MultiCare

FIRST EDITION

Responsabile Scientifico > Antonio Sagone

5-6 OTTOBRE 2018

Sesto San Giovanni (MI)
Grand Hotel Villa Torretta
Via Milanese, 3

Sessione 2

Fibrillazione atriale

Trattamento Clinico

Alessio Borrelli

Policlinico Casilino, Roma

Trattamento Clinico

I diagnosi

II Trattamento clinico od interventistico

III Prevenzione morbilità

Identificare il paziente

Identificare l’aritmia

Fibrillazione Atriale

- **Sintomatica**
- **Asintomatica o Silente**

Anamnesi

Quanto durano i sintomi
Ritmico od aritmico
Sempre uguale?
Durante la notte o di giorno
A riposo o da sforzo.
Sonno continuo o risvegli frequenti
Russamento?
Vita sportiva o sedentaria?

Triggers vagale – adrenergico – TPSV
altro

Observational Studies Show Greater AF Detection With longer monitoring

- 24-72 hr Holter monitoring studies — 5%
- 4-7 day monitoring studies — +6-8%
  - Stahrenberg et al 2010 (prospective 224)
  - Jaubadon et al, 2004 (prospetive, n 88)
  - Barthelemy et al, 2003 (prospective, n 60)
- 21-30 day monitoring studies — +5-20%
  - Miller et al, 2013 (retrospective, n=156)
  - Kamel et al, 2012 (pilot RCT, n=40)
  - Flint et al, 2012 (prospective n=239)
  - Sobocinski et al, 2012 (prospective, n=249)
  - Gaillard et al, 2010 (retrospective, n=98)
  - Elijovich et al, 2009 (retrospective, n=20)
  - Tayal et al, 2008 (retrospective, n=56)

- Serial monitoring studies — 14-29%
  - Dagayach et al, 2011 (retrospective n=298)
  - Wallmann et al, 2007 (prospective, n=127)

How many atrial fibrillation ablation candidates have an underlying supraventricular tachycardia previously unknown? Efficacy of isolated triggering arrhythmia ablation

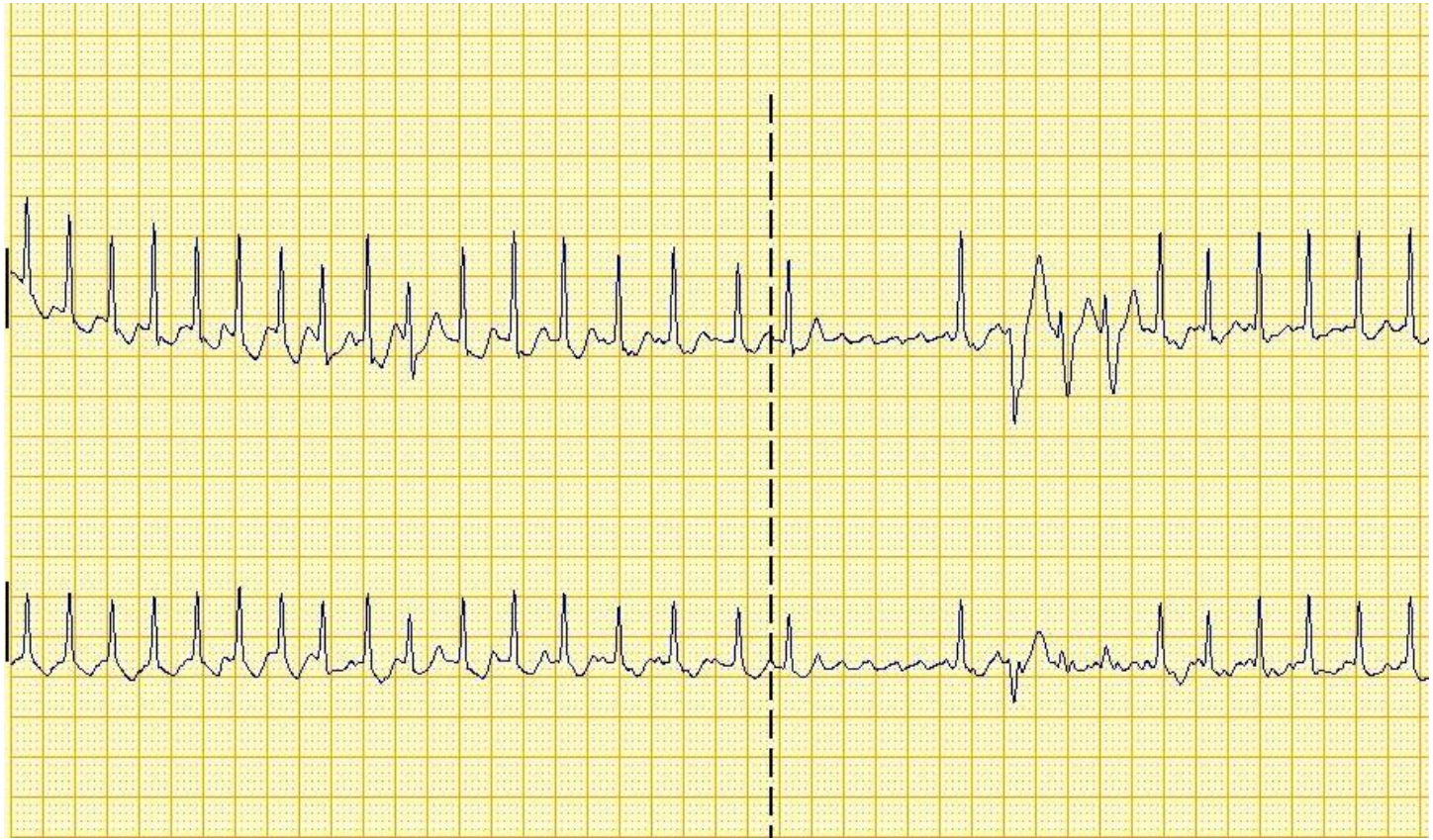
Luigi Sciarra[1]*, Marco Rebecchi[1], Ermenegildo De Ruvo[1], Lucia De Luca[1], Lorenzo Maria Zuccaro[1], Alessandro Fagagnini[1], Leonardo Corò[2], Giuseppe Allocca[2], Ernesto Lioy[1], Pietro Delise[2], and Leonardo Calò[1]

[1]Cardiology Department, Via Montaione 20 00139, Policlinico Casilino, Rome, Italy; and [2]Cardiology Department, Conegliano Hospital, Conegliano Veneto, Italy

Received 20 May 2010; accepted after revision 9 August 2010

Two hundred and fifty-seven patients (185 males; mean age: 53.4 ± 14.6 years) referred for AF ablation were studied. In all patients only AF relapses had been documented in the clinical history. Twenty-six patients (10.1%; mean age: 43.4 ± 13.3 years; 17 males) had inducible SVT during electrophysiological study and underwent an ablation targeted only at SVT suppression. Ablation was successful in all 26 patients. The ablative procedures are: 12 slow-pathway ablations for atrioventricular nodal re-entrant tachycardia; 9 concealed accessory pathway ablations for atrioventricular re-entrant tachycardia; and 5 focal ectopic atrial tachycardia ablations. No recurrences of SVT were observed during the follow-up (21 ± 11 months). Two patients (7.7%) showed recurrence of at least one episode of AF. Patients with inducible SVT had less structural heart disease and were younger than those without inducible SVT (interventricular septum thickness: 8.4 ± 1.6 vs. 11.0 ± 1.4 mm, $P < 0.01$; left atrial diameter: 37.0 ± 3.0 vs. 44.0 ± 2.2 mm, $P < 0.01$; age: 43.4 ± 13.3 vs. 57.3 ± 11.2 years, $P < 0.01$). Prevalence of paroxysmal AF was higher in patients with inducible SVT when compared with those with only AF (84.6 vs. 24.6%, $P < 0.01$).

External loop recorder



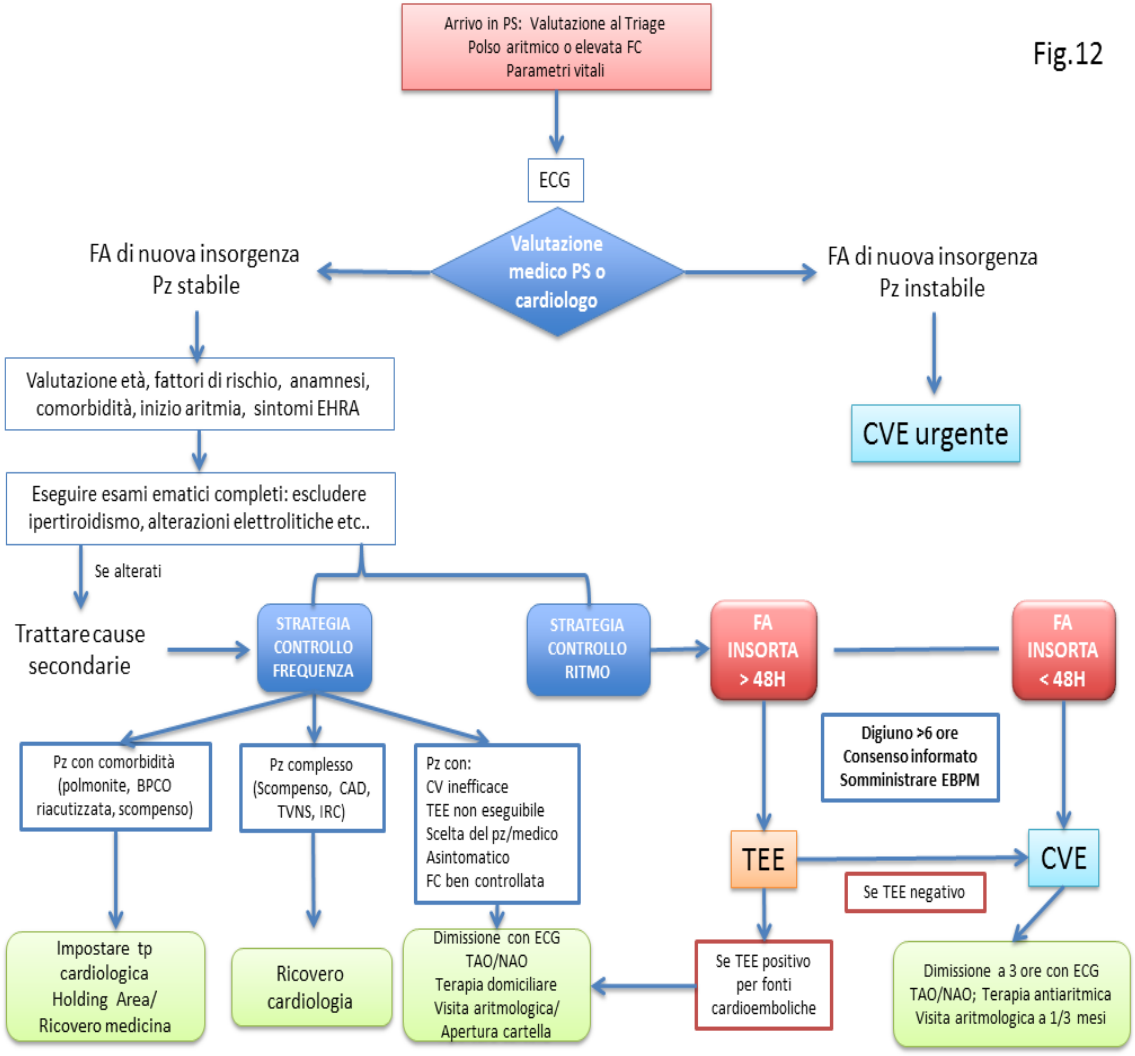
Trattamento acuto

CVE vs FARMACO

11% ricoveri FA 2016
< costi 120.00 euro

Algoritmo di trattamento FA in PS

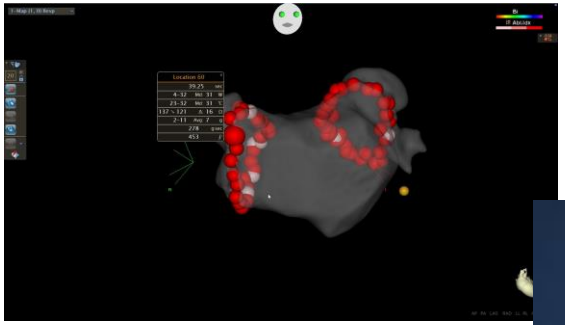
Fig.12



Trattamento Cronico

ATC vs FARMACO

Trattamento Clinico vs interventistico
1 soluzione per 1 problema



Recurrence of Atrial Arrhythmias in the Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial

Jeanne E. Poole MD, George Johnson BSEE, Kristi H. Monahan RN, Hoss Rostami BSMSE, Adam Silverstein MS, Hussein Al-Khalidi PhD, Mauri Wilson RN, Yves Rosenberg MD, MPH, Tristram D. Bahnson MD, Richard A. Robb PhD, Daniel B. Mark MD, MPH, Kerry L. Lee PhD, Douglas L. Packer MD for the CABANA Investigators and ECG Rhythm Core Lab

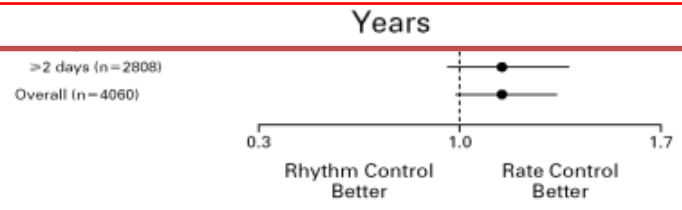
Studio AFFIRM

The New England
Journal of Medicine

VOLUME 347 DECEMBER 5, 2002 NUMBER 23

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

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



Un Anno dopo…

Relationships Between Sinus Rhythm, Treatment, and Survival … igation of

The association of SR but not AADs with improved survival may reflect the fact that currently available AADs are neither highly efficacious nor completely safe. One could

Implications

In patients with AF such as those enrolled in the AFFIRM Study, warfarin use improves survival. The presence of SR but not AAD use is associated with a lower risk of death. These results suggest that if an effective method for maintaining SR with fewer adverse effects were available, it might improve survival.

AFFIRM revised

Backgrounc … or stroke or death wit … ion-to-treat analysis. … d treatment as they cl …

Methods an … ine clinical variables, … d with an increased … or transient ischemic … t variables, the prese … mic drugs (AADs) … with the original intent … removed from the model.

Conclusions—W … a marker for other factors associ … model. Currently available AAI … rhythmic effects of AADs are off … erse effects were available, it m …

demographics were different from those in the AFFIRM Study. Most importantly, a requirement for high risk for stroke or death was not an entry criterion. Like our findings, these data require confirmation by … trolled clinical trials.

