

Fibrillazione Atriale & ↑ Mortalità: Causa o Associazione?

Antonio Raviele, MD, FESC, FHRS



All-cause mortality in 272 186 patients hospitalized with incident atrial fibrillation 1995–2008: a Swedish nationwide long-term case-control study

Tommy **Andersson**^{1*}, Anders Magnuson², Ing-Liss Bryngelsson³, Ole Frøbert¹, Karin M. Henriksson^{4,5}, Nils Edvardsson⁶, and Dritan Poçi¹

Eur Heart J 2013; 34: 1061-1067



Aims

To evaluate long-term all-cause risk of mortality in women and men hospitalized for the first time with atrial fibrillation (AF) compared with matched controls.

Methods and results

A total of 272 186 patients (44% women) ≤ 85 years at the time of hospitalization with incidental AF 1995–2008 and 544 344 matched controls free of in-hospital diagnosis of AF were identified. Patients were followed via record linkage of the Swedish National Patient Registry and the Cause of Death Registry. Using Cox regression models, the long-term relative all-cause mortality risk, adjusted for concomitant diseases, in women vs. controls was 2.15, 1.72, and 1.44 ($P < 0.001$) in the age categories ≤ 65 , 65–74, and 75–85 years, respectively. The corresponding figures for men were 1.76, 1.36, and 1.24 ($P < 0.001$). Among concomitant diseases, neoplasm, chronic renal failure, and chronic obstructive pulmonary disease contributed most to the increased all-cause mortality vs. controls. In patients with AF as the primary diagnosis, the relative risk of mortality was 1.63, 1.46, and 1.28 ($P < 0.001$) in women and 1.45, 1.17, and 1.10 ($P < 0.001$) in men.

Conclusion

Atrial fibrillation was an independent risk factor of all-cause mortality in patients with incident AF. The concomitant diseases that contributed most were found outside the thromboembolic risk scores. The highest relative risk of mortality was seen in women and in the youngest patients compared with controls, and the differences between genders in each age category were statistically significant.

