Bell LTE 08:26 100 %

PYEONGCHANG 2018

Ladies' Moguls - Finals

Freestyle Skiing

Ladies' Moguls

Finals | Bokwang Snow Park

FRA	CAN	KAZ
G	S	B
LAFFONT Perrine	**DUFOUR LA-POINTE** Justine	**GALYSHEVA** Yulia

Run 3 - Results

Official

Rk	Name	Score
1	LAFFONT P	**78.65**
2	DUFOUR LAPOINTE J	**78.56**
3	GALYSHEVA Y	**77.40**

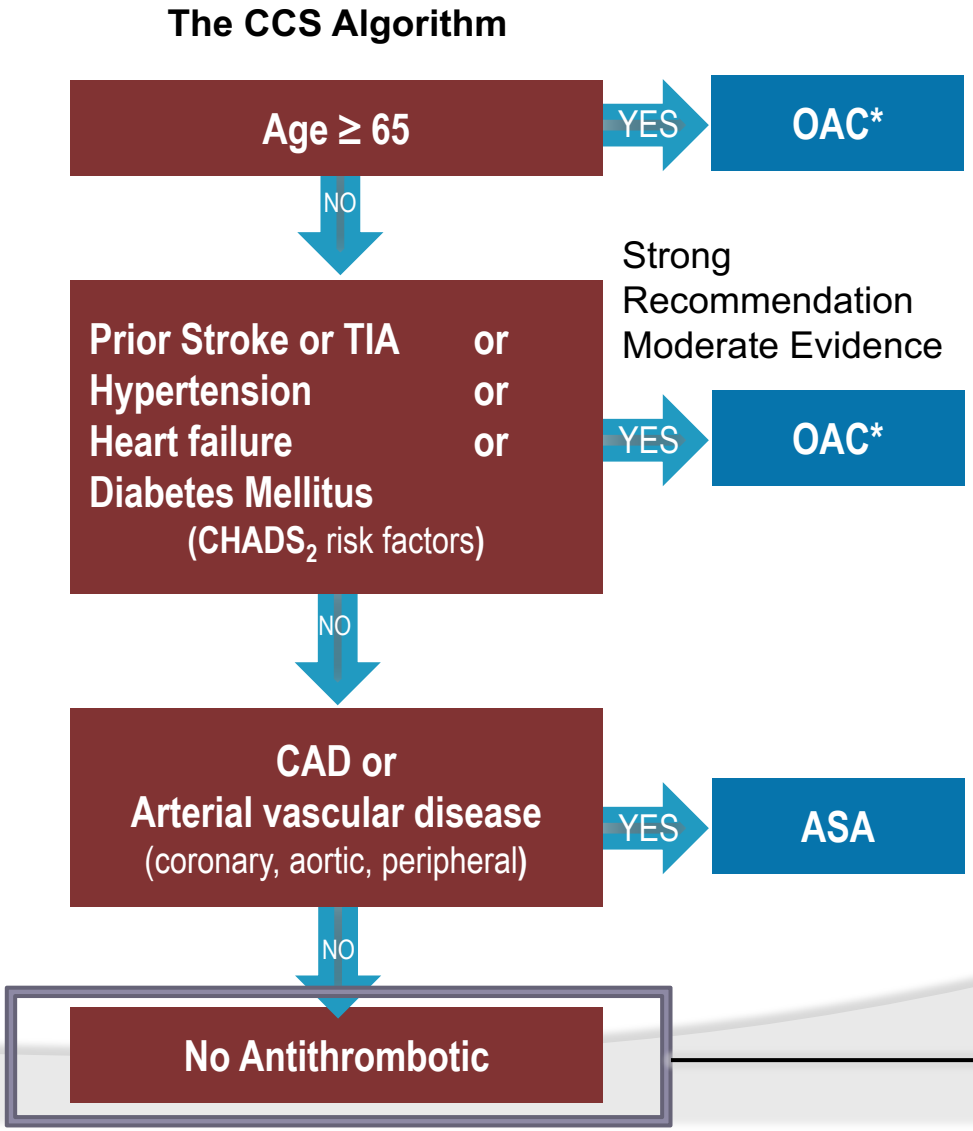
*B*linded *R*andomized trial of *A*nticoagulation to prevent *I*schemic stroke and *N*eurocognitive impairment in *A*trial *F*ibrillation

Steering committee:

Dr. L. Rivard, Dr. P. Khairy ,Dr. M. Talajic,, Dr. S. Black, Dr. L. Bherer,
Dr. S. Nattel, Dr. J. Andrade, Dr. F. Massoud, Dr. M.C. Guertin,
Dr. S. Lanthier, Dr. P. Dorian, Dr. J. Healey,
Dr. S. Kouz, Dr. I. Nault and Dr. D. Roy

Montreal Health Innovations Coordinating Center
A Division of the Montreal Heart Institute

Stroke Prevention - Therapy



Who is this group?