AFFIRM revised

Key Words: antiarrhythmia agents ■ anticoagulants ■ arrhythmia ■ fibrillation

Prevenzione farmacologica delle recidive di Fibrillazione Atriale dopo cardioversione elettrica

20% di tutti i casi di Fibrillazione atriale

Farmaco.	Persistenza del ritmo sinusale a 1 mese	a 3 mesi	a 6 mesi	a 12 mesi
Chinidina	65%	44-75%	27-58%	23-51%
Disopiramide	-	72%	44-50%	54%
Procainamide	-	39%	-	25%
Propafenone	54%	44%	40%	-
Flecainide	-	44%	-	34-42%
Amiodarone	-	-	75-78.5%	50-73%
Sotalolo	-	44-50%	46-50%	37-46%
Dofetilide	-	-	71%	66%
Placebo	58%	15-56%	19-35%	0-45%
Dronedarone	60%	43%	40%	22%

Up-dated Worldwide Survey on the Methods, Efficacy and Safety of Catheter Ablation for Human Atrial Fibrillation

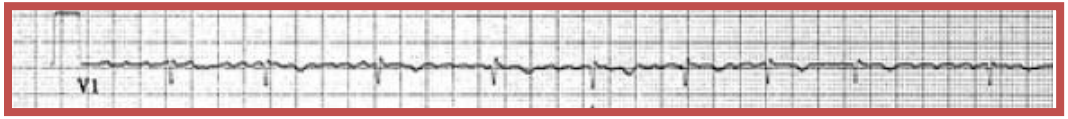
Cappato R et al. Circulation Arrh 2009

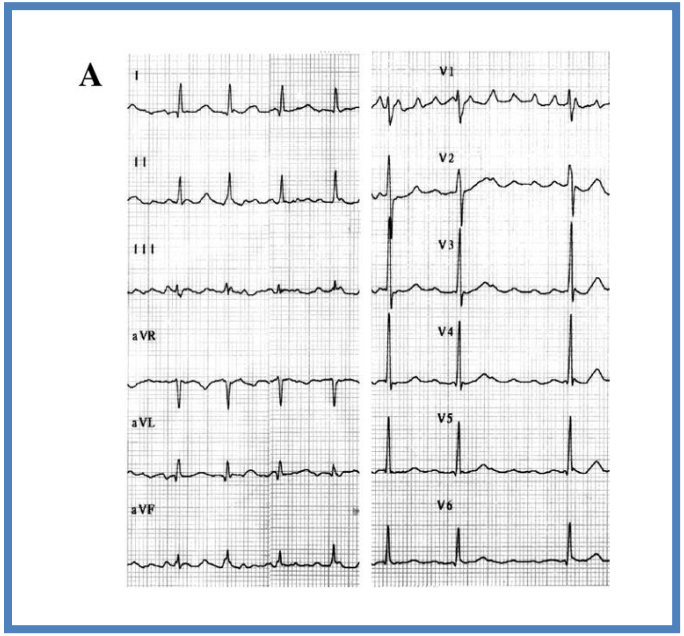
Type of AF	No. of Centers	No. of Pts	Success without AADs		Success with AADs		Overall Success	
			No. of Pts	Rate *Median [Interquartile range]	No. of Pts	Rate *Median [Interquartile range]	No. of Pts	Rate *Median [Interquartile range]
Paroxysmal	85	9,590	6,580	74.9 [64.9-82.6]	1,290	9.1 [0.2-14.7]	7,870	84.0 [79.7-88.6]
Persistent	73	4,712	2,800	64.8 [52.4-72.0]	595	10.0 [0.8-15.2]	3,395	74.8 [66.1-80.0]
Long-lasting	40	1,853	1,108	63.1 [53.3-71.4]	162	7.9 [0.9-15.9]	1,270	71.0 [67.4-76.3]

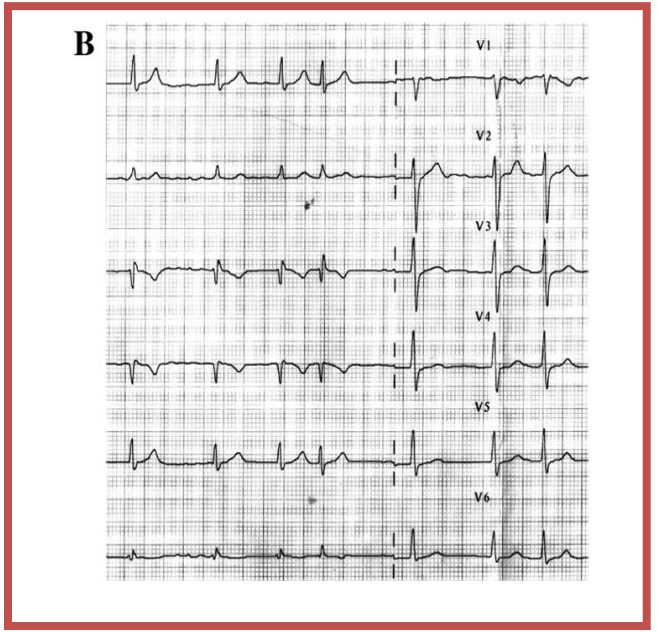

Per ogni problema complesso, c'è sempre una soluzione semplice. Che è sbagliata.
George Bernard Shaw

Uno nessuno 100.000

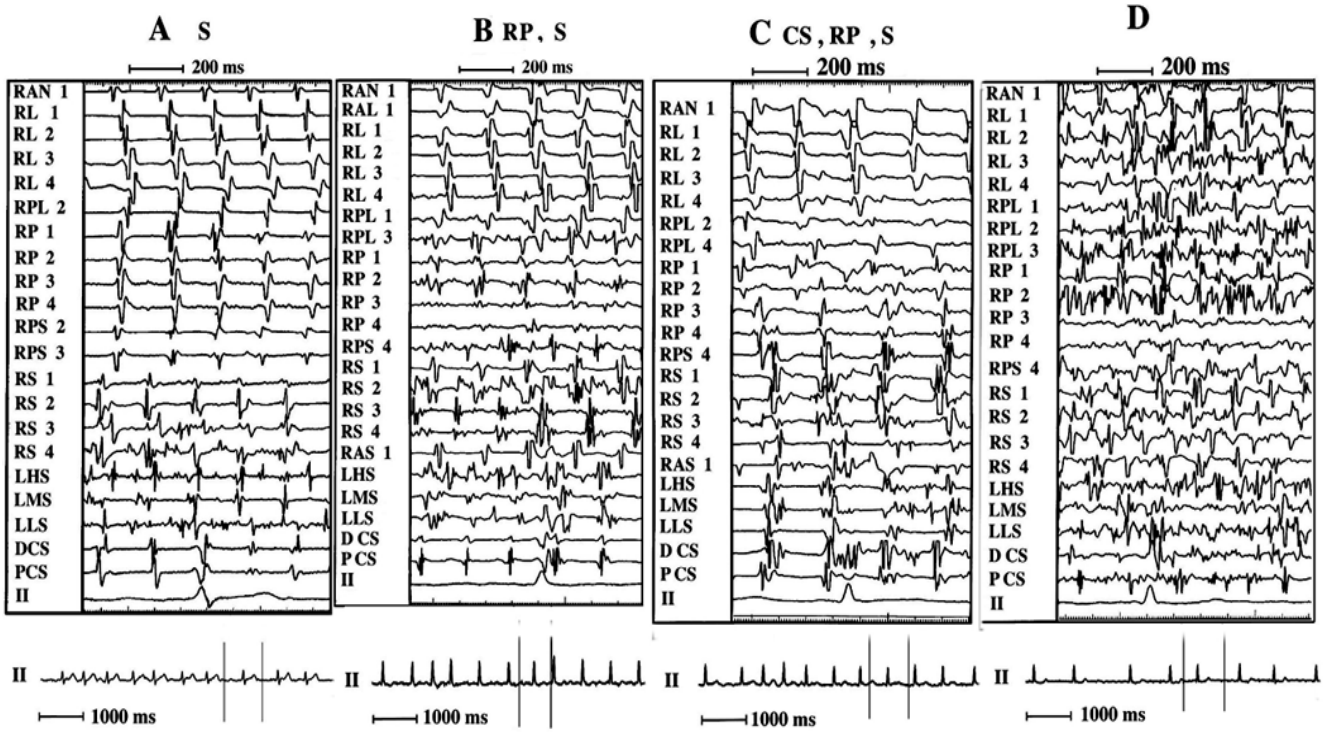
Different ecg and electrophysiological patterns







Different ecg and electrophysiological

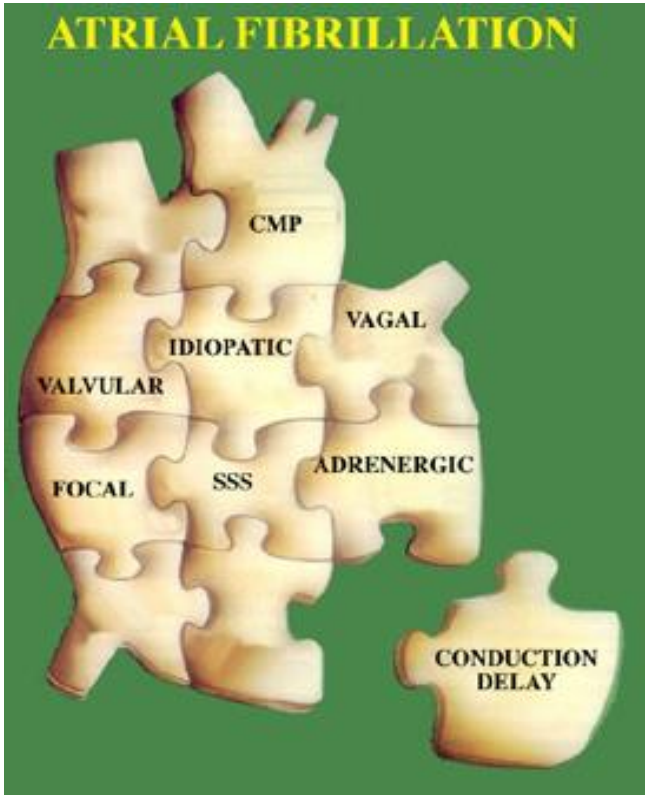


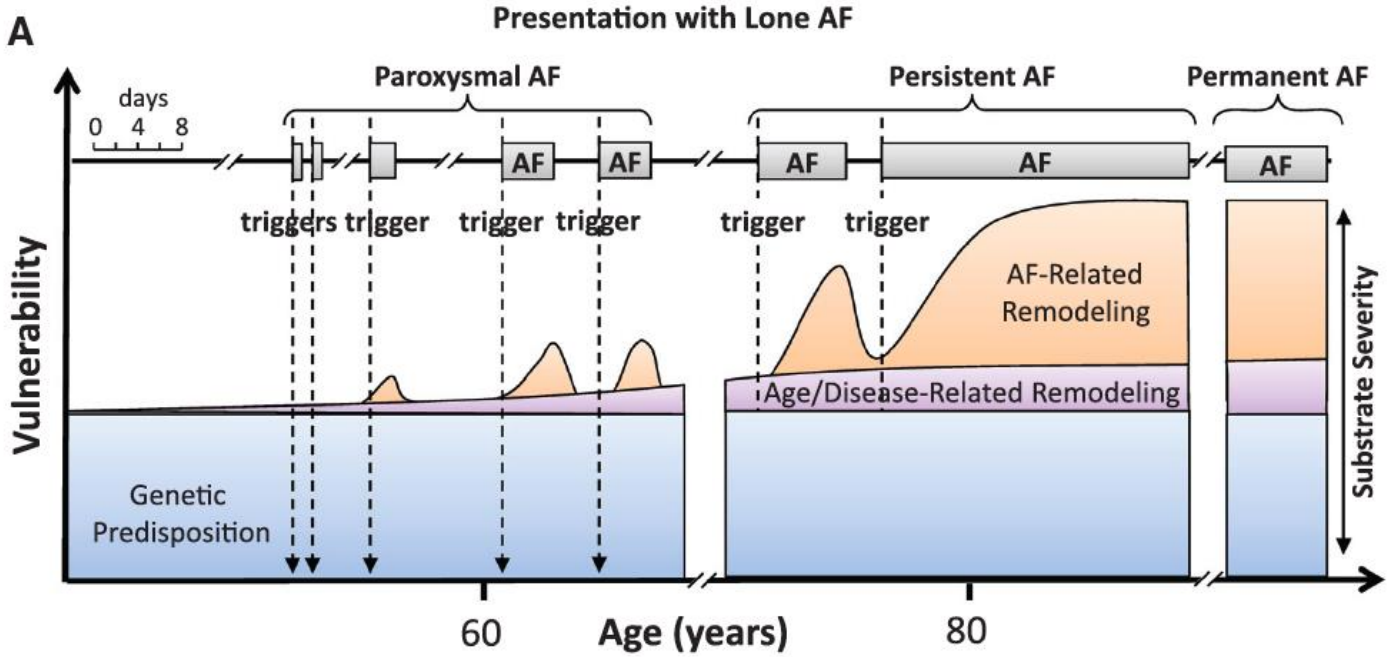
Gaita, Calo' et al, JACC 2001

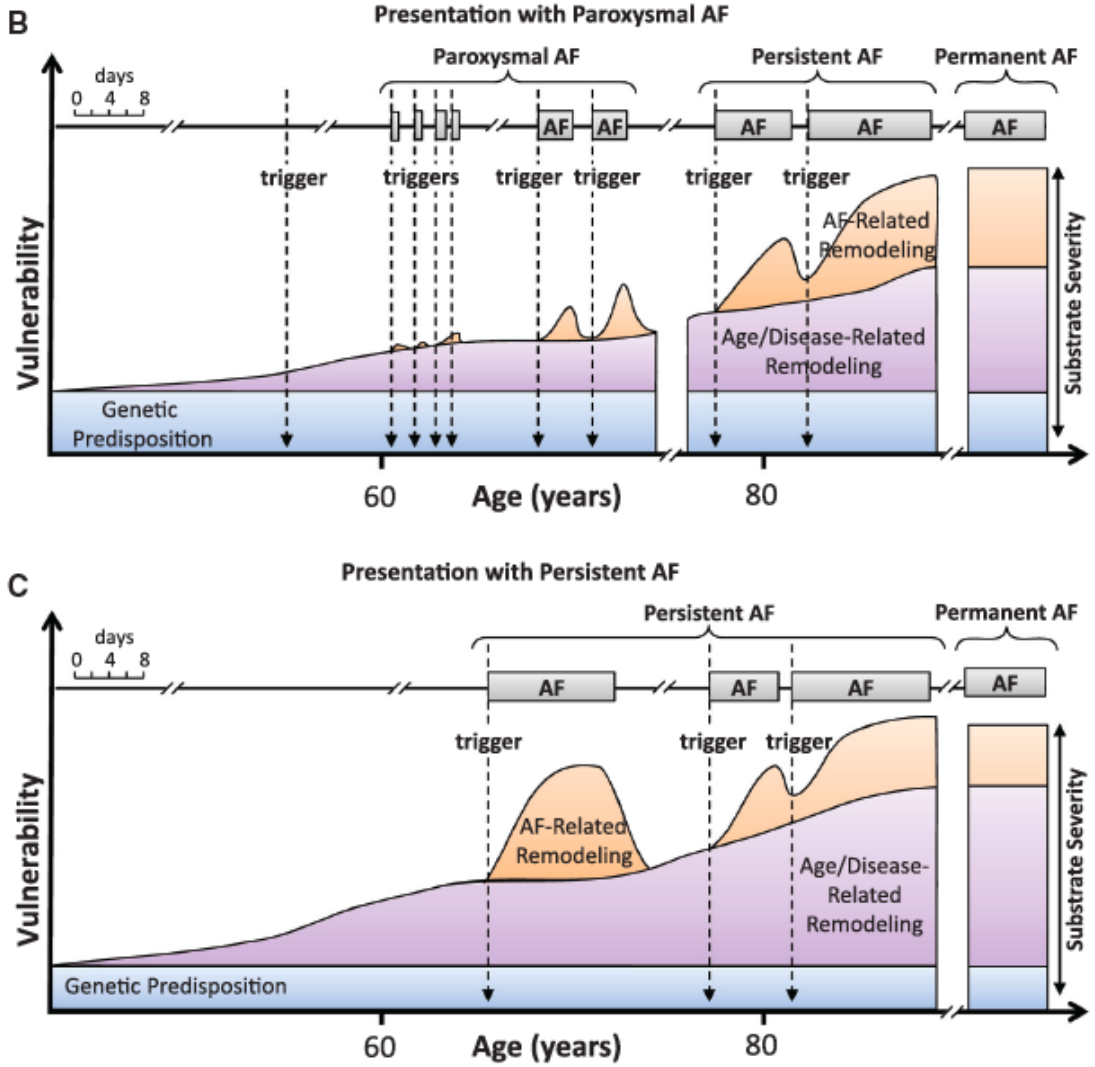
Quale FA?

