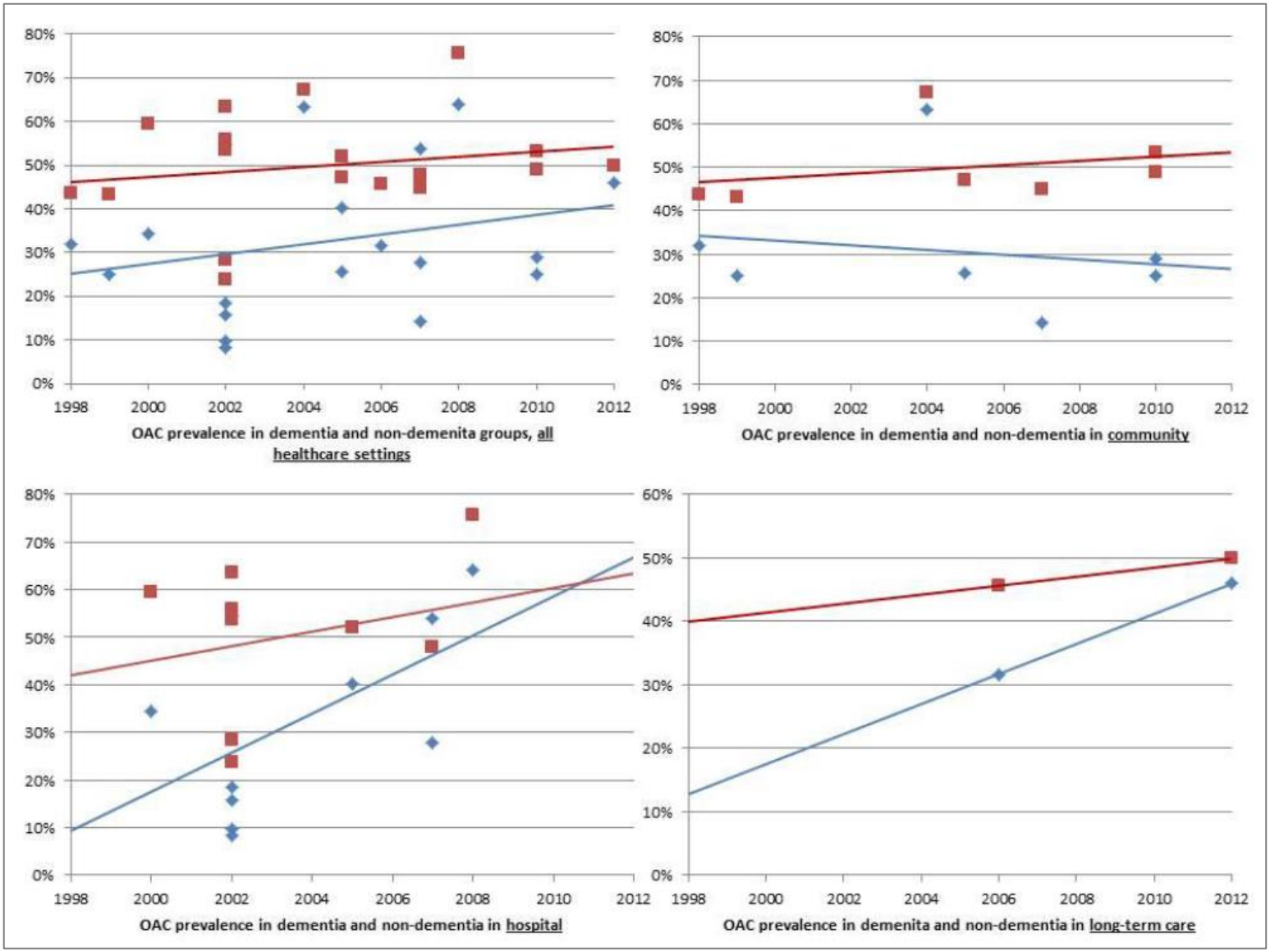
Prevalence, safety and effectiveness of oral anticoagulant use in people with and without dementia or cognitive impairment: a systematic review and meta-analysis

- 27 studies, published 2004-2017.



Fanning L, et al. J Alzheimers Dis. 2018;65(2):489-517. doi: 10.3233/JAD-180219.

OAC prevalence by mid-year of study observation period

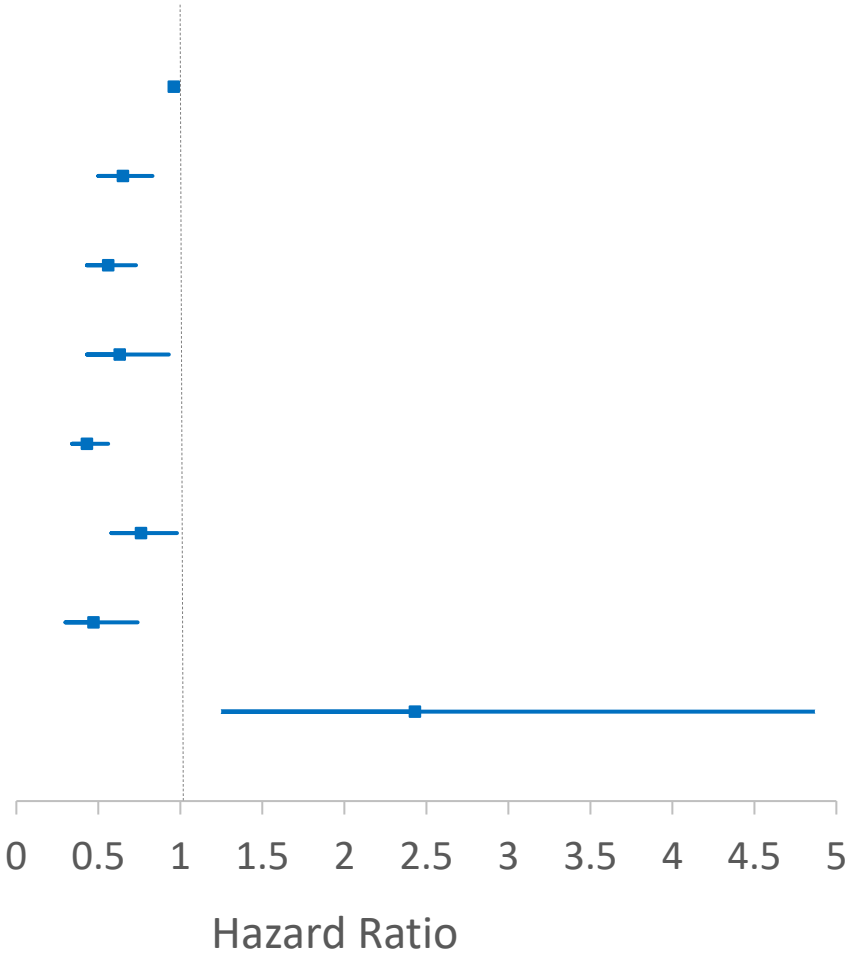


Horizontal-axis, publication year; Red square and trend line = non-dementia; Blue diamond and trend line = dementia/cognitive impairment; OAC = oral anticoagulation.

Fanning L, et al. J Alzheimers Dis. 2018;65(2):489-517. doi: 10.3233/JAD-180219.

Selected Factors Associated With OAC Prescription

Age at index (years)	**0.96 (0.94, 0.98)**
Female gender	**0.65 (0.50, 0.83)**
Major Bleed[a]	**0.56 (0.43, 0.73)**
Gastrointestinal Ulceration[a]	**0.63 (0.43-0.93)**
Drugs Pre-disposing to Bleeding[b]	**0.43 (0.34, 0.56)**
Falls[b]	**0.76 (0.58, 0.98)**
Care Home[b]	**0.47(0.30, 0.74)**
Polypharmacy[b,c]	**2.43 (1.21, 4.91)**



[a] Ever before index date. [b] One year prior to index date. [c] ≥4 repeat prescriptions