- CHADS 0
  - 20-40% of AF
  - 46% of those with AF <65y
- CHADSVASC 0
  - 7-22% of AF
- Risk of stroke is low but not negligible

(i.e., **0.5% to 1% per year**)

Europace. 2014 Feb; 16(2): 195–201.
CHEST 2011; 140(4):911–917
Chest. 2012 Jan;141(1):147-53.

Stroke Prevention - Therapy

brain AF

CHA_2DS_2-VASc

Risk Factor	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75	2
Diabetes Mellitus	1
Stroke/TIA/Thrombo-embolism	2
Vascular Disease	1
Age 65-74	1
Female	1
Maximum Score	9

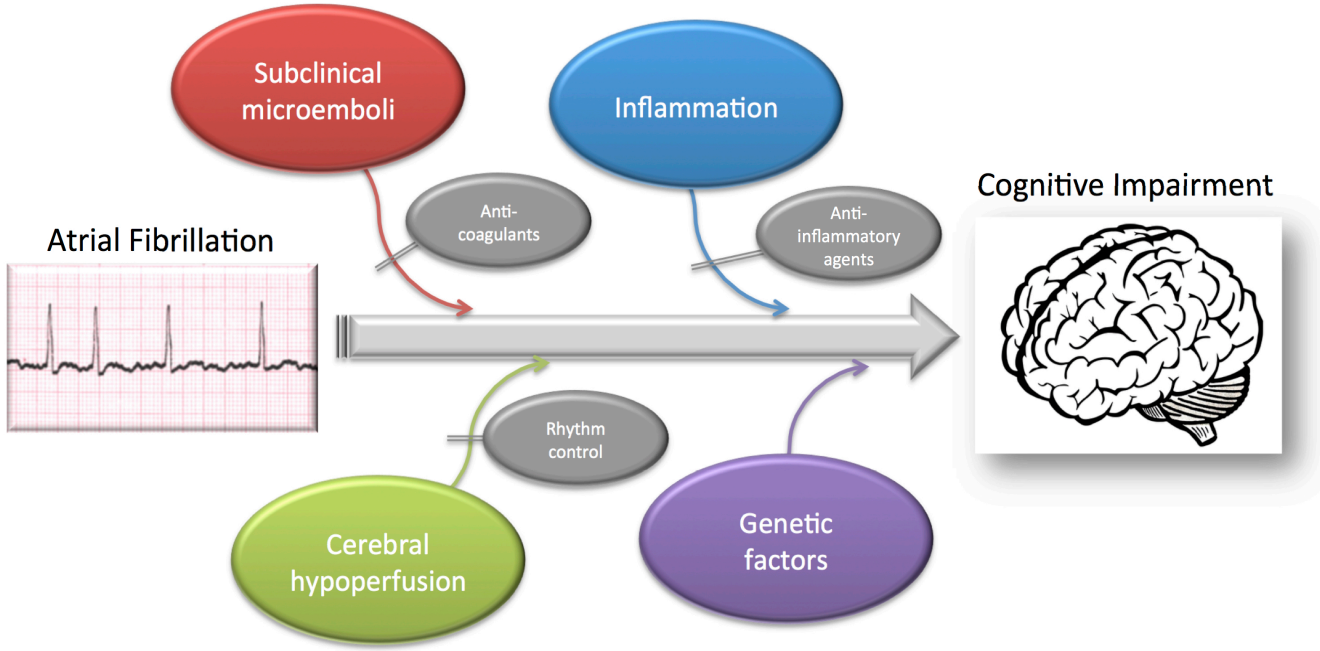
C statistic = 0.61

If score ≥ 1 → OAC

If score = 0 → Nothing

CCS Guidelines 2014 "*The greater safety of NOACs might alter the risk-benefit calculation for OAC use further (i.e.< 65 y) but data to allow this are presently insufficient".*