Conoscere il substrato.

Eterogeneous etiopathogenesis of atrial fibrillation




A
Presentation with Lone AF
Paroxysmal AF
Persistent AF
Permanent AF
days
0 4 8
AF
AF
AF
AF
AF
triggers trigger
trigger
trigger
trigger
trigger
AF-Related Remodeling
Age/Disease-Related Remodeling
Genetic Predisposition
Vulnerability
Substrate Severity
60
Age (years)
80


B
Presentation with Paroxysmal AF
Paroxysmal AF
Persistent AF
Permanent AF
days
0 4 8
AF
AF
AF
AF
AF
trigger
triggers
trigger
trigger
trigger
trigger
AF-Related Remodeling
Age/Disease-Related Remodeling
Genetic Predisposition
Vulnerability
Substrate Severity
60
Age (years)
80
C
Presentation with Persistent AF
Persistent AF
Permanent AF
days
0 4 8
AF
AF
AF
AF
trigger
trigger
trigger
AF-Related Remodeling
Age/Disease-Related Remodeling
Genetic Predisposition
Vulnerability
Substrate Severity
60
Age (years)
80

Alcune considerazioni

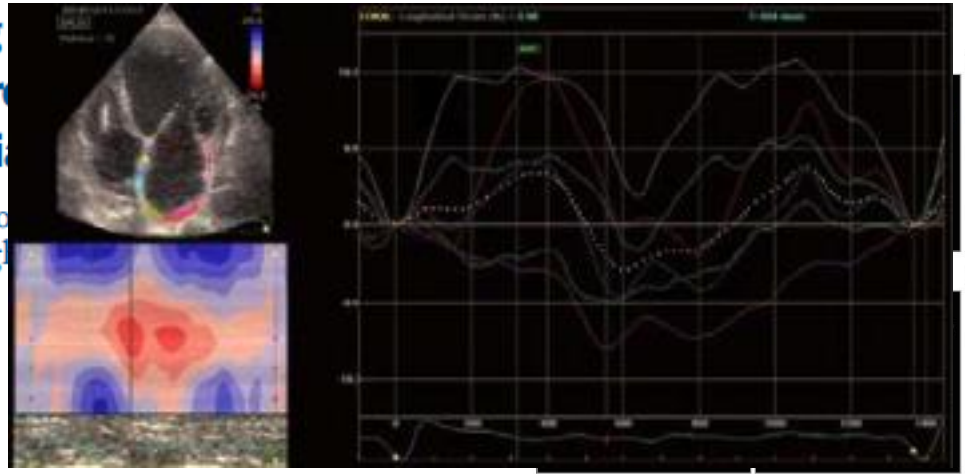
EDITORIAL COMMENT

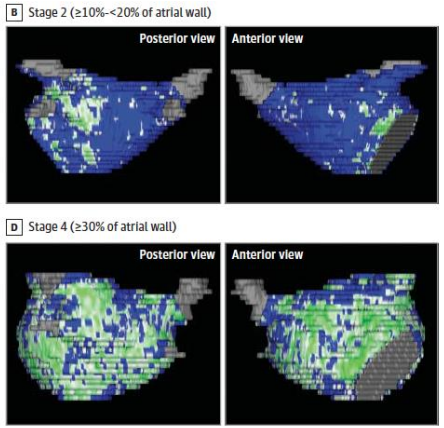
Differentiating
Paroxysmal Fr
Persistent Atri

Long-Term Electro
Monitoring Is Migl
Clinician*

Suneet Mittal, MD
Ridgewood, New Jersey

DEECAAF





Scarsa correlazione tra attribuzione tipologia FA e riconoscimento clinico

Alcune parossistiche hanno più fibrosi di alcune persistenti

Risk Factor	Potential Mechanism(s)
Age	Structural remodeling
Male sex	Ion currents governing repolarization
	Structural differences
Hypertension	Structural remodeling
Valve disease	Structural remodeling
Heart failure	Structural remodeling
	Abnormal calcium handling
Coronary artery disease	
Acute atrial ischemia	Conduction slowing, block
Prior atrial infarction	Structural remodeling, abnormal calcium handling
Obesity	Structural remodeling
Obstructive sleep apnea	Structural remodeling
Smoking	Structural remodeling
Endurance exercise	Autonomic changes, structural remodeling
Diabetes mellitus	Structural remodeling, autonomic changes
Thyroid disease	Structural remodeling, ion current remodeling, pulmonary vein activity, autonomic changes

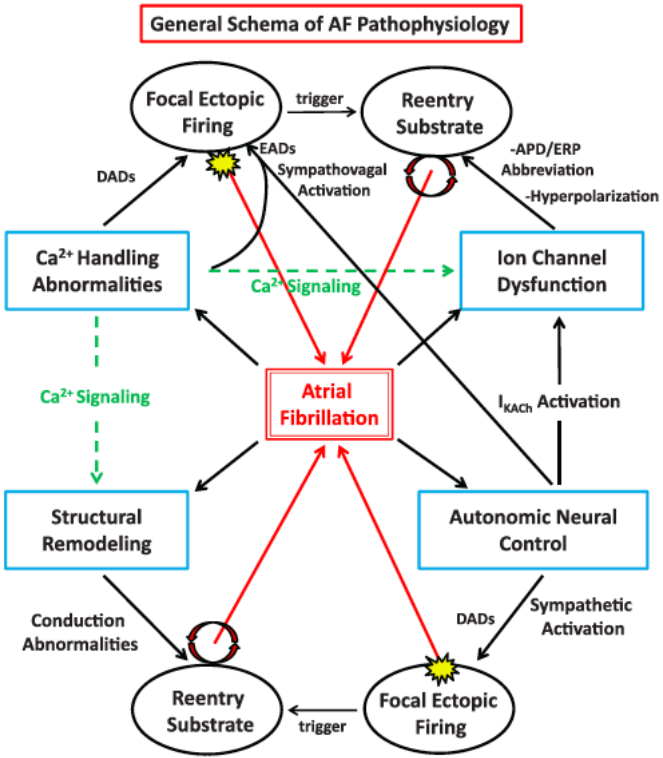
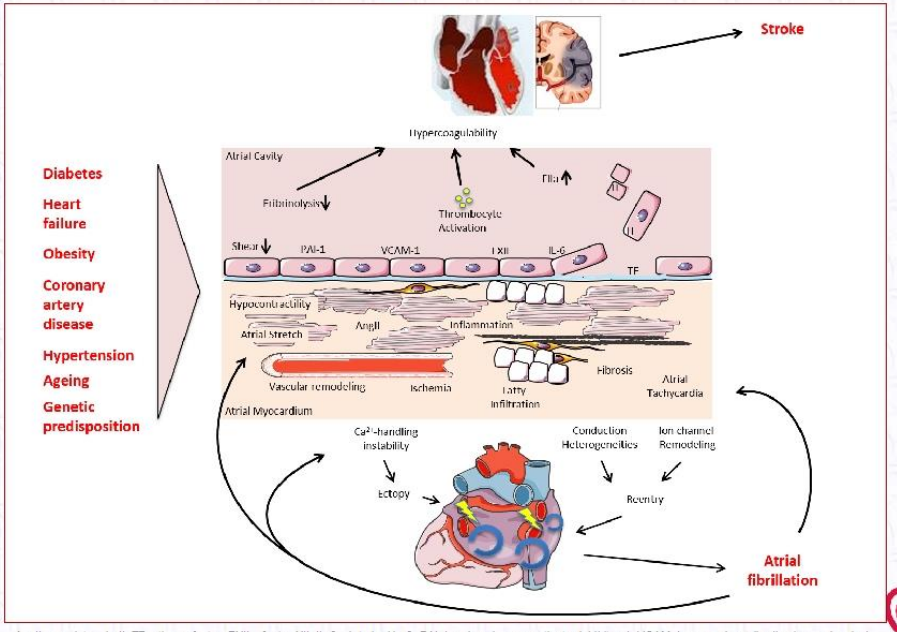


Table 1. AF Risk Factors

Risk Factor	Estimated Increased Risk	Comments
Established		
Age	≈2	Per decade
Male sex	1.5	
Hypertension	1.2–1.5	BP >140/90 mm Hg
Valvular heart disease	1.8–3.4	
LV systolic dysfunction	4.5–5.9	
Obesity	1.39–2.35	
Alcohol consumption	1.34–1.46	Heavy alcohol use (≥36 g/d)
Emerging		
Prehypertension	1.28	Systolic BP 130–139 mm Hg vs <120 mm Hg
Increased pulse pressure	1.26	Per 20-mm Hg increment
Obstructive sleep apnea	2.8–5.6	
Physical activity	2.87	Cumulative lifetime practice >1500 h
Diastolic dysfunction	3.33–5.26	
Familial and genetic	1.85	AF in ≥1 parent
Hypertrophic cardiomyopathy	4–6	
Congenital heart disease	N/A	
Potential		
Coronary artery disease	N/A	Data inconclusive
Chronic kidney disease	1.3–3.2	Graded risk
Inflammation	1.47–1.77	Independent predictive value unclear
Pericardial fat	1.28–5.30	Risk related to thickness and volume of pericardial fat
Tobacco use	1.51–2.05	

Major mechanisms causing atrial fibrillation to consider when deciding on management



AngII = angiotensin II; TF = tissue factor; FXII = factor XII; IL-6 = interleukin 6; PAI-1 = plasminogen activator inhibitor 1; VCAM-1 = vascular cell adhesion molecule 1.

www.escardio.org/guidelines

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Review

Chronic obstructive pulmonary disease and atrial fibrillation: An unknown relationship

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Cardiology Department, Serres General Hospital, Serres, Greece

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Keywords:
Chronic obstructive pulmonary disease
Atrial fibrillation
Pathophysiological mechanisms
Prognosis
Treatment

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is independently associated with atrial fibrillation (AF). Decreased oxygenation, hypercapnia, pulmonary hypertension, diastolic dysfunction, oxidative stress, inflammation, changes in atrial size by altered respiratory physiology, increased arrhythmogenicity from nonpulmonary vein foci commonly located in the right atrium, and respiratory drugs have been implicated in the pathogenesis of AF in COPD. The understanding of the relationship between COPD and AF is of particular importance, as the presence of the arrhythmia has significant impact on mortality, especially in COPD exacerbations. On the other hand, COPD in AF is associated with AF progression, success of cardioversion, recurrence of AF after catheter ablation, and increased cardiovascular and all-cause mortality. Treatment of the underlying pulmonary disease and correction of hypoxia and acid-base imbalance represents first-line therapy for COPD patients who develop AF. Cardioselective β-blockers are safe and can be routinely used in COPD. In addition, AF ablation was proved to be efficient and safe, and improves quality of life in these patients. This review presents the association between COPD and AF, describes the pathophysiological mechanisms implicated in AF development in COPD, underlines the prognostic significance of AF in COPD patients and vice versa, and highlights emerging therapeutic approaches in this setting.

Impact of Chronic Obstructive Pulmonary Disease on Prognosis in Atrial Fibrillation: A Report from the EURObservational Research Programme Pilot Survey on Atrial Fibrillation (EORP-AF) General Registry

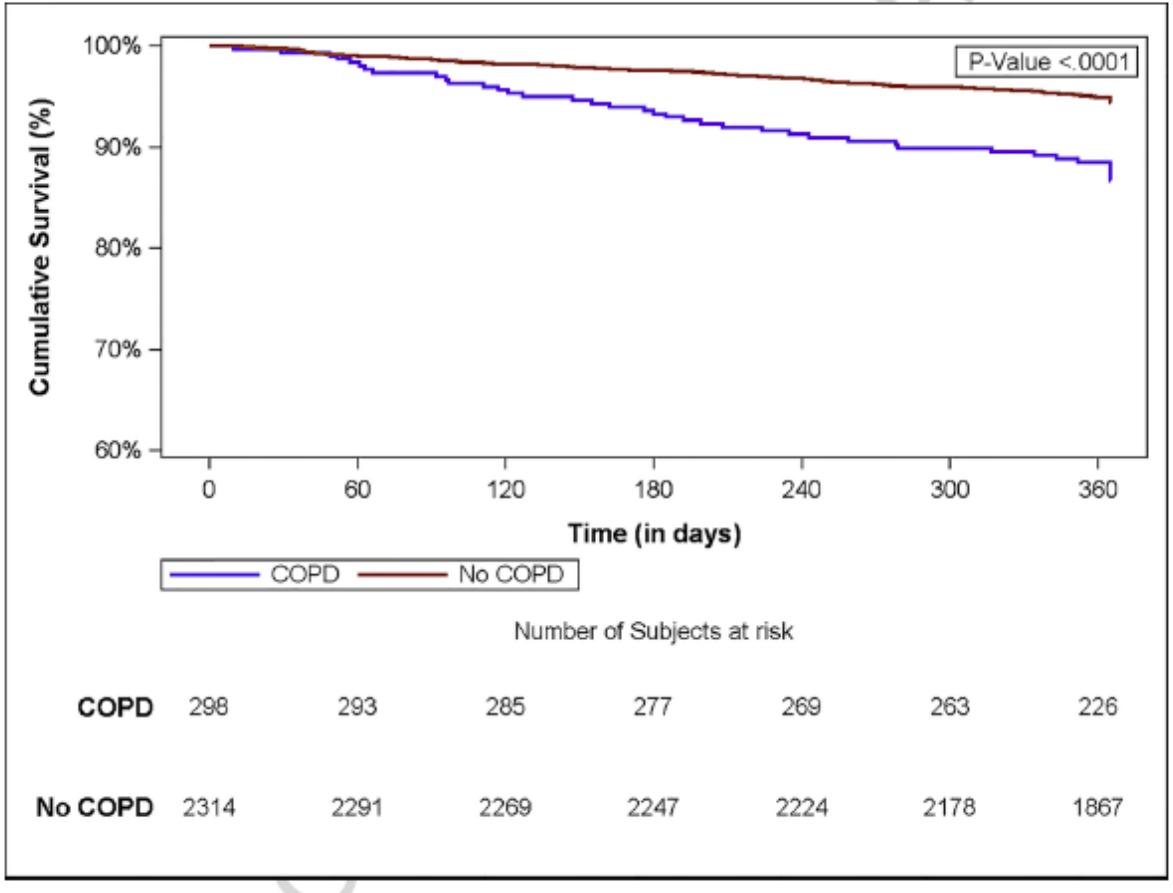
Marco Proietti, Cécile Laroche, Marcin Drozd, Johan Vijgen, Dragos C. Cozma, Jaroslaw Drozdz, Aldo P. Maggioni, Giuseppe Boriani, Gregory Y.H. Lip

PII: S0002-8703(16)30174-0
DOI: doi: 10.1016/j.ahj.2016.08.011
Reference: YMHJ 5270

To appear in: *American Heart Journal*

Received date: 1 May 2016
Accepted date: 23 August 2016

Figure 2: Kaplan-Meier curves for all-cause death at 1-year follow-up according to COPD presence



Thyroid Function Within the Normal Range, Subclinical Hypothyroidism, and the Risk of Atrial Fibrillation

Editorial, see p XXX

Christine Baumgartner, MD et al

BACKGROUND: Atrial fibrillation (AF) is a highly prevalent disorder leading to heart failure, stroke, and death. Enhanced understanding of modifiable risk factors may yield opportunities for prevention. The risk of AF is increased in subclinical hyperthyroidism, but it is uncertain whether variations in thyroid function within the normal range or subclinical hypothyroidism are also associated with AF.