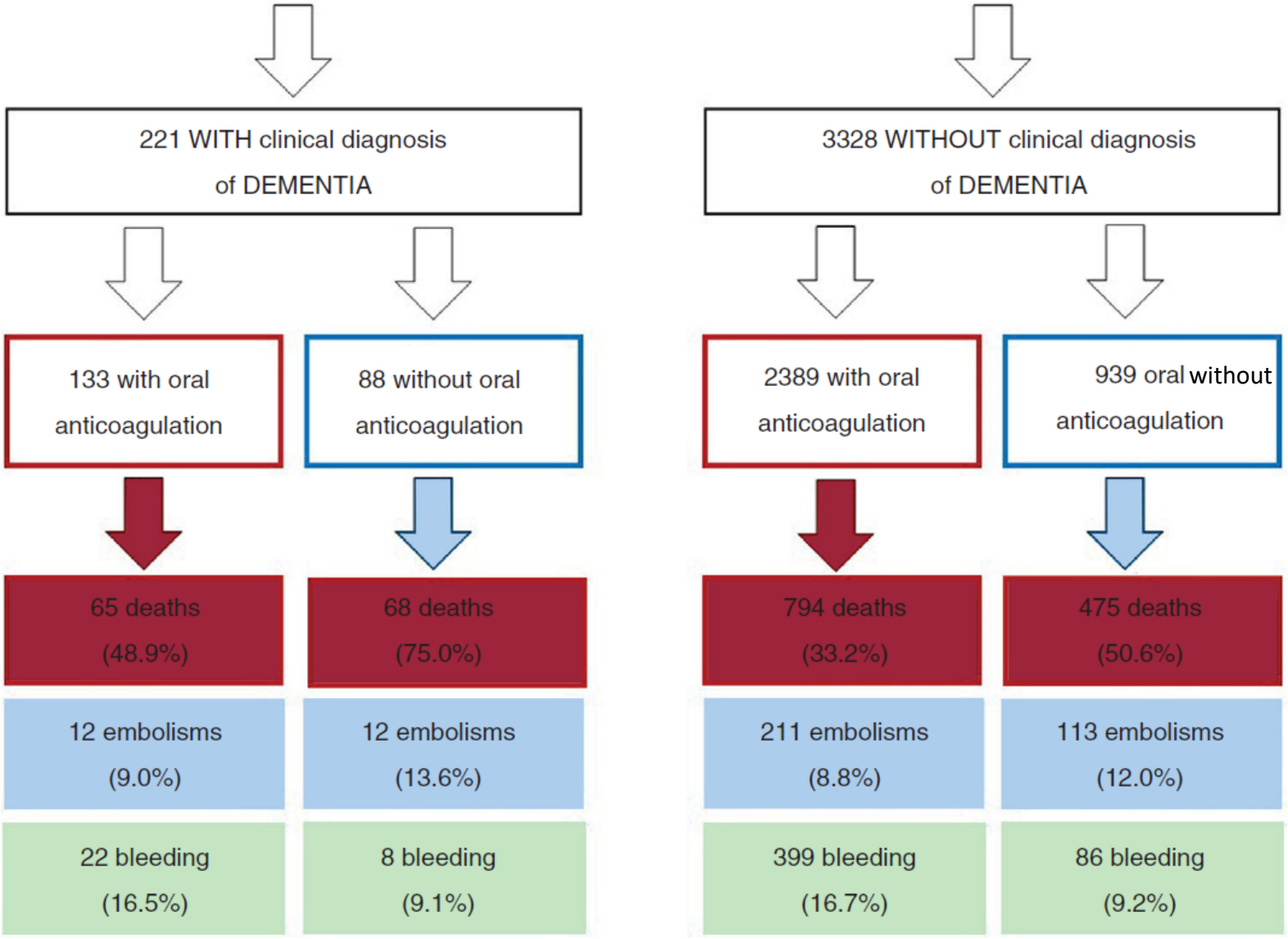
Adapted from Besford M, et al. Age Ageing. 2020 Apr 2. pii: afaa045. doi: 10.1093/ageing/afaa045. [Epub ahead of print].

Impact of anticoagulation in patients with dementia and atrial fibrillation. Results of the CardioCHUVI-FA registry

Rafael Cobas Paz,[a,*] Sergio Raposeiras Roubín,[a] Emad Abu Assi,[a] Cristina Barreiro Pardal,[b] Julio García Comesaña,[c] Alberto González-Carrero López,[d] Berenice Caneiro Queija,[a] María Cespón Fernández,[a] Isabel Muñoz Pousa,[a] Pablo Domínguez Erquicia,[a] Luis Manuel Domínguez Rodríguez,[a] Alberto Carpintero Vara,[e] Enrique García Campo,[a] Carlos Rodríguez Pascual,[e] and Andrés Íñiguez Romo[a]

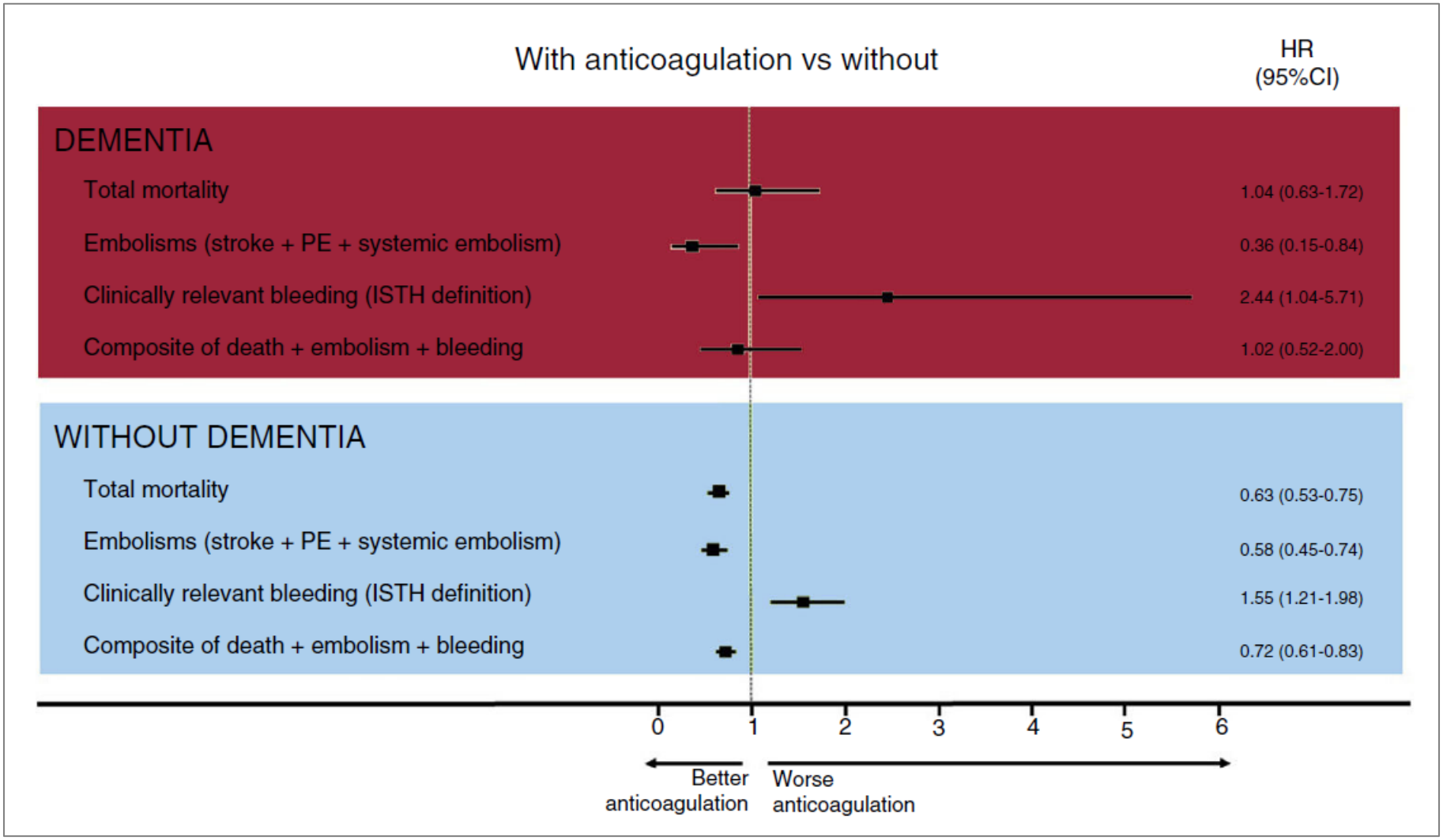
- **Study design**: a retrospective study, Spain, 2013-2018.
- **Study population**: 3,549 patients ≥85 years with AF:
  - 221/3,549 (6.1%) patients with moderate-severe dementia.
  - 3,328/3,549 (93.9%) patients without clinical dementia.
- **Outcomes**: total mortality, embolic and bleeding events.
- **Analyses**: propensity score matching; Cox regression analysis.
- **Follow-up**: mean, 2.8 years.

Cobas Paz R, et al. Rev Esp Cardiol (Engl Ed). 2020 Nov;73(11):877-884. English, Spanish. doi: 10.1016/j.rec.2019.10.025.



Adapted from Cobas Paz R, et al. Rev Esp Cardiol (Engl Ed). 2020 Nov;73(11):877-884. English, Spanish. doi: 10.1016/j.rec.2019.10.025.

- Fewer patients with dementia were receiving oral anticoagulants than patients without dementia (60.2% vs 71.8%; *P* < .001).



