ELECTRA & RHYTHM

18-21 MAY 2022

ELECTRA - SESSION CNCH : PREVENIR L'AVC SUR FA EN 2022

Fibrillation Atriale et Accident Vasculaire Cérébral : marqueur ou cause

Fabrice Extramiana

Hôpital Bichat - Paris

Marseille 20/05/2022

HÔPITAUX UNIVERSITAIRES PARIS NORD VAL DE SEINE
Bichat - Claude-Bernard

HÔPITAUX UNIVERSITAIRES PARIS OUEST
Corentin-Celton
Hôpital européen Georges-Pompidou
Vaugirard - Gabriel-Pallez

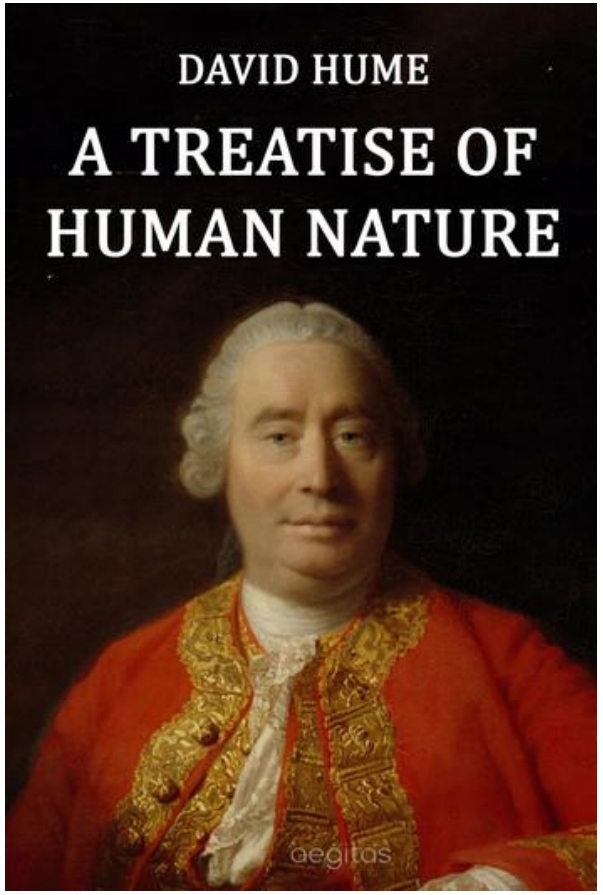
Université Paris Cité

Centre de Référence des Maladies Cardiaques Héréditaires ou Rares

cardiogen
filière nationale de santé maladies cardiaques héréditaires

Liens d'intérêts

- Bayer — honoraires, prise en charge congrès
- Microport — prise en charge congrès
- Mylan — honoraires
- Sanofi — honoraires, consultant, étude clinique, prise en charge congrès



Oxford University Press,
Oxford, 1888,
Second Edition, 1978
(original publication, 1739)

The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS
(*Professor Emeritus of Medical Statistics, University of London*)

(1) *Strength*. First upon my list I would put the strength of the association.

(2) *Consistency:* Next on my list of features to be specially considered I would place the *consistency*

(3) *Specificity:* One reason, needless to say, is the specificity of the association

(4) *Temporality:* My fourth characteristic is the temporal relationship of the association

(5) *Biological gradient:* Fifthly, if the association is one which can reveal a biological gradient, or dose-response curve,

(6) *Plausibility:* It will be helpful if the causation we suspect is biologically plausible. But this is a

(7) *Coherence:* On the other hand the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease

(8) *Experiment:* Occasionally it is possible to appeal to experimental, or semi-experimental, evidence.

(9) *Analogy:* In some circumstances it would be fair to judge by analogy.

Proc R Soc Med. 1965;58:295-300

(1) *Strength*. First upon my list I would put the strength of the association.

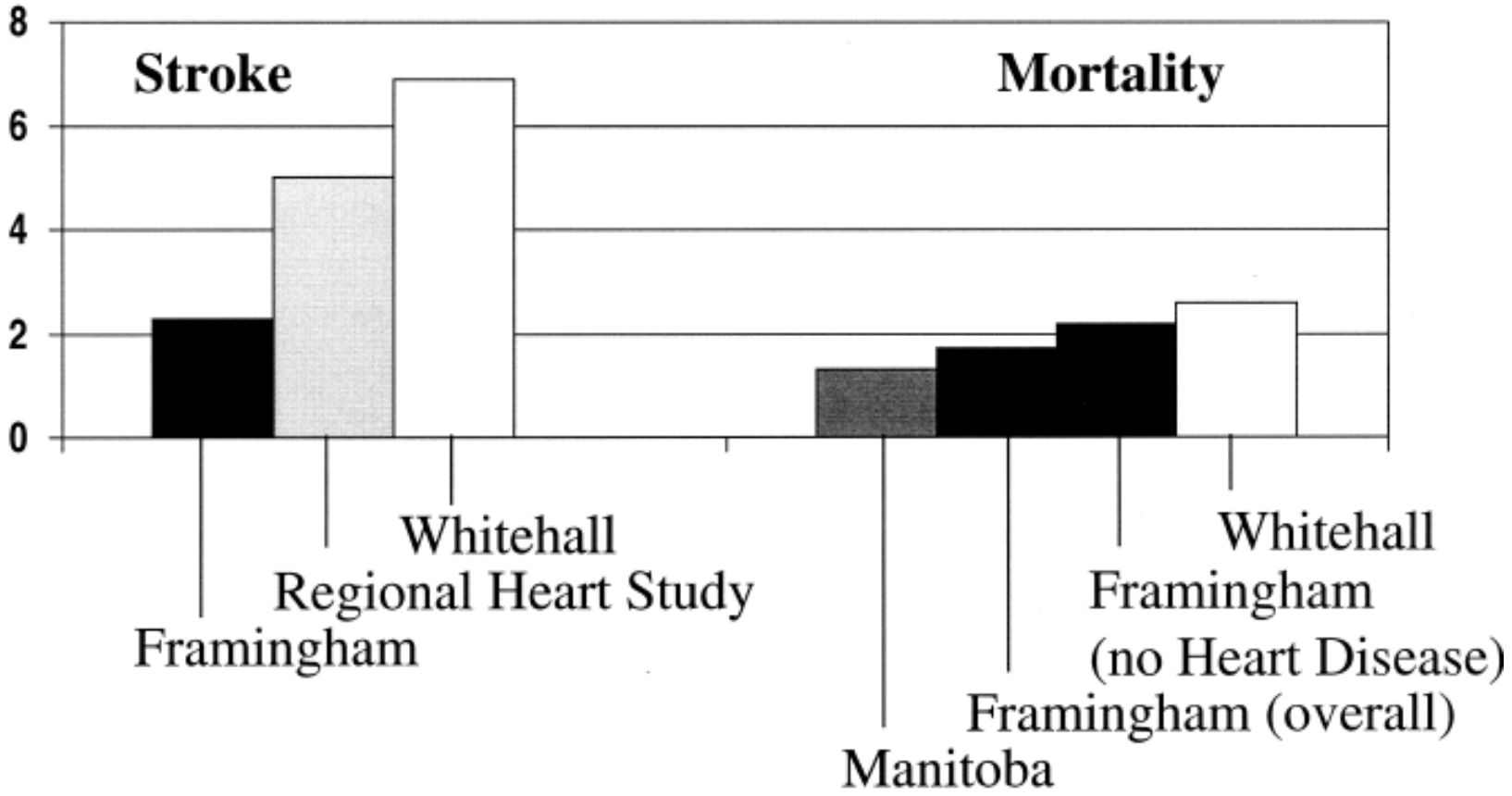
(2) *Consistency*: Next on my list of features to be specially considered I would place the *consistency*

