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

Dagress, Nikolaos; Chao, Tze-Fan; Fenelon, Guilherme; Aguinaga, Luis; Benhayon, Daniel; Benjamin, Emelia; Bunch, Jared; Chen, Lin Yee; Chen, Shih-An; Darrieux, Francisco; de Paola, Angelo; Fauchier, Laurent; Goette, Andreas; Kalman, Jonathan; Kalra, Lalit; Kim, Young-Hoon; Lane, Deirdre; Lip, Gregory; Lubitz, Steven; Marquez, Manlio

DOI: 10.1093/europace/euy046

License: Other (please specify with Rights Statement)

Document Version
Peer reviewed version

Citation for published version (Harvard):

Link to publication on Research at Birmingham portal

Publisher Rights Statement:
This is a pre-copyedited, author-produced PDF of an article accepted for publication in EP Europace following peer review. The version of record Nikolaos Dagress, Tze-Fan Chao, Guilherme Fenelon, Luis Aguinaga, Daniel Benhayon, Emelia J Benjamin, T Jared Bunch, Lin Yee Chen, Shih-An Chen, Francisco Darrieux, Angelo de Paola, Laurent Fauchier, Andreas Goette, Jonathan Kalman, Lalit Kalra, Young-Hoon Kim, Deirdre A Lane, Gregory Y H Lip, Steven A Lubitz, Manlio F Márquez, Tatjana Potpara, Domingo Luis Pozzer, Jeremy N Ruskin, Irina Savelieva, Wee Siong Teo, Hung-Fat Tse, Atul Verma, Shu Zhang, Mina K Chung,; European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on arrhythmias and cognitive function: what is the best practice?, EP Europace, euy046, https://doi.org/10.1093/europace/euy046 is available online at: https://doi.org/10.1093/europace/euy046

General rights
Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

• Users may freely distribute the URL that is used to identify this publication.
• Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
• User may use extracts from the document in line with the concept of ‘fair dealing’ under the Copyright, Designs and Patents Act 1988 (?)
• Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Download date: 10. Jan. 2020
EHRA/HRS/APHRS/LAHRS Expert Consensus on

Arrhythmias and cognitive function: What is the best practice?

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

1Department of Electrophysiology, University Leipzig - Heart Center, Leipzig, Germany; 2Taipei Veterans General Hospital, Taipei, Taiwan; 3Hospital Israelita Albert Einstein, São Paulo, Brazil; 4Centro Privado de Cardiología, Tucumán, Argentina; 5Cardiac and Vascular Institute, Memorial Health, Florida, US; 6Boston University Schools of Medicine and Public Health, Framingham Heart Study, Boston, MA, USA; 7Intermountain Medical Center, Murray, Utah, USA; 8Cardiovascular Division, Department of Medicine, University of Minnesota, USA; 9University Of Sao Paulo Medical School, Sao Paulo, Brazil; 10Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil; 11Service de Cardiologie, Centre Hospitalier Universitaire Trousseau, Université François Rabelais, Tours, France; 12Departement of Cardiology and Intensive Care Medicine, St. Vincenz-Hospital Paderborn, Working Group: Molecular Electrophysiology, University Hospital Magdeburg, Germany; 13University of Melbourne, Royal Melbourne Hospital, Melbourne, Victoria, Australia; 14King’s College London, London, UK; 15Korea University Medical Center, Seoul, Korea Republic of; 16Institute
of Cardiovascular Sciences, University of Birmingham, UK; Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; 17Massachusetts General Hospital, Boston, MA, USA; 18Instituto Nacional De Cardiologia, Electrocardiography, Mexico City, Mexico; 19School of Medicine, Belgrade University; Cardiology Clinic, Clinical Center of Serbia, Belgrade, Serbia; 20Instituto de Cardiología de Corrientes, Corrientes, Argentina; 21Cardiology Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St. George's University of London, UK; 22National Heart Centre, Singapore; 23Department of Medicine, The University of Hong Kong, Hong Kong; 24Southlake Regional Health Centre, Ontario, Canada; 25Beijing Fuwai Hospital, Beijing, China People's Republic of; 26Cleveland Clinic, Cleveland, OH, US.

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

*Corresponding author: Nikolaos Dagres, Department of Electrophysiology, University Leipzig - Heart Center, Leipzig, Germany. Tel: +493418651497; Fax: +493418651460; E-mail address: dagresnikolaos@gmail.com.
Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC), the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS).
## Table of Contents

1. Introduction .......................................................................................................................... 6

1.1. Evidence Review .................................................................................................................. 7

1.2. Relationships with Industry and Other Conflicts .............................................................. 9

2. Decline of Cognitive Function: Terminology and Epidemiology ......................................... 10

2.1 Terminology: Cognitive Decline, Mild Cognitive Impairment, and Dementia ................. 10

2.2 Epidemiology of Dementia .................................................................................................. 11

3. Methods for Assessment of Cognitive Function ................................................................. 15

4. Role of Imaging ..................................................................................................................... 19

5. Atrial fibrillation and cognitive function .............................................................................. 22

5.1 Atrial fibrillation, overt stroke and cognitive function ....................................................... 22

5.2 Atrial Fibrillation, Silent Stroke and Cognitive Function .................................................. 28

5.3 Atrial Fibrillation and Cognitive Function in the Absence of Stroke ............................... 30

5.4 Assessment of Cognitive Function in Atrial Fibrillation Patients in Clinical Practice .... 36

5.5 Prevention of Cognitive Dysfunction in Atrial Fibrillation Patients ............................... 37

6. Other arrhythmias and cognitive dysfunction ..................................................................... 41

6.1 Cognitive dysfunction in patients with regular supraventricular tachycardias .......... 41

6.2 Cognitive impairment after cardiac arrest ................................................................ ........ 41

6.3 Cardiac implantable electronic devices and cognitive dysfunction ............................... 45

6.4 Catheter Ablation ................................................................................................................ 46

6.5 Implications for EP Procedures and cognitive function .................................................... 50
1. Introduction

This expert consensus statement of the European Heart Rhythm Association (EHRA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and the Latin American Heart Rhythm Society (LAHRS) summarizes the consensus of the international writing group and is based on a thorough review of the medical literature regarding cognitive function in arrhythmias. The document is intended to describe the impact of different types of arrhythmias on cognitive function, to highlight possible risk markers for cognitive decline and to formulate implications for clinical practice regarding follow-up methods, prevention and treatment strategies. Our objective is to raise awareness of cognitive function among physicians treating patients with arrhythmias and to provide them with practical proposals that may lead to improvement of patient care in this regard.

This document reviews terminology and the epidemiology of cognitive dysfunction, methods for assessment of cognitive function and the role of imaging. Recent studies have suggested possible associations between cognitive decline and atrial fibrillation. We review the reported literature on atrial fibrillation and cognitive function, including the scenarios of atrial fibrillation with overt stroke, silent stroke, or no stroke, and then make recommendations for assessment of cognitive function and prevention of cognitive decline in patients with AF in clinical practice. The document also reviews the association of other arrhythmias and cognitive dysfunction, including settings such as post-cardiac arrest, cardiac implantable devices, such as implantable cardioverter-defibrillators (ICDs) and pacemakers, or ablation procedures. Implications for electrophysiological procedures and cognitive function are discussed. Long QT syndrome and cognitive function is not addressed in the document. For quick reference, sub-chapters are followed by a short section on consensus recommendations. The document
concludes with a summary of consensus statements, current knowledge gaps, and future directions of research.

1.1. Evidence Review

Members of the Task Force were asked to perform a detailed literature review, weigh the strength of evidence for or against a particular treatment or procedure, and include estimates of expected health outcomes for which data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that might influence the choice of particular tests or therapies are considered, as are frequency of follow-up and cost effectiveness. In controversial areas, or with regard to issues without evidence other than usual clinical practice, a consensus was achieved by agreement of the expert panel after thorough deliberations. This document was prepared by the Task Force with representation from EHRA, HRS, APHRS, and LAHRS. The document was peer-reviewed by official external reviewers representing EHRA, HRS, APHRS, and LAHRS.

Consensus statements are evidence-based and derived primarily from published data or determined through consensus opinion if data are not available. Current systems of ranking level of evidence are becoming complicated in a way that their practical utility might be compromised. In contrast to guidelines, we opted for an easier and user-friendly system of ranking using ‘coloured hearts’ that should allow physicians to easily assess the current status of the evidence and consequent guidance (Table 1). This EHRA grading of consensus statements does not have separate definitions of the level of evidence. This categorization, used for consensus statements, must not be considered as directly similar to that used for official society
guideline recommendations, which apply a classification (Class I-III) and level of evidence (A, B and C) to recommendations used in official guidelines.

Thus, a green heart indicates a ‘should do this’ consensus statement or indicated treatment or procedure that is based on at least one randomized trial, or is supported by strong observational evidence that it is beneficial and effective. A yellow heart indicates general agreement and/or scientific evidence favouring a ‘may do this’ statement or the usefulness/efficacy of a treatment or procedure. A ‘yellow heart’ symbol may be supported by randomized trials based on a small number of patients or which is not widely applicable. Treatment strategies for which there is scientific evidence of potential harm and should not be used (‘do not do this’) are indicated by a red heart.

**Table 1. Scientific rationale of recommendations**.

<table>
<thead>
<tr>
<th>Definitions related to a treatment or procedure</th>
<th>Consensus statement instruction</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific evidence that a treatment or procedure is beneficial and effective. Requires at least one randomized trial, or is supported by strong observational evidence and authors’ consensus (as indicated by an asterisk).</td>
<td>‘Should do this’</td>
<td><img src="image" alt="Green Heart" /></td>
</tr>
<tr>
<td>General agreement and/or scientific evidence favour the usefulness / efficacy of a treatment or procedure. May be supported by randomized trials based on a small number of patients or which is not widely applicable.</td>
<td>‘May do this’</td>
<td><img src="image" alt="Yellow Heart" /></td>
</tr>
<tr>
<td>Scientific evidence or general agreement not to use or recommend a treatment or procedure.</td>
<td>‘Do not do this’</td>
<td><img src="image" alt="Red Heart" /></td>
</tr>
</tbody>
</table>
*This categorisation for our consensus document should not be considered as being directly similar to that used for official society guideline recommendations which apply a classification (I-III) and level of evidence (A, B and C) to recommendations.

Finally, this is a consensus document that includes evidence and expert opinions from several countries. The pharmacological and non-pharmacological antiarrhythmic approaches discussed may, therefore include drugs that do not have the approval of governmental regulatory agencies in all countries.

1.2. Relationships with Industry and Other Conflicts

All members of the writing group, as well as reviewers, have disclosed any potential conflict of interest in detail, at the end of this document. All recommendations were voted upon by the writing committee independently and reached ≥80% consensus for inclusion in recommendations tables. Each partner society officially reviewed the document and all reviewer comments were addressed. The final document and recommendations were approved by each partner society.
2. Decline of Cognitive Function: Terminology and Epidemiology

2.1 Terminology: Cognitive Decline, Mild Cognitive Impairment, and Dementia

Cognitive decline that is greater than expected from normal aging can be ascertained from changes in standardized cognitive test scores over time. Examples of standardized cognitive tests that evaluate different cognitive domains include Delayed Word Recall test (short-term memory),
Digit Symbol Substitution test (executive function and processing speed), and Word Fluency test (executive function and expressive language).

