

# **DECLARATION OF CONFLICT OF INTEREST**

# Comparison of the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc prediction rules for stroke in patients with atrial fibrillation.

- The prospective Danish Diet, Cancer and Health (DCH) cohort study

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## Disclosures

- None to declare

## Aim of the study

- To assess the added predictive ability of the CHA<sub>2</sub>DS<sub>2</sub>VASc risk score for stroke and death in patients with atrial fibrillation

# Stroke risk stratification with CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores

<b>CHADS<sub>2</sub> acronym</b>	<b>Score</b>	<b>CHA<sub>2</sub>DS<sub>2</sub>-VASc acronym</b>	<b>Score</b>
Congestive heart failure	1	Congestive heart failure/LV dysfunction	1
Hypertension	1	Hypertension	1
<b>Aged ≥75 years</b>	<b>1</b>	<b>Aged ≥75 years</b>	<b>2</b>
Diabetes mellitus	1	Diabetes mellitus	1
Stroke/TIA/TE	2	Stroke/TIA/TE	2
		<b>Vascular disease (prior MI, PAD, or aortic plaque)</b>	<b>1</b>
		<b>Aged 65-74 years</b>	<b>1</b>
		<b>Sex category (i.e. female gender)</b>	<b>1</b>
Maximum score	6	Maximum score	9

# The Danish Diet, Cancer and Health (DCH) cohort study

- 27,178 men and 29,876 women enrolled
- Aged between 50 and 64 years
- Urban areas of Copenhagen and Aarhus
- Followed from 1993 – full follow up
- Detailed information on:
  - demographics
  - existing co-morbidities
  - individual risk factors
- Cross linkage of DCH with the National Registry of Patients and the Danish Prescription Database



## Case finding

- Incident cases of non VKA treated AF after recruitment
- Comorbidity and stroke: components of the CHA<sub>2</sub>DS<sub>2</sub>-VASc and CHA<sub>2</sub>DS<sub>2</sub>-VASc CHADS2 scores were determined at the time of AF diagnosis (ICD-8 and 10)
- Death: from the civil registration system

## Methods

- Incidence rates and COX-regression analysis
- Area under the ROC-curve (AUC) – C statistics; time dependent
- Negative Predictive Value (NPV); time dependent
- Net Reclassification Improvement (NRI); time dependent
- Bootstrap based confidence intervals

# ICD codes in the study

CHADS <sub>2</sub> & CHA <sub>2</sub> DS <sub>2</sub> VASC	ICD 8	ICD 10
Stroke*	433.09, 433.99, 434.09, 434.99, 436.01, 436.90	I63.0 – I63.9, I64.9
Transient ischemic attack	435.09, 435.99	G45.0 – G45.9**
Thromboembolism	444.00-444.99	I74.0 – I74.9
Congestive heart failure	427.09	I50.0 – I50.9, I11.0
Hypertension	400.09, 400.19, 400.29, 400.39, 400.99, 401.99, 402.99, 403.99, 404.99	I10.0, I10.9, I11.0, I11.9, I12.0, I12.9, I13.0 - I13.9, I15.0 – I15.9
Diabetes mellitus (type I)	249.00, 249.09	E10.0 – E10.9
Diabetes mellitus (type II)	250.08, 250.09	E11.0 – E11.9
Diabetes with no specification	-	E14.0 - E14.9
Acute myocardial infarction	410.09, 410.99	I21.0-I21.9, I22.0-I22.9
Peripheral arterial disease***	440.20, 443.99, 444.41	I70.2, I73.9, I74.5,
Arteriosclerosis of aorta	440.09	I70.0
Atrial fibrillation	427.93	I48.9
Atrial flutter	427.94	I48.9
<b>Other</b>		
Coronary artery disease	412.09, 412.99	I25.0, I25.1
Amaurosis fugax	377.02	G45.3
Thyrotoxicosis	242	E05
Pulmonary embolism	450	I26.0, I26.9
Deep venous thrombosis	451	I80.1–I80.9
Heavy smokers	Questionnaire (> 15 cigarettes per day)	Questionnaire (> 15 cigarettes per day)



# Net reclassification improvement

Case (c) Non case(nc)		Test 1		Total
		Abnormal	Normal	
Test 2	Abnormal	18	4	22
	Normal	2	6	8
Total		20	10	30
		10	60	70