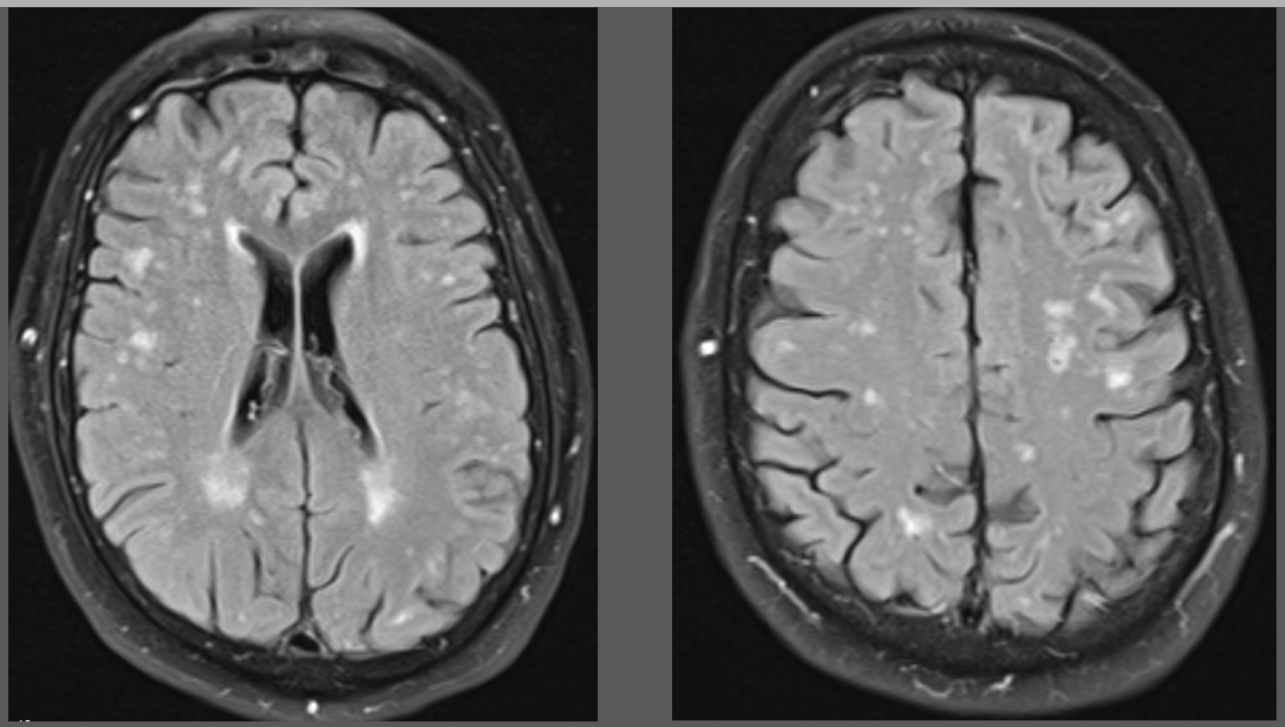
- Positive association between AF and cognitive impairment/dementia
- Microembolism is the main suspected mechanism



Rivard L, Khairy P . ***Mechanisms, Clinical Significance and Prevention of Cognitive Impairment in Atrial Fibrillation***
Canadian Journal of Cardiology (in press)

In patients with AF, silent cerebral ischemia is an important cause of cognitive impairment

59 year-old man with PAF, **CHA_2DS_2-VASc 0,** and mild cognitive impairment



Rivard L, Khairy P . ***Mechanisms, Clinical Significance and Prevention of Cognitive Impairment in Atrial Fibrillation***
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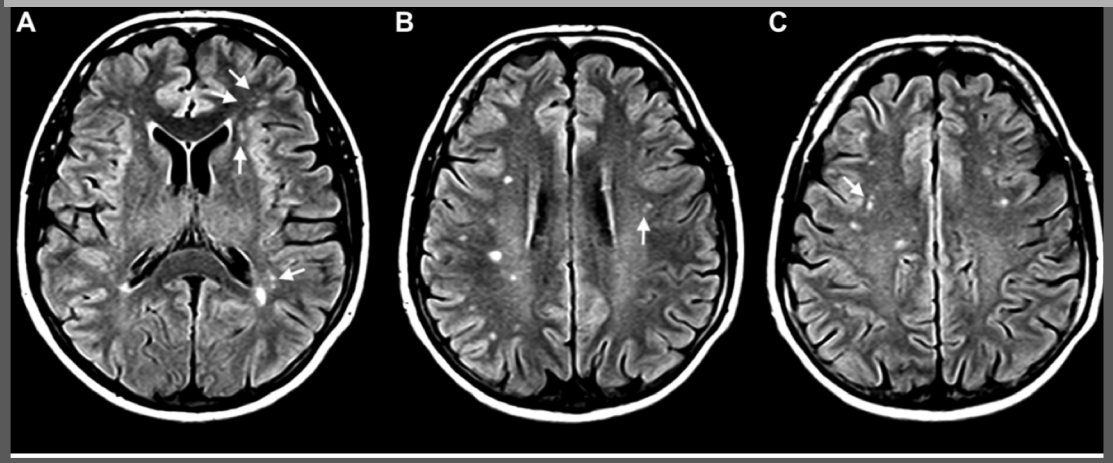
Prevalence of Silent Cerebral Ischemia in Paroxysmal and Persistent Atrial Fibrillation and Correlation With Cognitive Function

Gaita et al. JACC 2013

- 180 AF patients (**60.5% with CHA_2DS_2 VASc 0/1**) and 90 controls in SR, balanced for age, sex, risk factors, and education level

55-year-old man, with PAF and **CHA_2DS_2-Vasc 0**



CME

Prevalence of Silent Cerebral Ischemia in Paroxysmal and Persistent Atrial Fibrillation and Correlation With Cognitive Function

Fiorenzo Gaita, MD,* Laura Corsinovi, MD, PhD,* Matteo Anselmino, MD, PhD,* Cristina Raimondo, MD,* Martina Pianelli, MD,* Elisabetta Toso, MD,* Laura Bergamasco, Prof,† Carlo Boffano, MD,‡ Maria Consuelo Valentini, MD,§ Federico Cesarani, MD,‖ Marco Scaglione, MD¶