Cobas Paz R, et al. Rev Esp Cardiol (Engl Ed). 2020 Nov;73(11):877-884. English, Spanish. doi: 10.1016/j.rec.2019.10.025.

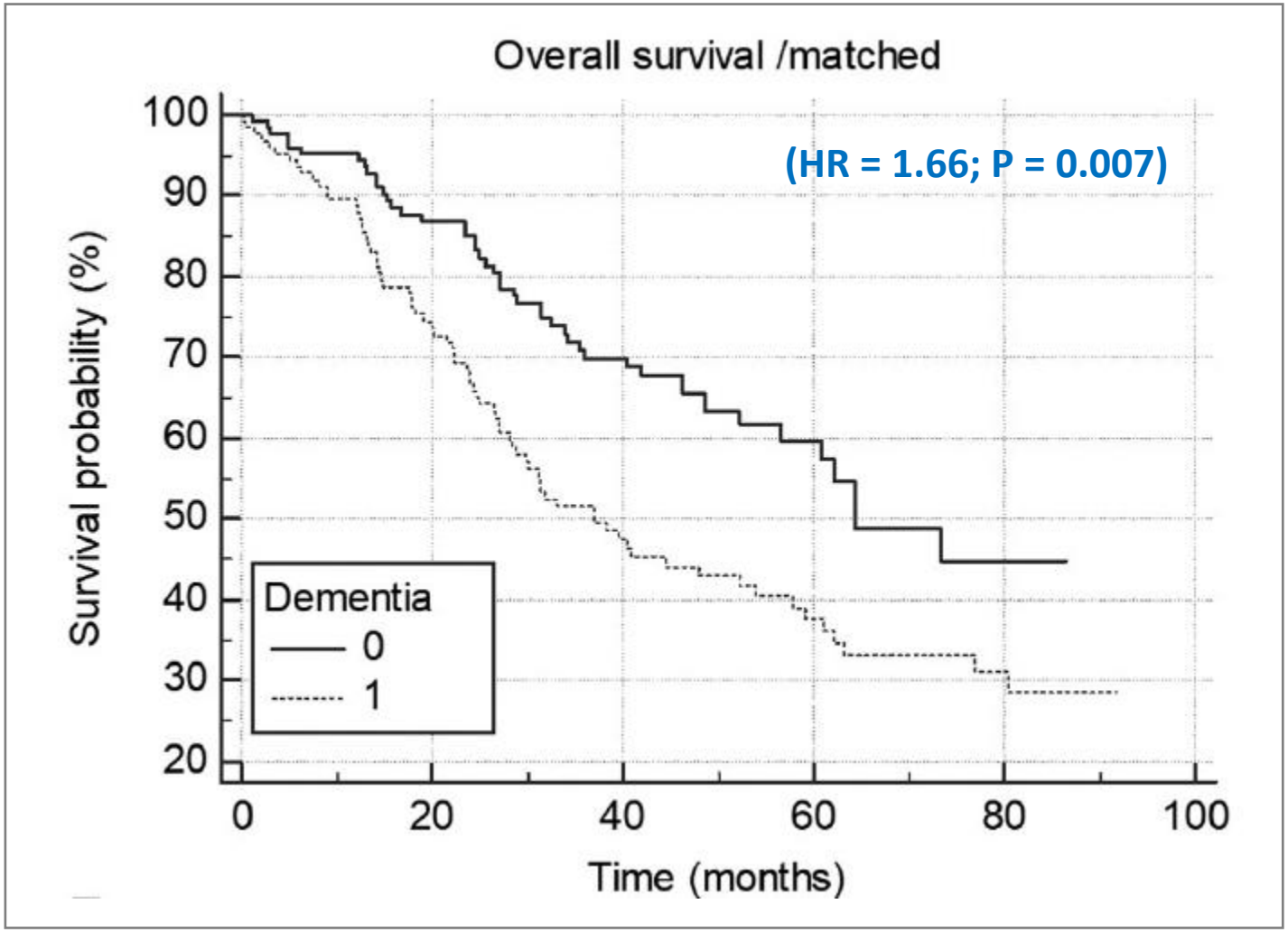
Patients with dementia and atrial fibrillation less frequently receive direct oral anticoagulants (DOACs) and experience higher thrombotic and mortality risk

Ivana Jurin, Marko Lucijanić, Vedran Radonić, Tomislav Letilović, Josip Pejić, Jelena Lucijanić, Ida Tješić-Drinković, Sanda Sokol Tomić & Irzal Hadžibegović

- **Study design**: a nested case-control study, Croatia, 2013-2018.
- **Study population**: 1,217 hospitalized AF:
  - 162/1,217 (13.3%) patients with dementia.
  - 1,055/1,217 (86.7%) patients without dementia.
- **Outcomes**: overall survival, thrombosis, major bleed, falls.
- **Analyses**: matching variables on CHA_2DS_2-VASC score, age, gender, LVEF and Cockcroft- Gault eGFR; Cox regression analysis.
- **Follow-up**: mean, 53 months.

Jurin I, et al. Acta Clin Belg. 2021 Apr 9:1-6. doi: 10.1080/17843286.2021.1913547.

- Patients with dementia were significantly less likely to receive DOACs compared to patients without dementia (27.2% vs 40.3%; *P* = 0.001)



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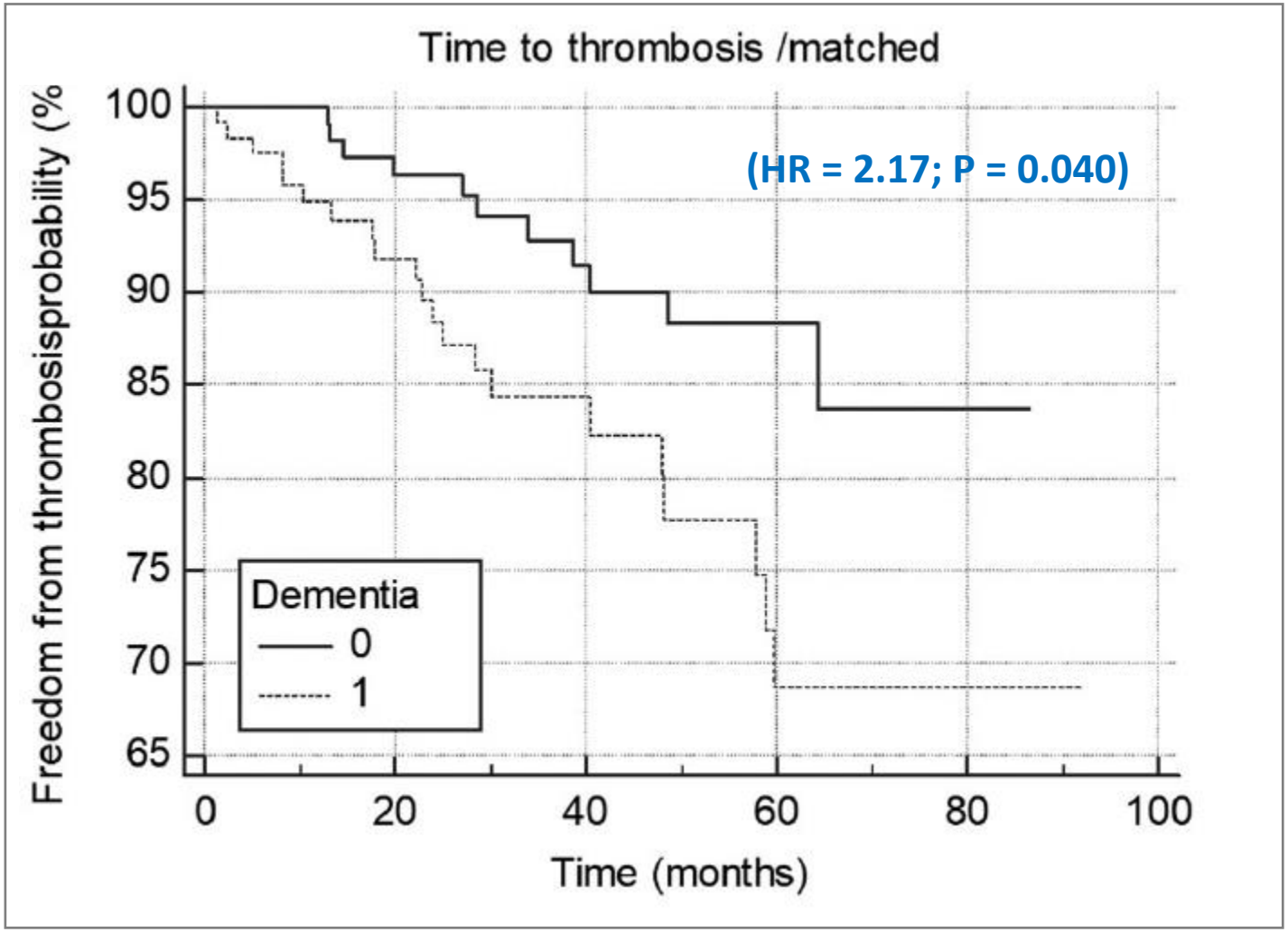