Strong & consistent association

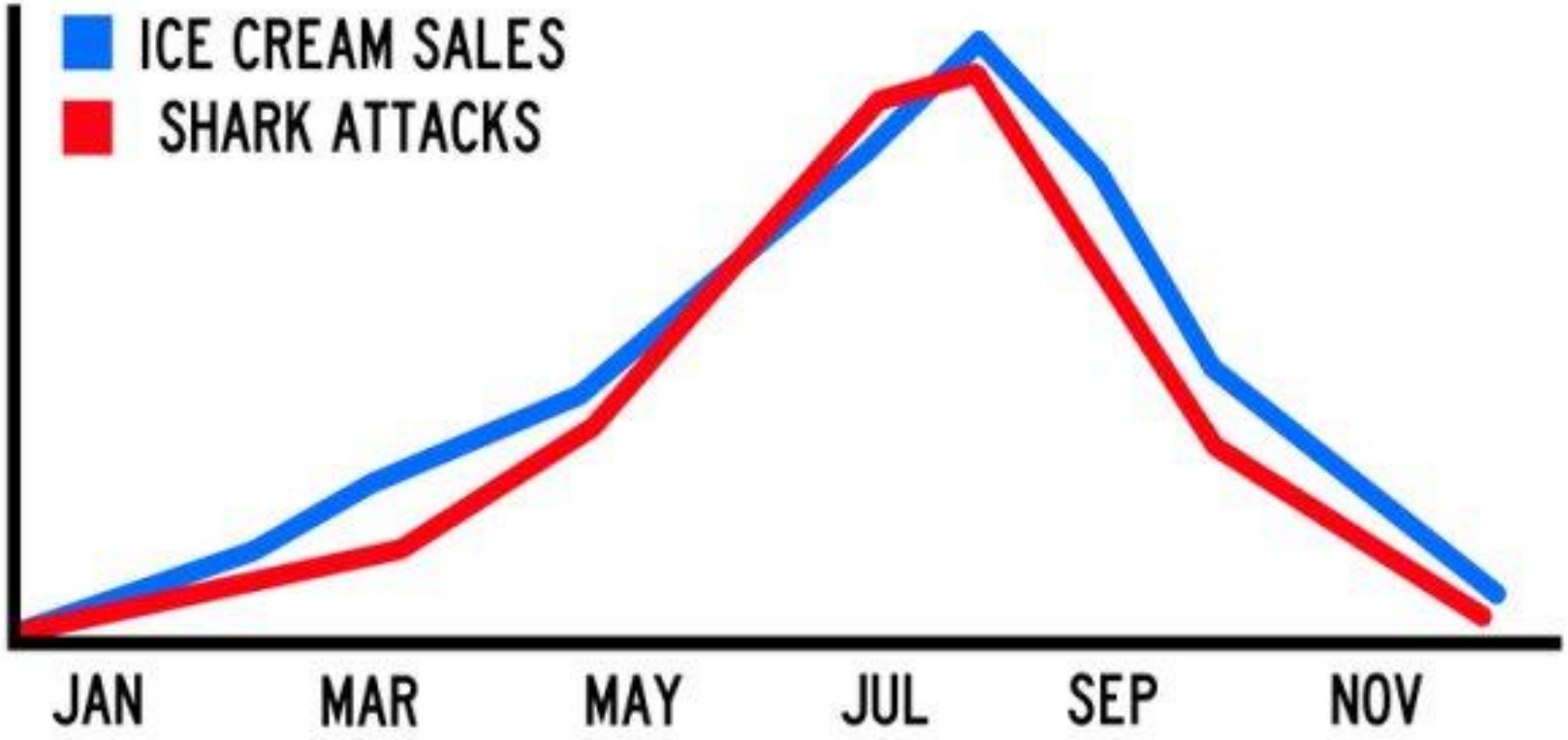
ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation

2001

Risques Relatifs



CORRELATION IS NOT CAUSATION!



Both ice cream sales and shark attacks increase when the weather is hot and sunny, but they are not caused by each other (they are caused by

(3) *Specificity:* One reason, needless to say, is the specificity of the association, the third characteristic which invariably we must consider.

Low specificity

Guidelines for the management of atrial fibrillation 2010

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score		
CHA_2DS_2-VASc score	Patients (n=7329)	Adjusted stroke rate (%/year)[b]
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

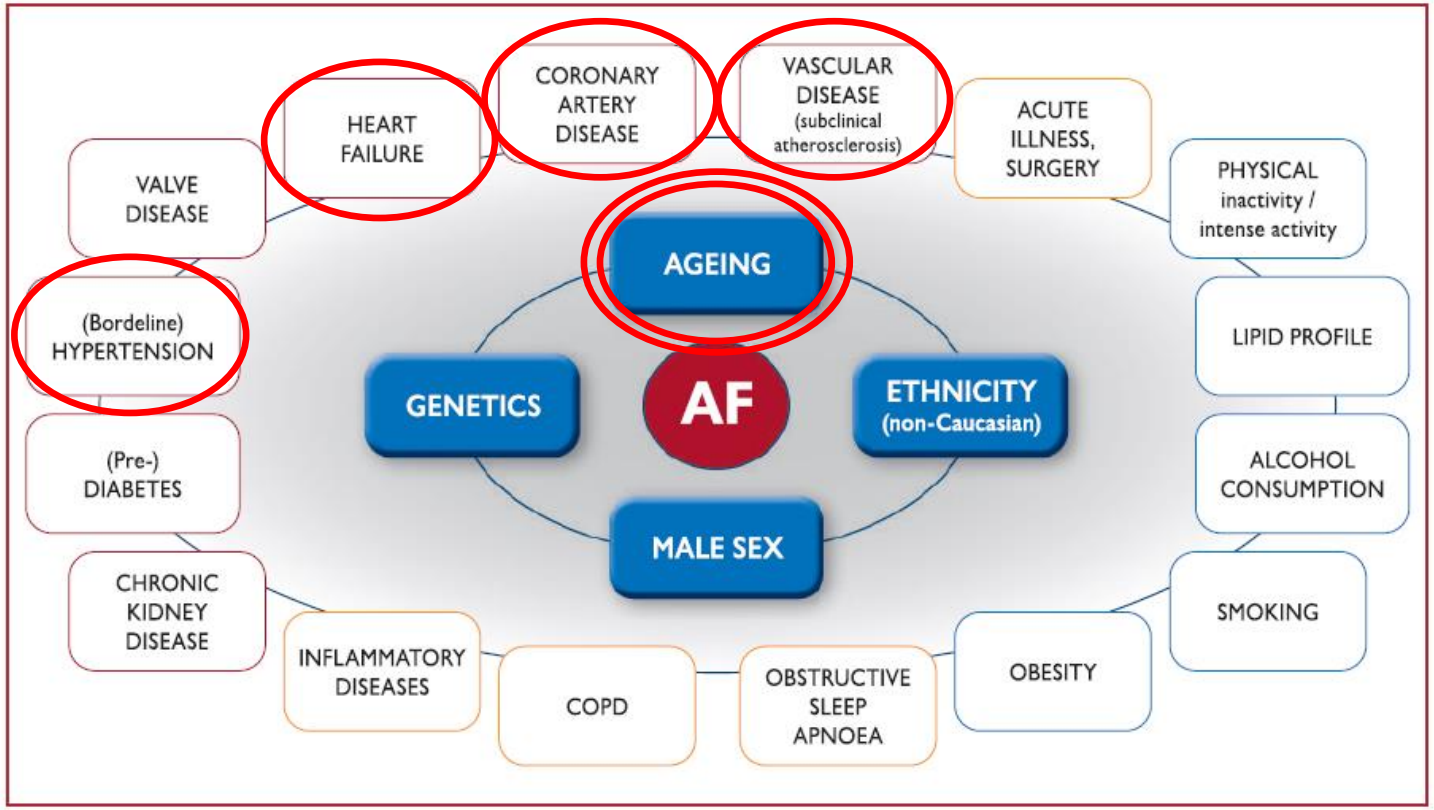
Table 3 Risk factors for ischaemic stroke/TIA/systemic embolism in patients with AF: the Swedish

	Multivariate hazard ratios (95% CI)
Age (years) <65 65–74 ≥75	 1.0 (Reference) 2.97 (2.54–3.48) 5.28 (4.57–6.09)
Female sex	1.17 (1.11–1.22)
Previous ischaemic stroke	2.81 (2.68–2.95)
Intracranial bleeding	1.49 (1.33–1.67)
Vascular disease (any) • Myocardial infarction • Previous CABG • Peripheral artery disease	1.14 (1.06–1.23) 1.09 (1.03–1.15) 1.19 (1.06–1.33) 1.22 (1.12–1.32)
Hypertension	1.17 (1.11–1.22)
Heart failure (history)	0.98 (0.93–1.03)
Diabetes mellitus	1.19 (1.13–1.26)
Thyroid disease Thyrotoxicosis	1.00 (0.92–1.09) 1.03 (0.83–1.28)

(3) *Specificity:* One reason, needless to say, is the specificity of the association, the third characteristic which invariably we must consider.