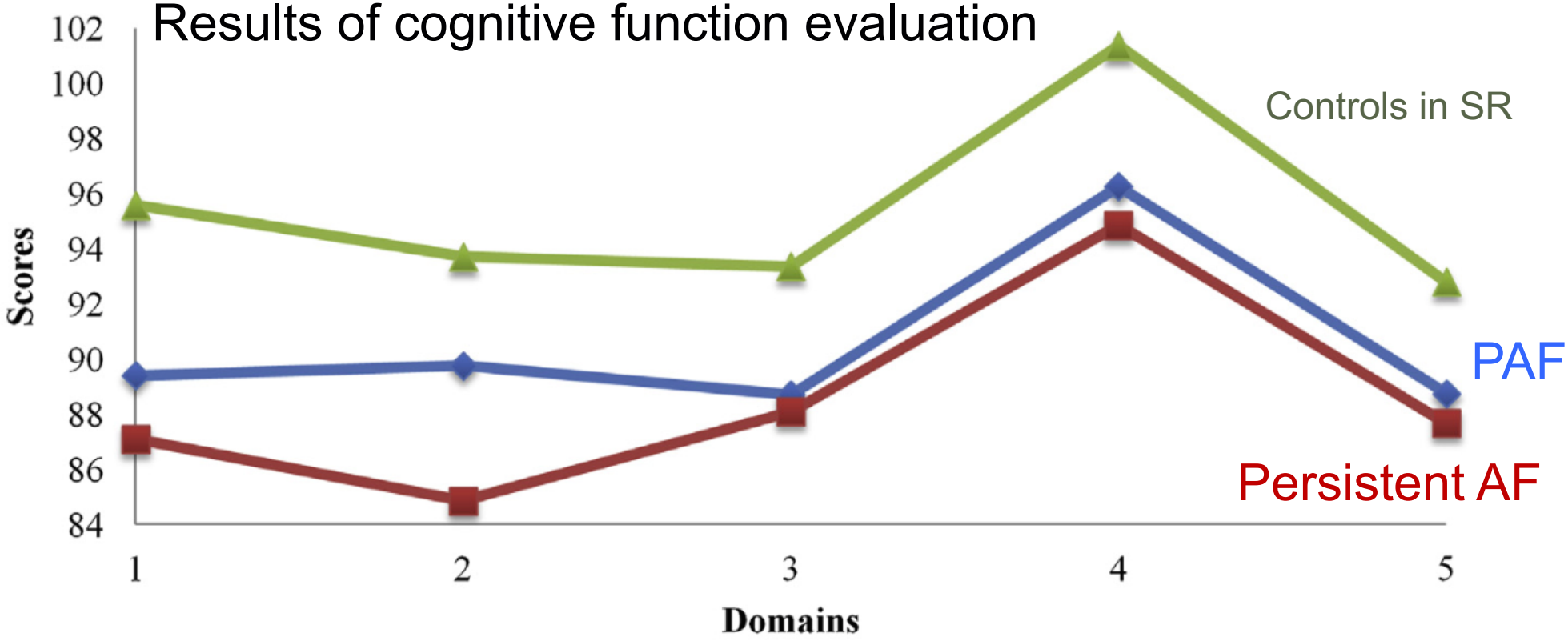
Turin, Milan, and Asti, Italy

brain AF

- Patients with AF had a higher prevalence of silence cerebral ischemia (SCI) and a worse cognitive performance compared to patients in sinus rhythm (SR) (odds ratio [OR], 11.2; 95% CI 6 to 21; $P<0.01$).

- Number of areas of SCI/pt was significantly higher in patients with AF than in controls (12.0±26.7; paroxysmal vs. controls and persistent vs. controls, $P<0.01$).

Results of cognitive function evaluation



	Controls (N = 90)	PRX AF (N = 90)	PER AF (N = 90)	p PRX / controls	p PER / controls	p PRX/ PER
Domains	92.4 ± 15.4	86.2 ± 13.8	82.9 ± 11.5	< 0.01	< 0.01	0.08
1-Immediate Memory	95.6 ± 17.5	89.9 ± 14.7	87.1 ± 16.9	0.02	< 0.01	0.24
2-Visuo-spatial abilities	93.8 ± 16.7	89.9 ± 18.2	84.8 ± 14.8	0.14	< 0.01	0.04
3-Language	92.9 ± 11.4	88.8 ± 9.1	88.1 ± 8.7	< 0.01	< 0.01	0.59
4-Attention	101.4 ± 21.2	96.6 ± 16.6	94.9 ± 15.6	0.09	0.02	0.47
5-Delayed memory	93.5 ± 11.7	88.7 ± 14.7	87.7 ± 14	0.02	< 0.01	0.64