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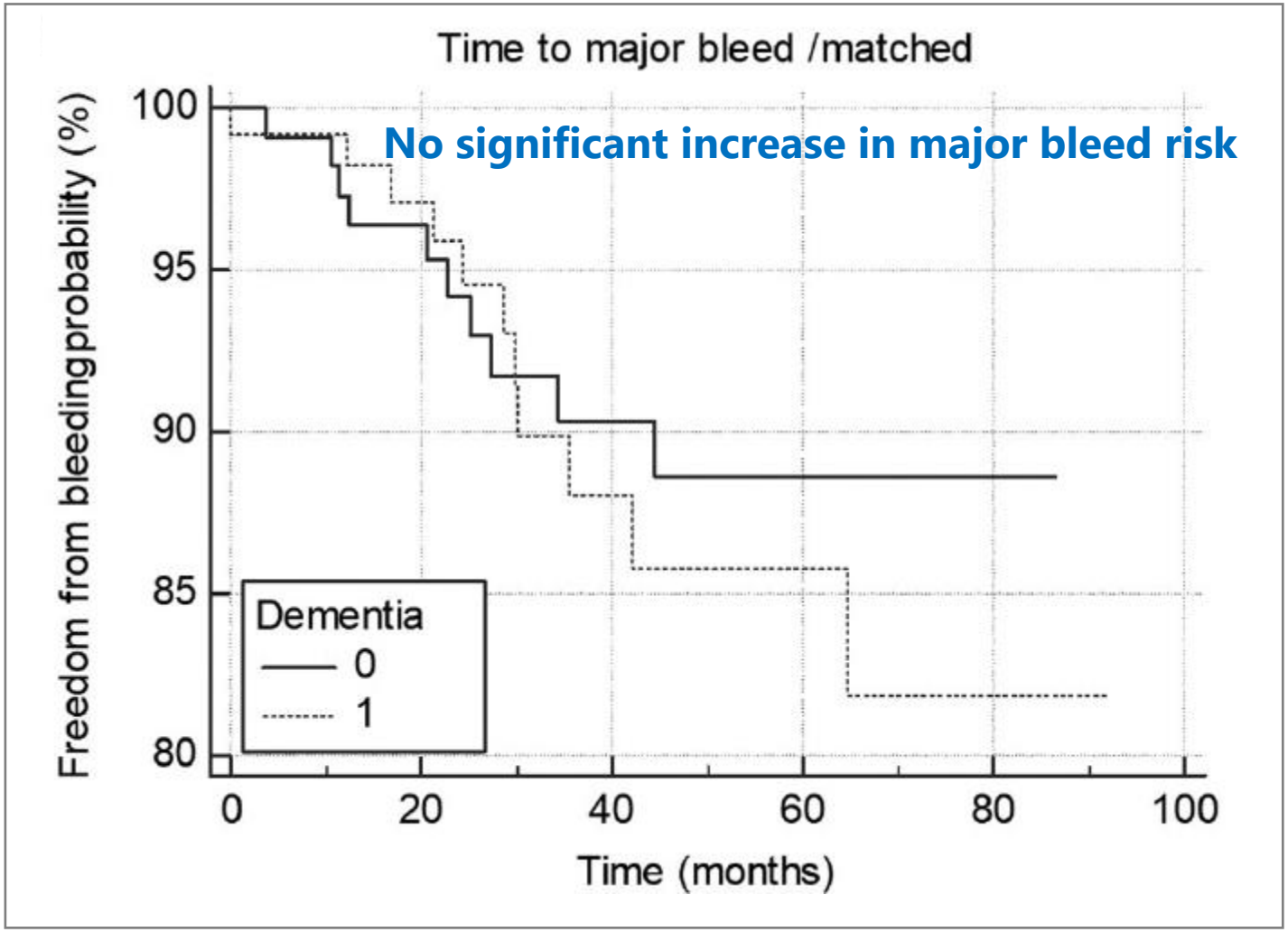

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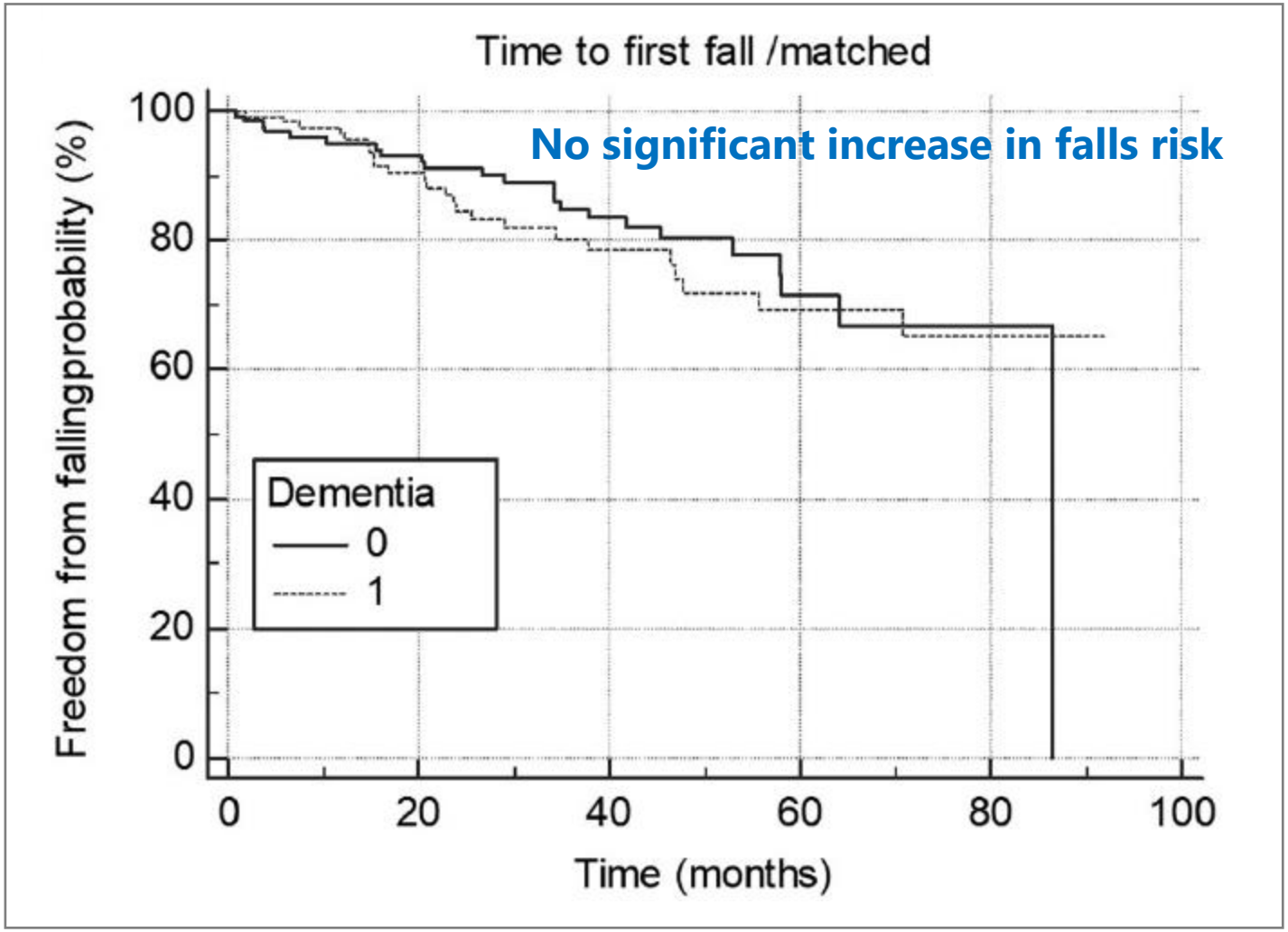


Adapted from Jurin I, et al. Acta Clin Belg. 2021 Apr 9:1-6. doi: 10.1080/17843286.2021.1913547.

Conclusions

field. Our findings speak in support of increased thrombotic and mortality risks associated with dementia which could be due to inadequate anticoagulation and higher number of comorbidities. This identifies AF patients with dementia as a high-risk subgroup of patients that requires special clinical concerns in everyday practice. Our suggestion is that physicians should prescribe DOACs more often in patients with dementia or at high risk of dementia development with aim of improving outcomes in these group of patients.

Jurin I, et al. Acta Clin Belg. 2021 Apr 9:1-6. doi: 10.1080/17843286.2021.1913547.