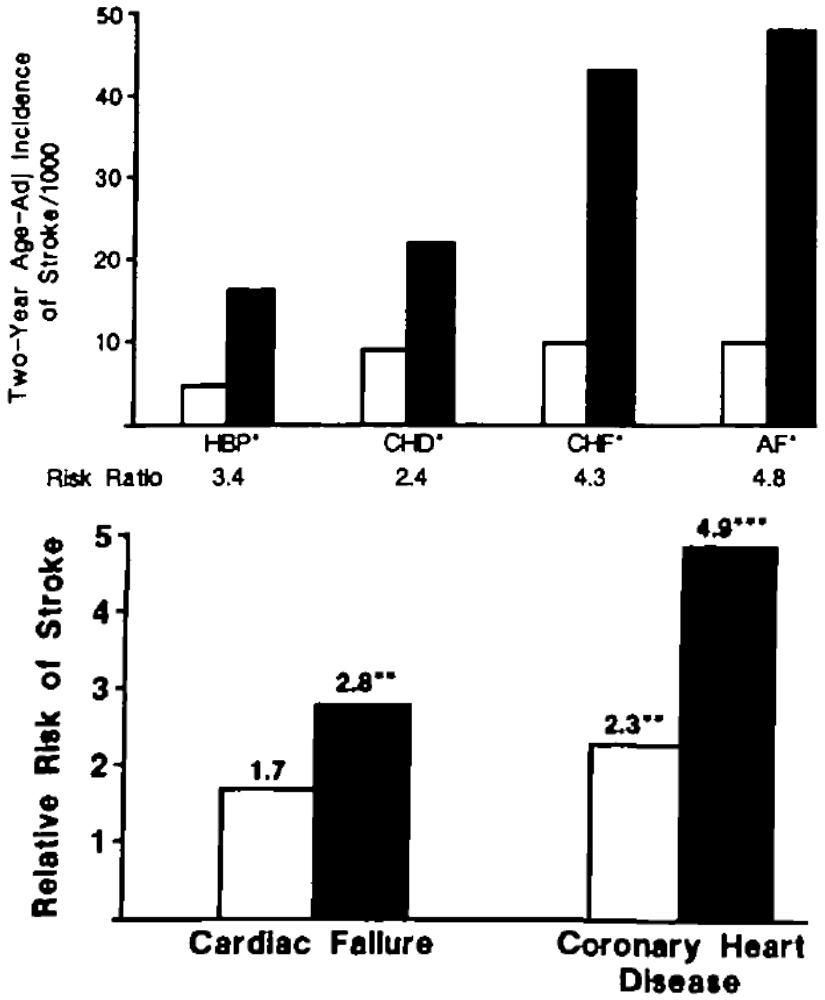
Low specificity

2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS)



Atrial Fibrillation as an Independent Risk Factor for Stroke: The Framingham Study

Philip A. Wolf, MD; Robert D. Abbott, PhD; and William B. Kannel, MD



Stroke 1991;22:983-8

(3) *Specificity:* One reason, needless to say, is the specificity of the association, the third characteristic which invariably we must consider.

Low specificity

Overlap of Diseases Underlying Ischemic Stroke

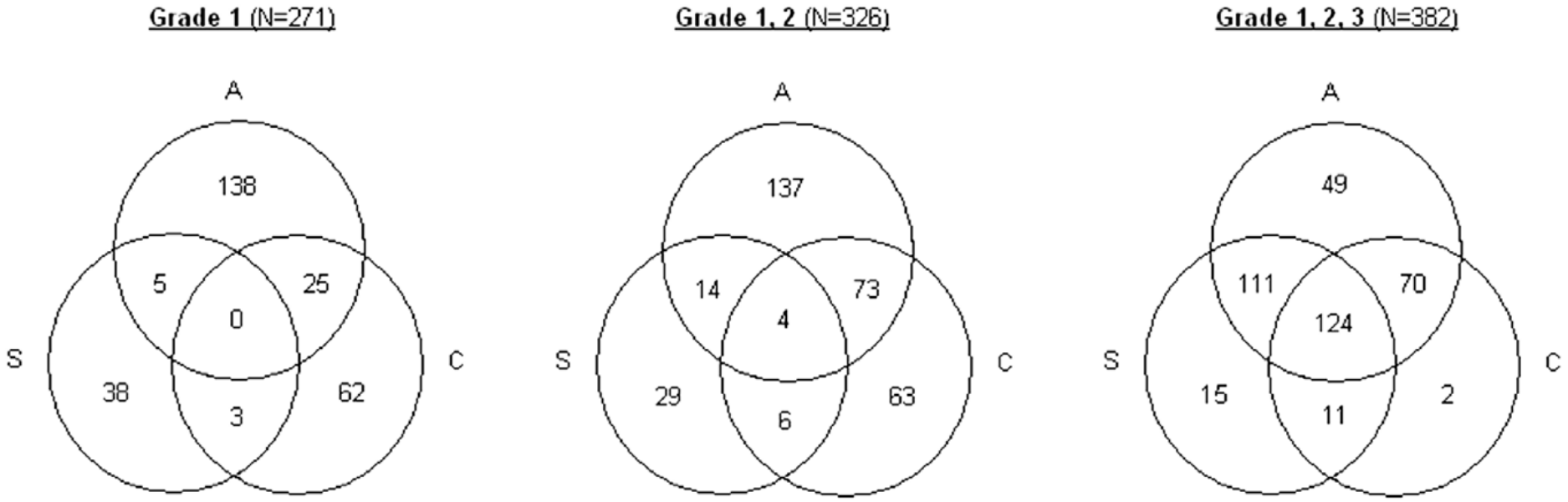
The ASCOD Phenotyping

Gaia Sirimarco, MD; Philippa C. Lavallée, MD; Julien Labreuche, BST; Elena Meseguer, MD; Lucie Cabrejo, MD; Céline Guidoux, MD; Isabelle F. Klein, MD, PhD; Jean-Marc Olivot, MD, PhD; Halim Abboud, MD; Valérie Adraï, MD; Jérôme Kusmierek, MD; Samina Ratani, MD; Pierre-Jean Touboul, MD; Mikael Mazighi, MD, PhD; Philippe Gabriel Steg, MD; Pierre Amarenco, MD

ASCOD phenotyping : to assign a degree of likelihood to every potential cause

1. Potential cause – 2. uncertain causality – 3. unlikely causal but present – 0. absence – 9. insufficient workup

Atherosclerosis
Small vessels
Cardiac
Other
Dissection



Stroke 2013;44:2427-33

(4) *Temporality:* My fourth characteristic is the temporal relationship of the association – which is the cart and which the horse?

Temporality?

Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices

on behalf of the IMPACT Investigators

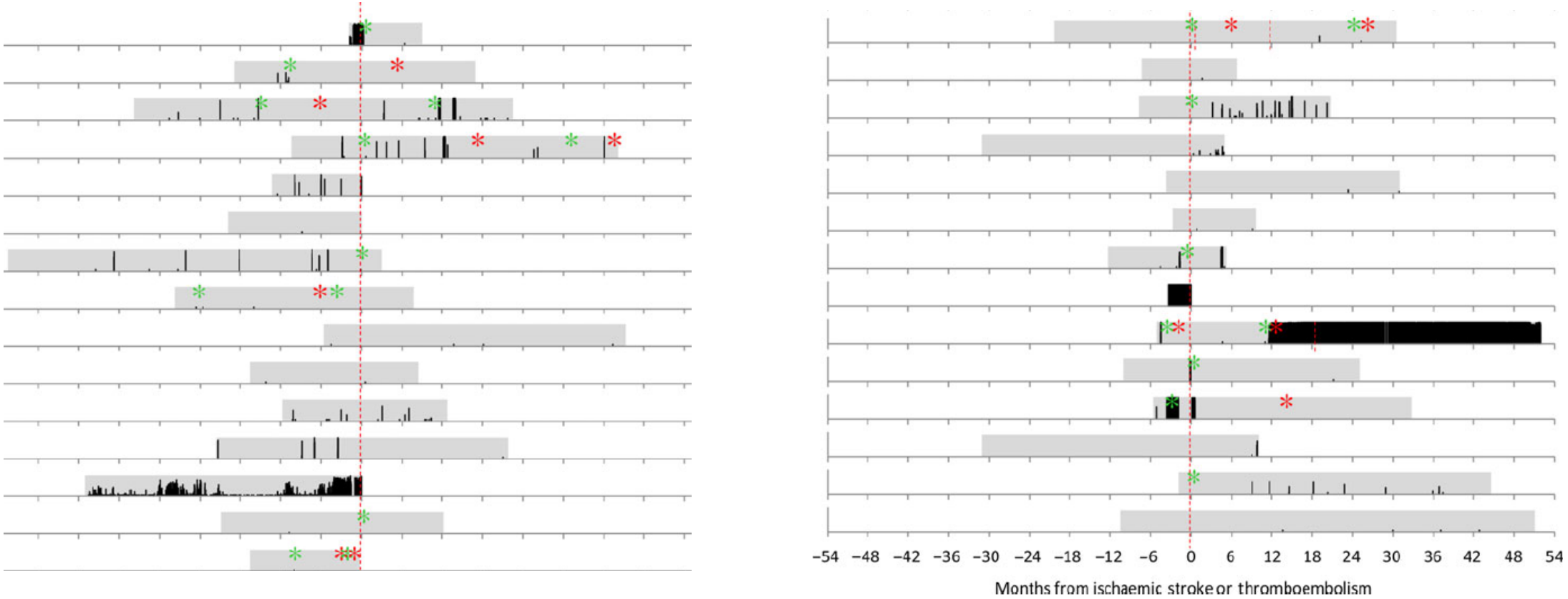


Figure 5 Temporal relationship between daily atrial tachyarrhythmia burden and clinical thromboembolism. Periods of remote monitoring are shown in grey, atrial tachyarrhythmia burden as vertical black lines (*y*-axis 0–100% burden, logarithmic scale), thromboembolic events in dashed red lines, oral anticoagulation starts as green asterisks and stops as red asterisks. Randomized group is denoted in ID column as subscripted C (control)

EHJ 2015;36:1660-8

(4) *Temporality:* My fourth characteristic is the temporal relationship of the association – which is the cart and which the horse? This is a question

Temporality?