Featured Article

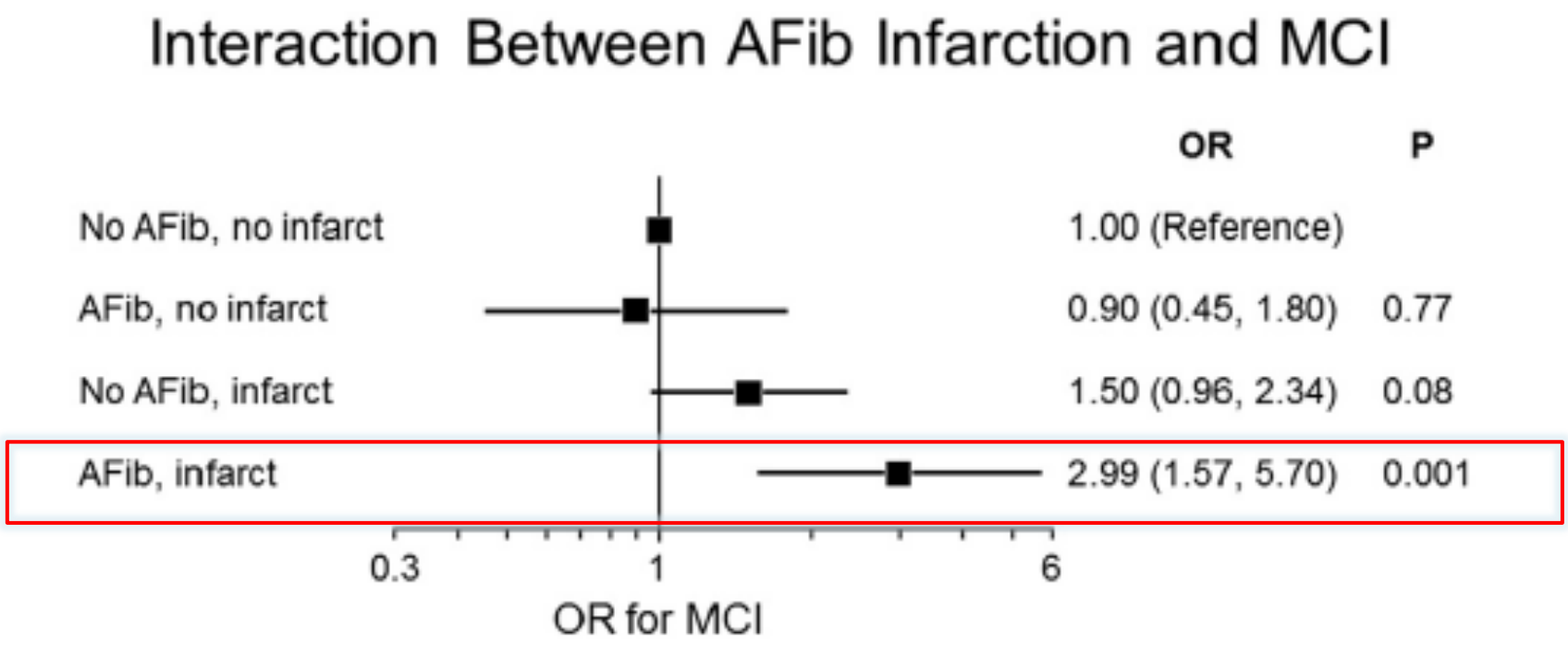
Atrial fibrillation, cognitive impairment, and neuroimaging

Jonathan Graff-Radford[a], Malini Madhavan[b], Prashanthi Vemuri[c], Alejandro A. Rabinstein[a], Ruth H. Cha[d], Michelle M. Mielke[a,d], Kejal Kantarci[c], Val Lowe[c], Matthew L. Senjem[c], Jeffrey L. Gunter[c], David S. Knopman[a], Ronald C. Petersen[a], Clifford R. Jack, Jr.,[d], Rosebud O. Roberts[a,d,*]

[a]*Department of Neurology, Mayo Clinic and Foundation, Rochester, MN, USA*
[b]*Department of Cardiology, Mayo Clinic and Foundation, Rochester, MN, USA*
[c]*Department of Radiology, Mayo Clinic and Foundation, Rochester, MN, USA*
[d]*Department of Health Sciences Research, Mayo Clinic and Foundation, Rochester, MN, USA*

Azheimer's & Dementia 2016

- Pts from the Mayo Clinic Study of Aging were invited to participate in the trial
- Cerebral MRI and cognitive testing (by a neuropsychometrist) in 1044 pts (141 with AF)



Patients with both AF and silent cerebral ischemia are more likely to suffer from MCI

Study Hypothesis

- **Pathophysiological hypothesis:** In patients with AF, silent cerebral microemboli are an important cause of cognitive impairment

Inclusion Criteria

- 30-62 years at consent
- Low risk of stroke
- Documentation of AF within the prior 18 months
  - ECG, intracardiac electrogram, or pacemaker/implantable cardioverter-defibrillator