Mild cognitive impairment is an intermediate stage between the expected cognitive decline of normal aging and the more serious abnormality of dementia. Mild cognitive impairment is characterized by declines in cognitive function and objective long-term cognitive deficit that does not affect activities of daily living.

Dementia is defined as deficits in ≥2 cognitive domains that represent a decline from previous level of functioning and that are sufficiently severe to affect activities of daily living. Both mild cognitive impairment and dementia can be further classified into subtypes. Mild cognitive impairment can be sub-typed into 4 groups (based on the scheme adopted by the National Institute on Aging Alzheimer’s Disease Centers Program for the Uniform Data Set) as amnestic or non-amnestic, single or multiple domain.

Dementia can be classified into etiologic diagnoses: Alzheimer’s disease, vascular dementia, Lewy body dementia, frontotemporal dementia, and other dementias.
2.2 Epidemiology of Dementia

A recent systematic review provided some insights into the contemporary (1980–2009) prevalence of dementia in individuals aged ≥60 years in 21 Global Burden of Disease regions: age-standardized prevalence for those aged ≥60 years varied in a narrow band (5%–7% in most world regions), with a higher prevalence in Latin America (8.5%), and a lower prevalence in the four sub-Saharan African regions (2%–4%).

Approximately 35.6 million people lived with dementia worldwide in 2010, with numbers expected to almost double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050. In 2010, 58% of all people with dementia lived in countries with low or middle incomes, with this proportion anticipated to rise to 63% in 2030 and 71% in 2050. Thus, dementia is a burgeoning global public health problem that prompts an urgent and more comprehensive understanding of its risk factors with the aim to discover novel prevention strategies.

The burden of dementia is rapidly increasing owing to the aging of the population. Other than advancing age, risk factors for dementia, particularly vascular dementia, have been extensively studied from an epidemiological perspective. Broadly, they can be classified as dementia due to non-modifiable risk factors, lifestyle factors, physiological risk factors, or clinical cardiovascular or cerebrovascular disease. Selected risk factors are shown in Table 2 and include many of the risk factors included in stroke risk scores in AF.

Table 2. Selected Risk Factors for Dementia

<table>
<thead>
<tr>
<th>Non-modifiable risk factors</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic factors</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Dementia prevalence increases exponentially</td>
</tr>
<tr>
<td></td>
<td>With age&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Dementia prevalence greater in women than men&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td>VaD risk greater in blacks than whites&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Genetic factors</strong></td>
<td>Genetic alterations may affect cognitive function, e.g., apolipoprotein E ε4 allele and ABCA7 are associated with increased risk of AD; C9ORF72, MAPT, GRN gene mutations associated with frontotemporal dementia; rs12007229 is associated with VaD&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Lifestyle factors</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>Lower education is associated with higher VaD risk&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Physical activity</strong></td>
<td>Increased physical activity is associated with lower risk of general dementia, Alzheimer’s dementia, and VaD risk, which was attenuated with further adjustment for baseline cognitive, psychosocial, and vascular factors. Review reported that 7 out of 8 studies found an association between increased physical activity and lower risk of cognitive decline&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td>U-shaped association between body mass index and dementia, with dementia risk higher</td>
</tr>
</tbody>
</table>

---

<sup>1. Data from [Source](#). 2. Data from [Source](#). 3. Data from [Source](#). 4. Data from [Source](#). 5. Data from [Source](#). 6. Data from [Source](#). 7. Data from [Source](#). 8. Data from [Source](#). 9. Data from [Source](#). 10. Data from [Source](#). 11. Data from [Source](#). 12. Data from [Source](#).</sup>
in individuals who were obese or underweight

**Smoking**

Meta-analysis reported that current smokers have higher risk of cognitive decline and dementia over follow up, than non-smokers or former smokers

**Social support and networks**

Compared with small social networks, larger social networks were associated with a lower risk of incident dementia over time.

### Cardiovascular risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>Higher mid-life blood pressure was associated with higher dementia risk and cognitive decline</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>Diabetes was associated with increased dementia risk and cognitive decline</td>
</tr>
<tr>
<td>Lipids</td>
<td>Higher total serum cholesterol was associated with higher VaD and AD risk</td>
</tr>
</tbody>
</table>

### Clinical cardiovascular or cerebrovascular disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>Stroke is associated with increased dementia risk</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>AF is associated with increased dementia risk</td>
</tr>
<tr>
<td>Vascular/Peripheral arterial disease</td>
<td>Carotid arterial disease is associated with</td>
</tr>
</tbody>
</table>
| | incident dementia risk and cognitive decline[^26],[^27] Lower ankle brachial index is associated with increased dementia risk[^28]  
| | Sleep apnoea | Sleep-disordered breathing is associated with an increased risk of cognitive impairment and a small worsening in executive function.[^29]  

[^1]: ABCA7, ATP-binding cassette transporter A7; AD, Alzheimer’s disease; AF, atrial fibrillation;  
[^2]: C9ORF72, chromosome 9 open reading frame 72; GRN, granulin; MAPT, microtubule-associated protein tau; VaD, vascular dementia
3. Methods for Assessment of Cognitive Function

Impairments of cognitive function often can be subtle and insidious, presenting as missed appointments, mislaying objects or minor problems at work or home, that are often attributed to stress, age or pressure of work. Any difference in appearance, behaviour or functioning reported by the patient or the family should alert the physician to the need for a formal assessment. The aim of this assessment is to examine higher cortical functions (attention, orientation, memory, language, praxis and executive function) from patient narrative, collateral information from families, clinical examination and standardized tests of cognitive function. For assessment of cognitive impairment a combination of tools and methods are used (Table 3).

During the assessment, particular attention needs to be paid to aspects such as vagueness with dates and events, repetition, inappropriate or fixed ideas. A collateral account from a caregiver can provide clarification of symptoms and their duration. Specific areas requiring attention include features of depression, neurological or psychiatric diseases, drug/medication use, uncorrected visual and hearing problems, infections, cardiac/respiratory/renal failure or fast atrial fibrillation, all of which potentially affect cognitive function. Investigations include complete blood count, blood glucose, creatinine, electrolytes, calcium, liver and thyroid function tests, serum folate and B₁₂ levels. Syphilis serology should be checked in high risk patients. Magnetic resonance imaging can be helpful to estimate cerebrovascular and degenerative disease load and exclude tumours or normal pressure hydrocephalus.

A list of cognitive assessment tools is provided in Table 4. Several tools are available for cognitive assessment, but there is no consensus on a preferred approach. The choice of tool should vary with the purpose of testing and other factors, such as availability, familiarity and feasibility. Common assessment tools are the two-step general practitioner assessment of
cognition (GPCOG) and the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE), both of which have been validated in large populations. Standardised assessment tools are not diagnostic instruments and results need to be interpreted in the context of all available evidence.

Table 3: Assessment of cognitive impairment

<table>
<thead>
<tr>
<th>Suspect</th>
<th>Patient history, appearance, changes in behaviour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm</td>
<td>Collateral history from family</td>
</tr>
<tr>
<td>Examine</td>
<td>Full medical examination, brief screening assessment</td>
</tr>
<tr>
<td>Investigate</td>
<td>Renal/liver/respiratory/thyroid compromise, B12, folate; syphilis serology (in high-risk patients)</td>
</tr>
<tr>
<td>Exclude</td>
<td>Depression, neurological/psychiatric disease, medication/drug use</td>
</tr>
<tr>
<td>Measure</td>
<td>Psychometric testing using validated battery</td>
</tr>
<tr>
<td>Image</td>
<td>Multimodal MRI (T1, T2, T2*, DWI) for brain changes</td>
</tr>
<tr>
<td>Establish</td>
<td>Diagnosis based on clinical + psychometric + imaging</td>
</tr>
</tbody>
</table>

Table 4: Comparison of commonly used brief cognitive assessment tools and a list of more complex cognitive assessments †

<table>
<thead>
<tr>
<th>Cognitive assessment tool</th>
<th>Number of items</th>
<th>Average completion time in elderly (≥65 years) patients, minutes</th>
<th>Equipment required</th>
<th>Cognitive domains assessed</th>
<th>Informant component</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMT45</td>
<td>4</td>
<td>1</td>
<td>Verbal</td>
<td>Memory</td>
<td>a0-4</td>
</tr>
<tr>
<td>Test</td>
<td>Items</td>
<td>Time</td>
<td>Format</td>
<td>Verbal</td>
<td>Motor</td>
</tr>
<tr>
<td>--------------</td>
<td>-------</td>
<td>------</td>
<td>-------------------------</td>
<td>--------</td>
<td>-------</td>
</tr>
<tr>
<td>SIS</td>
<td>6</td>
<td></td>
<td>paper</td>
<td>Verbal</td>
<td>-</td>
</tr>
<tr>
<td>Mini-Cog</td>
<td>6</td>
<td>3</td>
<td>Pen &amp; paper</td>
<td>Plus</td>
<td>-</td>
</tr>
<tr>
<td>AMT</td>
<td>10</td>
<td>3</td>
<td>Verbal</td>
<td>Plus</td>
<td>Plus</td>
</tr>
<tr>
<td>MIS</td>
<td>4</td>
<td>4</td>
<td>Verbal</td>
<td>-</td>
<td>Plus</td>
</tr>
<tr>
<td>6CIT</td>
<td>6</td>
<td>5-6</td>
<td>Pen &amp; paper</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>GPCOG</td>
<td>9</td>
<td>5-6</td>
<td>Pen &amp; paper</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>MMSE*</td>
<td>30</td>
<td>8</td>
<td>Pen, paper &amp; watch</td>
<td>-</td>
<td>Plus</td>
</tr>
<tr>
<td>MOCA</td>
<td>30</td>
<td>10</td>
<td>Pen &amp; paper</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>OCS</td>
<td>10</td>
<td>15-20</td>
<td>Pen &amp; paper</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>ACE</td>
<td>100</td>
<td>20</td>
<td>Pen, paper, watch &amp;</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

More complex and extended cognitive examinations‡:
- **3MS**: extension of MMSE including verbal fluency and further memory testing; overall score 0-100; score <78 for those aged ≥65 years
- **CAMCOG**: 80 mins, structured history taking from patient and informant, structured examination and mental state assessment
- **CASI**: 16-item informant questionnaire comparing patient cognition now to 10-years ago; each rated on 5-point Likert scale
- **IQCODE**: 16-item informant questionnaire comparing patient cognition now to 10-years ago; each rated on 5-point Likert scale

---

### Notes
- **3MS**: Modified Mini Mental Status Examination; **6CIT**: 6-item Cognitive Impairment Test; **ACE**: Addenbrooke’s Cognitive Examination; **AMT**: Abbreviated Mental Test; **CAMCOG**: Cambridge Cognitive Examination; **CASI**: Cognitive Abilities Screening Instrument; **CDT**: Clock Drawing Test; **GPCOG**: General Practitioner Assessment of Cognition; **InQ**: Informant
Questionnaire; MMSE, Mini Mental State Examination; MIS, Memory Impairment Screen; MOCA, Montreal Cognitive Assessment; OCS, Oxford Cognitive Screen; SIS, Six-Item Screener; STM, short-term memory: *Standardised MMSE is also available; †adapted from Woodford & George31; ‡ not an exhaustive list

| -   | not specifically tested |
| +   | minimal assessment      |
| ++  | moderate assessment     |
| +++ | relatively extensive assessment |
4. Role of Imaging

Brain imaging studies can identify vascular disease as a cause of dementia. In an autopsy study of patients with dementia, pathologic diagnoses implicated vascular disease in about 25% of subjects, half of whom had pure vascular disease. The three main causes of vascular cognitive impairment (VCI) are large vessel strokes, small vessel disease (SVD), and micro-haemorrhages. The preferred imaging modality, magnetic resonance imaging (MRI), has high specificity and sensitivity for detecting these changes and is an important adjunct to clinical and psychometric assessments. However, imaging findings need to be interpreted in the clinical context because of uncertain correlation with symptoms or psychometric test performance.