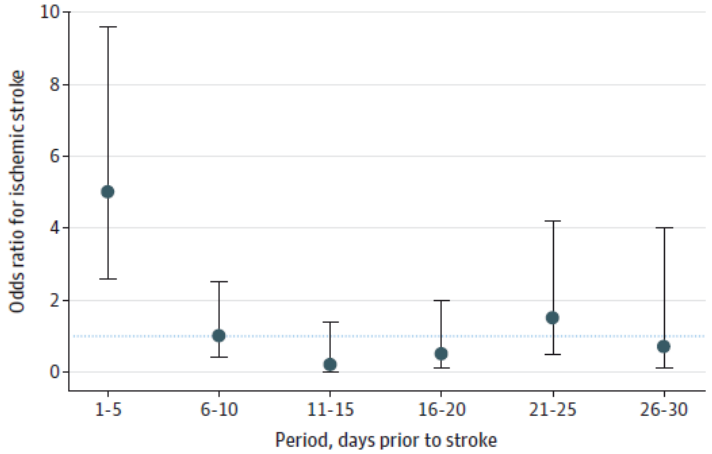
Temporal Association Between Episodes of Atrial Fibrillation and Risk of Ischemic Stroke

Daniel E. Singer, MD; Paul D. Ziegler, MS; Jodi L. Koehler, MS; Shantanu Sarkar, PhD; Rod S. Passman, MD, MSCE

Table 2. Association of Temporally Proximate Atrial Fibrillation (AF) With Risk of Stroke Stratified by Use of Anticoagulants: Comparing Occurrence of AF Above the Threshold 5.5 Hours or More on Any Day on Days 1 to 30 vs 91 to 120 Prestroke

	Patients, No.			
	Not taking anticoagulation		Taking anticoagulation	
Measure	Case period with AF	Case period with no AF	Case period with AF	Case period with no AF
Control period with AF	89	5[a]	54	9[a]
Control period with no AF	39[a]	570	13[a]	112
Odds ratio (95% CI)	7.80 (3.07-19.8)		1.44 (0.62-3.38)	

Figure. Odds Ratios for Ischemic Stroke for Sequential, Nonoverlapping 5-Day Intervals Containing at Least 1 Day With 5.5 Hours or More of Atrial Fibrillation



Five-day intervals proximate to the stroke were the case periods and were compared with corresponding matched within-patient 5-day control periods beginning 90 days earlier (days 1 to 5 prestroke were compared with days 91 to 95, days 6 to 10 were compared with days 96-100, and so on). Error bars indicate 95% CIs. The horizontal dotted line is the odds ratio of 1.0, ie, reflecting no association. Detailed results are provided in eTable 2 in the Supplement.

Table 3. Association of Temporally Proximate Atrial Fibrillation (AF) With Risk of Stroke: Exploring the Association of Mutually Exclusive Cumulative Amounts of AF on Any Given Day During the 30-Day Case Period vs the 30-Day Control Period[a]

AF threshold	Case period with AF	Case period with no AF	Odds ratio (95% CI)
0.5 to 1 h			
Control period with AF	1	3[b]	3.33 (0.92-12.11)
Control period with no AF	10[b]	638	
1 to 3 h			
Control period with AF	2	5[b]	1.60 (0.52-4.89)
Control period with no AF	8[b]	638	
3 to 6 h			
Control period with AF	2	2[b]	2.00 (0.37-10.92)
Control period with no AF	4[b]	638	
6 to 23 h			
Control period with AF	11	4[b]	2.75 (0.88-8.64)
Control period with no AF	11[b]	638	
>23 h			
Control period with AF	115	6[b]	5.00 (2.08-12.01)
Control period with no AF	30[b]	638	

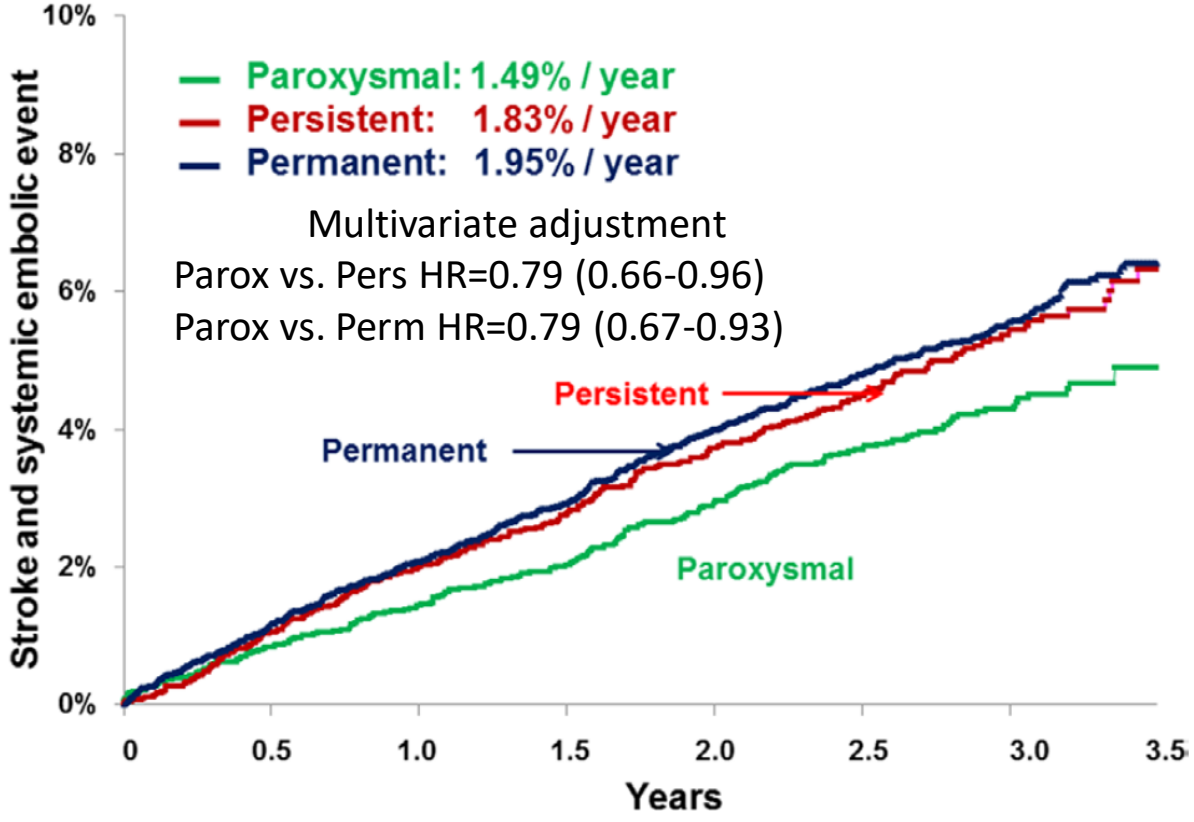
JAMA Cardiol. 2021
Doi:10.1001/jamacardio.2021.3702

(5) *Biological gradient:* Fifthly, if the association is one which can reveal a biological gradient, or dose-response curve, then we should look most carefully for such evidence.