Keywords

Atrial fibrillation • Mortality • Gender • Age • Long term

Table I Baseline characteristics

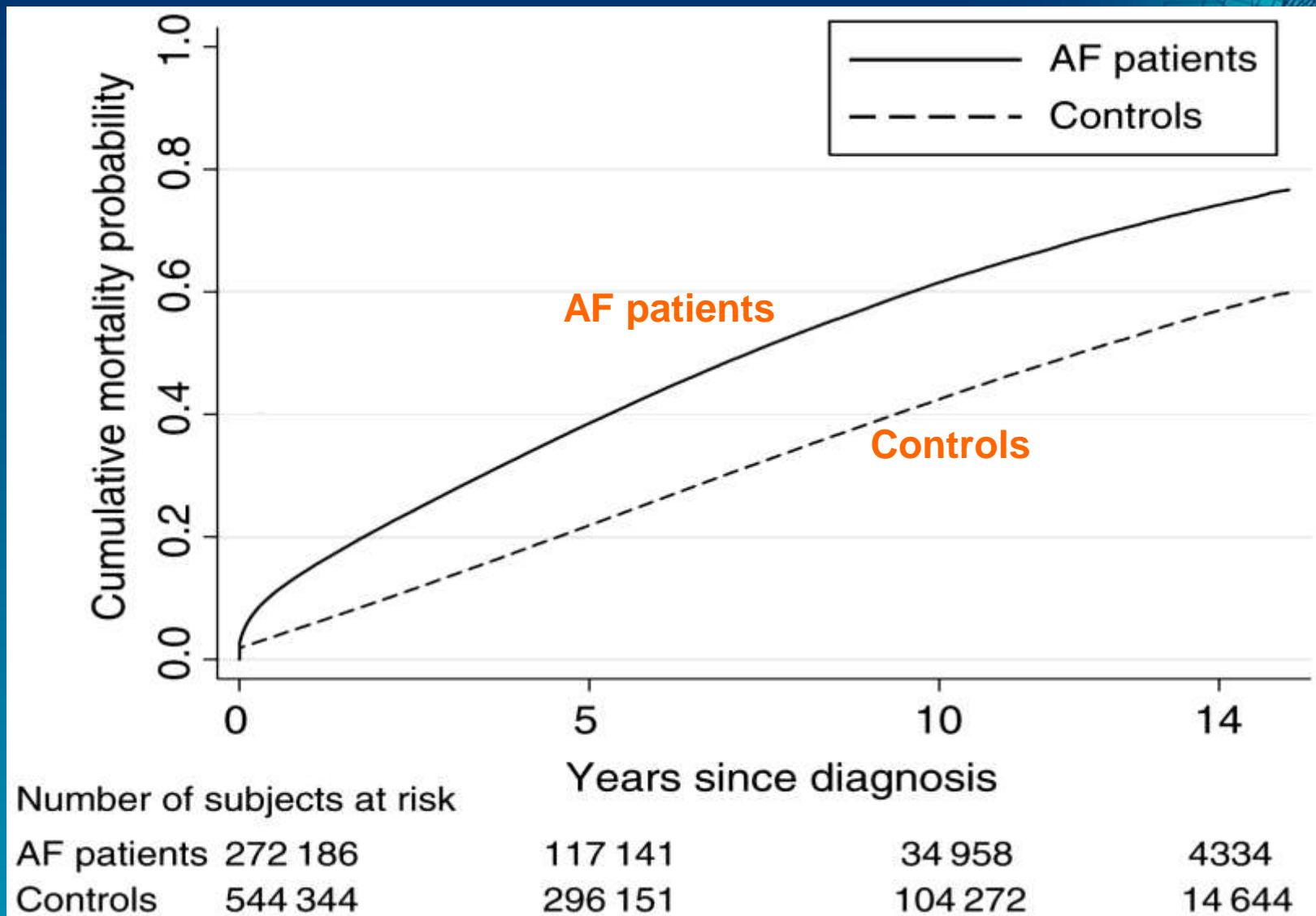
	Women		Men		All	
	AF patients	Controls	AF patients	Controls	AF patients	Controls
AF patients and matched controls						
	(n = 119 916)	(n = 239 818)	(n = 152 270)	(n = 304 526)	(n = 272 186)	(n = 544 344)
Age, mean (SD)	74.8 (9.3)	74.8 (9.3)	70.4 (11.7)	70.4 (11.7)	72.3 (10.9)	72.3 (10.9)
<65 (%)	13	13	26	26	20	20
65–74 (%)	25	25	29	29	27	27
75–85 (%)	62	62	45	45	53	53
Gender, women (%)					44	44
Concomitant diseases						
Any	70.6	27.8	68.6	26.7	69.5	27.2
Ischaemic heart disease (%)	22.8	6.2	28.6	9.5	26.0	8.0
Acute myocardial infarction (%)	10.3	2.4	13.6	4.4	12.2	3.6
Heart failure (%)	24.5	2.7	25.0	3.0	24.8	2.9
Stroke/TIA (%)	15.2	4.1	13.5	4.7	14.2	4.4
Stroke (%)	12.3	3.0	10.8	3.6	11.5	3.3
Hypertension (%)	27.7	7.3	23.5	6.5	25.4	6.8
COPD (%)	4.8	1.3	5.0	1.4	4.9	1.4
Diabetes mellitus (%)	12.8	4.8	13.8	5.5	13.4	5.2
Neoplasm (any) (%)	18.5	13.6	15.1	10.1	16.6	11.6
Chronic renal failure (%)	1.2	0.2	2.0	0.4	1.6	0.3



Patients with a primary diagnosis of AF and matched controls

	n = 54 022	n = 108 038	n = 65 609	n = 131 213	n = 119 631	n = 239 251
Age, mean (SD)	72.6 (10.2)	72.6 (10.2)	66.4 (13.0)	66.4 (13.0)	69.2 (12.2)	69.2 (12.2)
<65 (%)	19	19	39	39	30	30
65–74 (%)	29	29	30	30	29	29
75–85 (%)	52	52	31	31	41	41
Gender, women (%)					45	45
<hr/>						
Concomitant diseases						
Any	57.0	26.3	50.9	22.6	53.6	24.3
Ischaemic heart disease (%)	15.5	5.5	18.3	7.9	17.0	6.8
Acute myocardial infarction (%)	5.0	2.1	6.9	3.6	6.0	3.0
Heart failure (%)	16.7	2.2	16.1	2.3	16.3	2.3
Stroke/TIA (%)	6.8	3.6	5.7	3.8	6.2	3.7
Stroke (%)	4.7	2.6	3.9	2.9	4.3	2.7
Hypertension (%)	24.4	6.7	19.4	5.5	21.6	6.0
COPD (%)	3.0	1.2	3.0	1.1	3.0	1.2
Diabetes mellitus (%)	8.5	4.5	9.0	4.8	8.8	4.7
Neoplasm (any) (%)	15.8	13.4	10.3	8.5	12.8	10.7
Chronic renal failure (%)	0.7	0.2	1.1	0.3	0.9	0.3