Structural imaging is undertaken using T1- and T2-weighted spin echo sequences to identify infarcts and macro-haemorrhages, T2*-weighted gradient echo sequences for micro-haemorrhages, fluid-attenuated inversion recovery (FLAIR) imaging for incomplete infarcts and leukoaraiosis and diffusion weighted imaging (DWI) for visualising the integrity of functional network fibre tracts not captured by other imaging techniques. MRI provides several markers of micro- and macrostructural organization that are sensitive to change, related to clinical endpoints and has the potential to predict cognitive trajectories in individual patients.

MRI signs that predict potential cognitive impairments include a) large or bilateral infarcts due to large vessel disease; b) strategic infarcts secondary to embolization in regions as hippocampus, dominant thalamus, medial temporal, deep frontal; c) lacunes, white matter hyper-intensities (leukoaraiosis) and haemorrhages associated with small vessel disease; and d) lobar micro-haemorrhages representative of amyloid angiopathies. In addition, although global cerebral atrophy and/or medial-temporal lobe atrophy may suggest an element of Alzheimer’s
Disease (mixed cognitive impairment), subcortical infarcts, per se, may trigger progressive focal thinning and grey matter atrophy in connected temporal and frontal cortical areas.\textsuperscript{31}

Imaging of cerebral blood flow using arterial spin labelling (ASL), metabolic imaging with proton magnetic resonance spectroscopy (1H-MRS) and dynamic contrast-enhanced MRI (DCEMRI) can help estimate the extent of injury, vessel permeability and inflammation. Although these can differentiate between dementias and separate pathological changes from those due to aging, they remain research techniques with limited clinical application.

PET scans have also been used to assess brain metabolic function, inflammation, amyloid or tau protein, which may be helpful in differentiating some types of dementia.\textsuperscript{53} An overview of commonly used imaging modalities in cognitive impairment is provided in Table 5.

\textbf{Table 5: Commonly used brain imaging modalities in cognitive impairment}

<table>
<thead>
<tr>
<th>Modality</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>Large infarcts/haemorrhage, established small vessel disease, other pathologies, limited application</td>
</tr>
<tr>
<td>MRI</td>
<td>Imaging of choice for assessment of cognitive impairment\textsuperscript{53}</td>
</tr>
<tr>
<td>T1 &amp; T2 MRI</td>
<td>Highly sensitive to old and new infarcts, estimation of white matter disease load, other pathologies (e.g. malignancies, cerebral oedema)</td>
</tr>
<tr>
<td>T2* MRI</td>
<td>Blood and blood products (e.g. haemorrhages), micro-haemorrhages, haemosiderin deposition, amyloid angiopathies</td>
</tr>
<tr>
<td>DWI MRI</td>
<td>Extremely sensitive to early ischaemic changes (recent infarcts including micro-infarcts), integrity of fibre tracts, extensively used for tractography assessing the structural integrity of connecting white</td>
</tr>
<tr>
<td>1H-MRS</td>
<td>Measurement of neuronal damage, inflammation, gliosis, differentiation between pathology and normal aging</td>
</tr>
</tbody>
</table>

1H-MRS: Proton magnetic resonance spectroscopy; CT: computed tomography; DWI: Diffusion weighted imaging; MRI: magnetic resonance imaging
5. Atrial fibrillation and cognitive function

5.1 Atrial fibrillation, overt stroke and cognitive function

Evidence suggests that atrial fibrillation (AF) is associated with a higher risk for cognitive impairment and dementia, with or without a history of clinical stroke. Two meta-analyses that included both cross-sectional and prospective studies specifically examined the incidence of dementia in patients with AF and strokes. These meta-analyses found similar estimates of the risk ratios of cognitive impairment or dementia of 2.43 and 2.70 (Table 6).

It is uncertain whether or not risk of cognitive impairment and dementia vary by paroxysmal versus persistent AF. Many of the studies examining AF type were small and underpowered and the factors that impact progression, such as rhythm control approaches and physician approach to the patient management, can introduce study biases. In a small hypothesis generating cross-sectional study from the Atherosclerosis Risk in Communities Cohort persistent but not paroxysmal AF classified by ambulatory telemetry monitoring was associated with lower cognitive function. Another small cross-sectional study reported that cognitive performance did not significantly differ by AF burden, but the number of subclinical cerebral ischemia areas was higher in individuals with persistent compared to paroxysmal AF. More conclusive understanding of the relation of AF burden to cognitive decline and dementia will require larger and longitudinal studies. The relation between AF type and cognitive impairment and dementia is further complicated by the sometimes arbitrary definition of the AF type in the individual patient.

Unfortunately there are no randomized data examining the efficacy of therapies and in particular of individualised management to prevent dementia in individuals with AF. Of interest, the Framingham Heart Study has examined temporal trends in the incidence of dementia
and noted that the risk of dementia associated with AF declined over 3 decades (1970s to the early 2010s).\textsuperscript{58} One speculation is that improved anticoagulation and treatment of risk factors were responsible for the declining incidence of dementia in individuals with AF. Another piece of inferential evidence, supporting the benefit of preventing stroke as a strategy to prevent dementia in individuals with AF, are observational meta-analyses (Table 6). In individuals with AF but \textit{without} stroke at baseline the risk of dementia and cognitive decline is more modest (relative risk (RR) 1.37, 95% CI 1.08 to 1.73) than in individuals \textit{with} both AF and a history of stroke (RR 2.7, 95% CI 1.82 to 4.00).\textsuperscript{25}

Systemic anticoagulation remains the cornerstone of stroke prevention treatment. By meta-analysis, adjusted-dose warfarin is associated with a 64% (95% CI 49 to 74%) significantly lower risk of stroke (Table 7), whereas aspirin alone was associated with a 19% (95% CI -1 to 35%) non-significant lower stroke risk.\textsuperscript{59} In studies comparing warfarin and aspirin, warfarin was associated with a 38% (95% CI 18 to 52%) stroke reduction, when compared to aspirin alone.\textsuperscript{59}

A meta-analysis of the 4 randomized trials comparing the non-vitamin K antagonist oral anticoagulants (NOACs) to warfarin, demonstrated that the NOACs were associated with a significant risk reduction (RR 0.81, 95% CI 0.73 to 0.91) in overall stroke and systemic emboli, in part driven by the significant risk reduction (RR 0.48, 95% CI 0.39 to 0.59) in haemorrhagic stroke.\textsuperscript{60}

Since a prior stroke represents the strongest predictor of stroke recurrence, all patients who have AF and have had an ischemic stroke, should be anticoagulated, unless an absolute contraindication exists.\textsuperscript{61} Of interest, a recent observational study using a propensity score matched analysis reported that in individuals with a history of AF and dementia, persistent use of warfarin therapy was uncommon (16%), but was associated with the prevention of stroke (HR,
0.74; 95% CI, 0.54–0.996; P=0.047) and death (HR, 0.72; 95% CI, 0.67-0.87; P<0.001). A recent updated metaanalysis reported a significant reduction of stroke, stroke or systemic embolism, hemorrhagic stroke, and intracranial bleeding in AF patients with previous stroke or transient ischemic attack receiving NOACs compared with warfarin. 

63
Table 6. Meta-analyses relating atrial fibrillation to dementia and cognitive impairment

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Outcome</th>
<th>Inclusions/exclusions</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kwok et al., 2011$^{24}$</td>
<td>Meta-analysis cross-sectional and prospective studies</td>
<td>Dementia</td>
<td>Patients with H/o stroke</td>
<td>OR, 2.43; 95% CI, 1.70-3.46; p&lt;0.001; 7 studies; N=2425; $I^2=10%$</td>
</tr>
<tr>
<td>Kalantarian, et al. 2013$^{25}$</td>
<td>Meta-analysis cross-sectional and prospective studies</td>
<td>Cognitive impairment &amp; dementia</td>
<td>Patients with H/o stroke</td>
<td>RR, 2.70; 95% CI, 1.82-4.00; 7 studies; N=2409; $I^2=32.3%; p=0.18$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Excluding patients with or adjusting for H/o stroke</td>
<td>RR, 1.34; 95% CI, 1.13-1.5 10 studies</td>
</tr>
</tbody>
</table>

H/o: history of; OR: Odds Ratio; RR: Relative Risk

Table 7. Meta-analyses examining anti-coagulation strategies in atrial fibrillation relating to stroke

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Outcome</th>
<th>Inclusions/exclusions</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hart, et al. 2007$^{59}$</td>
<td>Meta-analysis adjusted dose warfarin &amp; aspirin</td>
<td>Stroke</td>
<td>6 RCTs Warfarin vs. Placebo N=2900</td>
<td>RR, 64% reduction; 95% CI, 49-74% Absolute reduction: 1º prevention 2.7%/yr</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Event Type</td>
<td>NOAC Group Size</td>
<td>Warfarin Group Size</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------</td>
<td>---------------------</td>
<td>-----------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Ruff, et al. 2014&lt;sup&gt;60&lt;/sup&gt;</td>
<td>Meta-analysis</td>
<td>Stroke &amp; Systemic Emboli</td>
<td>n=29,312 NOAC; n=29,272 Warfarin</td>
<td>RR, 0.81; 95% CI, 0.73–0.91; p&lt;0.001; I²=47%; p=0.13</td>
</tr>
<tr>
<td></td>
<td>Phase 3 RCTs:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-LY,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROCKET AF,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENGAGE AF–TIMI 48</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ischaemic stroke</td>
<td>n=29,292 NOAC; n=29,221 Warfarin</td>
<td>RR, 0.92; 95% CI, 0.83-1.02; p=0.10</td>
<td>P=32%; p=0.22</td>
</tr>
</tbody>
</table>