Biological gradient

Stroke and Mortality Risk in Patients With Various Patterns of Atrial Fibrillation

Results From the ENGAGE AF-TIMI 48 Trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48)



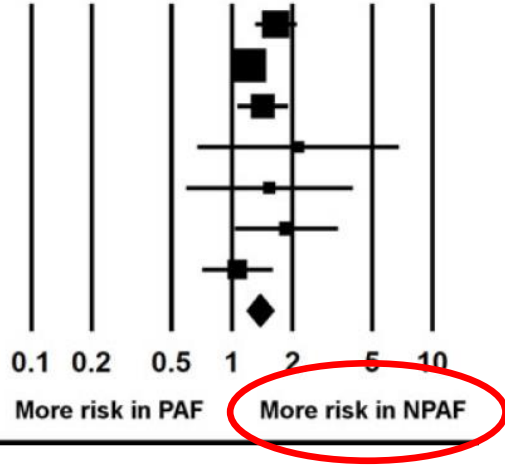
CircA&E 2017;10:e004267

The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis

B

Stroke or Systemic Embolism (adjusted)

Study name	Hazard ratio	Lower limit	Upper limit	p-Value
ACTIVE A/AVERROES	1.658	1.316	2.089	0.000
ROCKET-AF	1.220	1.060	1.403	0.006
ARISTOTLE	1.429	1.072	1.904	0.015
GISSI-AF	2.141	0.677	6.774	0.195
Euro Heart Survey	1.538	0.595	3.980	0.374
SPORTIF	1.870	1.041	3.359	0.036
Active W	1.064	0.714	1.586	0.761
OVERALL	1.384	1.191	1.608	0.000



NPAF = non paroxysmal AF

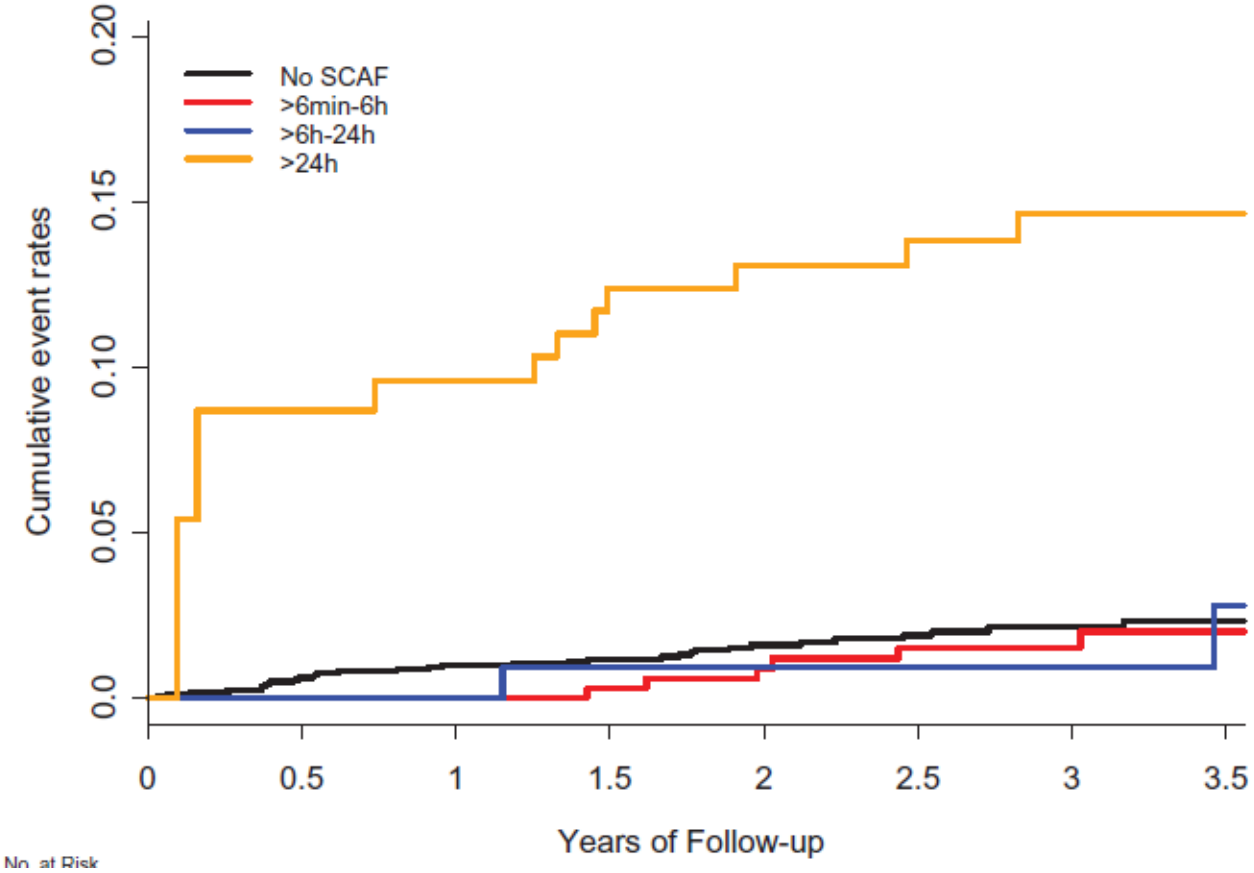
EHJ 2016;37:1591-602

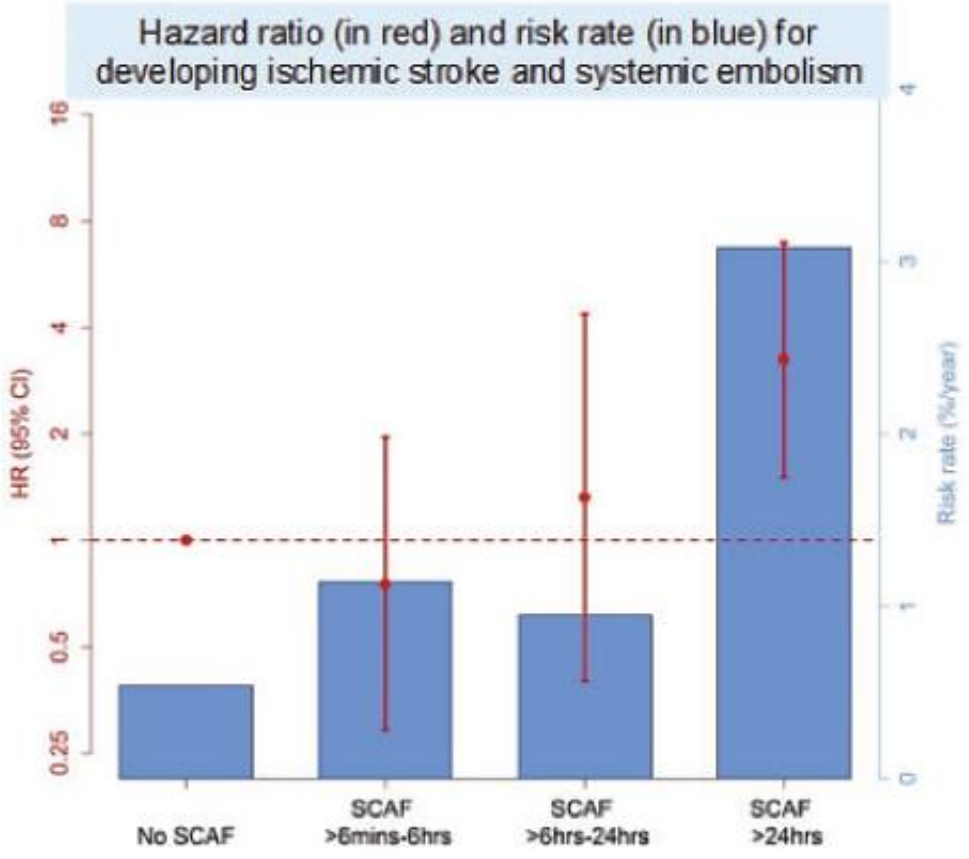
(5) *Biological gradient:* Fifthly, if the association is one which can reveal a biological gradient, or dose-response curve, then we should look most carefully for such evidence.

Biological gradient

Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT

Isabelle C. Van Gelder[1]*, Jeff S. Healey[2], Harry J.G.M. Crijns[3], Jia Wang[2], Stefan H. Hohnloser[4], Michael R. Gold[5], Alessandro Capucci[6], Chu-Pak Lau[7], Carlos A. Morillo[2], Anne H. Hobbelt[1], Michiel Rienstra[1], and Stuart J. Connolly[2]





EHJ. 2017;38:1339-44

(6) *Plausibility:* It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day.

(7) *Coherence:* On the other hand the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease

Plausibility ?