METHODS: We conducted a systematic review and obtained individual participant data from prospective cohort studies that measured thyroid function at baseline and assessed incident AF. Studies were identified from MEDLINE and EMBASE databases from inception to July 27, 2016. The euthyroid state was defined as thyroid-stimulating hormone (TSH) 0.45 to 4.49 mIU/L, and subclinical hypothyroidism as TSH 4.5 to 19.9 mIU/L with free thyroxine (fT4) levels within reference range. The association of TSH levels in the euthyroid and subclinical hypothyroid range with incident AF was examined by using Cox proportional hazards models. In euthyroid participants, we additionally examined the association between fT4 levels and incident AF.

RESULTS: Of 30 085 participants from 11 cohorts (278 955 person-years of follow-up), 1958 (6.5%) had subclinical hypothyroidism and 2574 individuals (8.6%) developed AF during follow-up. TSH at baseline was not significantly associated with incident AF in euthyroid participants or those with subclinical hypothyroidism. Higher fT4 levels at baseline in euthyroid individuals were associated with increased AF risk in age- and sex-adjusted analyses (hazard ratio, 1.45; 95% confidence interval, 1.26–1.66, for the highest quartile versus the lowest quartile of fT4; *P* for trend ≤0.001 across quartiles). Estimates did not substantially differ after further adjustment for preexisting cardiovascular disease.

CONCLUSIONS: In euthyroid individuals, higher circulating fT4 levels, but not TSH levels, are associated with increased risk of incident AF.

The full author list is available on page XX.

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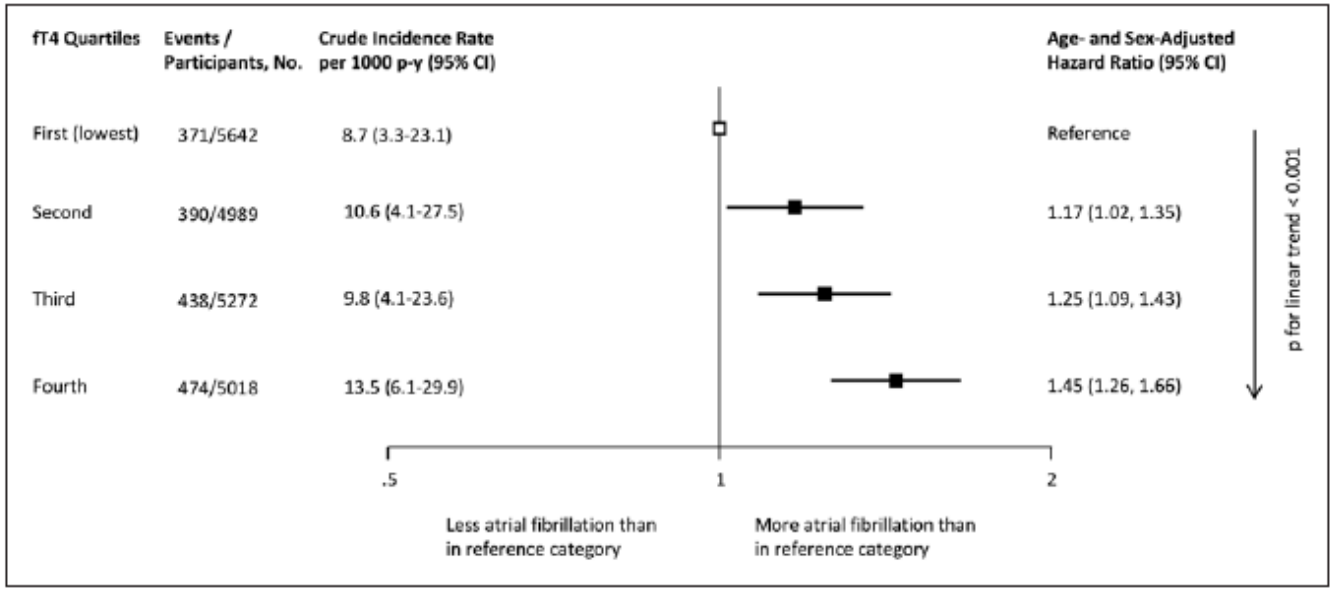
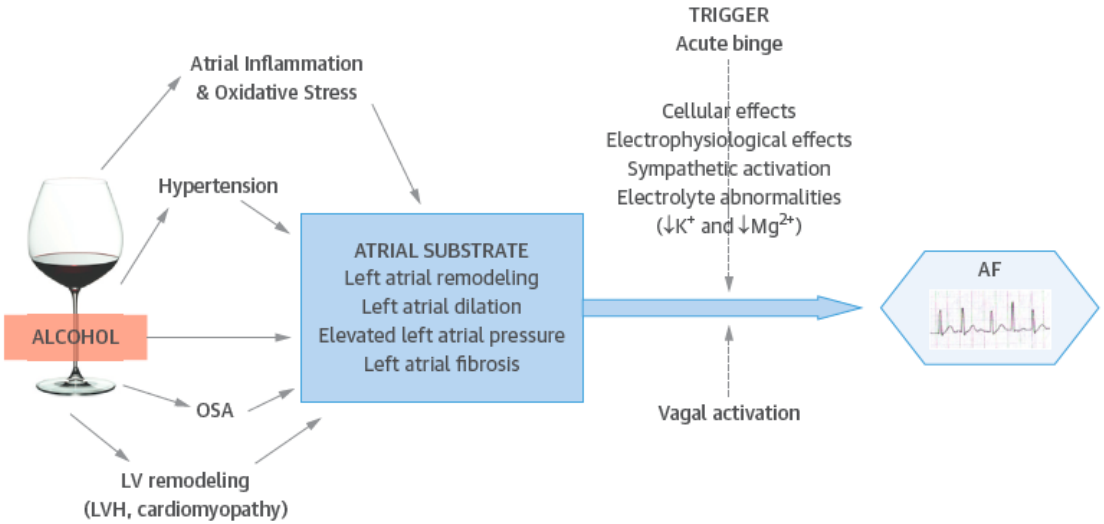
Sources of Funding, see page xxx


fT4 Quartiles
Events / Participants, No.
Crude Incidence Rate per 1000 p-y (95% CI)
Age- and Sex-Adjusted Hazard Ratio (95% CI)
First (lowest)
371/5642
8.7 (3.3-23.1)
Reference
Second
390/4989
10.6 (4.1-27.5)
1.17 (1.02, 1.35)
Third
438/5272
9.8 (4.1-23.6)
1.25 (1.09, 1.43)
Fourth
474/5018
13.5 (6.1-29.9)
1.45 (1.26, 1.66)
p for linear trend < 0.001
.5
1
2
Less atrial fibrillation than in reference category
More atrial fibrillation than in reference category



CELLULAR EFFECTS

- Damage to gap junction intercellular channels
- Direct myocyte injury and/or inflammation
- Acute oxidative stress

AUTONOMIC EFFECTS

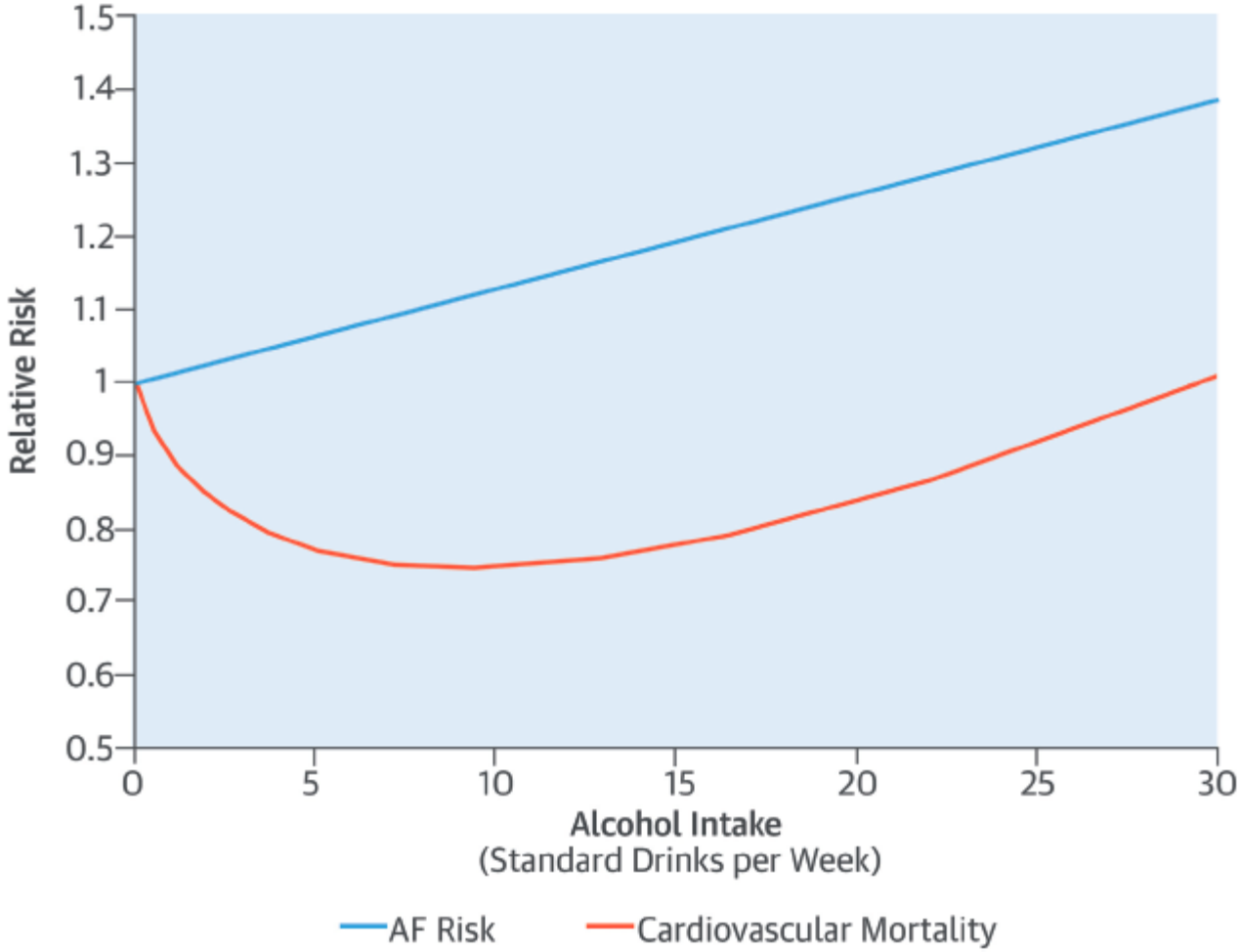
- Sympathetic activation (increased β receptor density)
- Vagal inhibition
- Reduced heart rate variability

ELECTROPHYSIOLOGICAL EFFECTS

- Shorter atrial and pulmonary vein action potential
- Shorter atrial effective refractory period
- Slowing of intra- and inter-atrial conduction
- Enhanced AV-nodal conduction

→ Re-entry

JACC VOL. 68, NO. 23, 2016
DECEMBER 13, 2016:2567–76



Voskoboinik, A. et al. J Am Coll Cardiol. 2016;68(23):2567–76.

Atrial fibrillation and the athletic heart

Calum J. Redpath[a] *and Peter H. Backx*[b]

Epidemiology

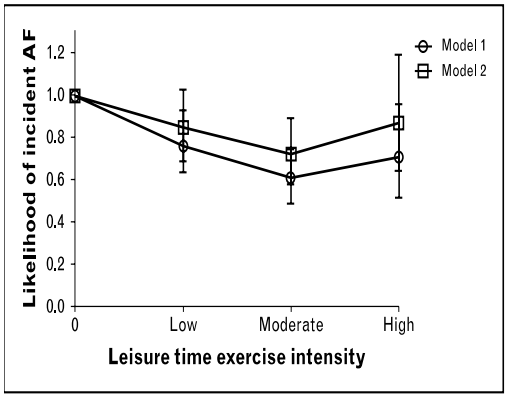
First author	Format	Athletes/Controls (*n*)	Sport	Odds ratio (confidence interval) for atrial fibrillation in athletes
Karjalainen [33]	Longitudinal	262/373	Orienteering	5.50 (1.3–24.4)
Elosua [34]	Retrospective	51/109	Various	2.87 (1.4–7.1)
Heidbuchel [35]	Retrospective	31/106	Various	1.81 (1.1–3.0)
Molina [36]	Longitudinal	252/305	Marathon running	8.80 (1.3–61.3)
Mont [37]	Prospective	107/107	Various	7.31 (2.3–22.9)
Mozaffarian [13]	Prospective	505/477	Various	0.87 (0.64–1.19)
Aizer [7]	Retrospective	2127/6321	Various	1.20 (1.02–1.41)

AF is 2–10 times more prevalent in active or former competitive athletes and those performing intense recreational endurance sports.

The reasons for this association are both functional (increased sympathetic activity, volume load during exercise, vagotonia at rest) and structural (atrial hypertrophy and dilatation).

The role of performance-enhancing drugs is largely unknown.

In population-based studies, the intensity of physical activity showed a U-shaped relationship with incident AF, which may indicate that the positive antiarrhythmic effects of physical activity are partially negated when exercise is too strenuous.