7 RCTs Aspirin vs. Placebo or no Rx
N=3900
RR, 19% reduction; 95% CI, -1 to 35%
1<sup>o</sup> prevention 0.8%/yr
2<sup>o</sup> prevention 2.5%/yr

8 RCTs Warfarin vs. aspirin Rx
N=3647
RR, 38% reduction; 95% CI, 18-52%
1<sup>o</sup> prevention 0.7%/yr
2<sup>o</sup> prevention 7.0%/yr
<table>
<thead>
<tr>
<th></th>
<th>Haemorrhagic stroke</th>
<th>RR, 0.49; 95% CI, 0.38–0.64; p&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=29,292 NOAC;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=29,221 Warfarin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I²=34%; p=0.21</td>
<td></td>
</tr>
</tbody>
</table>

H/o: history of; NOAC: Non-Vitamin K Antagonist Oral Anticoagulant; RCT: Randomized Clinical Trial; RR: Relative Risk
5.2 Atrial Fibrillation, Silent Stroke and Cognitive Function

It is well established that AF increases the risk of clinical stroke by four- to five-fold, and patients with a clinical history of stroke are at increased risk of developing dementia.\textsuperscript{64-67} However, AF is also associated with cognitive dysfunction ranging from mild impairment to overt dementia, independently of clinical stroke as well as multiple shared risk factors.\textsuperscript{64, 67} It is also well established that AF and cognitive impairment share common risk factors, including advanced age, diabetes, hypertension, sleep apnoea and chronic heart failure. Moreover, data have demonstrated a significant (34\%) increase in the risk of cognitive impairment in patients with AF in the absence of clinical stroke, even after adjustment for shared risk factors.\textsuperscript{64, 25} Thus, additional mechanisms beyond clinically recognized stroke and shared risk factors may link AF and cognitive impairment. One of the leading potential mechanisms is the occurrence of silent cerebral infarcts, which occur significantly more frequently than clinical stroke and are particularly common in patients with AF.\textsuperscript{68, 69}

Detection of cerebral ischemic events on MRI is based on acute hyperintense lesions on diffusion-weighted imaging. Brain MRIs reveal evidence of silent cerebral infarcts in a significant percentage of patients with AF.\textsuperscript{69} The incidence is related to specifications of MRI and depends on the definition applied.\textsuperscript{70} AF is associated with a more than two-fold increase in the risk of developing silent cerebral infarcts.\textsuperscript{69} Although silent infarcts are not associated with clinically apparent acute neurologic deficits, data suggest a significant association between silent infarcts and the development of cognitive decline and dementia.\textsuperscript{71-73} Silent infarcts in patients with AF are believed to be micro-embolic in origin and are identified as small, well-demarcated lesions, often in clusters, and are most prevalent in the frontal lobes.\textsuperscript{71} The pattern of silent infarct distribution is similar to that seen in vascular dementia, in which most silent strokes affect
frontal circuit components (frontal cortex, basal ganglia, thalamus) that play an important role in executive functioning.\textsuperscript{74} Thus, the term “silent infarct” is probably a misnomer. Because of their small size and location away from speech and motor centres, these micro-injuries do not cause clinically apparent acute focal neurological deficits. However, with the accumulation of silent infarcts and associated repetitive brain injuries over time, micro-injuries may contribute to the development of cognitive impairment. At least one study has specifically addressed the role of subclinical cerebrovascular disease as a mediator between AF and cognitive impairment. In a subset of stroke-free participants in the Atherosclerosis Risk in Communities (ARIC) study who underwent repeat brain magnetic resonance imaging after approximately 12 years, AF was associated with cognitive decline only in those patients who had developed incident silent cerebral infarcts.\textsuperscript{75}

There is a paucity of evidence regarding the effect of anticoagulation on silent cerebral infarcts and the risk of cognitive impairment. One recent study addressed this issue by evaluating the time in therapeutic range (TTR) as an indicator of the effectiveness of warfarin anticoagulation in patients with AF. These investigators observed a consistent increase in the risk of dementia as the percentage of TTR decreased.\textsuperscript{76} The association between warfarin therapy and dementia was “U”-shaped, with increased risk of dementia among patients with overexposure and underexposure to warfarin (i.e., supra-therapeutic and sub-therapeutic international normalized ratios [INRs]).\textsuperscript{76} This may be due to cumulative brain injury from cerebral micro-bleeds and silent infarcts, respectively. Recent observational data also suggest that delaying warfarin therapy in patients with AF and no history of dementia, including patients at low as well as high risk for stroke, significantly increases the risk for developing incident dementia.\textsuperscript{12, 77}

Whether the use of the NOACs will offer greater protection than warfarin in preventing AF-
related cognitive impairment and dementia remains to be determined. The significantly lower intracranial haemorrhage and microhemorrhage rates, the lower risk of mortality with intracranial haemorrhage with use of NOACs compared to warfarin, coupled with comparable degrees of protection against thromboembolic stroke and substantially lower variability in therapeutic anticoagulation effect over time with NOACs, offer reasons to hypothesize that these agents may be advantageous to warfarin regarding protection against cognitive impairment in patients with AF but this requires confirmation. Initial findings seem to confirm this hypothesis.

5.3 Atrial Fibrillation and Cognitive Function in the Absence of Stroke

Longitudinal studies have shown that dementia is more common in patients diagnosed with AF, even in the absence of stroke. A meta-analysis of 8 prospective studies evaluating the relationship between AF and incident dementia in patients without stroke and baseline normal cognitive function included a total of 77,668 patients of whom 15% had AF. After a mean follow-up of about 8 years, 6.5% of patients developed dementia. AF was independently associated with increased risk of incident dementia (HR 1.42 95% CI 1.17-1.72, p<0.001). This result was confirmed by a longitudinal analysis from the Cardiovascular Health Study including 5,150 participants without baseline history of stroke. Incident AF occurred in 11% of patients, with faster decline in mean cognitive function scores, measured using the Modified Mini Mental State Exam (3MSE), compared with patients in sinus rhythm. Although both AF and dementia are diseases of aging, in two large observational studies the highest relative risk of dementia was observed in younger AF patients <70 years of age. A recent cross-sectional study indicated that in individuals with heart failure with reduced and preserved systolic ejection fraction, AF
was associated with an adjusted higher odds of presence and severity of prevalent cognitive impairment. However, in very old individuals (≥80 years) the relationship between AF and dementia seems to be mostly mediated by concomitant risk factors.

The relationship between AF and cognitive decline may occur through a variety of pathological mechanisms. Given the relationship between AF and stroke, vascular dementia may be an obvious contributor to cognitive decline, encompassing both multi-infarct dementia and small vessel disease dementia. The second form of dementia in AF patients is Alzheimer’s disease, which is the most common type of dementia overall. AF has been identified as a risk factor for Alzheimer’s disease. Alzheimer’s disease is the result of accumulation of abnormally folded beta-amyloid and tau proteins forming cerebral plaques which exert cytotoxic effects leading to cerebral atrophy. Interestingly, misfolded atrial natriuretic peptides may lead to development of amyloid fibrils and deposits in the atria of elderly patients with AF causing a specific atrial cardiomyopathy classified as EHRAS IVa. However, if AF and Alzheimer’s disease share a common link with regards to protein misfolding and amyloidogenesis, it does not appear to be through the APOE ε4 allele. Other studies suggest that the occurrence of Alzheimer’s disease is related to hypoperfusion, inflammation, oxidative stress and endothelial dysfunction. All these factors may be induced by several non-cardiac diseases resulting in an atrial cardiomyopathy which in turn, leads to AF in the sense of both AF and Alzheimer's disease being the result of third confounding factors. Additionally, several circulating biomarkers of oxidative stress, inflammation and endothelial dysfunction are elevated during AF. These factors are also linked to cerebral small vessel disease; therefore, AF may provide a specific milieu for non-stroke related cognitive decline and dementia. For example, hippocampal atrophy in AF patients may be mediated by altered cerebral perfusion due to irregular RR
intervals, abnormal or rapid heart rate, and reduced blood pressure caused by AF, since the hippocampus is one of the most perfusion-sensitive structures of the brain\textsuperscript{95,99-102}.

Interestingly, patients with AF had lower total brain volume compared to those without AF, independent of cerebral emboli in a large cross sectional study\textsuperscript{103}. In addition, recently, AF was associated with a decrease in total cerebral blood flow and brain perfusion in an unselected elderly cohort\textsuperscript{104}. These results may, at least in part, explain the association of AF with reduced relative brain volume and cognitive impairment.

A schematic overview of the various mechanisms, through which AF may lead to cognitive impairment is illustrated in Figure 1.

A number of trials are currently examining, as the primary or secondary outcome, the effect of different therapies including anticoagulation and of different interventions on cognitive function in patients with AF. A non-exhaustive list of such studies is found in Table 8:
Table 8: Studies that are currently examining the effect of different therapies and interventions on cognitive function in patients with AF or atrial tachyarrhythmias

<table>
<thead>
<tr>
<th>Study name</th>
<th>Target population</th>
<th>Intervention</th>
<th>Cognitive function as outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impact of Anticoagulation Therapy on the Cognitive Decline and Dementia in Patients With Non-Valvular Atrial Fibrillation (CAF), NCT03061006</td>
<td>Non-valvular AF</td>
<td>Randomization to Dabigatran or Warfarin</td>
<td>Primary outcome: incident dementia and moderate decline in cognitive function</td>
</tr>
<tr>
<td>Comparison of Brain Perfusion in Rhythm Control and Rate Control of Persistent Atrial Fibrillation, NCT02633774</td>
<td>Persistent AF</td>
<td>Randomization to rhythm or rate control</td>
<td>Primary outcome: cognitive assessment</td>
</tr>
<tr>
<td>Cognitive Impairment Related to Atrial Fibrillation Prevention Trial (GIRAF), NCT01994265</td>
<td>AF patients &gt; 65 years old and CHA2DS2-VASc &gt; 1</td>
<td>Randomization to Dabigatran or Warfarin</td>
<td>Primary outcome: cognitive impairment</td>
</tr>
<tr>
<td>Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST), NCT01288352</td>
<td>AF patients</td>
<td>Randomization to early standardised rhythm control or usual care</td>
<td>Secondary outcome: cognitive function</td>
</tr>
<tr>
<td>Study Title</td>
<td>Eligibility</td>
<td>Randomization</td>
<td>Secondary Outcome</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Apixaban During Atrial Fibrillation Catheter Ablation: Comparison to Vitamin K Antagonist Therapy (AXAFA), NCT02227550</td>
<td>Patients undergoing catheter ablation of non-valvular AF</td>
<td>Randomization to Vitamin K antagonists or Apixaban</td>
<td>Secondary outcome: cognitive function change</td>
</tr>
<tr>
<td>NOACs for Stroke Prevention in Patients With Atrial Fibrillation and Previous ICH (NASPAF-ICH), NCT02998905</td>
<td>Patients with a high-risk of AF and previous intracerebral hemorrhage</td>
<td>Randomization to non-Vitamin-K-antagonist oral anticoagulant or acetylsalicylic acid</td>
<td>Secondary outcome: cognitive function</td>
</tr>
<tr>
<td>Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes (NOAH), NCT02618577</td>
<td>Patients with atrial high rate episodes and at least two stroke risk factors but without AF</td>
<td>Randomization to edoxaban or acetylsalicylic acid or placebo</td>
<td>Secondary outcome: cognitive function</td>
</tr>
<tr>
<td>Optimal Anticoagulation for Higher Risk Patients Post-Catheter Ablation for Atrial Fibrillation Trial (OCEAN), NCT02168829</td>
<td>Patients having undergone a successful AF catheter ablation</td>
<td>Randomization to rivaroxaban or acetylsalicylic acid</td>
<td>Secondary outcome: neuropsychological testing</td>
</tr>
<tr>
<td>Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive</td>
<td>Patients with non-valvular AF and with low risk of</td>
<td>Randomization to rivaroxaban or</td>
<td>Primary outcome: Composite endpoint of stroke, TIA and</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Study Description</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Secondary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impairment in AF (BRAIN-AF), NCT02387229</td>
<td>stroke</td>
<td>acetylsalicylic acid</td>
<td>neurocognitive decline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Secondary outcomes:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neurocognitive decline, new</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>onset of cognitive impairment</td>
</tr>
</tbody>
</table>
The results of these studies will help to improve our understanding of the relationship between AF and cognitive function and provide us with more data for possible prevention of cognitive decline by treatment of AF.