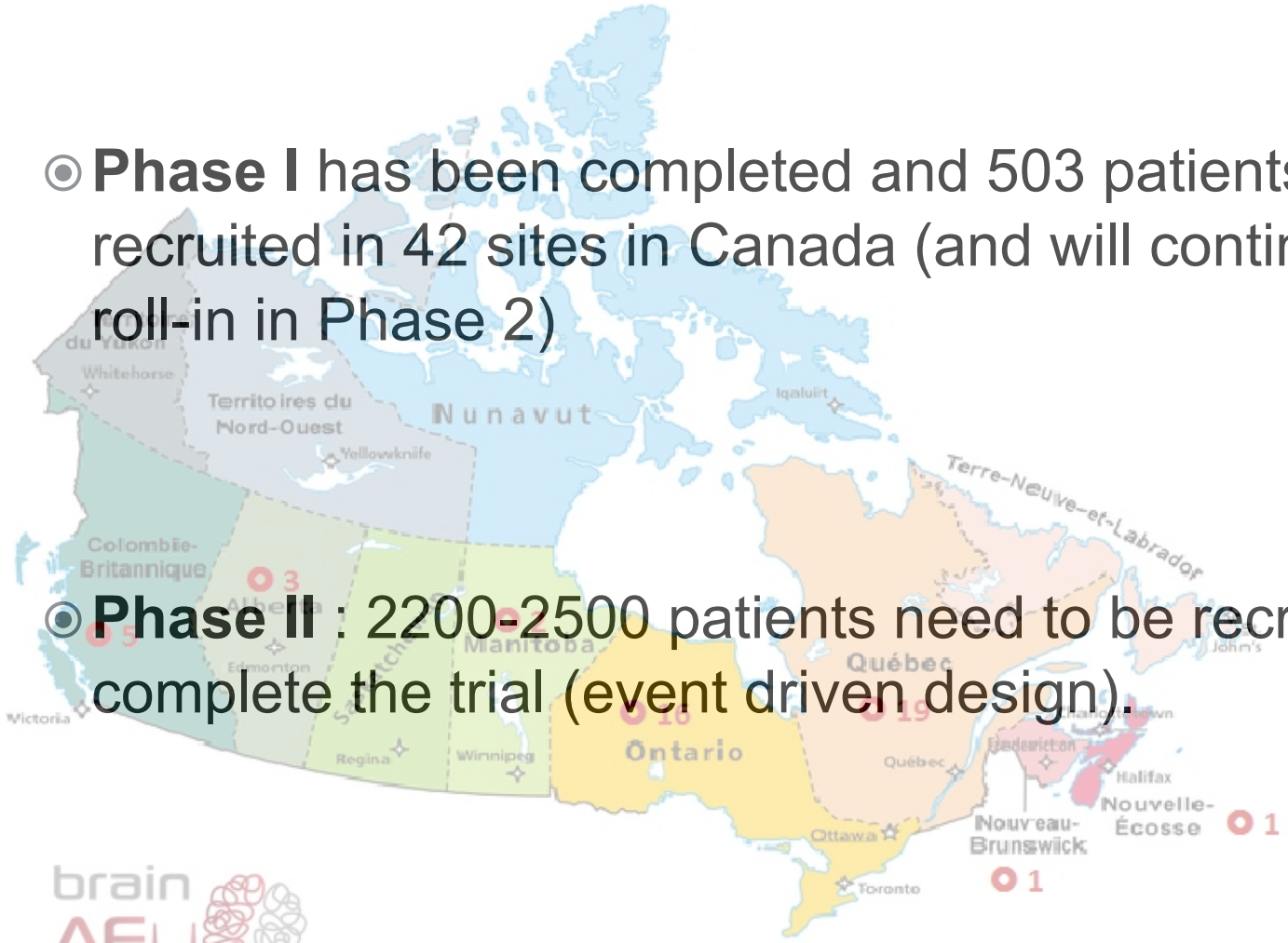
Exclusion Criteria

1. Known diagnosis of dementia;
2. Valvular AF (clinically significant) or hypertrophic cardiomyopathy;
3. Other indication for antiplatelet therapy or anticoagulation;
4. Conditions associated with an increased risk of bleeding;
5. History of gastro-intestinal bleeding;
6. Reversible cause of AF (e.g. cardiac surgery, pulmonary embolism, untreated hyperthyroidism);
7. Planned pulmonary vein ablation or surgery for treatment of AF;
8. Absence of AF recurrence ≥3 months post ablation