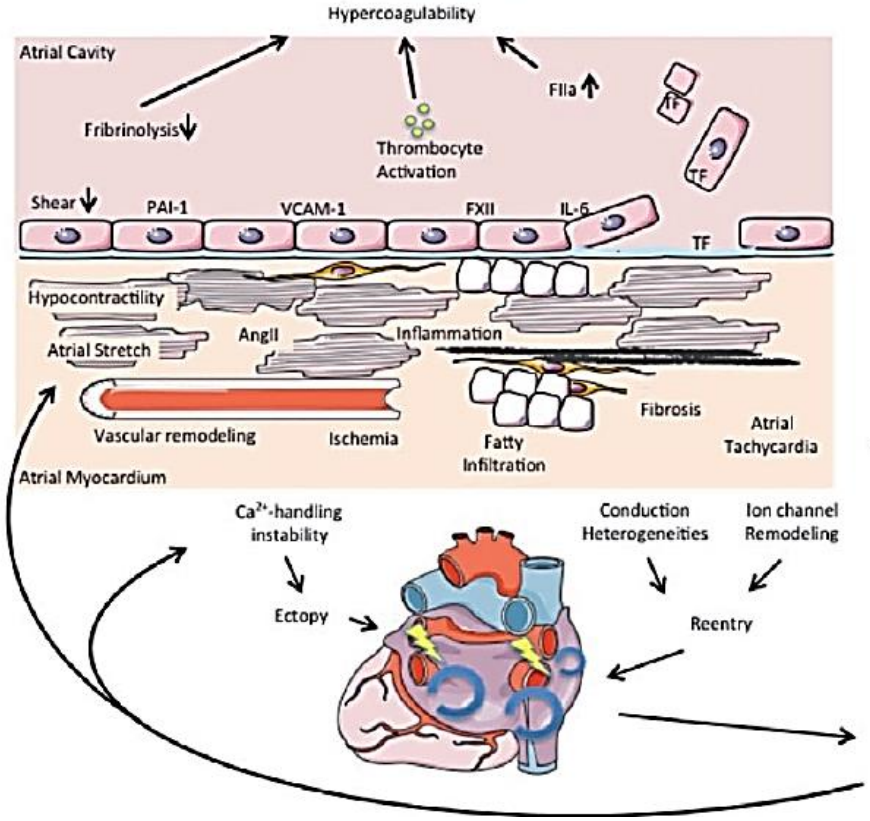
Coherence

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

Stroke

Patient effect

Diabetes
Heart failure
Obesity
Coronary artery disease
Hypertension
Ageing
Genetic predisposition



Substrat effect

= Atrial myopathy

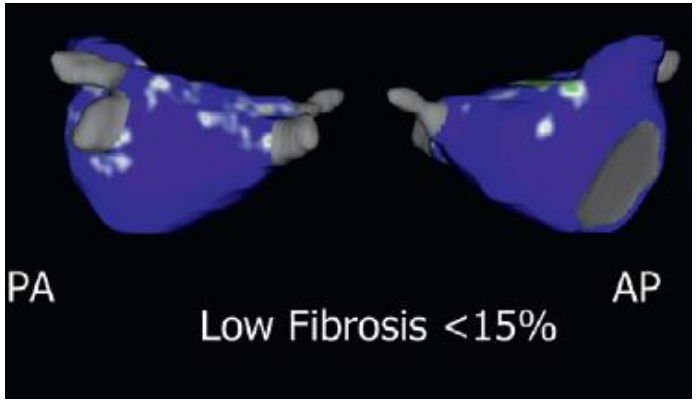
AF effect

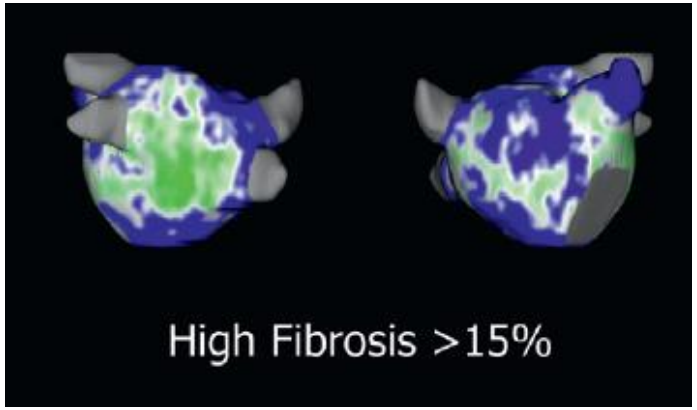
(6) *Plausibility:* It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day.

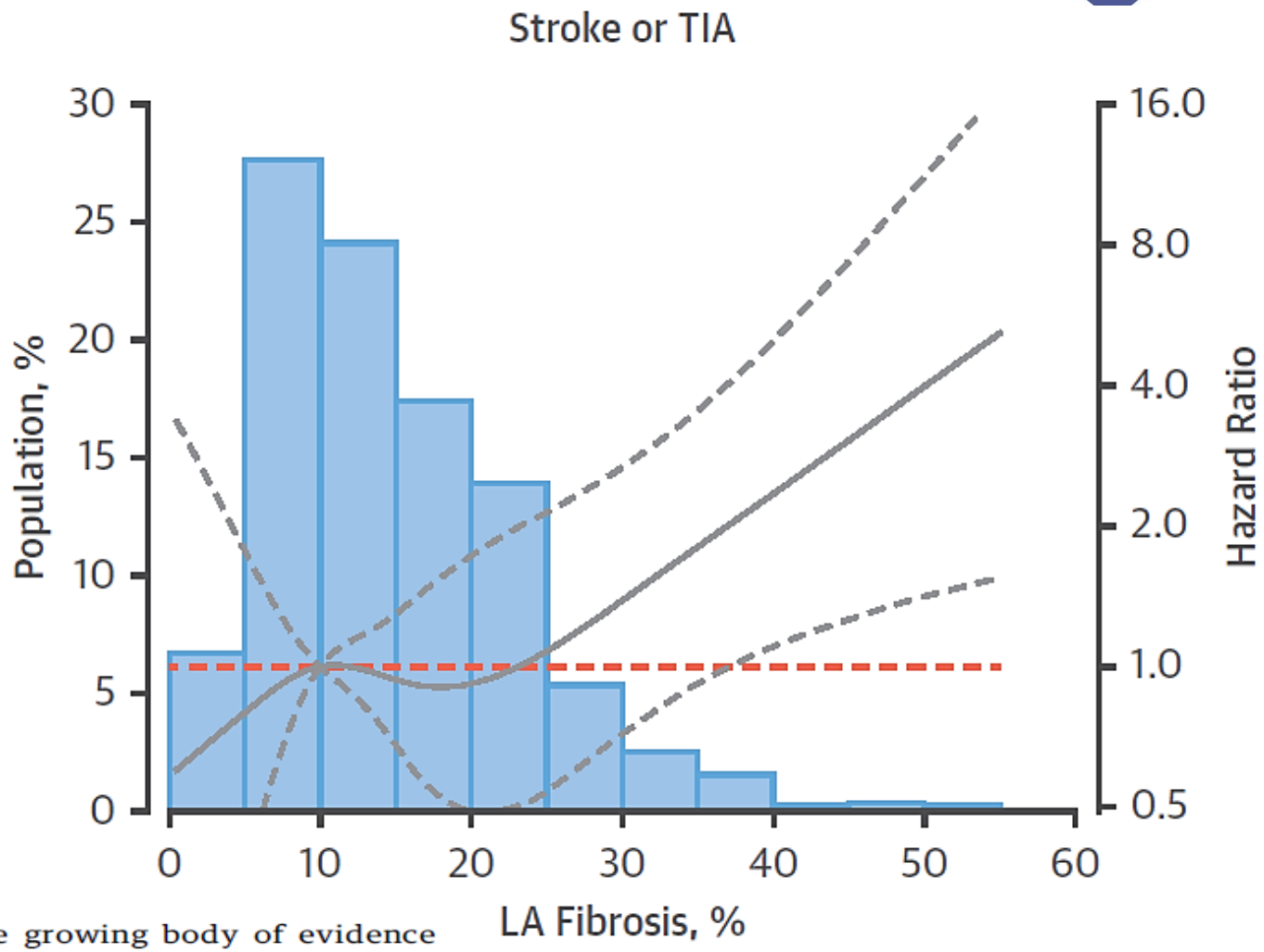
(7) *Coherence:* On the other hand the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease

Left Atrial Fibrosis and Risk of Cerebrovascular and Cardiovascular Events in Patients With Atrial Fibrillation

Retrospective Cohort







These results add to the growing body of evidence that suggests that atrial cardiomyopathy, as quantified by LA LGE severity, rather than the AF rhythm, might be the physiological trigger associated with adverse AF sequelae (16).

JACC 2017;70:1311-21

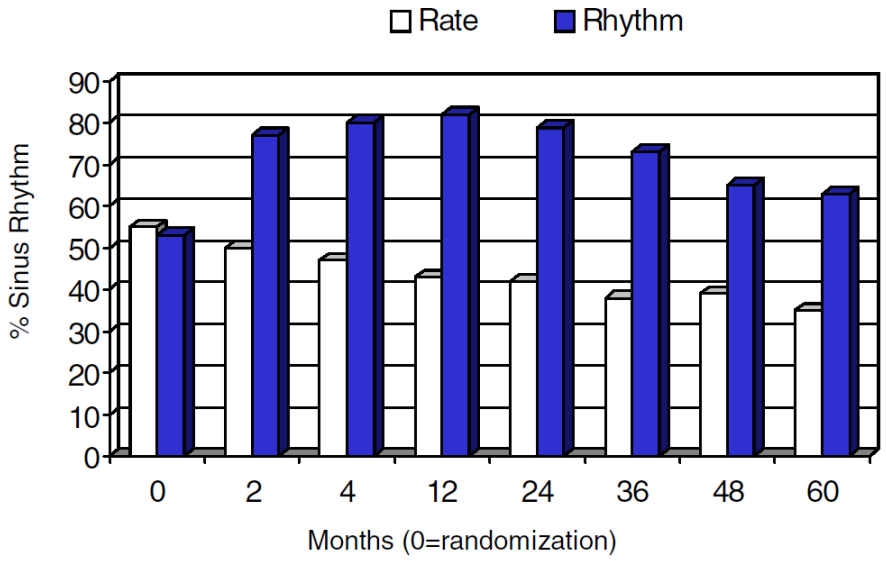
(8) *Experiment:* Occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association some preventive action is taken. Does it in fact prevent?