It has also to be noted that conversely, impairment of cognitive function per se might have a negative impact on therapy adherence, medication intake\textsuperscript{105, 106} and may thus adversely affect treatment effectiveness and outcome in patients with arrhythmias.

5.4 Assessment of Cognitive Function in Atrial Fibrillation Patients in Clinical Practice

Despite increasing awareness about the relationship between AF and cognitive decline\textsuperscript{75, 99, 107, 108}, clinical guidelines for the management of AF do not specifically include assessment of cognitive function in the diagnostic work-up. With increasing prevalence of cognitive impairment in the elderly\textsuperscript{109} and given that the highest relative risk of cognitive decline is in AF patients >70 years of age, healthcare professionals who treat AF patients should be able to diagnose, and assess risk factors for cognitive impairment appropriately.

Assessment of cognitive function should be multifaceted (see Table 3), and psychometric testing is just one component. Numerous validated tools are available to assess cognitive function, varying from brief screening tools, which take 1-8 minutes to complete among elderly patients, to more complex time-consuming neuropsychological batteries (see Table 4). Brief screening tools may be most applicable when cognitive impairment is suspected among AF patients, whereas more comprehensive assessments may be performed after appropriate referral to a geriatrician or neurologist. Other factors determining the choice of test include the time available with the patient, the setting (office-based or inpatient), the patient’s ability to speak English (some tools are not translated and/or validated in other languages), and the purpose of
the assessment (screening versus confirmatory). In practical terms, any of the brief tests could be used, although the most common is the GPCOG\textsuperscript{42}. In research settings, the Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MOCA) have been commonly used\textsuperscript{43, 44, 110}. Informant questionnaires, such as the second step of GPCOG or the IQCODE\textsuperscript{50}, provide important additive information, since they assess a patient’s change over time from someone who knows the person well. This level of detail may not always be feasible, however, and may be more suited for comprehensive geriatric or neurological assessment.

5.5 Prevention of Cognitive Dysfunction in Atrial Fibrillation Patients

Since the precise mechanism(s) of cognitive disorders in patients with AF is not fully known, the optimal way to prevent cognitive dysfunction for a given patient remains to be established. Considering the mechanisms of cognitive impairment described in the sections above, several therapies may be considered (see “Recommendations”). Both disease states share common risk factors that include aging, smoking, hypertension, diabetes, sleep apnoea, physical inactivity, vascular disease, inflammation, and heart failure. Many of these risk factors represent modifiable targets for preventative therapies and if treated early may lower the risk of both diseases.

Stroke prevention is the principal priority in the management of AF and integrated approaches such as the Atrial fibrillation Better Care (ABC) pathway (Avoid stroke, Better symptom management, Cardiovascular and comorbidity risk reduction) may improve AF management\textsuperscript{111}. Stroke prevention therapy, particularly oral anticoagulation, applied to the appropriate patients according to risk stratification proposed in scientific guidelines\textsuperscript{108} may reduce the risk of dementia. Fridberg and Rosenqvist studied 444,106 AF patients over 1.5 million years at risk. Anticoagulation use was in 202,946 (46%) of the patients with the primary
anticoagulant used warfarin (94%). In AF patients not treated with anticoagulation, 60% were on aspirin. In multivariate analysis, the strongest predictors of dementia were in order: age (hazard ratio (HR) per decade 2.19, 95% CI 2.16–2.22), Parkinson’s disease (HR 2.46, 95% CI 2.25–2.69), absence of oral anticoagulation treatment (HR 2.08, 95% CI 1.73–2.53), and alcohol abuse (HR 1.53, 95% CI 1.41–1.66).

In patients managed long term with vitamin K antagonists, for example, TTR is inversely associated with new-onset dementia. Risk of dementia is augmented in AF patients who are frequently over anticoagulated or receiving antiplatelet therapy. However, dementia can have a confounding effect on maintenance of TTR, and oral anticoagulation in AF patients has not been consistently associated with either improved cognitive function or less hippocampal atrophy. Anticoagulation with warfarin neither influenced the reduction of total brain volume nor cognitive function in individuals with AF. NOAC therapy may reduce the incidence of brain micro-haemorrhage compared to vitamin K antagonists, but whether NOACs improve long-term cognitive function is currently unknown. A recent community-based study provided some optimism in this regard and found that NOAC therapies were associated with lower stroke and dementia rates compared to warfarin. Considering the incidence of dementia in AF, only trials with large numbers of patients and extended long-term follow-up would be able to firmly establish the possible benefit of oral anticoagulation on the subsequent risk of cognitive decline.

Preventing early onset of AF through lifestyle or risk factor modification could delay the onset and progression of cognitive decline. Prevention and early management of smoking, excess alcohol consumption, hypertension, obesity, diabetes, and sleep apnoea may reduce the onset and/or progression of AF with concomitant reductions in stroke and possibly cognitive
function. However, such risk factor modifications may have independent positive effects on cognitive function regardless of the development of AF. It is also unclear if aggressive modification should start at the time of onset of AF. Lifestyle modification may also reduce the risk of cognitive decline in AF patients. Prevention of cognitive dysfunction may include general measures proposed in the treatment and management of vascular dementia or Alzheimer’s disease. Several trials have tested the effects of physical activity and cognitive training in Alzheimer’s disease and have shown some evidence of efficacy on cognitive endpoints. Most of the trials, however, had short follow-up periods. Further evidence is needed to confirm the optimal design and dose of interventions, the appropriate target population, and the efficacy of such interventions. Innovations such as the development of multi-domain interventions and the use of biomarkers or genetic profiles to better target higher-risk patients are being assessed in ongoing trials. However, differentiating the AF-dependent or AF-independent effects of lifestyle and risk factor modifications remains a major challenge.

There are no robust data to affirm that therapy for rhythm control with medication or "successful" AF catheter ablation can prevent cognition disorders in AF patients. AF catheter ablation may not eliminate AF in the majority of patients, but rather attenuate overall AF burden. Follow-up data beyond 5 or 10 years are limited, and suggest that 2-5% of “successfully” ablated patients will have recurrences annually. Furthermore, many of these recurrences may be asymptomatic and the prognostic implication of asymptomatic episodes on both stroke risk and cognitive function is unknown. Catheter ablation as a specific therapeutic approach to lower risk of stroke and dementia is discussed in the section “Catheter Ablation”.

In patients with persistent AF for whom which rhythm control is not pursued, AV node ablation with pacemaker implantation that restores a predictable R-R interval and heart rate has
been shown, in a small study, to improve frontal and temporal blood flow and improve memory and learning\textsuperscript{125}.

Recommendations on the prevention of cognitive dysfunction in AF patients are made in the section “Recommendations”. Most of these recommendations are consistent with those of international guidelines\textsuperscript{108} and are not necessarily unique to those patients with AF and cognitive dysfunction.
6. Other arrhythmias and cognitive dysfunction

6.1 Cognitive dysfunction in patients with regular supraventricular tachycardias

Recurrent supraventricular tachycardias in children and adolescents, mediated by AV nodal reentry or by accessory pathways, were shown to be associated with cognitive deficits in 48% of such patients, when assessed prior to catheter ablation.\textsuperscript{126} Whether an early catheter ablation of supraventricular arrhythmia would affect the cognitive status of such patients needs further investigation.

6.2 Cognitive impairment after cardiac arrest

\textit{Brain injury after non-fatal cardiac arrest.}

Cardiac arrest occurs in two different settings, in-hospital and out-of-hospital, with completely different prognosis, for obvious reasons: As cardiac arrests that occur in a hospital context are usually immediately attended, the primary focus of the study of brain injury after cardiac arrest has been among survivors of out-of-hospital cardiac arrest (OHCA).\textsuperscript{127} In this setting, brain damage is caused by cerebral hypoperfusion and its severity depends on the time of such deficit;\textsuperscript{128} the proportion of cardiac arrest survivors who present with some degree of brain damage ranges from 35\% to 100\%.\textsuperscript{129, 130} The working group of Chun-Lim and colleagues has delineated 3 scenarios that are clearly related to the duration of brain hypoperfusion: 1) patients with early recovery of brain function without any sequelae, usually associated with opportune resuscitation and/or early recovery of consciousness (less than 3 days after OHCA); 2) patients with extensive damage, associated with prolonged coma (more than 7 days after OHCA); and 3) an intermediate group between those extremes.\textsuperscript{131} They report that a coma duration of less than 3 days results in a better quality of life at 3 and 12 month follow-up, and that the manifestation of
severe cognitive impairment early on in recovery results in higher risk for permanent memory and motor impairment.

Clinical sequelae of brain damage after OHCA may range from mild memory impairment to severe physical and mental disability. As expected, if brain damage persists, it negatively impacts patients’ quality of life. Cognitive impairment could include limited attention span, personality disturbances, movement disorders (i.e. Parkinsonism), and even dementia; however, memory seems to be the cognitive function most affected in survivors of cardiac arrest. Neuropsychological studies have shown deficits in different cognitive areas including memory (64.3%), executive functioning (21.4%), language (21.4%), and perception (14.3%). In 1990, the Utstein style was developed in order to standardize the results of resuscitation studies; this includes neurological evaluation using either the Cerebral Performance Category (CPC) or the Modified Rankin Scale (mRS). CPC classifies patients on a scale from 1 to 5 (1= good cerebral performance; 5= deceased) while the mRS classifies patients on a 0 to 6 scale (0= asymptomatic; 6= deceased); CPC scores of 1-2 and mRS scores of 0-3 are considered favourable neurological outcomes. These criteria are included as a reminder of the risk of neurological dysfunction among survivors of cardiac arrest.