המלצות לביצוע MRI אמבולטורי בחולי שבץ מוחי

נכתב על ידי:

ד"ר חן הלוי
ד"ר ג'רמי מולד
ד"ר רוני אייכל
ד"ר רני ברנע
פרופ' אילן שלף
ד"ר איילת פרי-ערן
ד"ר אליאל (אלי) בן-דוד

בשם:

החברה הישראלית לשבץ מוחי, האיגוד הנוירולוגי בישראל
החוג לנוירורדיולוגיה, איגוד הרדיולוגים בישראל

נובמבר 2021

המכון לאיכות ברפואה

ההסתדרות הרפואית בישראל
המכון לאיכות ברפואה

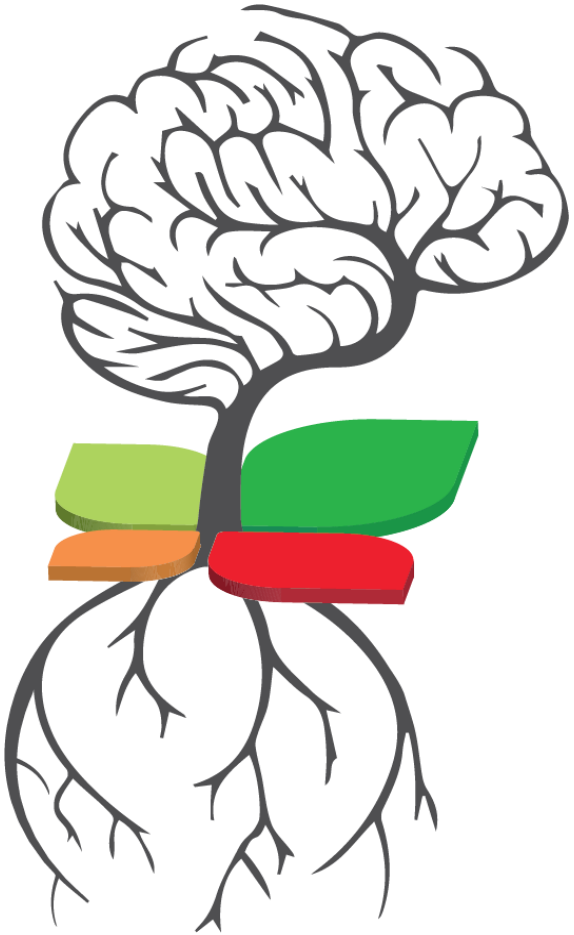
המלצות לביצוע MRI אמבולטורי בחולי שבץ מוחי

נכתב על ידי:
ד"ר חן הלוי
ד"ר ג'רמי מולד
ד"ר רוני אייכל
ד"ר רני ברנע
פרופ' אילן שלף
ד"ר איילת פרי-ערן
ד"ר אליאל (אלי) בן-דוד

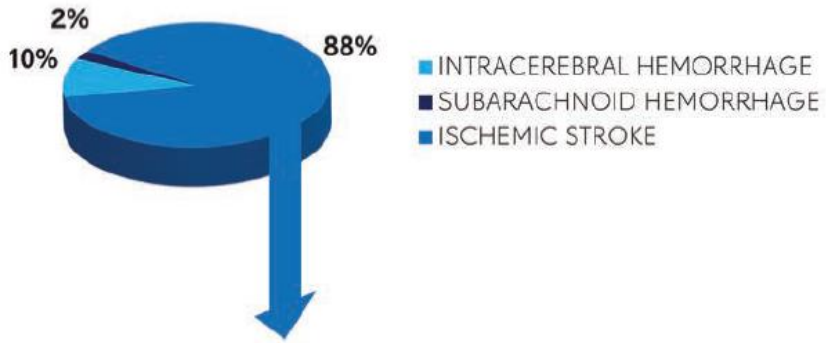
מניעה ראשונית של דמם תוך מוחי (ICH)

1. **מטופל עם התוויה לנוגדי קרישה (Oral Anticoagulants / Enoxaparin) באופן קבוע ובנוסף אחד מהבאים**[3]:
   א. נוכחות מיקרואנגיופתיה משמעותית ב-CT (לצורך הערכת CMBS) (B).
   ב. CMBS ידועים מבדיקה קודמת למעקב (B).
   ג. ממצאי CT המעלים חשד לקוורנומה או מום ווסקולרי אחר (A).
   ד. צורך קליני במשלב נוגד טסיות ונוגד קרישה באופן קבוע (B).
   ה. צורך בטיפול במשלב נוגדי טסיות מעבר ל-3 חודשים בהתוויה של מניעת שבץ-מוח (B).
   ו. ירידה קוגניטיבית (B).