Cardiorespiratory Fitness and Risk of Incident Atrial Fibrillation

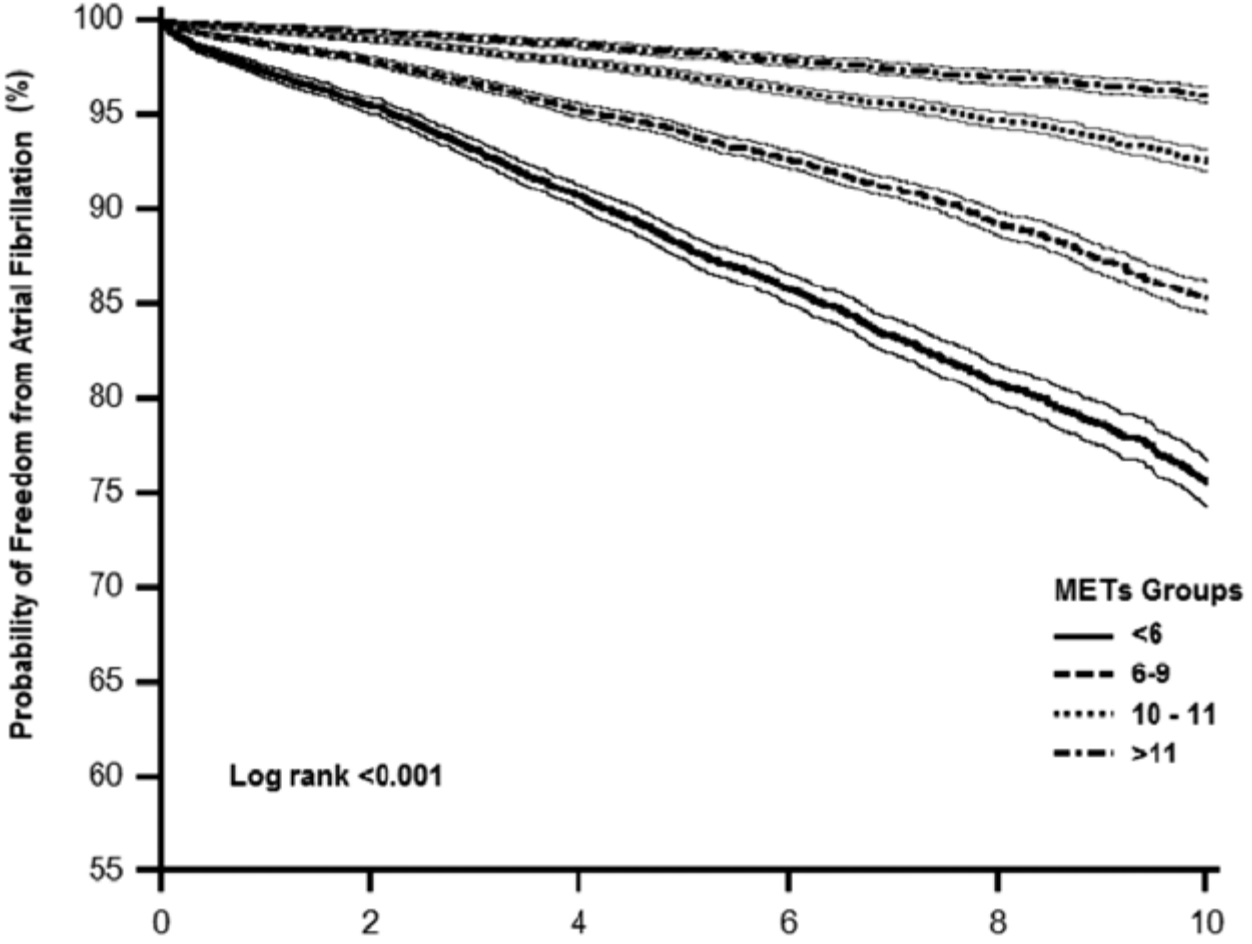
Results From the Henry Ford Exercise Testing (FIT) Project

Waqas T. Qureshi, MD, MS; Zaid Alirhayim, MD; Michael J. Blaha, MD, MPH; Stephen P. Juraschek, MD, PhD; Steven J. Keteyian, PhD; Clinton A. Brawner, PhD; Mouaz H. Al-Mallah, MD, MSc

Background—Poor cardiorespiratory fitness (CRF) is an independent risk factor for cardiovascular morbidity and mortality. However, the relationship between CRF and atrial fibrillation (AF) is less clear. The aim of this analysis was to investigate the association between CRF and incident AF in a large, multiracial cohort that underwent graded exercise treadmill testing.

Methods and Results—From 1991 to 2009, a total of 64 561 adults (mean age, 54.5±12.7 years; 46% female; 64% white) without AF underwent exercise treadmill testing at a tertiary care center. Baseline demographic and clinical variables were collected. Incident AF was ascertained by use of *International Classification of Diseases, Ninth Revision* code 427.31 and confirmed by linkage to medical claim files. Nested, multivariable Cox proportional hazards models were used to estimate the independent association of CRF with incident AF. During a median follow-up of 5.4 years (interquartile range, 3–9 years), 4616 new cases of AF were diagnosed. After adjustment for potential confounders, 1 higher metabolic equivalent achieved during treadmill testing was associated with a 7% lower risk of incident AF (hazard ratio, 0.93; 95% confidence interval, 0.92–0.94; $P<0.001$). This relationship remained significant after adjustment for incident coronary artery disease (hazard ratio, 0.92; 95% confidence interval, 0.91–0.93; $P<0.001$). The magnitude of the inverse association between CRF and incident AF was greater among obese compared with nonobese individuals (P for interaction=0.02).

Conclusions—There is a graded, inverse relationship between cardiorespiratory fitness and incident AF, especially among obese patients. Future studies should examine whether changes in fitness increase or decrease risk of atrial fibrillation. This association was stronger for obese compared with nonobese, especially among obese patients. **(*Circulation*. 2015;131:1827-1834. DOI: 10.1161/CIRCULATIONAHA.114.014833.)**


Probability of Freedom from Atrial Fibrillation (%)
100
95
90
85
80
75
70
65
60
55
0
2
4
6
8
10
METs Groups
<6
6-9
10 - 11
>11
Log rank <0.001

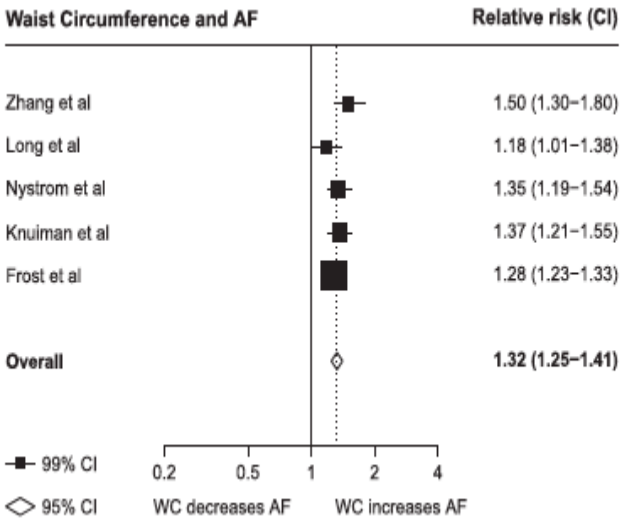
Associations of Epicardial, Abdominal, and Overall Adiposity With Atrial Fibrillation

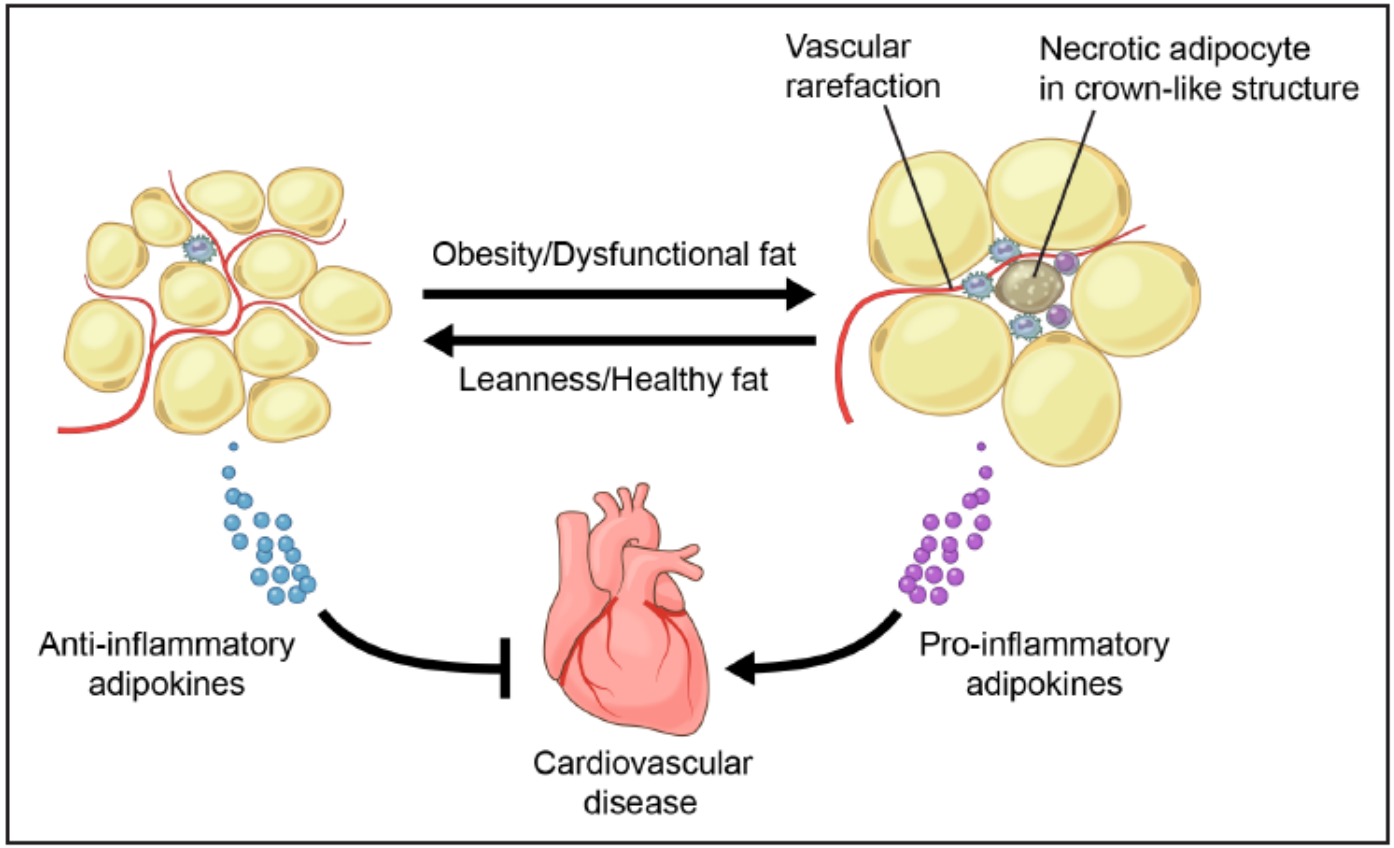
Christopher X. Wong, MBBS, MSc, MPH, PhD; Michelle T. Sun, MBBS; Ayodele Odutayo, MD, MSc; Connor A. Emdin, HBSc, DPhil; Rajiv Mahajan, MBBS, PhD; Dennis H. Lau, MBBS, PhD; Rajeev K. Pathak, MBBS, PhD; Dennis T. Wong, BMed, PhD; Joseph B. Selvanayagam, MBBS, DPhil; Prashanthan Sanders, MBBS, PhD; Robert Clarke, MD, FRCP

Background—Although adiposity is increasingly recognized as a risk factor for atrial fibrillation (AF), the importance of epicardial fat compared with other adipose tissue depots remains uncertain. We sought to characterize and compare the associations of AF with epicardial fat and measures of abdominal and overall adiposity.

Methods and Results—We conducted a meta-analysis of 63 observational studies including 352 275 individuals, comparing AF risk for 1-SD increases in epicardial fat, waist circumference, waist/hip ratio, and body mass index. A 1-SD higher epicardial fat volume was associated with a 2.6-fold higher odds of AF (odds ratio, 2.61; 95% confidence interval [CI], 1.89–3.60), 2.1-fold higher odds of paroxysmal AF (odds ratio, 2.14; 95% CI, 1.45–3.16) and, 5.4-fold higher odds of persistent AF (odds ratio, 5.43; 95% CI, 3.24–9.12) compared with sinus rhythm. Likewise, a 1-SD higher epicardial fat volume was associated with 2.2-fold higher odds of persistent compared with paroxysmal AF (odds ratio, 2.19; 95% CI, 1.66–2.88). Similar associations existed for postablation, postoperative, and postcardioversion AF. In contrast, associations of abdominal and overall adiposity with AF were less extreme, with relative risks per 1-SD higher values of 1.32 (95% CI, 1.25–1.41) for waist circumference, 1.11 (95% CI, 1.08–1.14) for waist/hip ratio, and 1.22 (95% CI, 1.17–1.27) for body mass index.

Conclusions—Strong and graded associations were observed between increasing epicardial fat and AF. Moreover, the strength of associations of AF with epicardial fat is greater than for measures of abdominal or overall adiposity. Further studies are needed to assess the mechanisms and clinical relevance of epicardial fat. **(*Circ Arrhythm Electrophysiol.* 2016;9:e004378. DOI: 10.1161/CIRCEP.116.004378.)**




Vascular rarefaction
Necrotic adipocyte in crown-like structure
Obesity/Dysfunctional fat
Leanness/Healthy fat
Anti-inflammatory adipokines
Pro-inflammatory adipokines
Cardiovascular disease

Human Connexin40 Mutations Slow Conduction and Increase Propensity for Atrial Fibrillation

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Peter Fahmy, PhD, MBBS, FRACP [a,b,c], Renuka Rao, PhD [a,b,c],
Jim Pouliopoulos, PhD, MSc(Med) [a,b,c],
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Background Patch clamping studies using non-cardiomyocytes revealed that the human connexin40 mutations P88S, G38D, and A96S are associated with reduced gap junction conductances compared to wild type connexin40 (wtCx40). Their effects within myocytes however are unclear. We aimed to characterise P88S, G38D, and A96S after expression in rat hearts and primary cardiomyocyte cultures.

Methods Adult Sprague-Dawley rat atria were transduced with a lentivector containing a transgene encoding wtCx40, P88S, G38D, A96S, or eGFP (n = 6 per transgene). Electrophysiology studies (EPS) were performed just prior to and seven days after surgery. Left atria were assessed for connexin expression, mRNA levels, inflammation and fibrosis. Primary cardiomyocyte cultures were also transduced with the abovementioned vectors (n = 6 per transgene) and monolayer conduction velocities (CV) and protein expression were assessed at 96 hours.

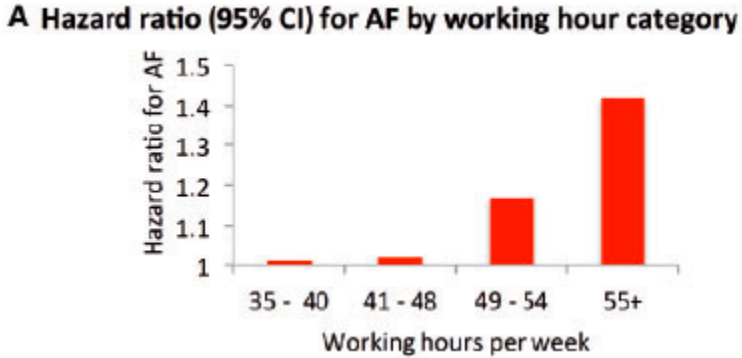
Results At day 7 EPS, P wave and induced atrial fibrillation (AF) durations were significantly longer in the mutant groups when compared to wtCx40 controls ($p < 0.05$). There were no significant differences in inflammation, fibrosis, or heart to body weight ratios. Monolayer CV's were reduced in the A96S group compared to the wtCx40 group. While similar to wtCx40 controls, P88S velocities were reduced compared to eGFP controls. G38D monolayers possessed spontaneous fibrillatory activity and could not be paced. Immunofluorescence revealed that P88S and G38D reduced native connexin43 myocyte coupling while A96S appeared to co-localise with connexin43 in gap junctions. Connexin43 mRNA levels were similar between groups.