Memory impairment after cardiac arrest.

In patients successfully treated for an OHCA in a rapid emergency response program, the long-term survival and quality of life are similar to age- and gender-matched controls. However, if cognitive assessment is evaluated in detail, memory loss is prevalent. Alexander et al. reported that among 30 selected patients (1 day of coma, with responsiveness after 24 hours but with remaining confusion for 7 days), only one third of the sample suffered from motor impairment.
after the event, but the total population showed at least a mild degree of memory impairment.\textsuperscript{138} Torgersen \textit{et al.} also reported that even after therapeutic hypothermia, 52\% of the patients who suffered cardiac arrest showed cognitive impairment, especially episodic memory dysfunction.\textsuperscript{139} This finding is not new, in 1996, Grubb \textit{et al.} demonstrated in a population of 35 patients that up to 37\% of the patients suffered chronic memory impairment after cardiac arrest, and that memory dysfunction was inversely proportional to the duration of the event.\textsuperscript{140}

Memory impairment after cardiac arrest does not seem to improve over time; a case-control study comparing OHCA patients with patients who suffered acute coronary syndrome without OHCA (controls) showed that memory impairment recorded at 3 month follow-up remained unchanged after 12 months, with just mild improvement of other functions.\textsuperscript{131} Further, only 16\% returned to work after the cardiac arrest whereas more than 94\% of controls returned to work.\textsuperscript{131} This study also evaluated quality of life among cardiac arrest survivors and controls; physical quality of life was not perceived as impaired in either group, however the ‘cases’ perceived a worse quality of life as a result of memory impairment.\textsuperscript{131}

\textit{Therapeutic hypothermia to prevent cognitive impairment after cardiac arrest.}

Although the effects of hypothermia have been evaluated in humans and experimental models before,\textsuperscript{141, 142} in 1956 Marchand and Allan developed an experimental model to measure the effects of hypothermia on the heart and brain.\textsuperscript{143} The first studies of therapeutic hypothermia in cardiac arrest patients were performed in the 1950s. Later, Zola-Morgan et al. reported that ischemic episodes damaged CA1 hippocampal cells.\textsuperscript{144} The benefits of induced hypothermia were demonstrated in animal models in the nineties.\textsuperscript{145} At the present time, compelling evidence supports the use of targeted therapeutic hypothermia. Effectiveness of therapeutic hypothermia to
prevent cognitive impairment has been reported with varying results among different authors.\textsuperscript{146} For example, Fugate \textit{et al.} followed 56 survivors of cardiac arrest treated with therapeutic hypothermia. Twenty-month follow-up interviews yielded results favouring the use of this therapy: 33 patients (60\%) were reported as being ‘cognitively normal’, with 79\% of working patients returning to their normal activities after the event.\textsuperscript{146} In contrast, a randomized clinical trial (RCT) of 70 patients comparing therapeutic hypothermia to a normothermic control group (without further intervention), found no statistically significant difference in cognitive function between the two groups, although the authors suggests that differences in the neuropsychological tests employed (previous prospective studies focusing on memory functions rather than executive functions) might explain the neutral findings in this RCT.\textsuperscript{147} Current guidelines for hospital care after cardiac arrest recommend the use of targeted therapeutic hypothermia between 32 and 34°C for 48 hours.\textsuperscript{148} After publication of these guidelines, a systematic review by Schenone \textit{et al.} reported that mortality was halved [OR = 0.51, 95\% CI (0.4, 0.64)] and neurological impairment caused by arrest-induced hypoxia was significantly lower [good neurological outcome OR = 2.48, 95\% CI (1.91, 3.22)] in patients who underwent therapeutic hypothermia compared to those who did not.\textsuperscript{149}

In summary, minimising and treating the complications originating from a cardiac arrest are almost as important as treating the arrest itself. Physicians should perform appropriate follow-up and referral to a specialized centre that can offer appropriate postcardiac arrest care in order to minimise the extent of brain damage and to avoid adverse outcomes, since the ultimate success of medical therapy is not only survival, but preservation of quality of life.
6.3 Cardiac implantable electronic devices and cognitive dysfunction

Patients requiring cardiac implantable electronic devices (CIED) are generally older and as such may have associated cognitive dysfunction. It has also been shown that patients with severe bradycardia or high-grade AV block may show impaired cognitive function.\textsuperscript{150-152}

Bradycardia is also more common in patients treated for dementia with cholinesterase inhibitor drugs (adjusted hazard ratio (HR) 1.4, 95% CI 1.1-1.6) and increases the risk of syncope, CIED need, and falls.\textsuperscript{153} A retrospective study showed that patients with cognitive dysfunction were more likely than those without cognitive deficits to be implanted with a pacemaker, even after adjusting for clinical risk factors.\textsuperscript{154} Treatment of both permanent or transient bradycardia with CIEDs has been shown to improve cognition in a number of small trials.\textsuperscript{151, 152, 155}

Although it may be inferred that patients with cognitive impairment and standard device indications may be at increased risk for device complications, this was not demonstrated in a study by Jama et al.\textsuperscript{156} However, the survival was lower than in matched controls suggesting that these patients may have more comorbidities. A small study suggested that the increase in cerebral blood flow after pacemaker implantation for symptomatic bradycardia resulted in improvement in cognitive function.\textsuperscript{152} Another small study showed that the improvement was, however, not significant over a 6-12 months follow-up after pacemaker implantation.\textsuperscript{151}

Ventricular pacing may result in impaired hemodynamics and has been associated with AF, which itself has been associated with multi-infarct dementia. Ventricular pacing was noted to show a trend towards a detrimental effect on the visual memory score.\textsuperscript{157} It is well known that CIED may have psychological side effects; this is particularly true for ICD and especially shock therapy.\textsuperscript{159, 160} Apart from this psychological effect, there may be a direct effect on cognitive
function. ICD implantation with defibrillation testing has been reported to initially result in cognitive dysfunction in 31-39% of patients, as determined by neuropsychological testing before and after ICD implantation in 52 patients, however most patients improve within a year.\textsuperscript{161} Another study in 115 ICD patients observed that cognitive function in memory was poor at baseline and decreased over 12 months post ICD implantation.\textsuperscript{162} In a small Polish study of 51 patients with primary prevention ICDs, 7 patients who received ICD shocks for ventricular fibrillation scored worse in neuropsychological measurements compared to patients without such shocks, suggesting greater cognitive impairment,\textsuperscript{163} which could be multifactorial. However, further studies are needed to demonstrate whether shock or VF prevention will prevent decline in cognitive function.

In contrast, there are several reports that cardiac resynchronization therapy may be associated with neurocognitive functional improvement.\textsuperscript{164-168} An early systematic review of 3 studies reported improvements in executive functioning and attention.

\textbf{6.4 Catheter Ablation}

With mounting evidence to suggest an association between arrhythmias and cognitive decline and dementia, treatment of these arrhythmias has been considered as an option to lower risk of cognitive decline. As antiarrhythmic drug therapies have variable efficacy and are associated with many side effects, and medications can directly influence quality of life, mood, and function\textsuperscript{170}, catheter ablation is often employed as a durable non-pharmacological option.

The majority of evidence that catheter ablation may impact cognition is derived from observational studies of AF management. Outcomes in a consecutive series of 4,212 patients who underwent AF ablation were compared (1:4) to 16,848 age/gender matched controls with
AF (no ablation) and 16,848 age/gender matched controls without AF. In this analysis, stroke outcomes of patients with AF, and an ablation, were better than patients with AF and no ablation, but similar to patients without AF\textsuperscript{171}. Similarly, long-term outcomes of cognition were better in AF ablation patients compared to AF patients who did not undergo ablation, including lower rates of Alzheimer’s, senile, and vascular dementia. Cognitive outcomes between those patients that received an ablation were similar to patients without a history of AF, including all subtypes of dementia. In patients with atrial flutter stroke rates post ablation are significantly lower compared to AF patients treated with ablation\textsuperscript{172}. However, as these were not RCTs, better outcomes could have been related to selection bias rather than impact of ablation.

Dementia has not been a traditional endpoint in observational studies of outcomes after AF ablation. However, stroke and transient ischemic attack (TIA) are commonly reported endpoints. Long-term cognitive deficits are common after stroke with up to 10% of patients developing dementia after their first stroke with an incidence that increases to 30-40% with recurrent stroke\textsuperscript{173}. In a propensity-matched study of 969 consecutive AF ablation patients with a CHA\textsubscript{2}DS\textsubscript{2}VASc score $\geq 2$, AF ablation was associated with a long-term reduced risk of stroke [HR: 0.62 (95% CI 0.47-0.82)] and TIA [HR: 0.47 (95% CI 0.20-0.78)].\textsuperscript{174} In a separate observational study, AF ablation was associated with lower rates of stroke/TIA compared to AF patients not treated with ablation across all age and CHADS\textsubscript{2} strata including patients considered at high risk for stroke and patients with prior stroke.\textsuperscript{175} In this study, stroke rates in all groups increased with higher CHADS\textsubscript{2} scores, including non-AF patients, consistent with the influence of systemic risk factors on stroke risk beyond that of AF.

Catheter ablation of all arrhythmias has peri-procedural risks that may have long-term significant consequences with regard to cognition and dementia risk. Procedural risk with all
cardiac left sided procedures may impact long-term cognition due to the presence of peri-procedural thrombus, atheroemboli, cerebral hypoperfusion, sheath and wire manipulation and management, and anaesthesia. In patients that undergo right sided cardiac procedures the risk is anticipated to be lower although paradoxical thromboembolism can occur in the presence of a septal defect.\textsuperscript{172} The risk of stroke during left atrial catheter ablation is estimated at approximately 0.5-1%.\textsuperscript{122} However asymptomatic or subclinical ischemic lesions develop in up to 41% of AF ablation patients with an incidence that varies with anticoagulation approach, ablation tool used, and cranial scan protocol.\textsuperscript{122, 123, 176, 177} In addition, when peri-procedural transcranial Doppler analysis is used during AF ablation to monitor for emboli, sheath manipulation, removal and insertion of tools, and using of multiple tools within the left atrium are significantly associated with microembolic events.\textsuperscript{178} The risk of these lesions is higher (up to 63%) during ventricular arrhythmia ablation with retro-aortic access and long sheaths in the aorta being unique risk factors.\textsuperscript{179}

To put these incidences in context with other cardiovascular procedures, the estimated incidence of new brain lesions has been reported to be 8-18% after AF ablation, 11-17% after coronary angiography or percutaneous coronary intervention, 16-51% after coronary artery bypass graft, 38-47% after surgical aortic valve replacement, 68-91% after transaortic valve implantation, 4-34% after carotid endarterectomy, 15-67% after carotid artery stenting, 11-20% after cerebral angiography, and 10-64% after endovascular aneurysm procedures.\textsuperscript{180}

The long-term consequences of asymptomatic or subclinical cerebral ischemic events are unknown. It stands to reason that cranial injury of any type, if persistent or accumulative can impact function. However, cognition is not often tested serially after ablation and the mechanisms that underlie the genesis of these cranial lesions are not fully understood. In the
prospective Mesh Ablator versus Cryoballoon Pulmonary Vein Ablation of Symptomatic Paroxysmal Atrial Fibrillation (MACPAF) study, high-resolution diffusion-weighted MRI imaging, performed within 48 hours after ablation, showed that new brain lesions (range: 1-17) were present in 43.2% of patients. Follow-up MRI at 6 months found that 12.5% of the acute brain lesions after ablation formed a persistent scar. Neuropsychological assessment at 6 months found that there was not a significant consequence of these lesions on attention or executive functions, short-term memory, or learning. However, other studies such as the ERACE study reported much lower rates of permanent scar indicating the uncertainty in this area.