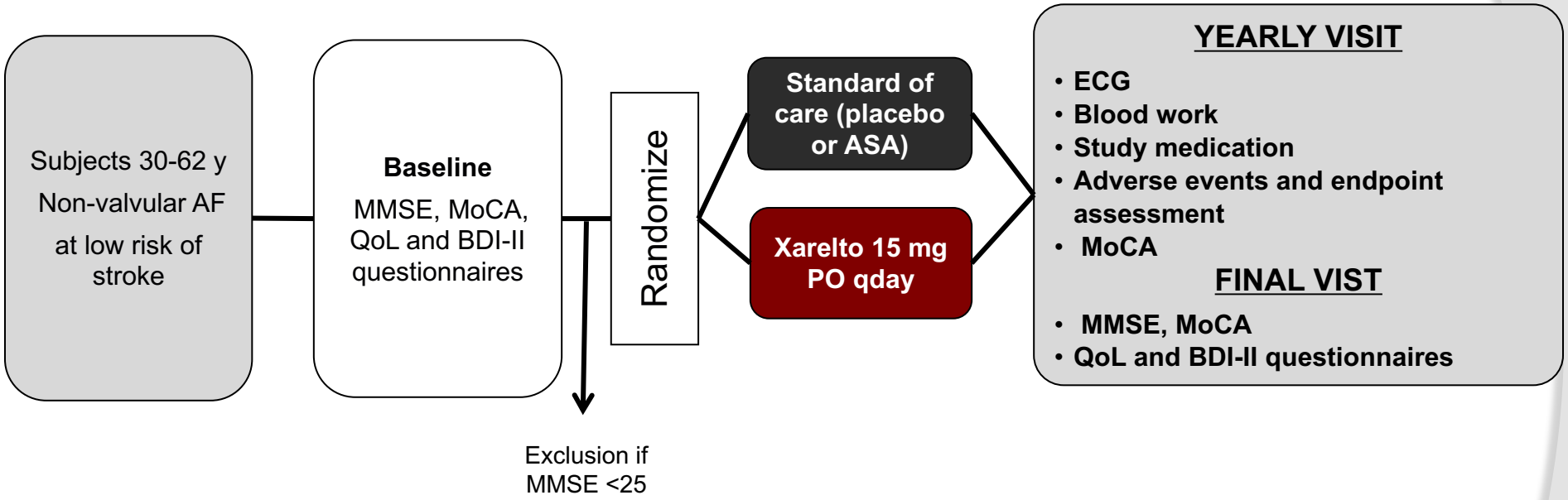
Exclusion Criteria

9. Severe renal impairment (creatinine clearance 30 mL/min or less);
10. Active infective endocarditis;
11. Active liver disease (e.g. acute clinical hepatitis, chronic active hepatitis, cirrhosis), or ALT >3 times the upper limit of normal;
12. Women who are pregnant or of childbearing potential not using a medically acceptable form of contraception;
13. Women who are breastfeeding;
14. Anemia or thrombocytopenia (according to the normal range values of the local laboratory);
15. Investigational drug received in the past 30 days;
16. Patients considered unreliable, or having a life expectancy of less than 3 years;
17. Known diagnosis of major depression within the past year.

- **Phase I** has been completed and 503 patients have been recruited in 42 sites in Canada (and will continue FU with roll-in in Phase 2)
- **Phase II** : 2200-2500 patients need to be recruited to complete the trial (event driven design).



PHASE II: STUDY SCHEME



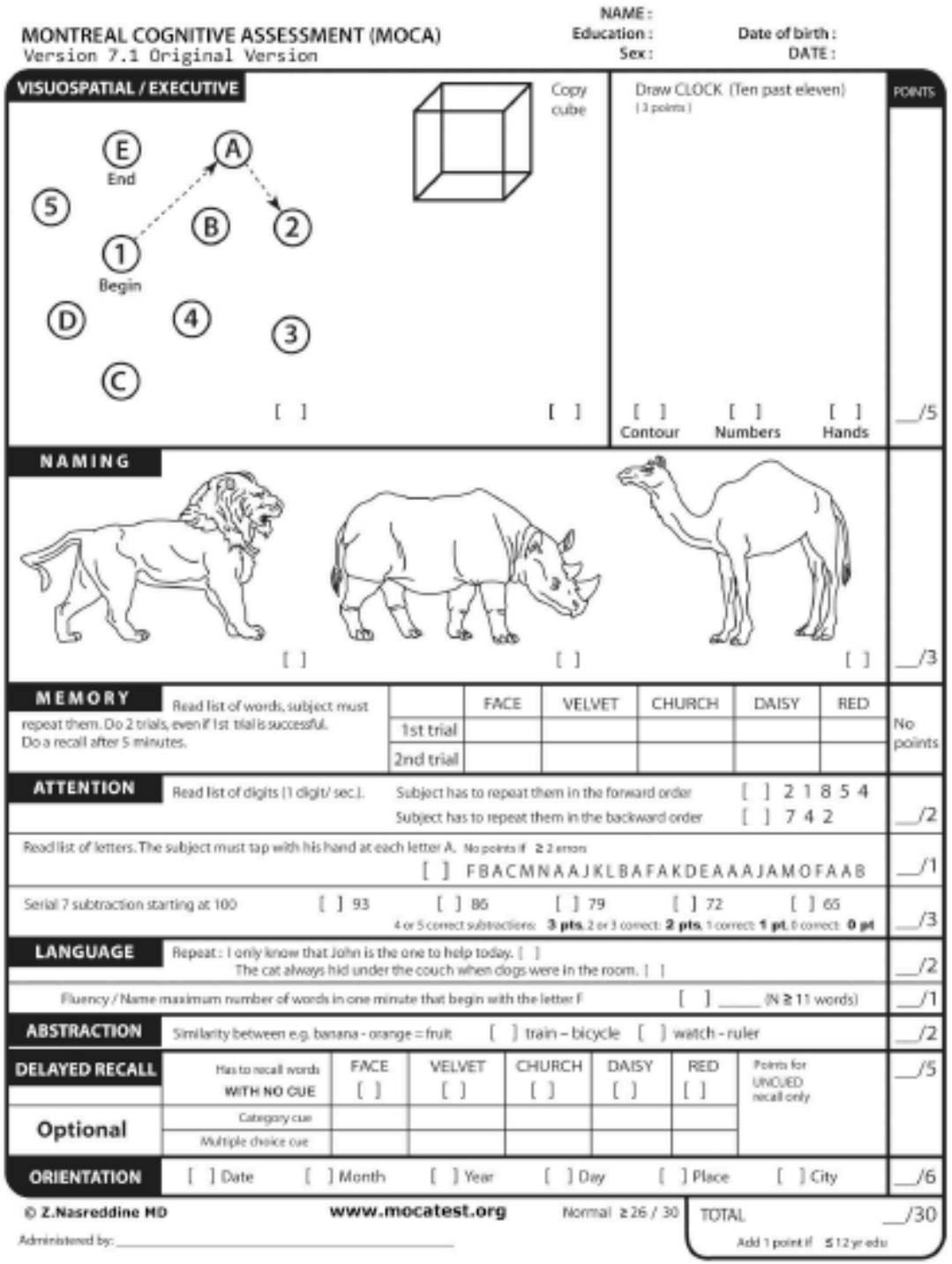
- Important modifications include:
  - *Primary outcome*: neurocognitive decline measured by MoCA instead of 3MS
  - *Treatment arm*: Xarelto 15 mg PO day versus standard of care, with stratified randomization to ASA if vascular disease or placebo in the absence of vascular disease to comply with current guidelines
  - Major streamlining and simplification of *follow-up and eCRF* to facilitate recruitment
  - Event-driven design trial