All-cause mortality in patients with a diagnosis of AF vs. controls



Unadjusted all-cause mortality risk

All-cause mortality risk adjusted for concomitant diseases

	Age < 65 yrs	Age 65-74 yrs	Age 75-85
All patients			
- Women	3,57 2,15	2,55 1,72	1,94 1,44
- Men	2,80 1,76	2,03 1,36	1,72 1,24
Patients with primary diagnosis of AF			
- Women	2,20 1,63	1,76 1,46	1,43 1,28
- Men	1,91 1,45	1,44 1,17	1,25 1,10



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Atrial fibrillation • Mortality • Gender • Age • Long term



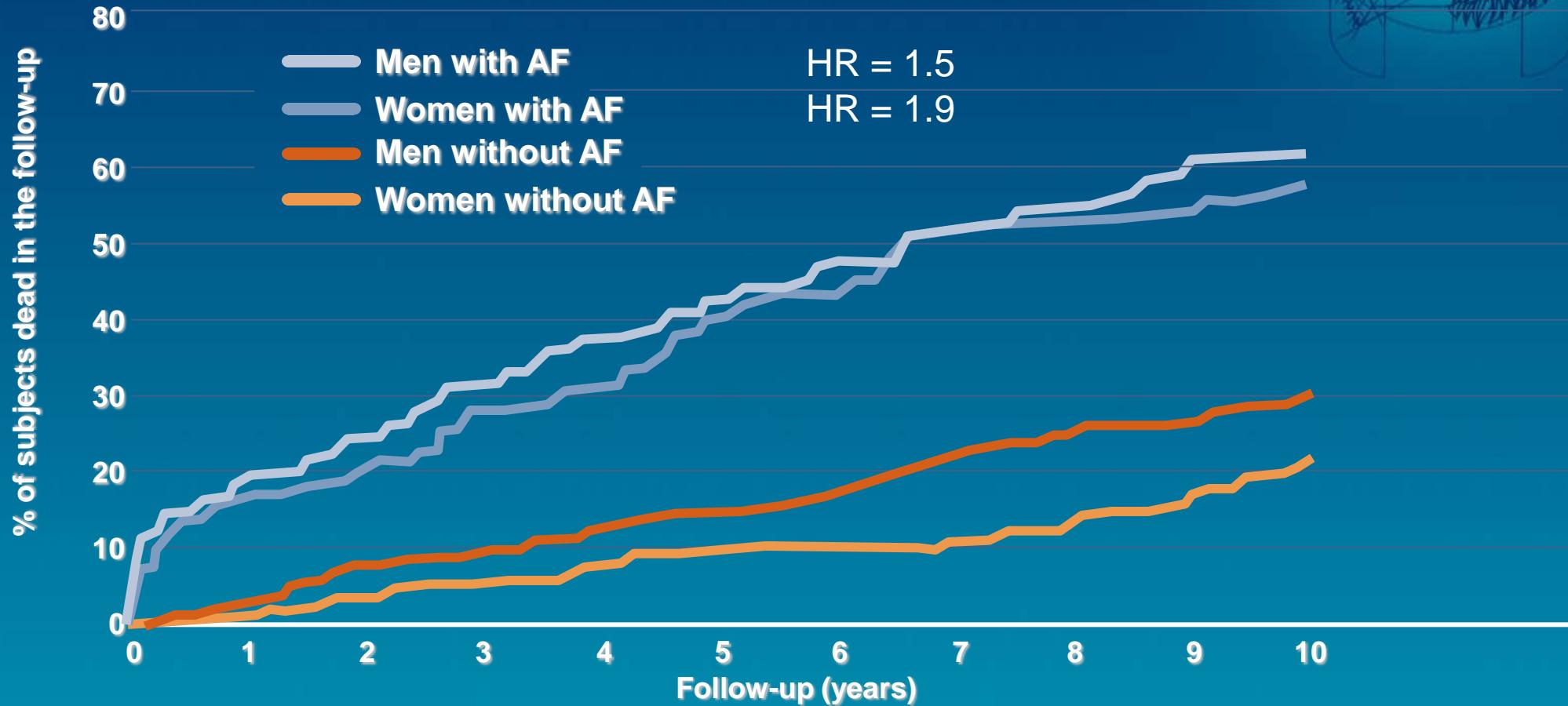
Impact of Atrial Fibrillation on the Risk of Death