Conclusions The A96S, G38D, and P88S Cx40 mutations slow conduction and increased the propensity for inducible AF.

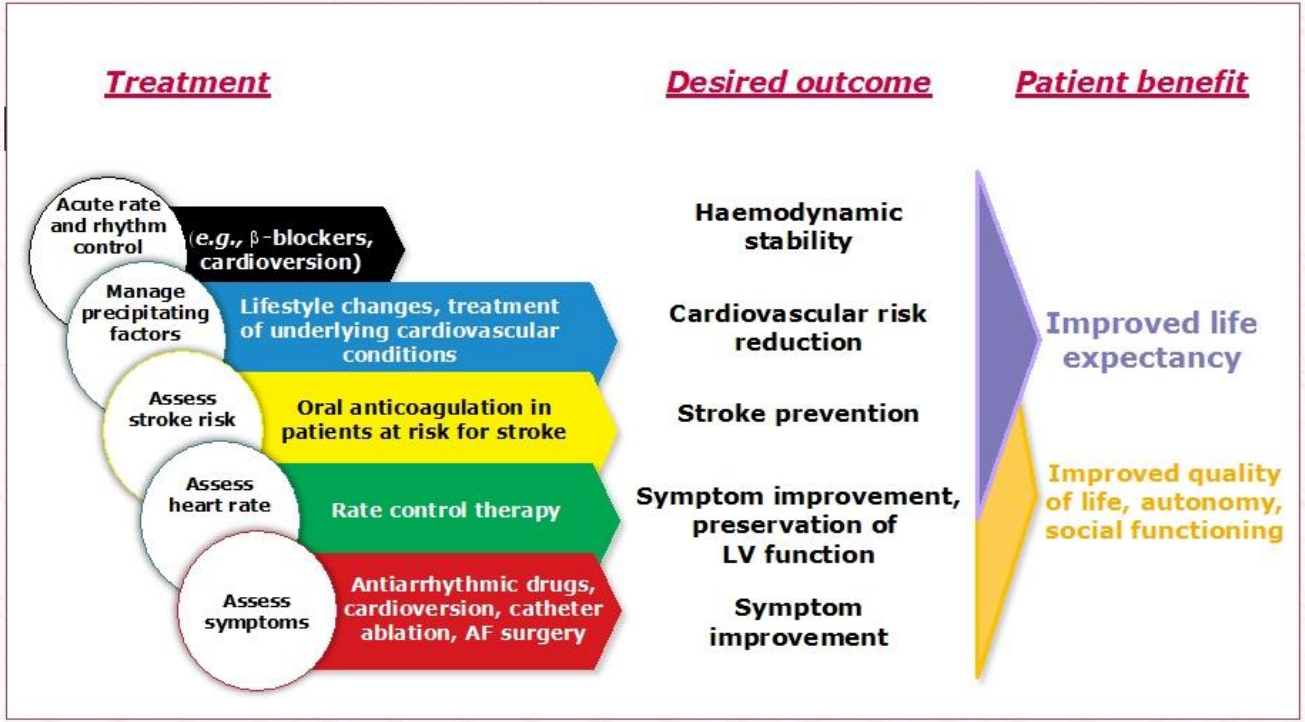
Keywords Connexin40 • Gene mutation • Atrial fibrillation • Cardiac electrophysiology

ESC European Society of Cardiology
European Heart Journal (2017) **38**, 2621–2628
doi:10.1093/eurheartj/ehx324

Long working hours as a risk factor for atrial fibrillation: a multi-cohort study



The Five Domains of Integrated AF Management



European Heart Journal - doi:10.1093/eurheartj/ehw210

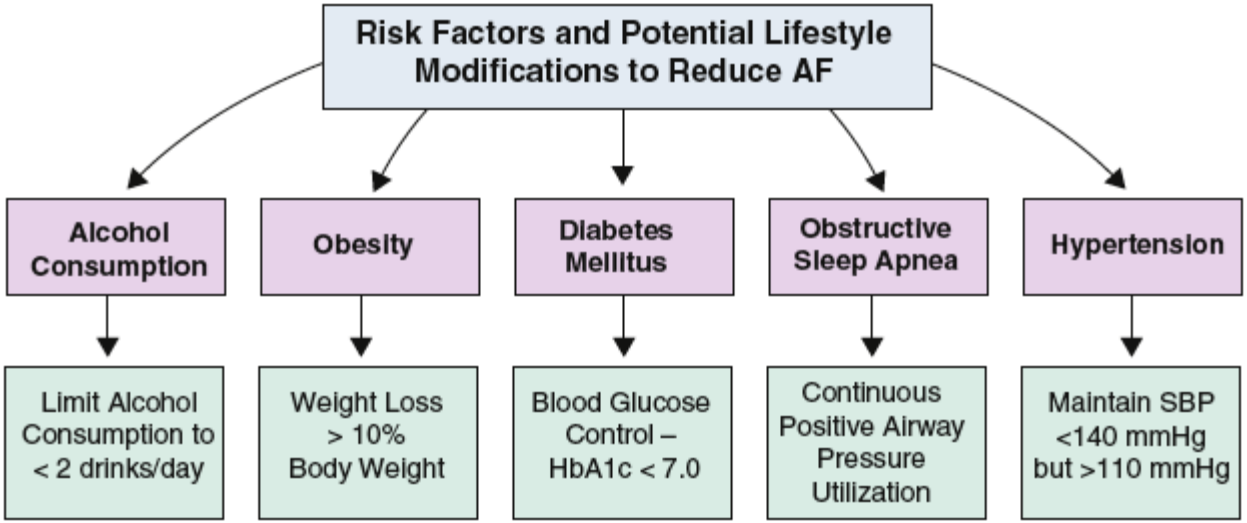
Providing integrated care for AF patients

Integrated AF management			
Patient involvement	**Multidisciplinary teams**	**Technology tools**	**Access to all treatment options for AF**
• Central role in care process. • Patient education. • Encouragement and empowerment for self-management. • Advice and education on lifestyle and risk factor management. • Shared decision making. • ***Informed, involved, empowered patient.***	• Physicians (general physicians, cardiology and stroke AF specialists, surgeons) and allied health professionals work in a collaborative practice model. • Efficient mix of communication skills, education, and experience. • ***Working together in a multi-disciplinary chronic AF care team.***	• Information on AF. • Clinical decision support. • Checklist and communication tools • Used by healthcare professionals and patients. • Monitoring of therapy adherence and effectiveness. • ***Navigation system to support decision making in treatment team.***	• Structured support for lifestyle changes. • Anticoagulation. • Rate control. • Antiarrhythmic drugs. • Catheter and surgical interventions (ablation, LAA occluder, AF surgery, etc.). • ***Complex management decisions underpinned by an AF Heart Team***

To support integrated AF care, the ESC Guidelines task force and the CATCH ME consortium (www.catch-me.info) have developed state-of-the-art interactive tools underpinning integrated AF management. A first version including an overall treatment manager is integrated into the AF section of the ESC pocket guidelines app. Further CATCH ME tools for healthcare professionals and an associated app for AF patients will be released in late 2016 / early 2017.

CATCH ME is supported by the European Union grant agreement No 633196 [CATCH ME].

European Heart Journal - doi:10.1093/eurheartj/ehw210


Risk Factors and Potential Lifestyle Modifications to Reduce AF
Alcohol Consumption
Obesity
Diabetes Mellitus
Obstructive Sleep Apnea
Hypertension
Limit Alcohol Consumption to < 2 drinks/day
Weight Loss > 10% Body Weight
Blood Glucose Control – HbA1c < 7.0
Continuous Positive Airway Pressure Utilization
Maintain SBP <140 mmHg but >110 mmHg

Casi particolari

AF AND CHF: CHICKEN AND EGG HISTORY. WHO CAMES THE FIRST ?

Il ritmo sinusale è associato a meno sintomi nei pazienti con scompenso cardiaco

Table 3 NYHA status in the 2 original rate control and rhythm control arms by intention to treat

Arm	N of records	NYHA (0 + I) N of records	NYHA (0 + I) %	NYHA (II + III) N of records	NYHA (II + III) %
Rate control	20,672	18,754	90.7	1,905	9.2
Rhythm control	20,843	19,087	91.6	1,746	8.4*

Abbreviations as in Table 1.
*$P < .01$.

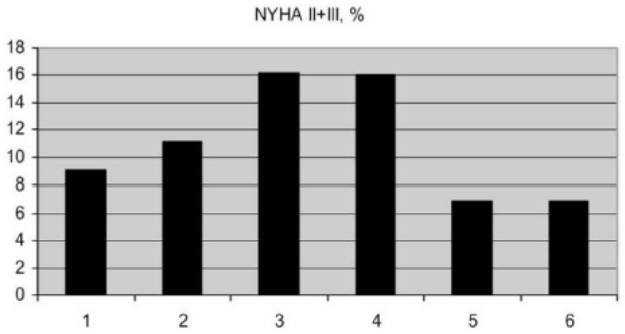


Table 5 Symptomatic HF in groups with different AF burdens

		N of records	NSR/AF	NYHA II + III, %	Odds ratio (95% confidence interval)	*P*
1	Rate	17,967	0.63	9.1	1.35 (1.12–1.63)	.0018
2	Rhythm to rate	5,894	0.75	11.1	1.69 (1.3–2.19)	<.0001
3	Rhythm to rate to rhythm	973	0.85	16.2	2.61 (1.76–3.89)	<.0001
4	Rate to rhythm to rate	712	2.15	16.0	2.56 (1.49–4.4)	.0007
5	Rate to rhythm	1,732	4.41	6.9	1.01 (0.66–1.53)	.9727
6	Rhythm	14,237	10.76	6.9	1	

Abbreviations as in Table 4.

Guglin M et. al, Heart Rhythm 2010;7:596–601

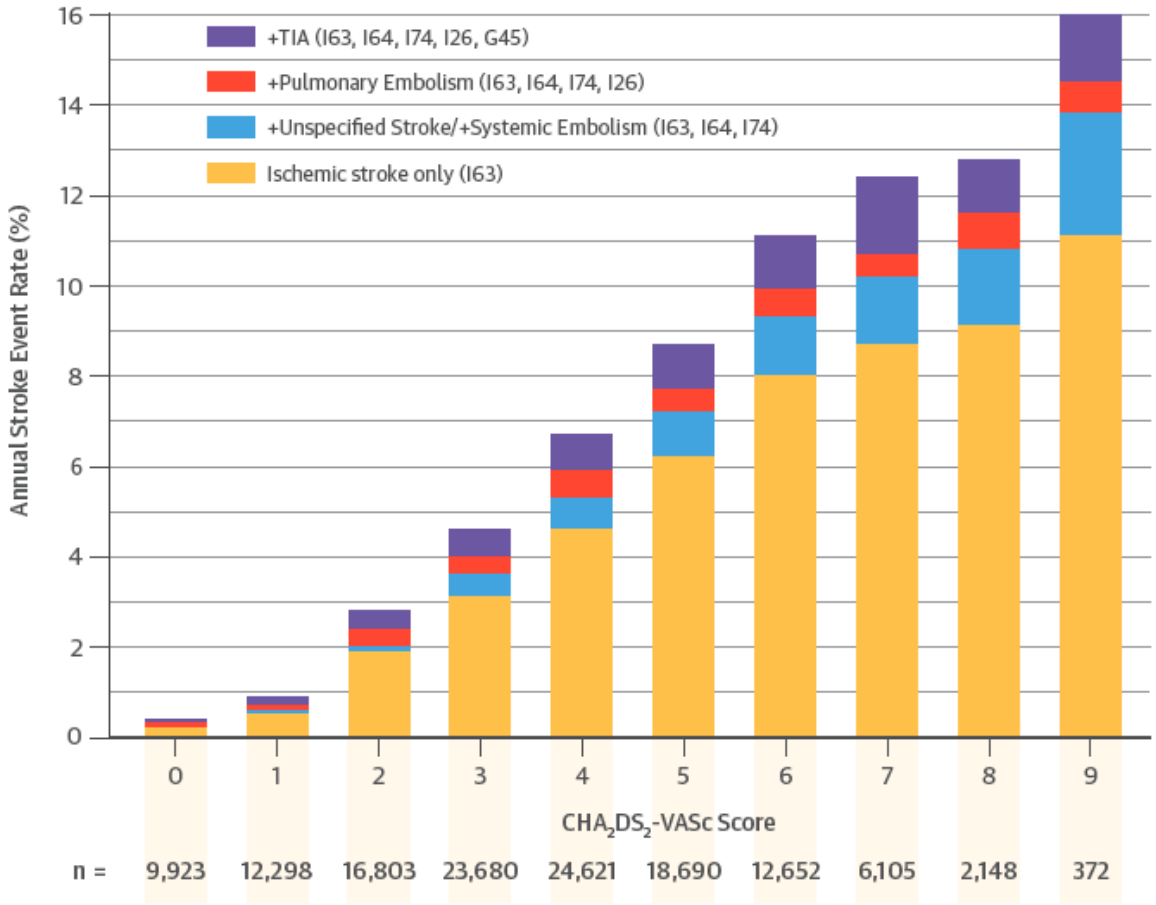
Anticoagulare

Chi come quando e per quanto

To anticoagulate or not to anticoagulate that is the problem?

Above all WHO?????

CENTRAL ILLUSTRATION **Annual Event Rates**



Friberg, L. et al. J Am Coll Cardiol. 2015; 65(3):225-32.

Stroke Association UK

Many common Factors

CHADSVASC = 2 > F + H
H + A
A > 74
D + C
S
H + V
etc. etc.

TABLE 3. Proportional Hazards Models For Ischemic Stroke Outcome

	Relative Risk (95% Confidence Intervals)	
	All Stroke	Fatal Stroke
Demographic		
Age	1.06 (1.04–1.09)*	1.10 (1.06–1.14)*
Female sex	0.52 (0.38–0.70)*	0.45 (0.25–0.79)†
Currently married	0.70 (0.54–0.91)†	0.46 (0.28–0.76)†
Cardiovascular risk factors		
Prior stroke	3.27 (2.39–4.47)*	3.07 (1.81–5.21)*
Prior CHD	1.15 (0.87–1.51)	1.03 (0.64–1.71)
Diabetes	1.23 (0.82–1.84)	0.97 (0.43–2.16)
Blood pressure medication	1.37 (1.04–1.80)‡	1.44 (0.87–2.38)
SBP 140–159 or DBP 90–94	1.01 (0.74–1.37)	1.03 (0.59–1.81)
SBP 160–199 or DBP 95–99	1.26 (0.92–1.72)	1.06 (0.60–1.88)
SBP $ 200 or DBP $ 100	1.67 (1.09–2.57)‡	2.08 (1.01–4.29)‡
Atrial fibrillation	1.58 (0.91–2.75)§	3.11 (1.38–7.00)‡
Total cholesterol	1.02 (0.92–1.14)	0.95 (0.78–1.17)
HDL cholesterol	0.64 (0.44–0.94)‡	0.54 (0.27–1.07)§
Triglycerides	1.06 (0.97–1.16)	1.09 (0.92–1.29)
Smoking		
Former	0.94 (0.70–1.26)	0.91 (0.53–1.58)
Current	1.14 (0.78–1.67)	1.07 (0.52–2.18)
Body mass index	0.96 (0.93–0.99)‡	0.87 (0.81–0.93)*

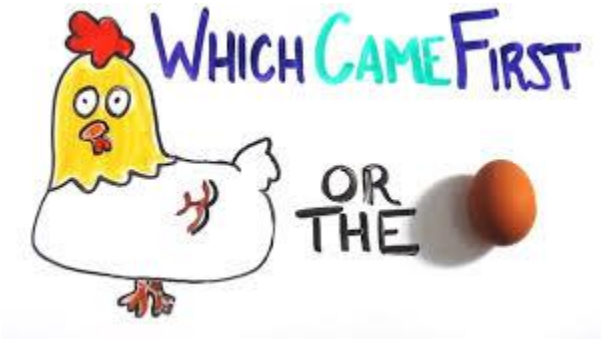
Modifiable: risk factors under your control [72]	**Non modifiable:** risk factors out of your control [72]
High blood pressure	Age
High blood cholesterol	Ethnicity
Diabetes (type 2)	Gender
Being overweight	Family history of heart disease
Smoking	History of heart disease
Alcohol consumption	PFO (hole in the heart)
Drug use	Diabetes (type 1)
No physical exercise	Atrial Fibrillation

Invited Commentary

When Does High Risk for Stroke Become Low Risk After Atrial Fibrillation Ablation?