PHASE I: BASELINE CHARACTERISTICS

Characteristic	N = 415
Type of AF Paroxysmal Persistent Permanent	 74.3% 11.9% 13.8%
Prior AF ablation	11.2%
Family history of AF (first degree)	26.1%
Family history of dementia (first degree)	21.5%
Known sleep apnea	16.8%

10% at high risk

Data as of August 02, 2017



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE
Copy cube
Draw CLOCK (Ten past eleven) (3 points)
POINTS
End
Begin
Contour
Numbers
Hands
/5

NAMING
/3

MEMORY
Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.
FACE VELVET CHURCH DAISY RED
1st trial
2nd trial
No points

ATTENTION
Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2
/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B
/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**
/3

LANGUAGE
Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ]
/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)
/1

ABSTRACTION
Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler
/2

DELAYED RECALL
Has to recall words WITH NO CUE
FACE [ ] VELVET [ ] CHURCH [ ] DAISY [ ] RED [ ]
Points for UNCUED recall only
Optional
Category cue
Multiple choice cue
/5

ORIENTATION
[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City
/6

© Z.Nasreddine MD
www.mocatest.org
Normal ≥ 26 / 30
TOTAL /30
Add 1 point if ≤ 12 yr edu
Administered by: _____

brain AF

- MoCA is a screening tool developed specifically for detection of MCI
- Using a cut-of point of 26/30, sensitivity=80-100% and specificity=50-76%[1]
- Using a cut-of point of 24/30, specificity increases to 87%[2]

1-Smith 2007- Nasreddine 2005
2-Cecato 2011

PHASE I: BASELINE CHARACTERISTICS

Characteristics	N = 415	
MoCA	Range 21-30 out of 30	
MoCA <26*		PAF vs Persistent/Permanent P=0.05
Paroxysmal AF	13.1% (mean age 55.7)	
Persistent AF	20.4% (mean age 55.9)	
Permanent AF	21.1% (mean age 56.6)	
MoCA <24**		PAF vs Persistent/Permanent P=0.03
Paroxysmal AF	3.9% (mean age 55.0)	
Persistent AF	8.2% (mean age 52.4)	
Permanent AF	10.5% (mean age 54.7)	

Data as of August 02, 2017

In short, baseline characteristics confirm a high degree of cognitive pathology in this young population with AF, with a "dose-response" relationship

PHASE I: OUTCOMES (BLINDED)

Efficacy outcomes at 1 year follow-up	N=277
Cognitive decline (primary endpoint)	18 (6.5%)
Stroke/TIA	2 (0.7%)

No overlap between the two

Safety outcomes (per patient)	N=497
Death	1 (motorcycle accident)
Major bleeding	1 (post surgery, off-study drug)
Non-major clinically relevant bleeding (NMCRB)	20 (4.0%)
Minimal bleeding	29 (5.8%)
Bleeding in pts with a minimal FU of 12 months (N=277)	NMCRB 19 (6.9%) Minimal 26 (9.4%)

2018

In summary, a 7.2%/year rate of the primary outcome was observed, with an excellent safety profile (no major bleeds on study drugs)

In conclusion

- Growing evidence that AF may contribute to cognitive impairment independently of clinical stroke as a result of subclinical emboli

- Important study evaluating whether anticoagulation could reduce neurocognitive decline/cerebral ischemia in patients with non-valvular AF and no current indication for oral anticoagulation

Treat the Heart, Help the Brain