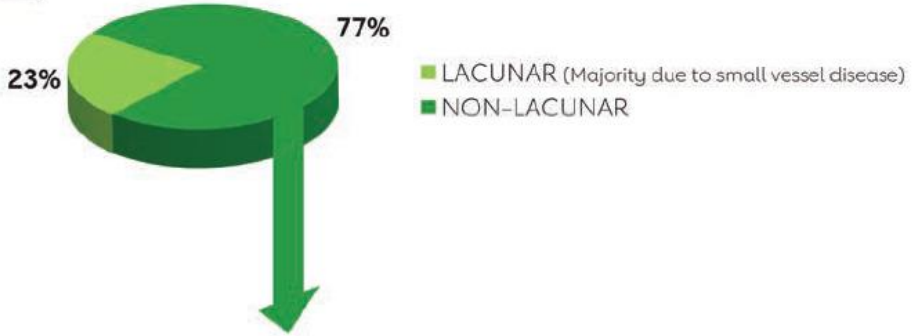
תודה רבה



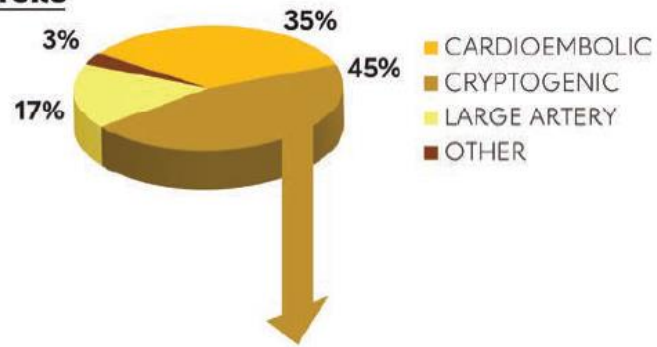
Stroke



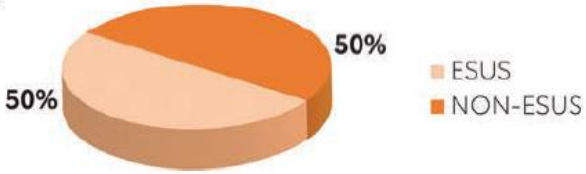
Ischemic Stroke

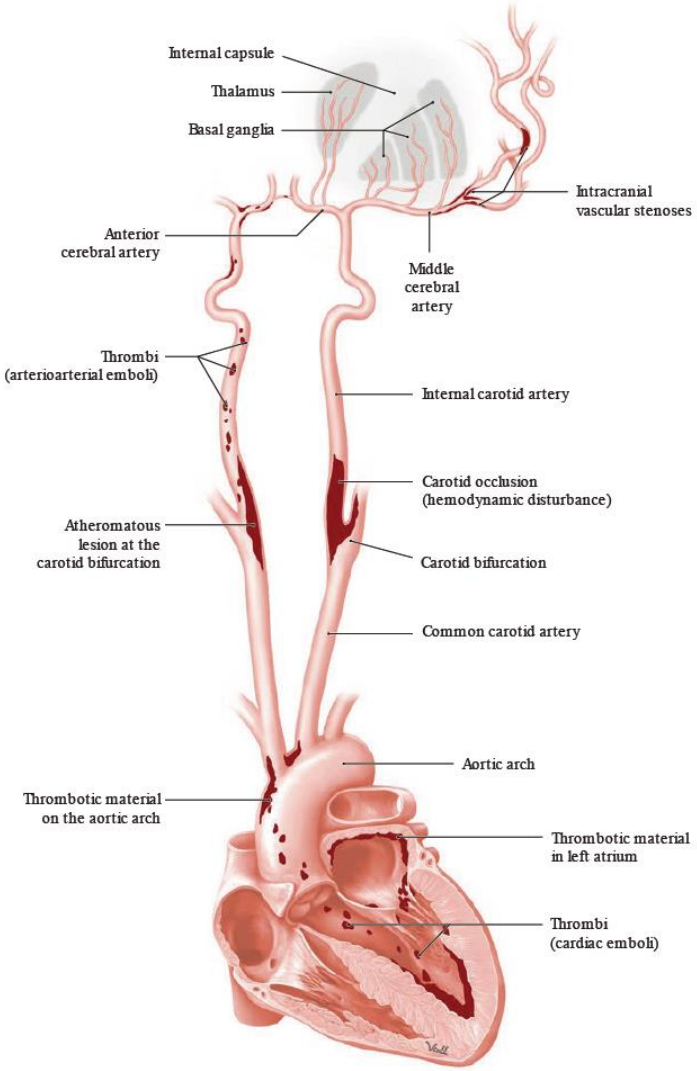


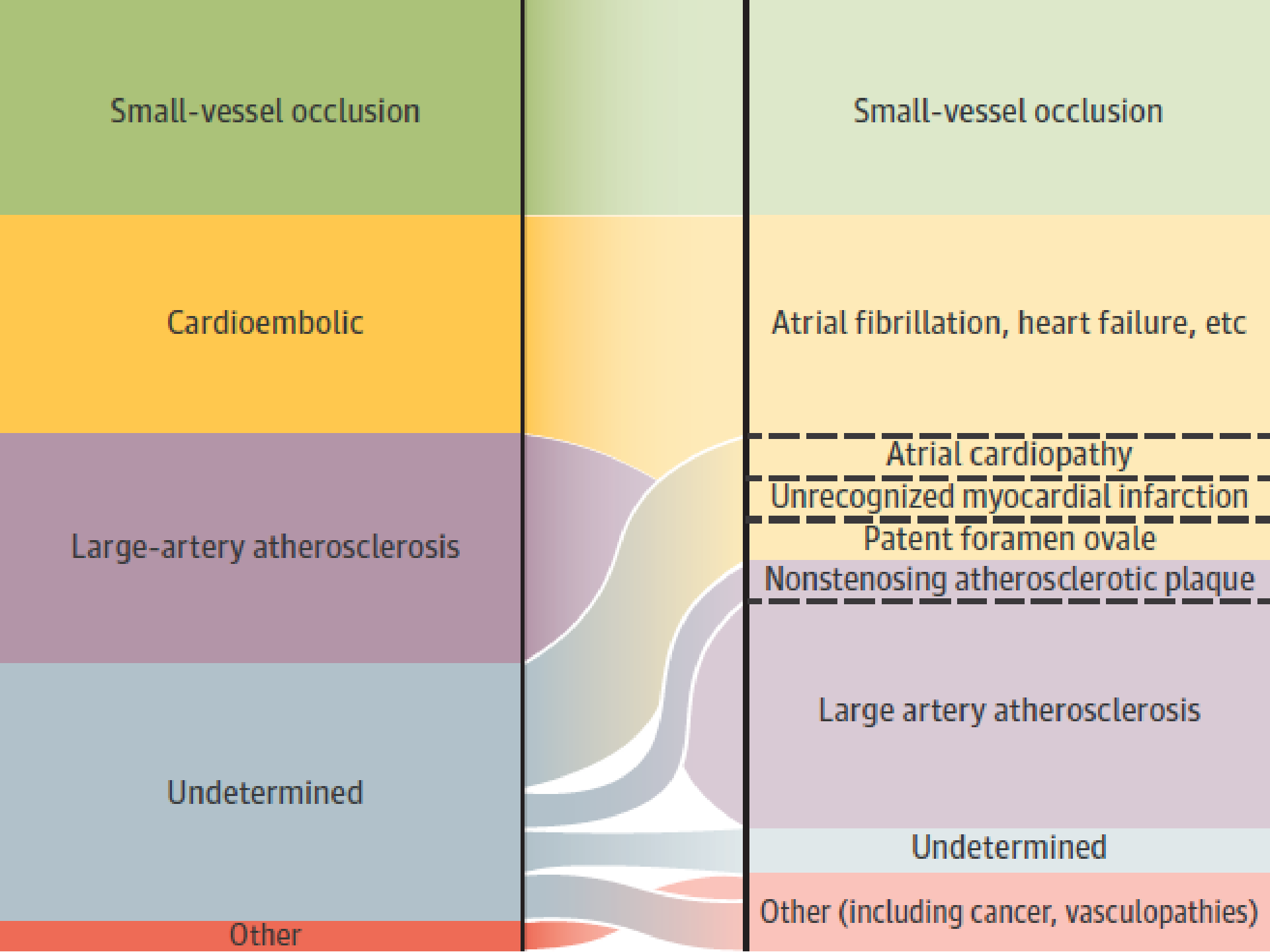
Non-lacunar Stroke



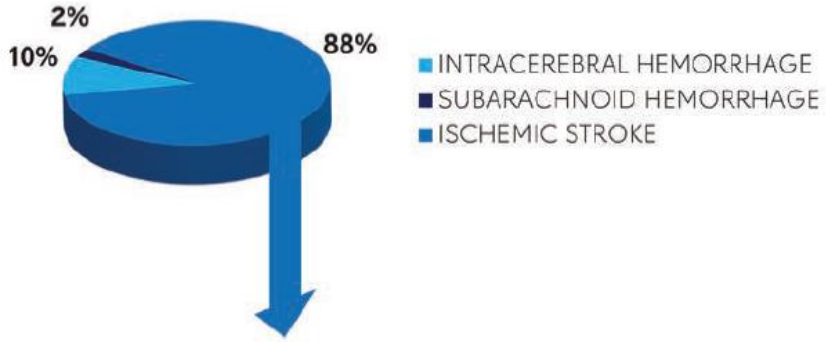
Cryptogenic Stroke

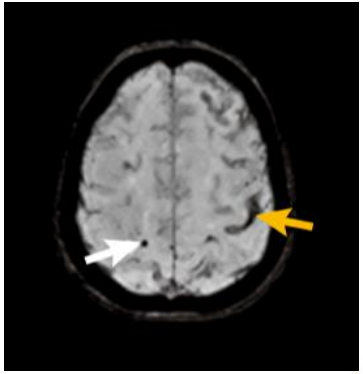




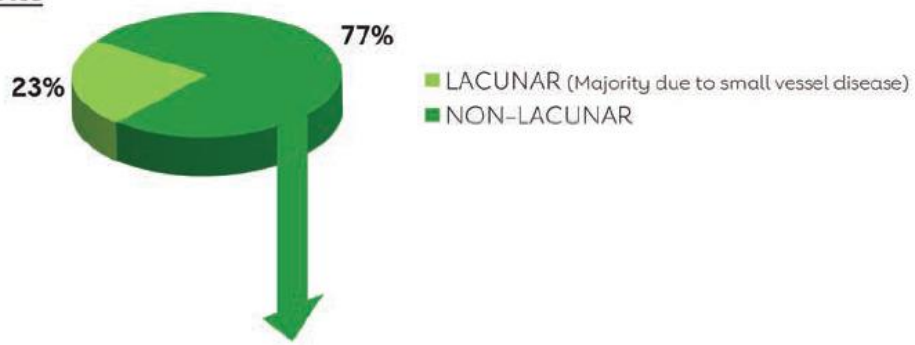

Small-vessel occlusion
Cardioembolic
Large-artery atherosclerosis
Undetermined
Other
Small-vessel occlusion
Atrial fibrillation, heart failure, etc
Atrial cardiopathy
Unrecognized myocardial infarction
Patent foramen ovale
Nonstenosing atherosclerotic plaque
Large artery atherosclerosis
Undetermined
Other (including cancer, vasculopathies)