Francis E. Marchlinski, MD; Pasquale Santangeli, MD, PhD

If I’m on anticoagulants for AF, but I’ve no more AF Why should I take AC?



ASSERT: Relationship between AHRE and Stroke

- In ASSERT, 59 patients had stroke or SE
- 30 had no AHRE
  - 9 had AHRE but only AFTER their stroke
- 20 patients had at least one AHRE > 6 minutes prior to their stroke or SE
  - 3 developed persistent AF at least one month before, but only recognized clinically in 1 pt.
  - 2 patients had 9-day long episodes 1-2 weeks prior
  - 1 patient had 2.7 hour episode beginning 48 hours prior
  - ***None of remaining 14 pts. had ANY AHRE > 6 minutes in 30 days before stroke or SE***

Evaluating the Atrial Myopathy Underlying Atrial Fibrillation

Identifying the Arrhythmogenic and Thrombogenic Substrate

Jeffrey J. Goldberger, MD, MBA; Rishi Arora, MD; David Green, MD, PhD; Philip Greenland, MD; Daniel C. Lee, MD, MSc; Donald M. Lloyd-Jones, MD, ScM; Michael Markl, PhD; Jason Ng, PhD; Sanjiv J. Shah, MD

Abstract—Atrial disease or myopathy forms the substrate for atrial fibrillation (AF) and underlies the potential for atrial thrombus formation and subsequent stroke. Current diagnostic approaches in patients with AF focus on identifying clinical predictors with the evaluation of left atrial size by echocardiography serving as the sole measure specifically evaluating the atrium. Although the atrial substrate underlying AF is likely developing for years before the onset of AF, there is no current evaluation to identify the preclinical atrial myopathy. Atrial fibrosis is 1 component of the atrial substrate that has garnered recent attention based on newer MRI techniques that have been applied to visualize atrial fibrosis in humans with prognostic implications regarding the success of treatment. Advanced ECG signal processing, echocardiographic techniques, and MRI imaging of fibrosis and flow provide up-to-date approaches to evaluate the atrial myopathy underlying AF. Although thromboembolic risk is currently defined by clinical scores, their predictive value is mediocre. Evaluation of stasis via imaging and biomarkers associated with thrombogenesis may provide enhanced approaches to assess risk for stroke in patients with AF. Better delineation of the atrial myopathy that serves as the substrate for AF and thromboembolic complications might improve treatment outcomes. Furthermore, better delineation of the pathophysiologic mechanisms underlying the development of the atrial substrate for AF, particularly in its earlier stages, could help identify blood and imaging biomarkers that could be useful to assess risk for developing new-onset AF and suggest specific pathways that could be targeted for prevention. (*Circulation*. 2015;132:278-291. DOI: 10.1161/CIRCULATIONAHA.115.016795.)

Future Cardiol. 2015 May ; 11(3): 323–331. doi:10.2217/fca.15.22.

Atrial Cardiopathy: A Broadened Concept of Left Atrial Thromboembolism Beyond Atrial Fibrillation

Hooman Kamel, MD[1], **Peter M. Okin, MD**[2], **W. T. Longstreth Jr., MD, MPH**[3], **Mitchell S.V. Elkind, MD, MS**[4], and **Elsayed Z. Soliman, MD, MSc, MS**[5]

Atrial Fibrillation May Not Account for All Cases of Left Atrial Thromboembolism

- Given its paroxysmal nature, AF may not be recognized as the cause of stroke because a patient may be in normal sinus rhythm upon presentation with stroke. Prolonged continuous heart-rhythm monitoring after stroke of undetermined cause may often reveal paroxysmal AF. However, most patients with cryptogenic stroke will not manifest AF, indicating that other embolic sources are likely.

Left Atrial Thromboembolism in the Absence of Atrial Fibrillation

- Recent evidence links other markers of left atrial abnormality to an increased risk of stroke. ECG-defined left atrial abnormality, left atrial enlargement on echocardiogram, and elevated NT-proBNP have all been associated with stroke independently of AF. This suggests that left atrial thromboembolism may occur even in the absence of AF.

The Concept of Atrial Cardiopathy as the Source of Thromboembolism

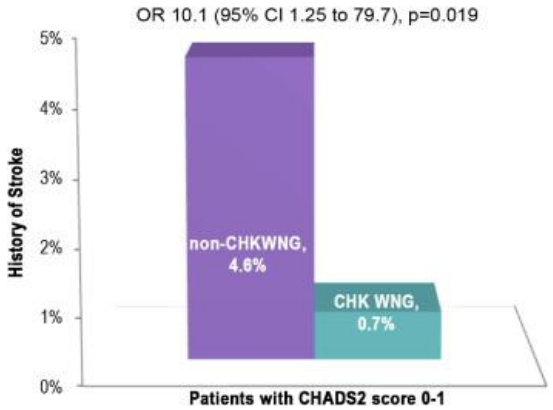
- We suggest that the concept of atrial cardiopathy, rather than AF, may better explain the phenomenon of left atrial embolisation. Rather than viewing AF as the necessary and sufficient cause of the thromboembolic risk seen in patients with AF, it may be more helpful to view both AF and thromboembolism as common manifestations of an underlying atrial cardiopathy. In this formulation, the driving force of thromboembolism is not the dysrhythmia but rather a host of underlying pathological tissue changes.

Implications of the Atrial Cardiopathy Model

- The concept of atrial cardiopathy would explain several puzzling observations about AF and stroke: namely, the lack of a temporal or dose-response relationship between AF and stroke.
- The concept of atrial cardiopathy may allow better screening for thromboembolic risk than the current approach of relying on the identification of AF, which can be difficult to document given its paroxysmal nature, and which may miss some patients with left atrial abnormality but no dysrhythmia.
- The concept of atrial cardiopathy may also serve as a valid therapeutic target for anticoagulant drugs, and such a hypothesis will require testing in randomized clinical trials.

AURICOLA SINISTRA
MORFOLOGIA

La morfologia dell'auricola può predire il anche nei pazienti a **basso CHADS score**



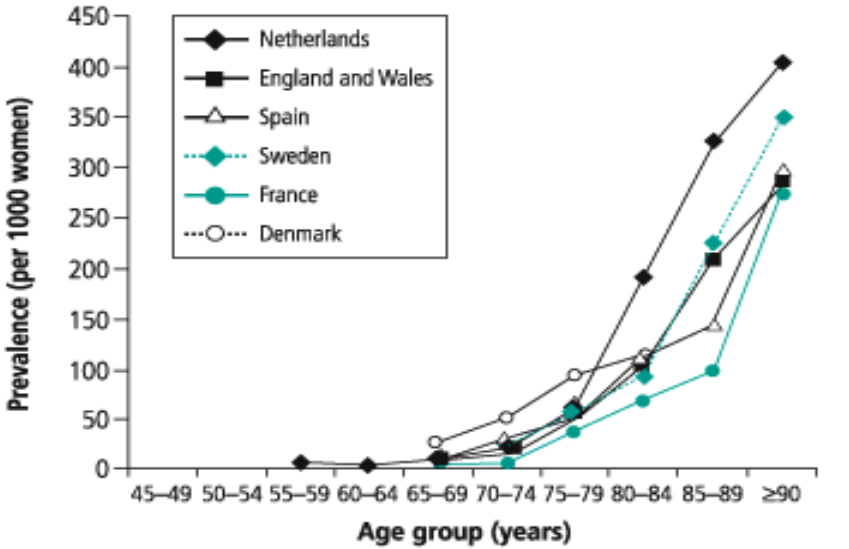
Gaita et al. J Am Coll Cardiol 2012

	Total	Control	Stroke	P value	OR (95% CI)
Cactus	4 (5)	2 (2.5)	2 (2.5)	0.596	1.71 (0.23 - 12.85)
Cauliflower	32 (40)	14 (17.5)	18 (22.5)	0.005	3.86 (1.48 - 10.04)
Chicken Wing	14 (17.5)	11 (13.8)	3 (3.8)	0.171	0.39 (0.10 - 1.55)
Windsock	30 (37.5)	23 (28.8)	7 (8.8)	0.043	0.36 (0.13 - 0.98)
Volume (cm^3)	16.1 ± 7.5	16.7 ± 8.6	15.1 ± 5.2	0.34	N/A
LA size (cm)	3.9 ± 0.7	3.9 ± 0.8	4.0 ± 0.5	0.631	N/A
LAA flow (cm/sec)	52.0 ± 19.4	52.6 ± 19.0	51.0 ± 20.4	0.74	N/A

Kimura et al.
Heart Rhythm 2013

Prevalence of Dementia

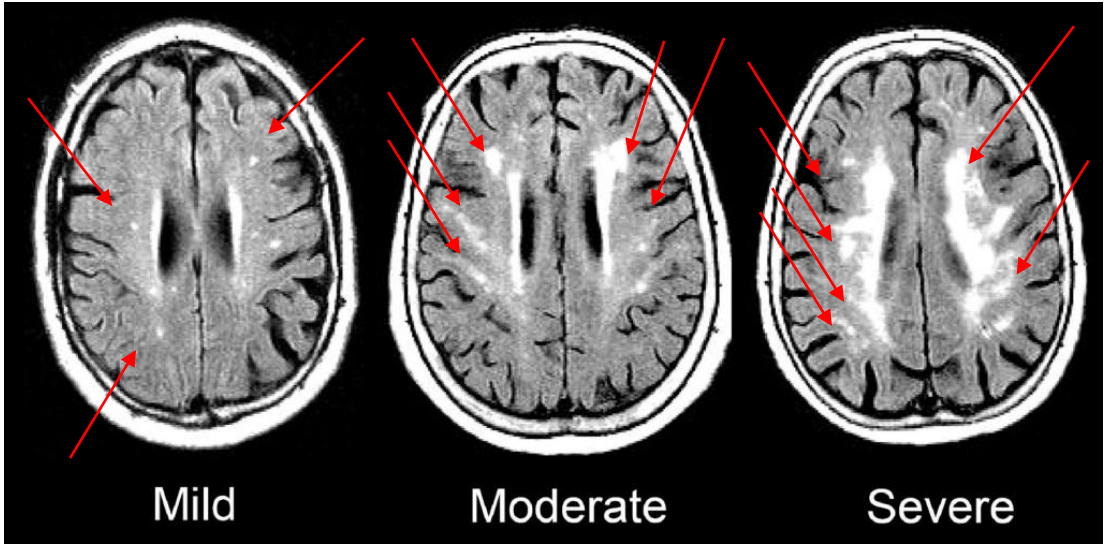
Fig. 2. **Observed prevalence of dementia among females in Denmark, England and Wales, France, the Netherlands, Spain, and Sweden**



WHO 02.142

North America: 6.9% prevalence; 63% increase 2010-2030; 151% increase 2010-2050

Silent Cerebral Ischaemia



European Heart Journal (2016) 37, 2893–2962
doi:10.1093/eurheartj/ehw210

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

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

Endorsed by the European Stroke Organisation (ESO)

Authors/Task Force Members: Paulus Kirchhof* (Chairperson) (UK/Germany), Stefano Benussi*[1] (Co-Chairperson) (Switzerland), Dipak Kotecha (UK), Anders Ahlsson[1] (Sweden), Dan Atar (Norway), Barbara Casadei (UK), Manuel Castella[1] (Spain), Hans-Christoph Diener[2] (Germany), Hein Heidbuchel (Belgium), Jeroen Hendriks (The Netherlands), Gerhard Hindricks (Germany), Antonis S. Manolis (Greece), Jonas Oldgren (Sweden), Bogdan Alexandru Popescu (Romania), Ulrich Schotten (The Netherlands), Bart Van Putte[1] (The Netherlands), and Panagiotis Vardas (Greece)

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file of anticoagulation in ablated patients need to be considered. In the absence of controlled trial data, OAC after catheter ablation should follow general anticoagulation recommendations, regardless of the presumed rhythm outcome.

Table 8 Cardiovascular and other conditions independently associated with atrial fibrillation

Characteristic/comorbidity	Association with AF
Genetic predisposition (based on multiple common gene variants associated with AF)[64]	HR range 0.4–3.2
Older age[19] 50–59 years 60–69 years 70–79 years 80–89 years	HR: 1.00 (reference) 4.98 (95% CI 3.49–7.10) 7.35 (95% CI 5.28–10.2) 9.33 (95% CI 6.68–13.0)
Hypertension (treated) vs. none[19]	HR 1.32 (95% CI 1.08–1.60)
Heart failure vs. none[19]	HR 1.43 (95% CI 0.85–2.40)
Valvular heart disease vs. none[205]	RR 2.42 (95% CI 1.62–3.60)
Myocardial infarction vs. none[19]	HR 1.46 (95% CI 1.07–1.98)
Thyroid dysfunction[206,207] Hypothyroidism Subclinical hyperthyroidism Overt hyperthyroidism	(reference: euthyroid) HR 1.23 (95% CI 0.77–1.97) RR 1.31 (95% CI 1.19–1.44) RR 1.42 (95% CI 1.22–1.63)
Obesity[19,208] None (BMI <25 kg/m^2) Overweight (BMI 25–30 kg/m^2) Obese (BMI ≥31 kg/m^2)	HR: 1.00 (reference) 1.13 (95% CI 0.87–1.46) 1.37 (95% CI 1.05–1.78)
Diabetes mellitus vs. none[19]	HR 1.25 (95% CI 0.98–1.60)
Chronic obstructive pulmonary disease[209] FEV1 ≥80% FEV1 60–80% FEV1 <60%	RR: 1.00 (reference) 1.28 (95% CI 0.79–2.06) 2.53 (95% CI 1.45–4.42)
Obstructive sleep apnoea vs. none[210]	HR 2.18 (95% CI 1.34–3.54)
Chronic kidney disease[211] None Stage 1 or 2 Stage 3 Stage 4 or 5	OR: 1.00 (reference) 2.67 (95% CI 2.04–3.48) 1.68 (95% CI 1.26–2.24) 3.52 (95% CI 1.73–7.15)
Smoking[212] Never Former Current	HR: 1.00 (reference) 1.32 (95% CI 1.10–1.57) 2.05 (95% CI 1.71–2.47)
Alcohol consumption[213] None 1–6 drinks/week 7–14 drinks/week 15–21 drinks/week >21 drinks/week	RR: 1.00 (reference) 1.01 (95% CI 0.94–1.09) 1.07 (95% CI 0.98–1.17) 1.14 (95% CI 1.01–1.28) 1.39 (95% CI 1.22–1.58)
Habitual vigorous exercise[214] Non-exercisers <1 day/week 1–2 days/week 3–4 days/week 5–7 days/week	RR: 1.00 (reference) 0.90 (95% CI 0.68–1.20) 1.09 (95% CI 0.95–1.26) 1.04 (95% CI 0.91–1.19) 1.20 (95% CI 1.02–1.41)

AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; HR = hazard ratio; OR = odds ratio; RR = risk ratio.