Diagonal labels:   
 Top-right: Correct (4) / Incorrect (2)   
 Bottom-left: Incorrect (2) / Correct (8)

## Change in Sn + Sp:

Test 1: 66.7% + 85.7% = 152.4%

Test 2: 73.3% + 91.4% = 164.7%

Change in Sn + Sp = 12%

## NRI for test 2:

$NRI_c = (4-2)/30 = 0.067$

$NRI_{nc} = (8-4)/70 = 0.057$

Sum = 0.12

## Net proportion of patients reclassified correctly by Test 2:

$((4-2) + (8-4))/100 = 6\%$

Suggested reading: Pencina et al. Stat Med. 2008;27:157-72

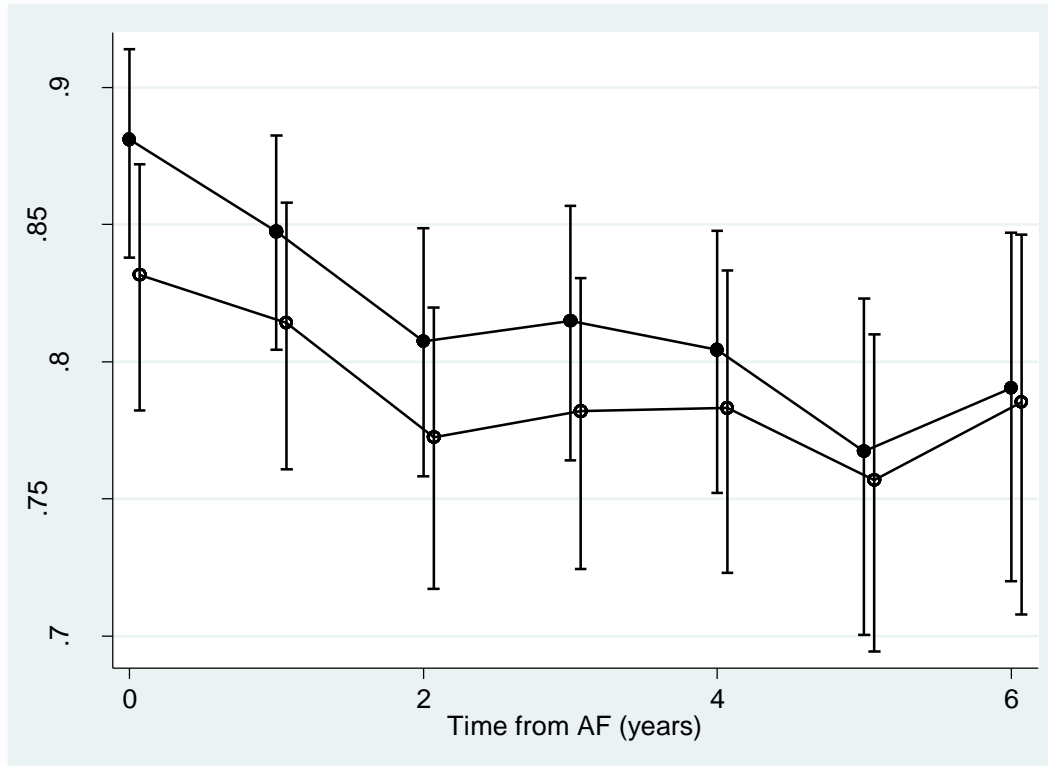
# Results

<b>(a)Clinical Characteristics</b>	<b>Whole cohort Median (p10;p90)</b>
Number of participants (N)	1,682
Age, years (at time of AF)	66.7 (59.2; 74.3)
Age ≥75 years	8.0 (135)
Age 65-74 years	53.4 (898)
Women	39.5 (665)
Follow up time (years):	5.4 (0.9;11.0)
<b>Past medical history</b> (at time of atrial fibrillation)	<b>% (N)</b>
Congestive heart failure:	22.6 (379)
Hypertension	28.6 (481)
Diabetes	9.0 (151)
Stroke history	9.5 (160)