Emelia J. Benjamin, Philip A. Wolf, Ralph B. D'Agostino, Halit Silbershatz, William B. Kannel, and Daniel Levy

Circulation 1998; 98: 946-952

Impact of AF on the risk of death: the Framingham study

N = 5209; follow-up: 40 years



(Benjamin EJ et al. Circulation 1998; 98: 946-952)

Associazione tra FA & Mortalità



✓ Popolazione Generale

✓ Specifiche Situazioni Cliniche

- Scompenso Cardiaco
- Infarto miocardico
- Insufficienza renale
- Stroke
- Ipertensione
- Diabete mellito
- Post-cardiochirurgia



Temporal Relations of Atrial Fibrillation and Congestive Heart Failure and Their Joint Influence on Mortality

The Framingham Heart Study

Thomas J. Wang, MD; Martin G. Larson, ScD; Daniel Levy, MD; Ramachandran S. Vasan, MD;
Eric P. Leip, MS; Philip A. Wolf, MD; Ralph B. D'Agostino, PhD; Joanne M. Murabito, MD, ScM;
William B. Kannel, MD; Emelia J. Benjamin, MD, ScM

Circulation 2003;107:2920-2925



TABLE 2. Cox Multivariable Proportional Hazards Models Examining the Impact of the Comorbid Condition on Mortality

Models	Men, Adjusted HR (95% CI)	Women, Adjusted HR (95% CI)
Comorbid condition as a time-dependent variable		
(A) Mortality after AF		
Impact of Incident CHF	2.7 (1.9 to 3.7)*	3.1 (2.2 to 4.2)*
(B) Mortality after CHF		
Impact of Incident AF	1.6 (1.2 to 2.1)†	2.7 (2.0 to 3.6)*

Wang TJ et al. Circulation 2003; 107: 2920-25



Risk of Death and Cardiovascular Events in Initially Healthy Women With New-Onset Atrial Fibrillation

David Conen, MD, MPH; Claudia U. Chae, MD, MPH; Robert J. Glynn, ScD; Usha B. Tedrow, MD, MSc; Brendan M. Everett, MD, MPH; Julie E. Buring, ScD; Christine M. Albert, MD, MPH

JAMA. 2011; 305: 2080-2087

**Table 3.** Risk of Death Among Women With New-Onset AF**FU = 15.4 years**

Outcome	No Incident AF (n = 33711)	Incident AF (n = 1011)
All-cause mortality (n = 1602)		
No. of events	1539	63
Incidence rate (95% CI) ^a	3.1 (2.9-3.2)	10.8 (8.1-13.5)
Hazard ratio (95% CI)		
Age-adjusted model (n = 34 722)	1 [Reference]	2.19 (1.69-2.83)
Multivariable-adjusted model 1 (n = 33 840) ^b	1 [Reference]	2.14 (1.64-2.77)
Multivariable-adjusted model 2 (n = 33 840) ^c	1 [Reference]	1.70 (1.30-2.22)



Atrial fibrillation is associated with increased mortality: causation or association?