Stroke

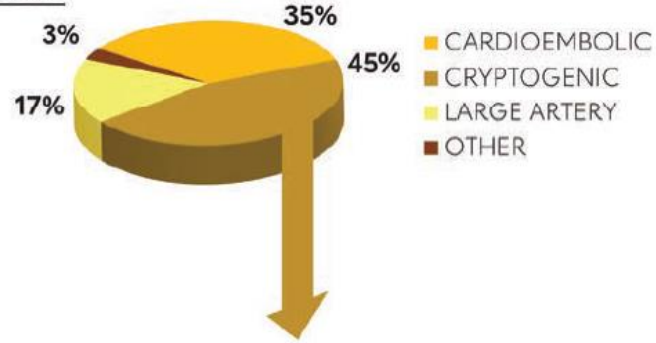




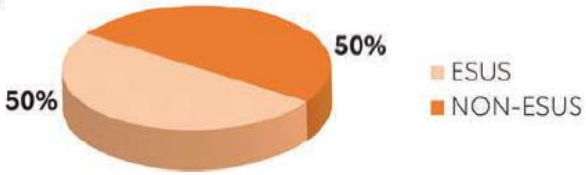
Ischemic Stroke

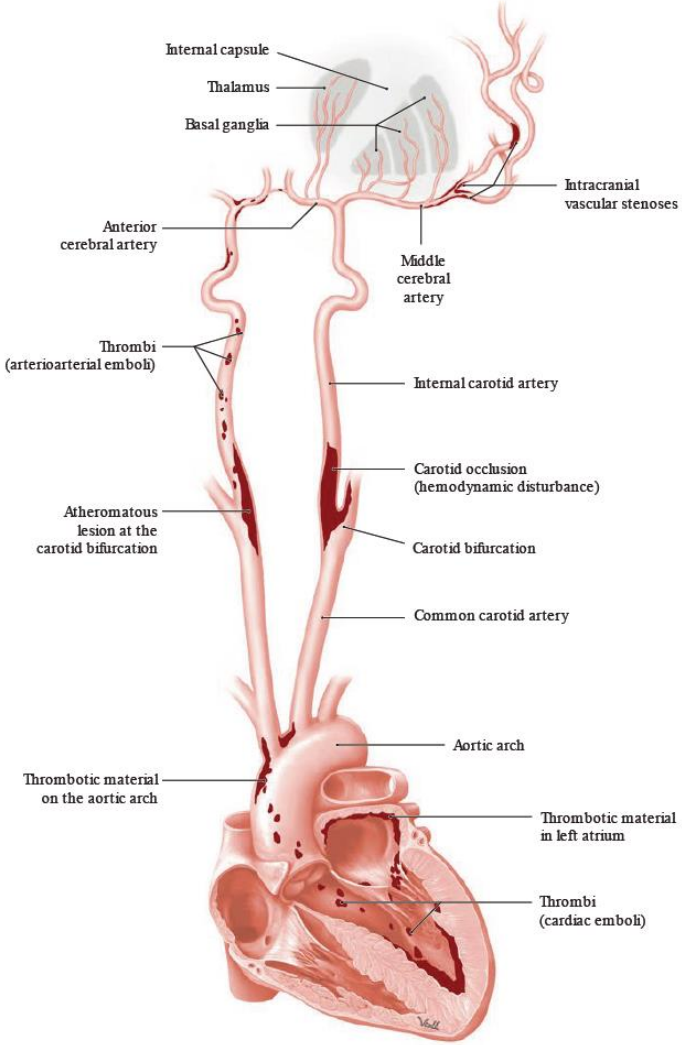


Non-lacunar Stroke



Cryptogenic Stroke





Effect of apixaban on brain infarction and microbleeds: AVERROES-MRI assessment study

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Background Clinical and subclinical (covert) stroke is a cause of cognitive loss and functional impairment. In the AVERROES trial, we performed serial brain magnetic resonance imaging (MRI) scans in a subgroup to explore the effect of apixaban, compared with aspirin, on clinical and covert brain infarction and on microbleeds in patients with atrial fibrillation.

Methods We performed brain MRI (T1, T2, fluid-attenuated inversion recovery, and T2* gradient echo sequences) in 1,180 at baseline and in 931 participants at follow-up. Mean interval from baseline to follow-up MRI scans was 1.0 year. The primary outcome was a composite of clinical ischemic stroke and covert *embolic pattern infarction* (defined as infarction >1.5 cm, cortical-based infarction, or new multiterritory infarction). Secondary outcomes included new MRI-detected brain infarcts and microbleeds and change in white matter hyperintensities.

Results Baseline MRI scans revealed brain infarct(s) in 26.2% and microbleed(s) in 10.5%. The rate of the primary outcomes was 2.0% in the apixaban group and 3.3% in the aspirin group (hazard ratio [HR] 0.55; 0.27-1.14) from baseline to follow-up MRI scan (mean duration of follow-up: 1 year). In those who completed baseline and follow-up MRI scans, the rate of new infarction detected on MRI was 2.5% in the apixaban group and 2.2% in the aspirin group (HR 1.09; 0.47-2.52), but new infarcts were smaller in the apixaban group ($P = .03$). There was no difference in proportion with new microbleeds on follow-up MRI (HR 0.92; 0.53-1.60) between treatment groups.

Conclusions Apixaban treatment was associated with a nonsignificant trend toward reduction in the composite of clinical ischemic stroke and covert embolic-pattern infarction and did not increase the number of microbleeds in patients with atrial fibrillation compared with aspirin. (Am Heart J 2016;178:145-50.)

JAMA Neurol. 2015;72(11):1288-1294. doi:10.1001/jamaneurol.2015.2161
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Original Investigation

Association Between Atrial Fibrillation and Dementia in the General Population

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Table 2. Atrial Fibrillation and the Risk of Dementia

	Dementia			Alzheimer Disease		
		HR (95% CI)			HR (95% CI)	
Characteristic	Cases, No. (%)	Model I[a]	Model II[b]	Cases, No. (%)	Model I[a]	Model II[b]
Including Stroke						
Atrial fibrillation						
Prevalent (n = 6514)	994 (15.3)	1.34 (1.03-1.74)	1.33 (1.02-1.73)	787 (12.1)	1.30 (0.96-1.75)	1.29 (0.95-1.75)
Incident (n = 6194)	932 (15.0)	1.13 (0.90-1.41)	1.23 (0.98-1.56)	741 (12.0)	1.09 (0.85-1.40)	1.18 (0.91-1.54)
Censored for Stroke						
Atrial fibrillation						
Prevalent (n = 6314)	844 (13.4)	1.35 (1.01-1.81)	1.33 (0.99-1.78)	705 (11.2)	1.31 (0.94-1.81)	1.28 (0.93-1.78)
Incident (n = 6019)	793 (13.2)	1.14 (0.89-1.49)	1.24 (0.96-1.61)	665 (11.0)	1.08 (0.82-1.42)	1.15 (0.87-1.54)

Abbreviation: HR, hazard ratio.

[a] Model I was adjusted for age and sex.

[b] Model II was additionally adjusted for diabetes mellitus, smoking, total cholesterol and high-density lipoprotein cholesterol levels, lipid-lowering medication, systolic and diastolic blood pressure, blood pressure–lowering medication, body mass index, educational level, ever use of oral anticoagulant medication, coronary heart disease, heart failure, and apolipoprotein E ε4 carrier status.

Table 1. Baseline Characteristics

Characteristic	Atrial Fibrillation, No. (%)[a]		
	Not Prevalent (n = 6196)	Prevalent (n = 318)	*P* Value for Difference[b]
Age, mean (SD), y	68.3 (8.5)	75.7 (8.1)	<.001
Female, sex	3678 (59.4)	161 (50.6)	<.001
BMI, mean (SD)	26.3 (3.7)	26.0 (3.6)	.48
Blood pressure, mm Hg, mean (SD)			
Systolic	139 (22)	142 (25)	.40
Diastolic	74 (11)	73 (13)	.52
Blood pressure–lowering medication	1367 (22.1)	109 (34.9)	<.001
Diabetes mellitus	609 (9.9)	64 (20.1)	<.001
Cholesterol, mean (SD), mg/dL			
Total	258.7 (46.3)	239.4 (46.3)	<.001
HDL	54.1 (15.4)	46.3 (11.6)	<.001
Lipid-lowering medication	151 (2.4)	9 (2.8)	.09
Smoking			
Former	2548 (42.2)	136 (44.3)	.74
Current	1429 (23.3)	56 (18.2)	.35
Apolipoprotein E ε4 carrier	1646 (27.8)	82 (26.5)	.95
Educational level			
Primary	2235 (36.6)	126 (40.8)	1 [Reference]
Lower vocational	1006 (16.5)	51 (16.5)	.08
Lower secondary	673 (11.0)	29 (9.4)	.68
Intermediate vocational	1463 (24.0)	80 (25.9)	.09
General secondary	198 (3.2)	6 (1.9)	.54
Higher vocational	470 (7.7)	16 (5.2)	.63
University	64 (1.0)	1 (0.3)	.32
Ever use of oral anticoagulant medication	1386 (22.4)	87 (27.4)	<.001
Coronary heart disease	468 (7.9)	53 (18.0)	<.001
Heart failure	152 (2.5)	58 (18.8)	<.001

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Effects of Hypoperfusion in Alzheimer's Disease

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The role of hypoperfusion in Alzheimer's disease (AD) is a vital component to understanding the pathogenesis of this disease. Disrupted perfusion is not only evident throughout disease manifestation, it is also demonstrated during the pre-clinical phase of AD (i.e., mild cognitive impairment) as well as in cognitively healthy persons at high-risk for developing AD due to family history or genetic factors. Studies have used a variety of imaging modalities (e.g., SPECT, MRI, PET) to investigate AD, but with its recent technological advancements and non-invasive use of blood water as an endogenous tracer, arterial spin labeling (ASL) MRI has become an imaging technique of growing popularity. Through numerous ASL studies, it is now known that AD is associated with both global and regional cerebral hypoperfusion and that there is considerable overlap between the regions implicated in the disease state (consistently reported in precuneus/posterior cingulate and lateral parietal cortex) and those implicated in disease risk. Debate exists as to whether decreased blood flow in AD is a cause or consequence of the disease. Nonetheless, hypoperfusion in AD is associated with both structural and functional changes in the brain and offers a promising putative biomarker that could potentially identify AD in its pre-clinical state and be used to explore treatments to prevent, or at least slow, the progression of the disease. Finally, given that perfusion is a vascular phenomenon, we provide insights from a vascular lesion model (i.e., stroke) and illustrate the influence of disrupted perfusion on brain structure and function and, ultimately, cognition in AD.