## Incidence rates per 100 person years (95 % CI) for stroke among 1,682 patients after incident atrial fibrillation

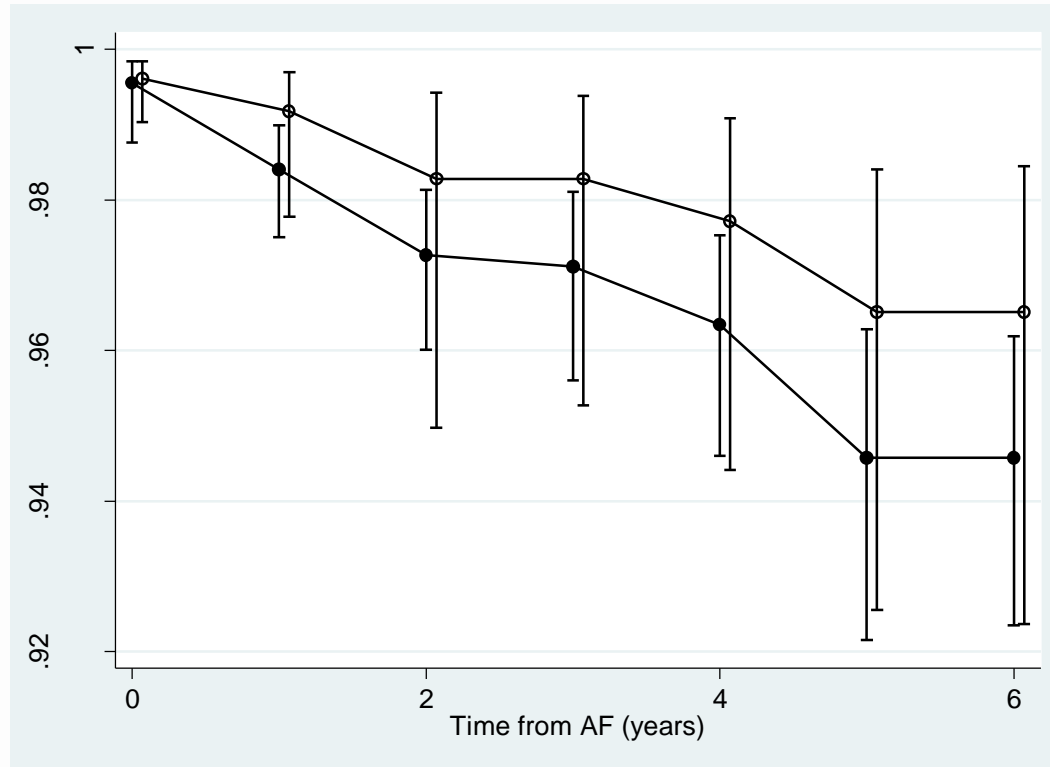
Score value	Incidence rates for CHADS <sub>2</sub>		Incidence rates for CHA <sub>2</sub> DS <sub>2</sub> VASc	
	One year follow up	Full follow up	One year of follow up	Full follow up
0	1.5 (0.9;2.7)	0.9 (0.7;1.2)	0.9 (0.2;3.4)	0.5 (0.3;1.04)
1	1.1 (0.4;3.0)	1.6 (1.0;2.3)	1.5 (0.7;3.2)	0.7 (0.6;1.3)
2	29.7 (22.1;39.9)	10.8 (8.3;14.2)	3.5 (2.0;6.1)	2.3 (1.7;3.2)
3	55.1 (39.1;77.4)	19.9 (14.4;27.3)	14.4 (10.0;20.1)	5.4 (4.0;7.5)
4	63.6 (36.1;110)	28.2 (17.0;46.8)	28.6 (19.9;41.2)	11.4 (8.2;15.8)
5	48.6 (12.1;190)	36.7 (11.8;110)	46.6 (30.4;71.5)	17.5 (11.7;26.1)
6	0.0	0.00	61.9 (25.8;150)	34.6 (15.6;77.1)
7	-	-	48.4 (12.1;190)	35.8 (11.6;110)
8	-	-	0.00	0.00
9	-	-	0.00	0.00
Test for trend	p<0.0001	p<0.0001	p<0.0001	p<0.0001