Effect of anticoagulant?

A COMPARISON OF RATE CONTROL AND RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

NEJM 2002;347:1825-33

THE ATRIAL FIBRILLATION FOLLOW-UP INVESTIGATION OF RHYTHM MANAGEMENT (AFFIRM) INVESTIGATORS*



157 ischemic strokes

OAC: 85% rate control

70% rhythm control

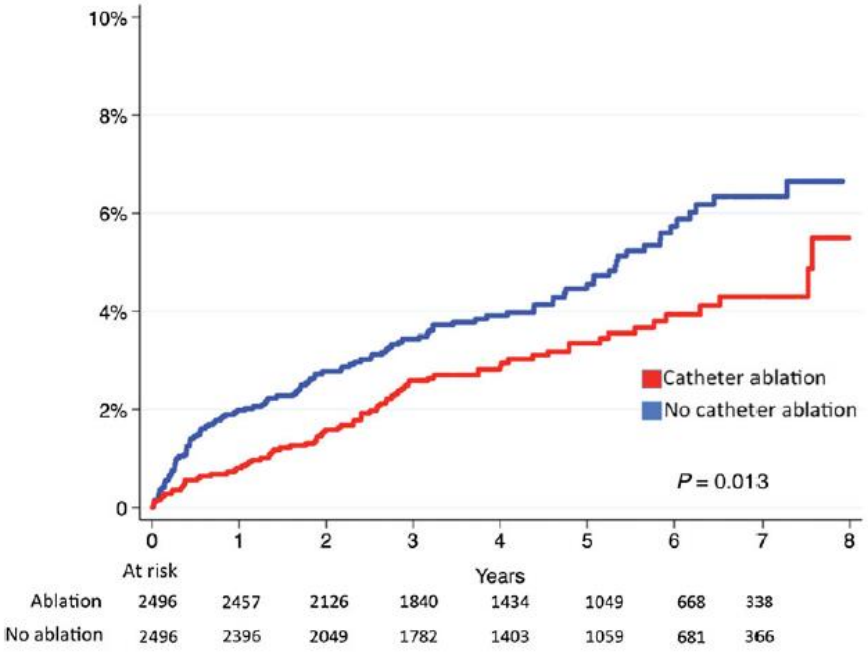
	Overall (N=4060)	Rate-Control Group (N=2027)	Rhythm-Control Group (N=2033)	P Value
		no. of patients (%)		
Central nervous system event				
Total	211 (8.2)	105 (7.4)	106 (8.9)	0.93
Ischemic stroke§	157 (6.3)	77 (5.5)	80 (7.1)	0.79
After discontinuation of warfarin	69	25	44	
During warfarin but with INR <2.0	44	27	17	
Concurrent atrial fibrillation	67	42	25	
Primary intracerebral hemorrhage	34 (1.2)	18 (1.1)	16 (1.3)	0.73
Subdural or subarachnoid hemorrhage	24 (0.8)	11 (0.8)	13 (0.8)	0.68

(8) *Experiment:* Occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association some preventive action is taken. Does it in fact prevent?

Effect of anticoagulant?

Catheter ablation for atrial fibrillation is associated with lower incidence of stroke and death: data from Swedish health registries

	Propensity score matched			All patients		
	Ablation (n = 2496)	No ablation (n = 2496)	*P*-value	Ablation (n = 3120)	No ablation (n = 295 877)	*P*-value
Age, years mean ± SD	59.97 ± 10.20	59.55 ± 12.83	0.207	58.73 ± 10.465	74.67 ± 12.366	<0.001
CHA_2DS_2-VASc score, mean ± SD	1.62 ± 1.44	1.70 ± 1.55	0.068	1.51 ± 1.39	3.58 ± 1.90	<0.001
CHA_2DS_2-VASc score ≥2	46.6%	44.7%	0.173	42.5%	84.7%	<0.001
HAS-BLED score, mean ± SD	1.41 ± 1.12	1.38 ± 1.16	0.275	1.33 ± 1.10	2.50 ± 1.21	<0.001
Years since first AF diagnosis	3.56 ± 3.30	4.28 ± 3.92	<0.001	3.95 ± 3.38	1.72 ± 3.08	<0.001
Heart failure	15.2%	16.0%	0.458	15.6%	29.4%	<0.001
Hypertension	47.5%	48.6%	0.428	46.9%	63.3%	<0.001
Diabetes	10.0%	10.3%	0.779	8.9%	17.7%	<0.001
Ischaemic stroke	5.3%	5.2%	0.949	4.7%	13.7%	<0.001
Thromboembolism (arterial)	9.3%	9.2%	0.922	8.4%	21.5%	<0.001
Myocardial infarction	7.9%	7.4%	0.558	6.5%	17.4%	<0.001
Ischaemic heart disease	15.0%	15.8%	0.456	14.0%	29.4%	<0.001
Peripheral arterial disease	3.0%	2.8%	0.671	2.5%	6.6%	<0.001
Drug purchase ≤5 months before index						
Warfarin	81.8%	81.3%	0.636	85.3%	44.1%	<0.001
Dabigatran/rivaroxaban/apixaban	0.4%	0.4%	1.000	0.4%	0.3%	0.184



EHJ 2016;37:2478-87

(8) *Experiment:* Occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association some preventive action is taken. Does it in fact prevent?

Effect of anticoagulant

Early Rhythm-Control Therapy in Patients with Atrial Fibrillation

P. Kirchhof, A.J. Camm, A. Goette, A. Brandes, L. Eckardt, A. Elvan, T. Fetsch, I.C. van Gelder, D. Haase, L.M. Haegeli, F. Hamann, H. Heidbüchel, G. Hindricks, J. Kautzner, K.-H. Kuck, L. Mont, G.A. Ng, J. Rekosz, N. Schoen, U. Schotten, A. Suling, J. Taggeselle, S. Themistoclakis, E. Vettorazzi, P. Vardas, K. Wegscheider, S. Willems, H.J.G.M. Crijns, and G. Breithardt, for the EAST-AFNET 4 Trial Investigators*

Medication at discharge — no./total no. (%)§§		
Oral anticoagulation with NOAC or VKA	1267/1389 (91.2)	1250/1393 (89.7)

Table 2. Efficacy Outcomes.*

Sinus rhythm — no. of patients with feature/total no. (%)	921/1122 (82.1)	687/1135 (60.5)	3.13 (2.55 to 3.84)††

Outcome	Early Rhythm Control	Usual Care	Treatment Effect
First primary outcome — events/person-yr (incidence/100 person-yr)	249/6399 (3.9)	316/6332 (5.0)	0.79 (0.66 to 0.94)†
Components of first primary outcome — events/person-yr (incidence/100 person-yr)			
Death from cardiovascular causes	67/6915 (1.0)	94/6988 (1.3)	0.72 (0.52 to 0.98)‡
Stroke	40/6813 (0.6)	62/6856 (0.9)	0.65 (0.44 to 0.97)‡
Hospitalization with worsening of heart failure	139/6620 (2.1)	169/6558 (2.6)	0.81 (0.65 to 1.02)‡
Hospitalization with acute coronary syndrome	53/6762 (0.8)	65/6816 (1.0)	0.83 (0.58 to 1.19)‡

ELECTRA 2017

13es JOURNEES PRATIQUES DE RYTHMOLOGIE ET DE STIMULATION CARDIAQUE
01 & 02 DÉCEMBRE 2017 - MARSEILLE CHANOT

→ ELECTRA 2022

The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS
(*Professor Emeritus of Medical Statistics, University of London*)

FA : cause d'AVC ?

(1) *Strength*. First u list I would put the strength of the asso **Yes**

(2) *Consistency:* Next list of features to be specially considered I place the *consistency* **Yes**

(3) *Specificity:* One r needless to say, is the specificity of the asso **No**

(4) *Temporality:* ic is the temporal relatior **No → Debated**

(5) *Biological gradient:* Fifthly, if the association is one which can r dient, or dose-response curv **Yes (?) → Yes**

(6) *Plausibility:* It will pful if the causation we suspect is biologic usible. But this is a **Yes**

(7) *Coherence:* On the hand the cause-and-effect interpretation data should not seriously conflict with the generally known facts of the natural history and biology of the disease **Yes**

(8) *Experiment:* C appeal to experin evidence. **Possibly → Probable**

(9) *Analogy:* In some circumstances it would be fair to judge by analogy.