ESC European Society of Cardiology

Europace (2018) **20**, 1252–1258
doi:10.1093/europace/eux220

Atrial fibrillation is associated with decreased total cerebral blood flow and brain perfusion

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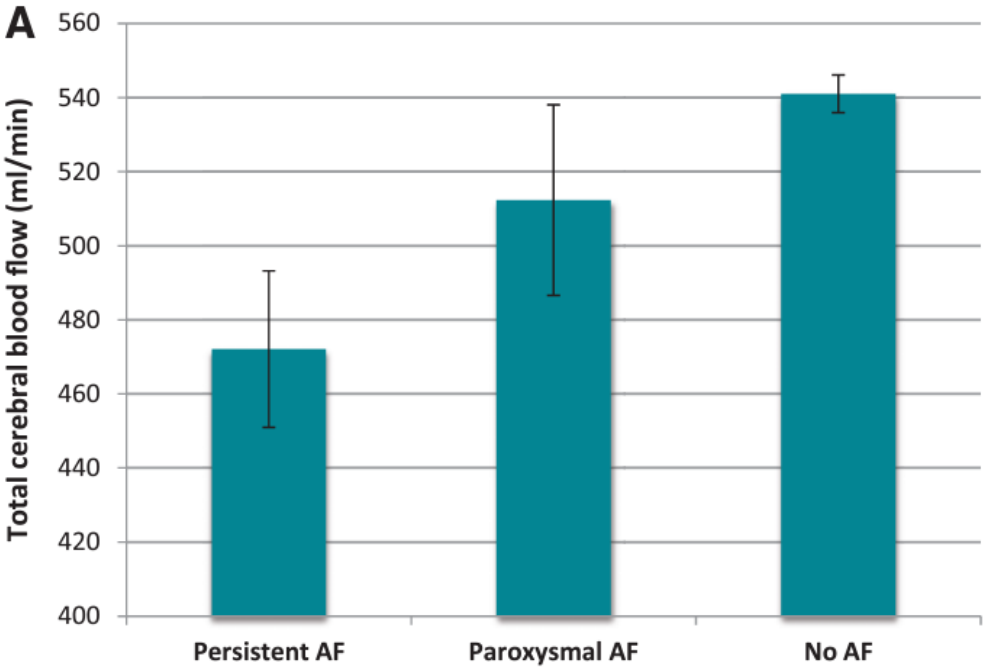

Definitions and Assessment of Cognitive Function

Domains	Assessment
Cognitive domains	Attention
	Memory
	Executive function, which is a set of mental skills that includes working memory, flexible thinking, and self-control (eg, skills to plan, organize, shift from 1 activity to another, pay attention)
	Language
	Visuospatial processing
Cognitive decline	Change in cognitive function that is greater than expected from normal aging
	Can be diagnosed through changes in standardized cognitive test scores over time
Mild cognitive impairment	Characterized by cognitive decline that is greater than expected from normal aging, but without affecting activities of daily living
Amnestic	Characterized by memory complaints
	High risk of progression toward Alzheimer disease
Single domain amnestic	Isolated memory impairment
Multiple domain amnesic	Memory impairments and deficits in one or more cognitive domains
Dementia	Defined as deficits in at least 2 cognitive domains that represent a decline from a previous level of functioning and that are sufficiently severe to affect activities of daily living

Rivard L, et al. Circulation. 2022 Feb;145(5):392-409. doi: 10.1161/CIRCULATIONAHA.121.055018.

Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia

Heart Rhythm, Vol 7, No 4, April 2010

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BACKGROUND The aging population has resulted in more patients living with cardiovascular disease, such as atrial fibrillation (AF). Recent focus has been placed on understanding the long-term consequences of chronic cardiovascular disease, such as a potential increased risk of dementia.

OBJECTIVE This study sought to determine whether there is an association between AF and dementia and whether their coexistence is an independent marker of risk.

METHODS A total of 37,025 consecutive patients from the large ongoing prospective Intermountain Heart Collaborative Study database were evaluated and followed up for a mean of 5 years for the development of AF and dementia. Dementia was sub-typed into vascular (VD), senile (SD), Alzheimer's (AD), and nonspecified (ND).

RESULTS Of the 37,025 patients with a mean age of 60.6 ± 17.9 years, 10,161 (27%) developed AF and 1,535 (4.1%) developed dementia (179 VD, 321 SD, 347 AD, 688 ND) during the 5-year follow-up. Patients with dementia were older and had higher rates of hypertension, coronary artery disease, renal failure, heart failure, and prior strokes. In age-based analysis, AF independently was significantly associated with all dementia types. The highest risk was in the younger group (<70). After dementia diagnosis, the presence of AF was associated with a marked increased risk of mortality (VD: hazard ratio [HR] = 1.38, $P = .01$; SD: HR = 1.41, $P = .001$; AD: HR = 1.45; ND: HR = 1.38, $P < .0001$).

CONCLUSION AF was independently associated with all forms of dementia. Although dementia is strongly associated with aging, the highest risk of AD was in the younger group, in support of the observed association. The presence of AF also identified dementia patients at high risk of death.

KEYWORDS Atrial fibrillation; Dementia; Alzheimer's; Hypertension; Aging; Stroke

ABBREVIATIONS **AD** = Alzheimer's disease; **AF** = atrial fibrillation; **HR** = hazard ratio; **ICD** = International Classification of Diseases; **ND** = nonspecified dementia; **SD** = senile dementia; **VD** = vascular dementia

(Heart Rhythm 2010;7:433–437)

RESEARCH ARTICLE OPEN ACCESS

Atrial Fibrillation, Stroke, and Silent Cerebrovascular Disease

A Population-based MRI Study

Lina Rydén, MD, Simona Sacuiu, MD, PhD, Hanna Wetterberg, MSc, Jenna Najar, MD, Xinxin Guo, MD, PhD, Silke Kern, MD, PhD, Anna Zettergren, PhD, Sara Shams, MD, PhD, Joana B. Pereira, PhD, Lars-Olof Wahlund, MD, PhD, Eric Westman, PhD, and Ingmar Skoog, MD, PhD

Neurology® 2021;97:e1608-e1619. doi:10.1212/WNL.0000000000012675

	Atrial fibrillation (n = 65)	No atrial fibrillation (n = 711)	*p* Value
Female, n (%)	25 (38.5)	386 (54.3)	0.019
More than mandatory education, n (%)	54 (83.1)	630 (88.7)[c]	0.224
Smoking status, n (%)			
Never smoker	21 (32.3)	273 (38.6)[e]	
Former smoker	38 (58.5)	380 (53.7)[e]	
Current smoker	6 (9.2)	54 (7.6)[e]	0.589
Alcohol risk consumption, n (%)	22 (33.8)	218 (30.8)[e]	0.675
BMI, mean ± SD, kg/m^2	26.6 ± 4.8[c]	25.9±(4.3)[f]	0.218
Heart disease, n (%)	17 (26.2)	49 (6.9)	<0.001
Hypertension, n (%)	42 (64.6)	417 (58.7)[c]	0.429
Diabetes, n (%)	14 (21.5)	83 (11.7)[c]	0.013
Hypercholesterolemia, n (%)	48 (73.8)	416 (58.6)[c]	0.017
Dementia, n (%)	2 (3.1)	8 (1.1)[c]	0.202
***APOE* ε4 allele, n (%)**	24 (38.1)[d]	230 (33.0)[g]	0.407
CHA_2DS_2-VASc score, mean ± SD	3.2 ± 1.6	2.4 ± 1.0[c]	<0.001
Anticoagulants, n (%)	34 (52.3)	7 (1.0)[c]	<0.001
Warfarin	25	6	—
NOACs	9	1	—
Symptomatic stroke, n (%)	13 (20.0)	31 (4.4)	<0.001
Infarcts on brain MRI, n (%)[a]			
Large infarcts	6 (9.2)	9 (1.3)	<0.001
ICH	0 (0)	4 (0.6)	—
Lacunes	12 (18.5)	45 (6.3)	0.002
Silent brain infarcts, n (%)[b]			
Silent large infarcts	2 (3.8)	3 (0.4)	0.043
Silent lacunes	11 (21.2)	43 (6.3)	<0.001