In conclusione

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

Precision Medicine — Personalized, Problematic, and Promising

J. Larry Jameson, M.D., Ph.D., and Dan L. Longo, M.D.

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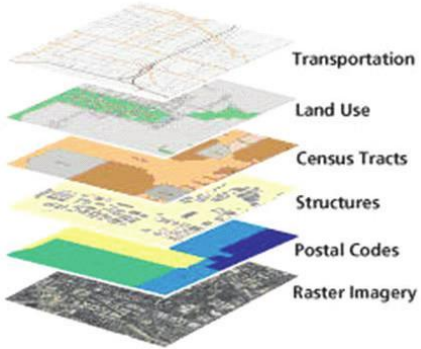
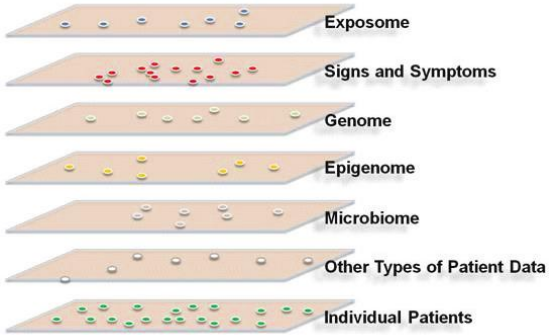
Geographical **I**nformation **S**ystem

Google Maps: GIS layers
Organized by Geographical Positioning



System **M**edicine

Information Commons
Organized Around Individual Patients



COMMENT

STATISTICS A call to police the whole data-analysis pipeline, not just *P* values **p.612**

SPRING BOOKS Does Nicholas Stern's global vision admit ground truth? **p.614**

SPRING BOOKS Metaphor pile-up obscures the meaning of junk DNA **p.615**

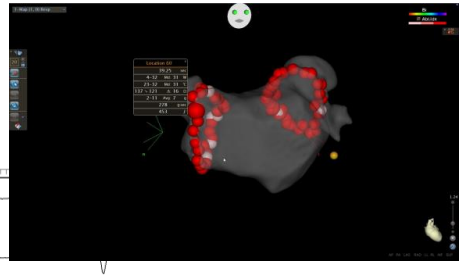
SPRING BOOKS Grind, politics and dirty tricks in life of polio-vaccine pioneer **p.620**

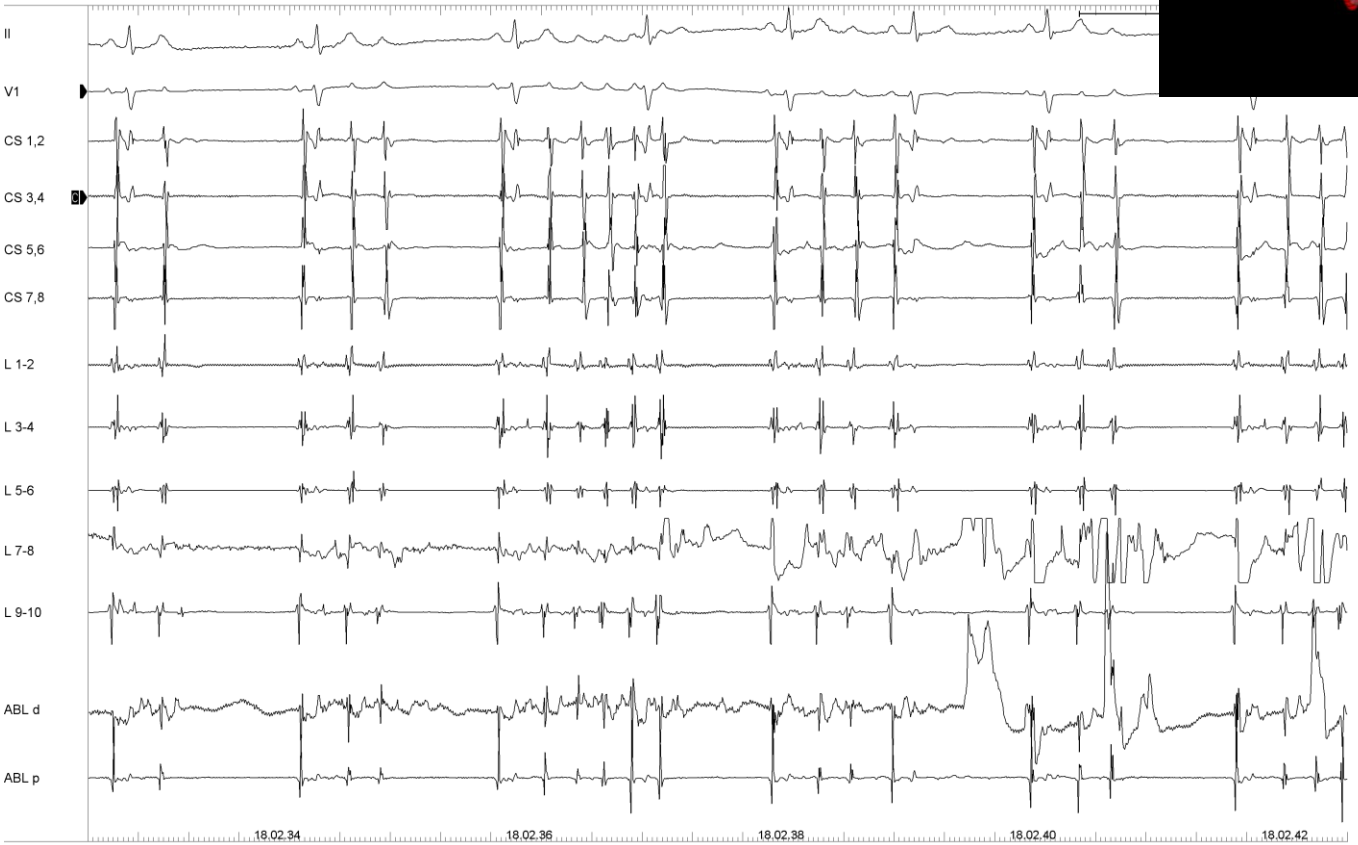
ILLUSTRATION BY GREG CLARKE

Time for one-person trials

Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy, says **Nicholas J. Schork**.

Focal AF




II
V1
CS 1,2
CS 3,4
CS 5,6
CS 7,8
L 1-2
L 3-4
L 5-6
L 7-8
L 9-10
ABL d
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18.02.34
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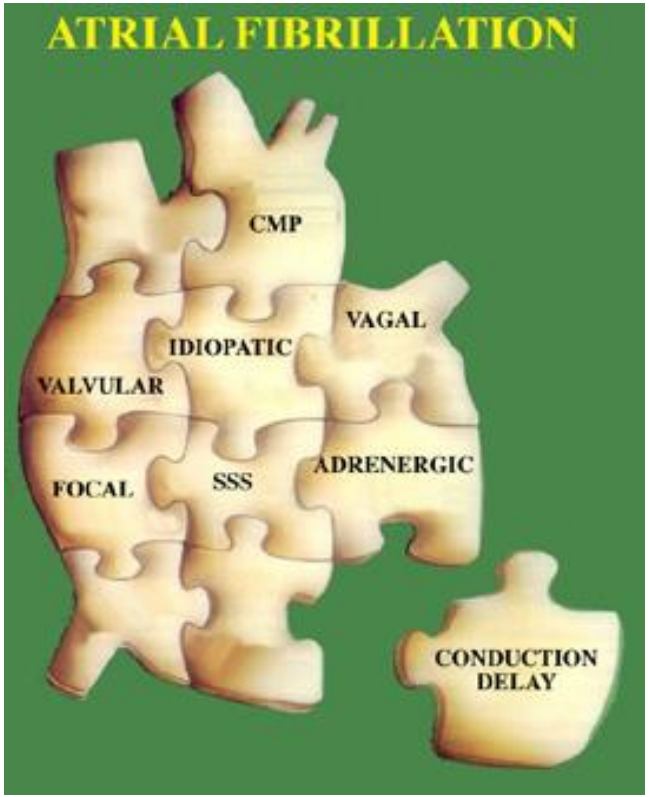
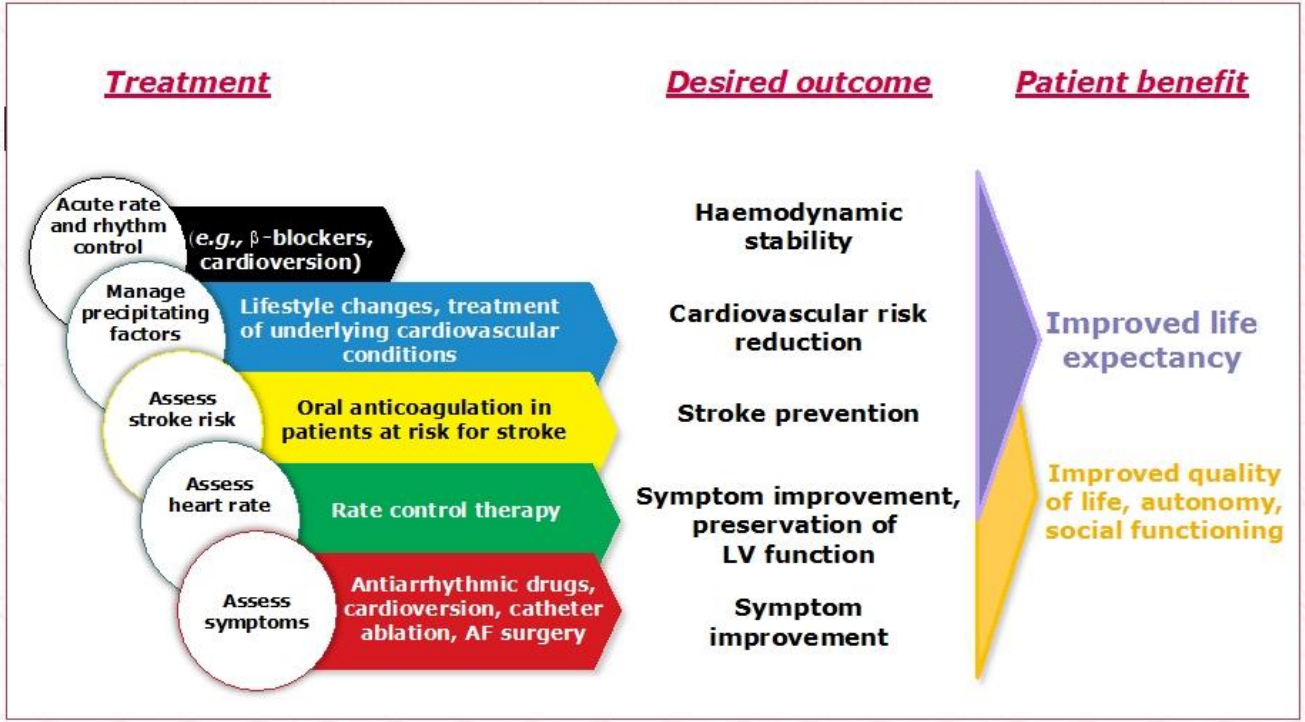
Eterogeneous etiopathogenesis of atrial fibrillation

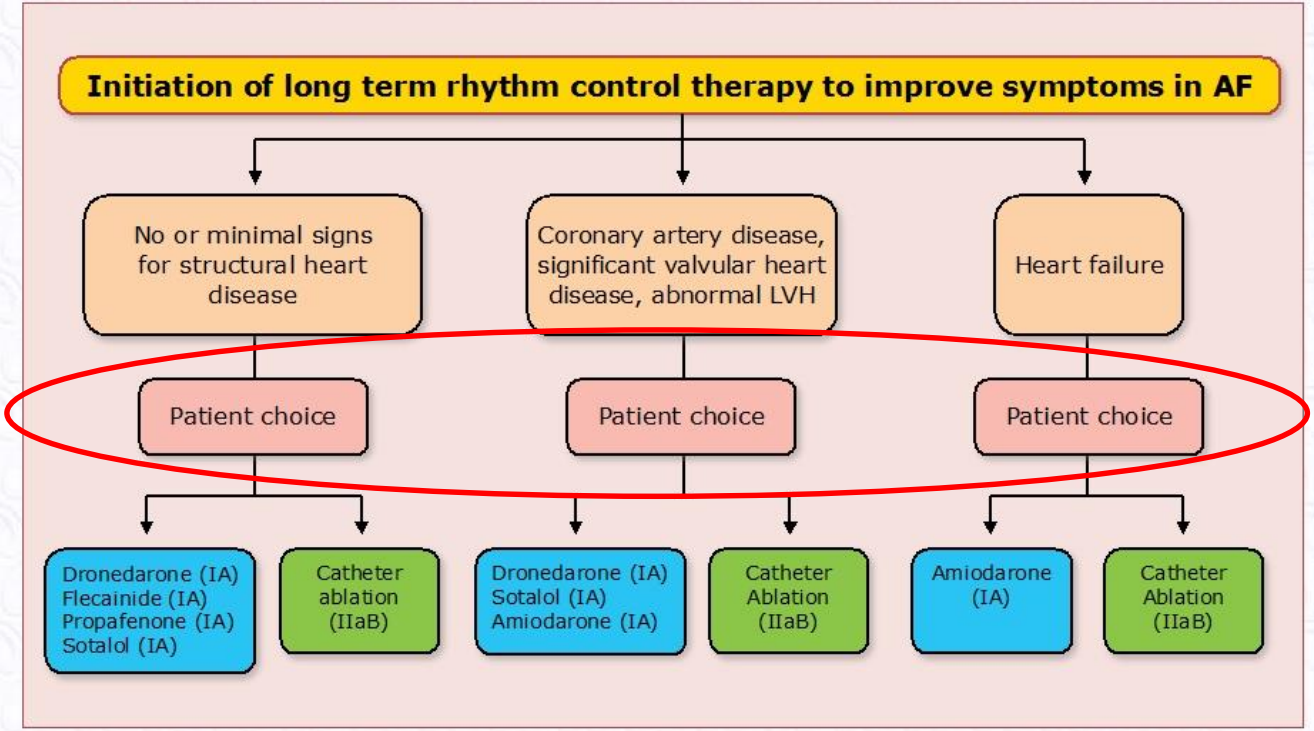


The Five Domains of Integrated AF Management



European Heart Journal - doi:10.1093/eurheartj/ehw210

Initiation of long term rhythm control therapy in symptomatic patients with atrial fibrillation



European Heart Journal - doi:10.1093/eurheartj/ehw210

Thank you for attention

I can resist everything except temptation

O. Wilde