Darryl P. Leong^{1,2*}, John W. Eikelboom¹, Jeff S. Healey¹, and Stuart J. Connolly¹

Eur Heart J 2013; 34: 1027-1030

Considerazioni

- ✓ E' importante stabilire se l'eccesso di mortalità
è causato direttamente dalla fibrillazione atriale
o se si tratta semplicemente di un'associazione

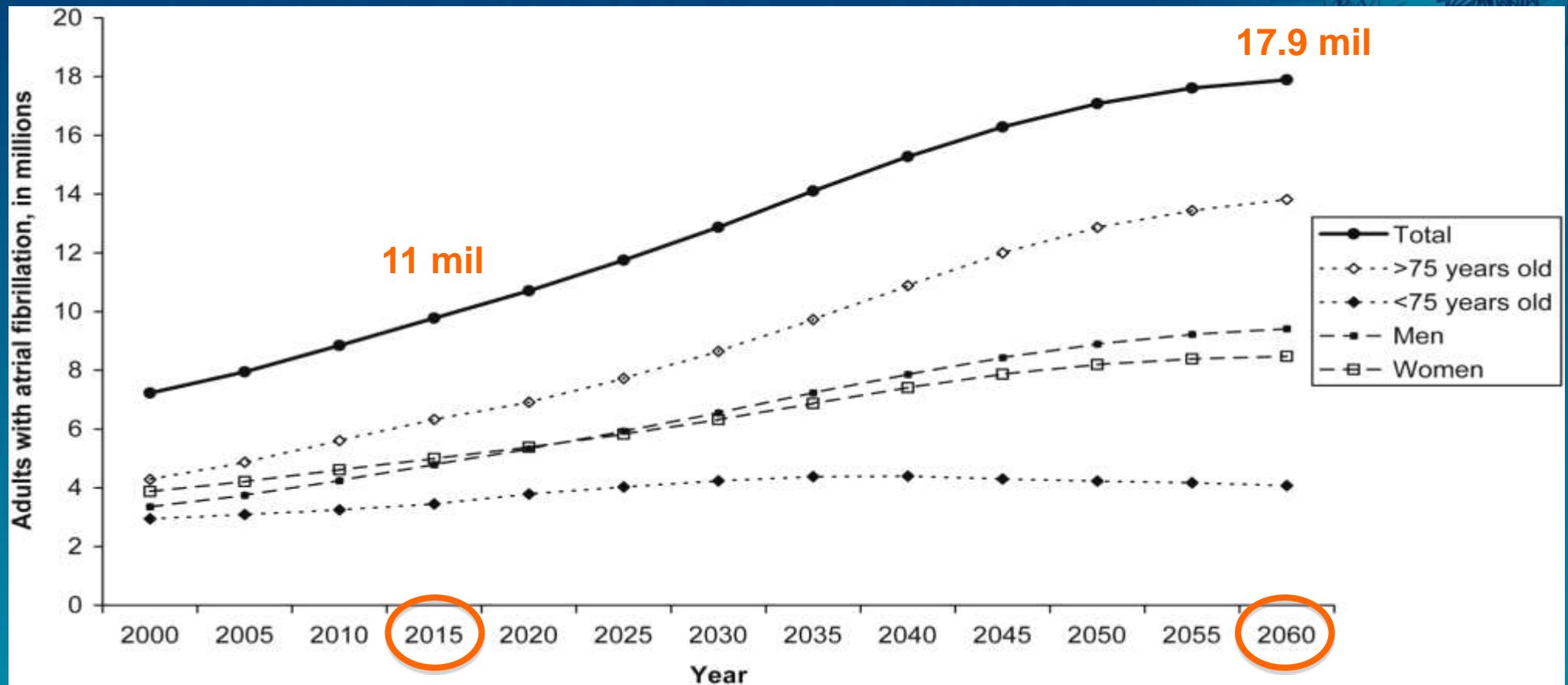


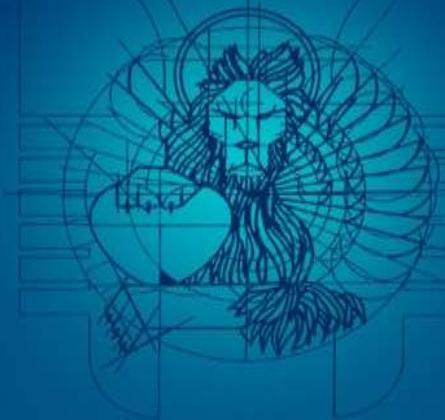
Considerazioni



- ✓ **La FA è una condizione clinica molto diffusa**
e la mortalità legata a questa patologia è in crescita
- ✓ **Se la FA è la responsabile diretta di morte,**
allora l'uso di terapie per sopprimere la FA - pittosto
che l'uso di terapie per prevenirne i sintomi – è da
preferire