Based on the limited available data, post AF ablation cognitive dysfunction seems to be common. In a study of 150 patients who underwent ablation, cognitive dysfunction was evident in 28% with paroxysmal AF, 27% with persistent AF, and 13% with supraventricular tachycardia and 0% in control patients with AF who did not undergo ablation. Although these incidences decreased to 13%, 20%, and 3% at 90 days, measurable cognitive dysfunction persisted; access time in the left atrium was the most significant procedural variable of risk. Unfortunately in this study, MRI imaging was not performed to determine and correlate this dysfunction with peri-procedural cranial lesions. Neuropsychological outcomes were sought at 3 months in a small study of 23 patients who underwent ablation with post-procedure diffusion weighted MRI cranial imaging. New cranial lesions were detected in 3 patients (14%) and one patient suffered a clinical stroke. Residual cognitive defects were noted at 3 months with neuropsychological testing, in particular, in verbal memory (one of five cognitive domains); deterioration was observed in 56.5% of ablation patients compared to 17.4% of controls.
6.5 Implications for EP Procedures and cognitive function

As described in the preceding sections, emerging evidence suggests that various EP procedures may be associated with cerebral injury and the potential of cognitive decline therefore, it is timely to consider current evidence and guidelines to minimise these risks.

Over recent years considerable research has focused on how to minimise these procedural risks during left sided catheter ablation and in particular AF ablation. The routine use of transesophageal echocardiography (TEE) to identify pre-existing thrombus at the time of AF ablation remains controversial particularly in an era where most EP procedures will be performed on uninterrupted anti-coagulation. However, TEE studies have demonstrated that up to 2% of anticoagulated AF patients may have left atrial appendage thrombus or sludge with risk varying according to CHA2DS2-VASc score. In the most recent AF ablation HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement guidelines, 51% of the writing group members perform a TEE in all patients presenting for AF ablation regardless of presenting rhythm and anticoagulation status: 71% perform a TEE in patients presenting in AF even on therapeutic anticoagulation, and 78% perform a TEE in patients not previously anticoagulated even in sinus rhythm. Computed tomography and intra-cardiac echocardiography have both also been used to screen for thrombus but evidence from large comparative studies is lacking.

Evidence suggests that patients with an anticoagulation window period or those requiring bridging are at increased risk of peri-procedural events. Uninterrupted anticoagulation ensures the full anticoagulant effect in the early post-procedural phase when embolic events are most likely to occur. In this context, in recent years it had become routine to perform AF ablation on uninterrupted warfarin with a therapeutic INR. Until recently there were little data to
support this practice for NOACs however, emerging data from both meta-analyses and a recent large randomized study support the safety of this approach.\textsuperscript{183} This practice is likely to gain increasing acceptance particularly as reversal agents become more widely available for all NOACs.

Intra-procedurally, a strategy of more aggressive heparin dosing has evolved over the past decade in the light of data that patients who have an Activated Clotting Time (ACT) of <300 s during the procedure have an increased risk of silent cerebral infarction. The current consensus document recommends an ACT target of 300-400 with repeated checks at 15-20 minute intervals. In addition, echocardiographic data have demonstrated that thrombus may form on sheaths immediately following trans-septal puncture; as such 77\% of Consensus Document Writing Group\textsuperscript{185} members give heparin prior to the trans-septal puncture.

Less data exist for ablation of ventricular arrhythmias although a recent study demonstrated the presence of new silent cerebral infarction in 7/12 patients having ablation of ventricular tachycardia originating from the left ventricle. The majority of these patients underwent ablation via a retrograde trans-aortic approach and the target ACT was 300-400 seconds. Whether the incidence would be lower using a trans-septal approach is unknown.

Similarly, limited data exist regarding the impact of device implantation on cognitive function and these have been discussed in Section 6.2. Until more comprehensive data are available it seems prudent to follow recommendations in the 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing even though data that such an approach minimises cognitive impact are lacking. These include the 2A recommendation that: “It is reasonable to omit defibrillation efficacy testing in patients undergoing initial left pectoral
transvenous ICD implantation procedures where appropriate sensing, pacing, and impedance values are obtained with fluoroscopically well-positioned right ventricular leads”; and the Class 3 recommendation that “Defibrillation efficacy testing at the time of implantation of a transvenous ICD should not be performed on patients with a documented nonchronic cardiac thrombus, AF or atrial flutter without adequate systemic anticoagulation, critical aortic stenosis, unstable coronary artery disease, recent stroke or TIA, hemodynamic instability, or other known morbidities associated with poor outcomes”.

Regarding the impact of left atrial appendage occlusion (LAAO) procedures on cognitive function, MRI-detected new acute brain lesions were detected in 12 of 23 patients (52%) after LAAO procedures using the Amulet, Occlutech or LAmbre devices. New brain lesions were associated with a higher number of left atrial appendage angiographies although there was no apparent impact on cognitive testing. Procedural stroke, typically related to air embolism, has also been reported with the Watchman device in the PROTECT trial, although impact on long term cognition is unknown. However, any long term impact on cognition has not been reported.
7. **Current knowledge gaps, future directions and areas for research**

Global management of dementia syndromes has been recently set as a public health priority, and the World Health Organization has prioritized seven research domains to reduce the global burden of dementia\(^{189}\): 1) Prevention, identification, and reduction of risk; 2) Quality of care for people with dementia and their carers; 3) Delivery of care and services for people with dementia and their carers; 4) Diagnosis, biomarker development, and disease monitoring; 5) Pharmacological and non-pharmacological clinical–translational research; 6) Public awareness and understanding, and 7) Physiology and progression of normal ageing and disease pathogenesis. Other expert groups have also provided recommendations for further progress and improvements in dementia-related research\(^{190}\) and highlighted knowledge gaps in cardiovascular care of the elderly, including those with cognitive impairment\(^{191}\). Declining incidence and age-specific prevalence of dementia in high-income countries\(^{192-195}\) implies that dementia risk is modifiable, likely through improved management of cardiovascular risk factors\(^{196}\) and psychosocial factors\(^{190, 197-199}\). Although dementia-prevention RCTs failed to confirm many signals from observational studies, those RCTs highlighted some key methodological issues to be considered in contemporary trials (Table 9).

Elderly patients with cognitive impairment commonly have mixed pathologies, including cardiovascular disease (e.g., AF and heart failure)\(^{81, 86, 200-202}\) but the complexity of shared pathological pathways and risk factors is still poorly understood and warrants further research. Better understanding of the mechanisms and determinants of AF-related cognitive impairment/dementia beyond aging and stroke would inform AF-specific preventive strategies to attenuate and/or postpone cognitive deterioration. Prospective studies addressing the long-term effects of AF treatments directed towards rhythm control, reduction of total AF burden and
improvement in cardiac function (i.e., catheter ablation and pharmacotherapy) on cognitive function are needed. Inherent to achieving these targets is consistent utilization of well-validated neurocognitive measures. Also, the effects of lifestyle changes resulting in weight loss, improvement in overall cardio-metabolic risk profile and reduced AF burden need to be investigated. Further research is needed to optimise rate control in AF relative to cognitive function.

Cognitive endpoints were not addressed in the recent large RCTs of OAC (VKA or NOACs) for thromboprophylaxis in AF, with one exception, the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) which reported better cognitive function in elderly patients receiving warfarin compared to aspirin\textsuperscript{114}. In retrospective observational studies the risk of dementia increased with poor management of VKA (a low TTR)\textsuperscript{76, 113}, whilst NOAC use was associated with lower risk for dementia compared to warfarin\textsuperscript{115}. Observational data on AF patients diagnosed with dementia consistently shows significant VKA underuse or discontinuation\textsuperscript{62} even post-stroke\textsuperscript{203}, despite similar VKA-related bleeding risk irrespective of the cognitive status. Large prospective studies with pre-specified cognitive outcomes are needed to identify optimal thrombo-prophylactic strategies for AF patients with cognitive impairment/dementia. Importantly, the effects of early AF treatment or primary AF prevention on cognitive deterioration in patients at risk for both conditions remain to be elucidated.

Elderly patients and those with cognitive impairment/dementia were generally under-represented in catheter ablation and CIED (i.e., ICD and CRT) trials. Studies are needed to better define the risks and benefits of cardiac arrhythmias ablation or CIED implantation, long-term effects of these interventions on cognitive status and optimal strategies for shared decision-making and end-of-life decisions in these patients (Table 9).
Table 9. Knowledge gaps and areas for further research.