# Time dependent area under the ROC curve for Stroke



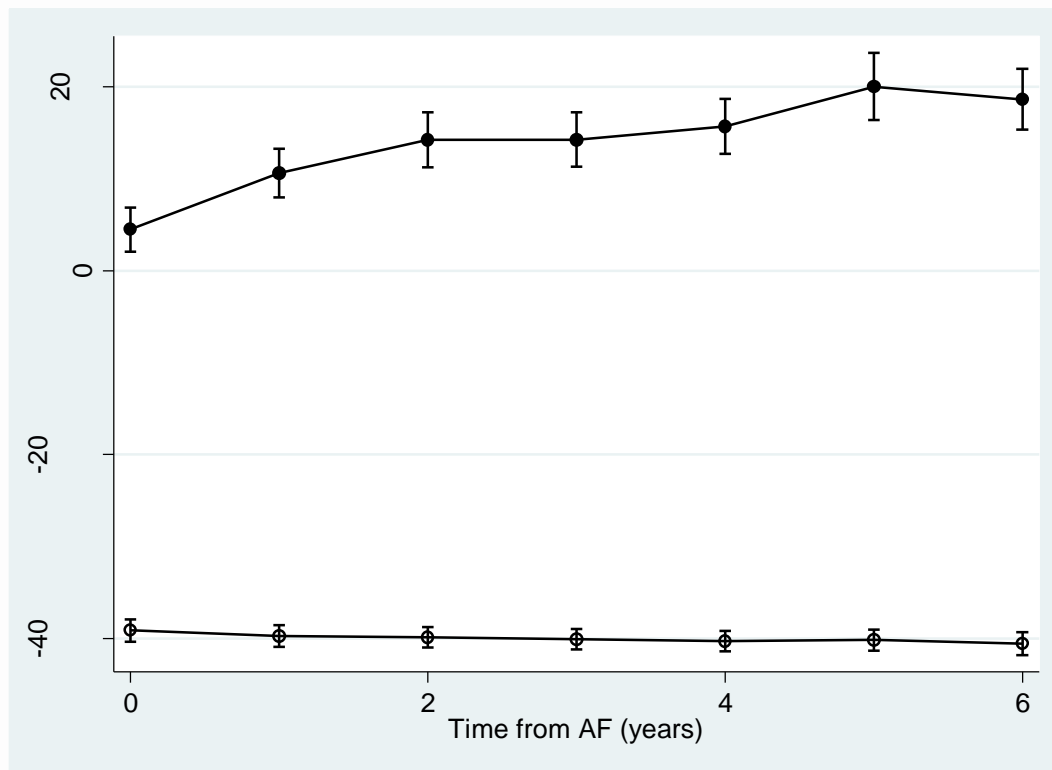
The solid dots are CHADS<sub>2</sub> and the circles are CHA<sub>2</sub>DS<sub>2</sub>VASc (all values from CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc are used to calculate the area under the ROC curve)

# Negative predictive value for zero as cut off value for the endpoint Stroke



The solid dots are CHADS<sub>2</sub> and the circles are CHA<sub>2</sub>DS<sub>2</sub>VASc

## Net Reclassification Index for cases and non-cases of stroke comparing the 'in-risk' scoring of CHADS<sub>2</sub> with CHA<sub>2</sub>DS<sub>2</sub>VASc using score $\geq 1$ as threshold for 'in-risk'.



The solid dots are NRI cases and the circles are NRI non-cases

Positive NRI means overweight of correct reclassified subjects. Negative NRI means overweight of incorrect reclassified subjects. NRI is stated in terms of the proportion of reclassified out of the population according to the endpoint status.

# What does CHA<sub>2</sub>DS<sub>2</sub>VASc add?

After 1 year



54 in VKA treatment to protect 1

After 5 years



14 in VKA treatment to protect 1

## Conclusions

- CHADS<sub>2</sub> as well as the CHA<sub>2</sub>DS<sub>2</sub>VASc risk score can exclude a large proportion of patients from having high risk of stroke or death.
- Using the CHA<sub>2</sub>DS<sub>2</sub>VASc risk score, less patients will fulfil the criterion for low risk (and are 'truly low risk') and the predictive negative value is increased.
- Use of NRI seems to be a valuable supplement to the c-statistic and NPV in evaluating the added predictive ability of the CHA<sub>2</sub>DS<sub>2</sub>VASc score and to contribute to a meaningful estimate of the clinical utility of this new risk score.



## Clinical implications

- Many of the patients at low risk according to CHADS<sub>2</sub> are not at “truly low risk”
- Given the high mortality and morbidity associated with AF-related thromboembolism, the CHA<sub>2</sub>DS<sub>2</sub>VASc stroke risk score is more inclusive of common stroke risk factors and would have ‘flagged up’ for anticoagulant treatment, which would have the potential to reduce stroke risk in these individuals.

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