Proc R Soc Med. 1965;58:295-300

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

Table 3 Cardiovascular morbidity and mortality associated with atrial fibrillation

Event	Association with AF
Death	Increased mortality, especially cardiovascular mortality due to sudden death, heart failure or stroke.
Stroke	20–30% of all strokes are due to AF. A growing number of patients with stroke are diagnosed with 'silent', paroxysmal AF.
Hospitalizations	10–40% of AF patients are hospitalized every year.
Quality of life	Quality of life is impaired in AF patients independent of other cardiovascular conditions.
Left ventricular dysfunction and heart failure	Left ventricular dysfunction is found in 20–30% of all AF patients. AF causes or aggravates LV dysfunction in many AF patients, while others have completely preserved LV function despite long-standing AF.
Cognitive decline and vascular dementia	Cognitive decline and vascular dementia can develop even in anticoagulated AF patients. Brain white matter lesions are more common in AF patients than in patients without AF.

2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS)

AF-related OUTCOMES

AF-Related Outcome	Frequency in AF	Mechanism(s)
Death	1.5 - 3.5 fold increase	Excess mortality related to: • HF, comorbidities • Stroke
Stroke	20-30% of all ischaemic strokes, 10% of cryptogenic strokes	• Cardioembolic, or • Related to comorbid vascular atheroma
LV dysfunction / Heart failure	In 20-30% of AF patients	• Excessive ventricular rate • Irregular ventricular
Cognitive decline / Vascular dementia	HR 1.4 / 1.6 (irrespective of stroke history)	
Depression	Depression in 16-20% (even suicidal ideation)	• Severe symptoms and decreased QoL • Drug side effects
Impaired quality of life	>60% of patients	• Related to AF burden, comorbidities, psychological functioning and medication • Distressed personality type
Hospitalizations	10-40% annual hospitalization rate	• AF management, related to HF, MI or AF related symptoms • Treatment-associated complications

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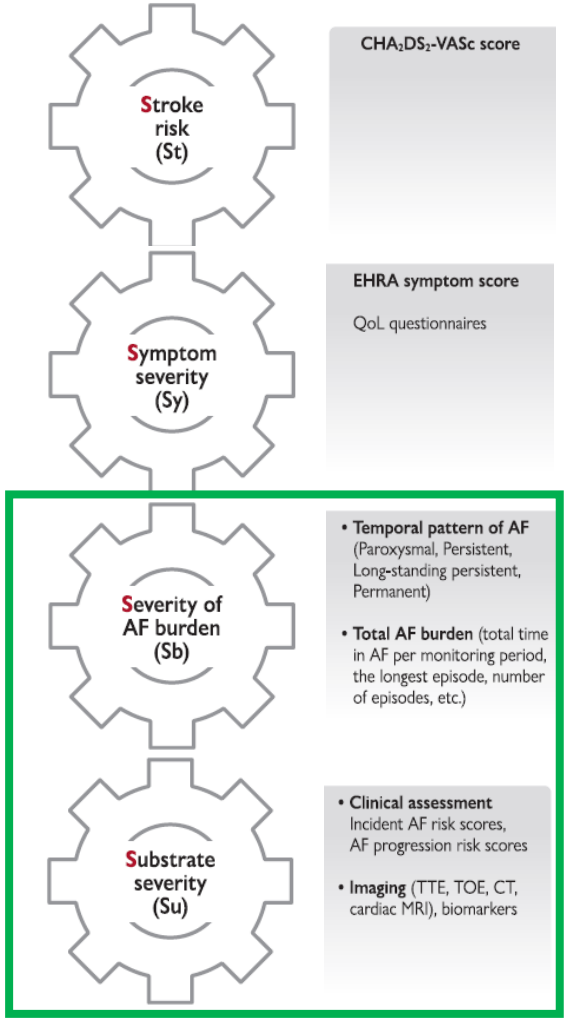
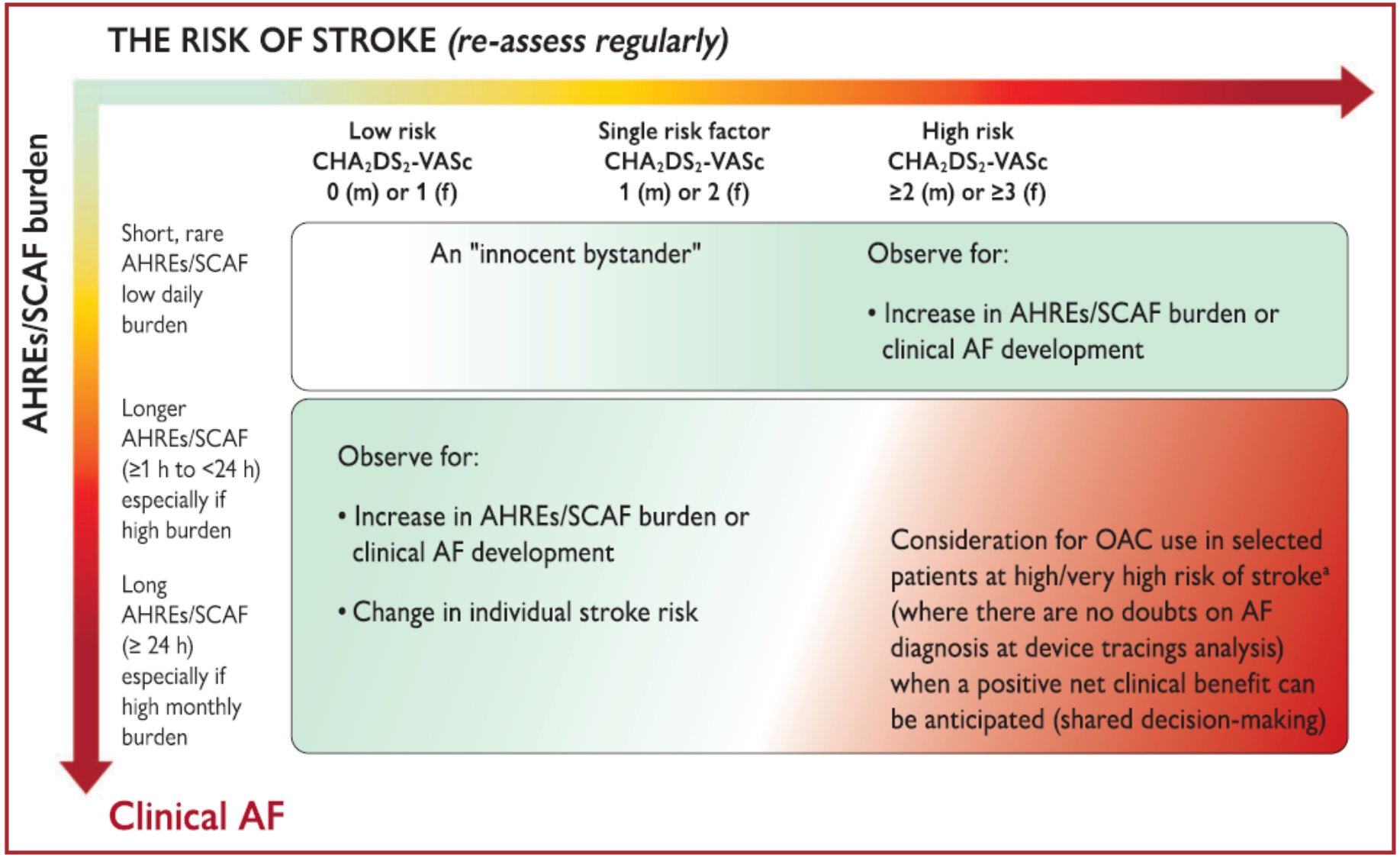
+ Substrate severity ?





Fibrillation Atriale & AVC: marqueur ou cause ?

- FA associée aux AVCI – risque diminué +++ par les anticoagulants
- Relation FA et AVCI complexe :

  FA = marqueur du risque d'AVC **ET** FA = cause d'AVC
- Concept du « Quantitatively additive risk »
  - Charge en FA
  - Terrain de survenue de la FA (myopathie atriale…)
- Implications potentielles (futures ?):
  - **Pas d'argument pour modifier la stratégie d'anticoagulation après « contrôle du rythme »**
  - **Tenir compte de la charge & du terrain pour statuer sur l'indication du traitement anticoagulant**
  - **Cibler le dépistage de la FA (adéquation population / sensibilité de dépistage)**
  - **Prévenir la myopathie atriale ?**
  - **Stratégies à reconsidérer avec les anti-XIa**