<table>
<thead>
<tr>
<th>General dementia-related research domains*</th>
<th>Knowledge gap(s)</th>
<th>Further research</th>
</tr>
</thead>
</table>
| Distinguishing progression of normal aging from pre-clinical cognitive decline | Physiology of normal aging /pathological neurodegenerative processes.          | • Large international population-based longitudinal studies of aging and dementia  
• Contribution of vascular conditions, inflammation, oxidative stress, and the immune system to neurodegenerative processes causing dementia |
| Identification of the risk factors and risk reduction | Interactions of shared pathological pathways and risk factors.                    | • Interactions of modifiable and non-modifiable dementia risk factors in population-based studies  
• Feasibility, administration and effectiveness of interventions addressing dementia risk factors |
| Early diagnosis, biomarkers and disease monitoring | Effective strategies for cognitive surveillance; Early detection of cognitive impairment; Monitoring of disease progression. | • Interventions for timely and accurate diagnosis of cognitive impairment or dementia at the primary health-care level. Better characterization of different dementia types  
• Strategies for longitudinal surveillance of healthy individuals to distinguish (and timely diagnose) pre-clinical neurodegenerative diseases with cognitive impairment versus normal aging  
• Validation and standardization of available cerebrospinal fluid and brain imaging biomarkers of dementia for research and clinical use  
• Development and validation of novel biological, genetic, behavioural or cognitive biomarkers with predictive value at pre-dementia stages |
| Prevention of cognitive impairment/dementia | Effective preventive strategies in general population.                             | • Exploring single- and multi-domain approaches for primary and secondary prevention of dementia based on evidence on risk / protective factors and the relationship with other chronic diseases  
• Prevention studies need to start in mid-life and have a long follow-up to identify “windows of opportunity” for effective interventions |
| Pharmacological and non-pharmacological | Effective dementia-related strategies | • Identification, validation and implementation of better defined outcome |
| Pharmacological clinical-translational research on dementia diagnosis and treatment | Specific therapies are not available yet. | Measures for clinical trials of cognition, function and other biomarkers of neurodegenerative diseases causing dementia  
- Improvement in differentiation of dementia types  
- Improvement in the selection of patients eligible for clinical trials of cognitive impairment or dementia  
- Investigation of combination therapies for dementia and diversification of investigational therapeutic approaches (pharmacological and non-pharmacological interventions) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AF-specific research domains</strong></td>
<td><strong>Knowledge gap(s)</strong></td>
<td><strong>Further research</strong></td>
</tr>
<tr>
<td>Association of AF with cognitive impairment or dementia</td>
<td>Underlying mechanisms beyond clinically overt strokes, silent strokes and aging are poorly understood.</td>
<td></td>
</tr>
</tbody>
</table>
- Significance and contribution of cerebral hypoperfusion due to irregular heart rhythm and impaired cardiac function in AF patients, AF-associated hypercoagulability and OAC-related cerebral micro-bleeds to cognitive deterioration and development of dementia  
- Association of AF burden (i.e., paroxysmal versus non-paroxysmal AF) with cognitive status  
- Potential role of atrial cardiomyopathy in the development of cognitive impairment/dementia |
| Time-course of cognitive impairment in AF patients | Mechanism(s) of accelerated development of dementia in AF patients. |  
- Large prospective population-based studies on AF and non-AF patients to identify the time-course of cognitive deterioration by AF status and risk factors for accelerated dementia, thus providing a roadmap for prevention strategies  
- Identification and validation of clinical predictors and biomarkers to identify AF patients at increased risk of cognitive impairment/dementia |
| Rhythm control and other strategies, including ablation, for AF burden | Short- and long-term effects on cognitive function in AF patients |  
- Better representation of elderly and other AF patients with, or at risk for cognitive impairment or dementia in future rhythm control and AF ablation studies |
| Reduction | • Prospective investigation of the effects of rhythm control, AF ablation and other strategies for AF burden reduction on cognitive function and prevention, attenuation or delay of cognitive impairment/dementia  
• Prospective investigation of the effects of different ablation energy sources (e.g., radiofrequency, cryoablation) on cognitive function |
|-----------------|---------------------------------------------------------------|
| Pharmacological rate control therapies in AF; AV node ablation with permanent pacemaker implantation for rate control in AF | Short- and long-term effects on cognitive function in AF patients  
• Prospective investigation of the effects of strict versus lenient rate control on cognitive function in AF patients including those with cognitive impairment or dementia  
• Better representation of elderly and other AF patients with, or at risk for cognitive impairment or dementia in future prospective studies investigating the effects of AV node ablation with permanent pacemaker implantation on cognitive function and prevention, attenuation or delay of cognitive impairment or dementia |
| VKA, NOACs and non-pharmacological (LAAO) thromboprophylaxis in AF | Long-term effects on cognitive function in AF patients  
• Prospective studies of VKA, NOACs and LAAO long-term effects on cognitive function in AF patients with baseline normal cognitive status, cognitive impairment or dementia  
• Assessment of benefits of VKA, NOACs for reduction of cognitive decline among patients with micro-haemorrhages  
• Identification and validation of clinical/biomarker predictors of cognitive impairment/dementia in anticoagulated AF patients or those with LAAO  
• Studies on the consequences of non-adherence or permanent OAC discontinuation in AF patients with cognitive impairment or dementia |
| Screening for asymptomatic AF | Asymptomatic AF-associated risk of cognitive impairment  
• Assessment of cognitive impairment and dementia in patients with asymptomatic AF  
• Assessment of the effect of asymptomatic AF treatment on prevention, attenuation or delay of cognitive impairment or dementia |
<p>| Early AF detection and effects of early | • Studies with pre-specified primary endpoint of cognitive function |</p>
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Aggressive rhythm control on cognitive function</th>
<th>• Inclusion of elderly and other AF patients with, or at risk for cognitive impairment or dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prevention of AF</td>
<td>Effective interventions for primary prevention (ongoing research)</td>
<td>• Effects of dietary intervention, improved blood pressure control and other risk factors control on cognitive function in patients at risk of AF and cognitive impairment/dementia, and in non-AF patients with cognitive impairment/dementia</td>
</tr>
<tr>
<td>Other arrhythmia-specific research domains</td>
<td>Knowledge gap(s)</td>
<td>Further research</td>
</tr>
<tr>
<td>SCD risk assessment and SCD prevention</td>
<td>Effective strategies in individuals with cognitive limitations</td>
<td>• Improvement of non-invasive risk assessment and identification of screening tools applicable to older and other patients with, or at risk for cognitive impairment or dementia</td>
</tr>
<tr>
<td>Catheter ablation of ventricular arrhythmias</td>
<td>Short and long-term effects in individuals with cognitive limitations</td>
<td>• Better understanding of the role of catheter ablation of ventricular arrhythmias in older and other patients with, or at risk for cognitive impairment/dementia, including studies of competing risk of death caused by ventricular arrhythmias versus other causes</td>
</tr>
<tr>
<td>ICD for primary and secondary prevention</td>
<td>Short- and long-term effects in patients with cognitive limitations</td>
<td>• Studies on ICD implantation outcomes including procedural complications, QALY gain, healthcare costs and competing risk of death in patients with cognitive impairment or dementia</td>
</tr>
<tr>
<td>CRT</td>
<td>Effects in patients with</td>
<td>• Studies of the impact of CRT, with or without ICD, on QoL and cognitive function</td>
</tr>
<tr>
<td>cognitive limitations</td>
<td>function in patients with, or at risk for cognitive impairment or dementia</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>&quot;Compiled and modified from the References 132-134 [189-191] (for details on the quality of care, delivery of care and services for individuals with dementia and public awareness and understanding see the cited documents). AF: Atrial fibrillation; AV: atrioventricular; CRT: Cardiac resynchronization therapy; ICD: Implantable cardioverter defibrillator; LAAO: Left atrial appendage occlusion; NOAC: Non-VKA oral anticoagulant; QALY: Quality-adjusted life-years; QoL: Quality of life; SCD: Sudden cardiac death; VKA: Vitamin K antagonist.&quot;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
8. Recommendations

Interventions that can be considered for prevention of cognitive dysfunction in atrial fibrillation patients are summarized in Table 10. The writing committee reached consensus on recommendations summarized in Table 11.

Table 10. Interventions to be considered for prevention of cognitive dysfunction in atrial fibrillation patients

<table>
<thead>
<tr>
<th>Pharmacological interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• In relation to AF management:</td>
</tr>
<tr>
<td>- Oral anticoagulation (early identification of appropriate candidates; improving drug adherence, avoiding warfarin in those with poor TTR, optimal TTR management)</td>
</tr>
<tr>
<td>- Rhythm control</td>
</tr>
<tr>
<td>- Antihypertensive treatment</td>
</tr>
<tr>
<td>- Treatment of concomitant heart failure</td>
</tr>
<tr>
<td>• Non-specific pharmacological interventions:</td>
</tr>
<tr>
<td>- Glycaemic control</td>
</tr>
<tr>
<td>- Hormone replacement therapy</td>
</tr>
<tr>
<td>- Avoid aspirin therapy unless specific clinical indication present</td>
</tr>
<tr>
<td>• Alzheimer’s disease-specific pharmacological interventions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multifactorial vascular risk factor management</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Targeting blood pressure, cholesterol, diabetes, sleep apnoea, and obesity via diet, medication, smoking cessation, and physical activity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nutritional interventions</th>
</tr>
</thead>
</table>
- Low levels of vitamin D and B\(_{12}\), and folate increase risk, but the value of supplementation remains unproven. Calcium supplementation in women has been associated with increased dementia risk.\(^{204-206}\) The value of modulating cognitive function based on educational interventions is uncertain.

- Weight loss in obesity\(^{207}\)

<table>
<thead>
<tr>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Cognitive activities or training</td>
</tr>
<tr>
<td>- Physical exercise</td>
</tr>
<tr>
<td>- Multi-domain interventions</td>
</tr>
</tbody>
</table>
Table 11: Recommendations for measures to prevent cognitive dysfunction in AF patients.

<table>
<thead>
<tr>
<th>Preventive Measures of Cognitive Dysfunction in Patients with Atrial Fibrillation</th>
<th>Class</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate anticoagulation in patients with AF and stroke risk factors should be applied for the prevention of cognitive dysfunction.</td>
<td></td>
<td>108, 112</td>
</tr>
<tr>
<td>Consider NOAC instead of VKA when using oral anticoagulation for the prevention of stroke in AF, which may have a beneficial effect on subsequent cognitive disorders.</td>
<td></td>
<td>108, 115</td>
</tr>
<tr>
<td>In patients with AF managed with long term VKA, a high anticoagulation time in therapeutic range may be beneficial for optimal prevention of new-onset dementia.</td>
<td></td>
<td>76, 108</td>
</tr>
<tr>
<td>General health measures (prevention of smoking, hypertension, obesity and diabetes, sleep apnoea, and appropriate control of all risk factors) may reduce the concomitant risks of AF (new onset or recurrences) and stroke, with a putative benefit on cognitive function.</td>
<td></td>
<td>108, 116</td>
</tr>
<tr>
<td>Prevention of cognitive dysfunction in AF may include general measures proposed in vascular dementia or Alzheimer’s disease.</td>
<td></td>
<td>117</td>
</tr>
<tr>
<td>Cognitive assessment should be performed in AF patients where there is suspicion of cognitive impairment.</td>
<td></td>
<td>208</td>
</tr>
</tbody>
</table>
AF: atrial fibrillation; NOAC: non-vitamin-K antagonist oral anticoagulant; VKA: vitamin-K-antagonist
Figure Legends

Figure 1.
Different mechanisms through which atrial fibrillation may contribute to cognitive impairment. Potential interventions are shown in red.
CO: cardiac output; CRP: C-reactive protein; DM: diabetes mellitus; HF: heart failure; HTN: hypertension; IL: Interleukin; OSA: obstructive sleep apnoea
*Some of the reported brain morphometric changes include: hippocampus atrophy, white matter hyperintensities, and frontal medial lobe atrophy. Reproduced with permission.⁶⁴
Figure 1. Potential mechanisms for the association between atrial fibrillation and cognitive impairment.
References


67
[18] Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for
dementia and related pathologies - The Honolulu-Asia Aging Study. Diabetes 2002; 51: 1256-
1262.

161: 785-U768.

between Serum Cholesterol and Risk of Late-Life Dementia: Review and Meta-Analysis. J

Clinical science 2017; 131: 1561-1578.


[23] Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-
stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet Neurol 2009; 8:
1006-1018.


[26] Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of


Gress DR. The problem with asymptomatic cerebral embolic complications in vascular procedures: what if they are not asymptomatic? *Journal of the American College of Cardiology* 2012; **60**: 1614-1616.


[208] This panel of experts.