Projected number of adults with atrial fibrillation in the European Union between 2000 and 2060



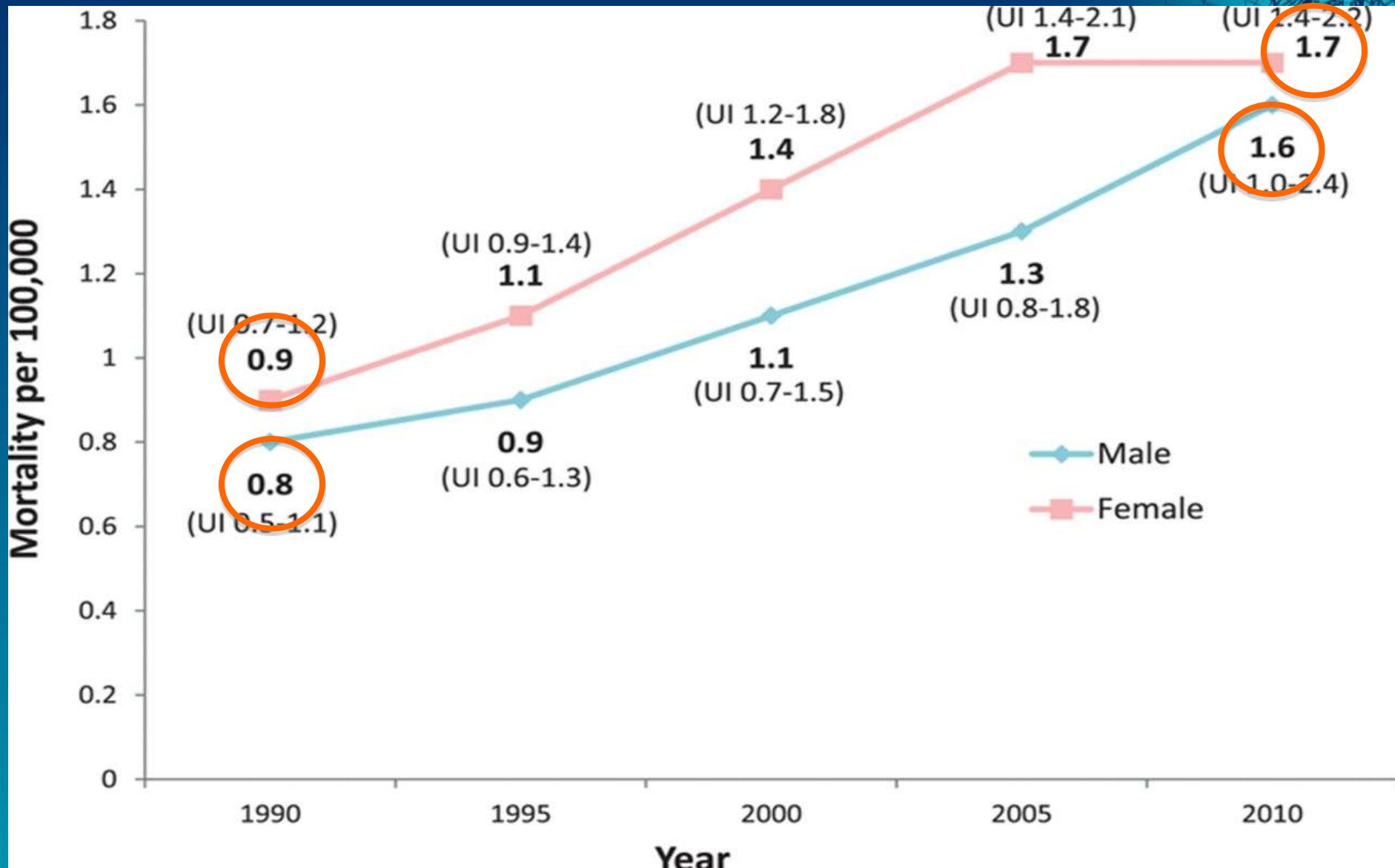


Worldwide Epidemiology of Atrial Fibrillation

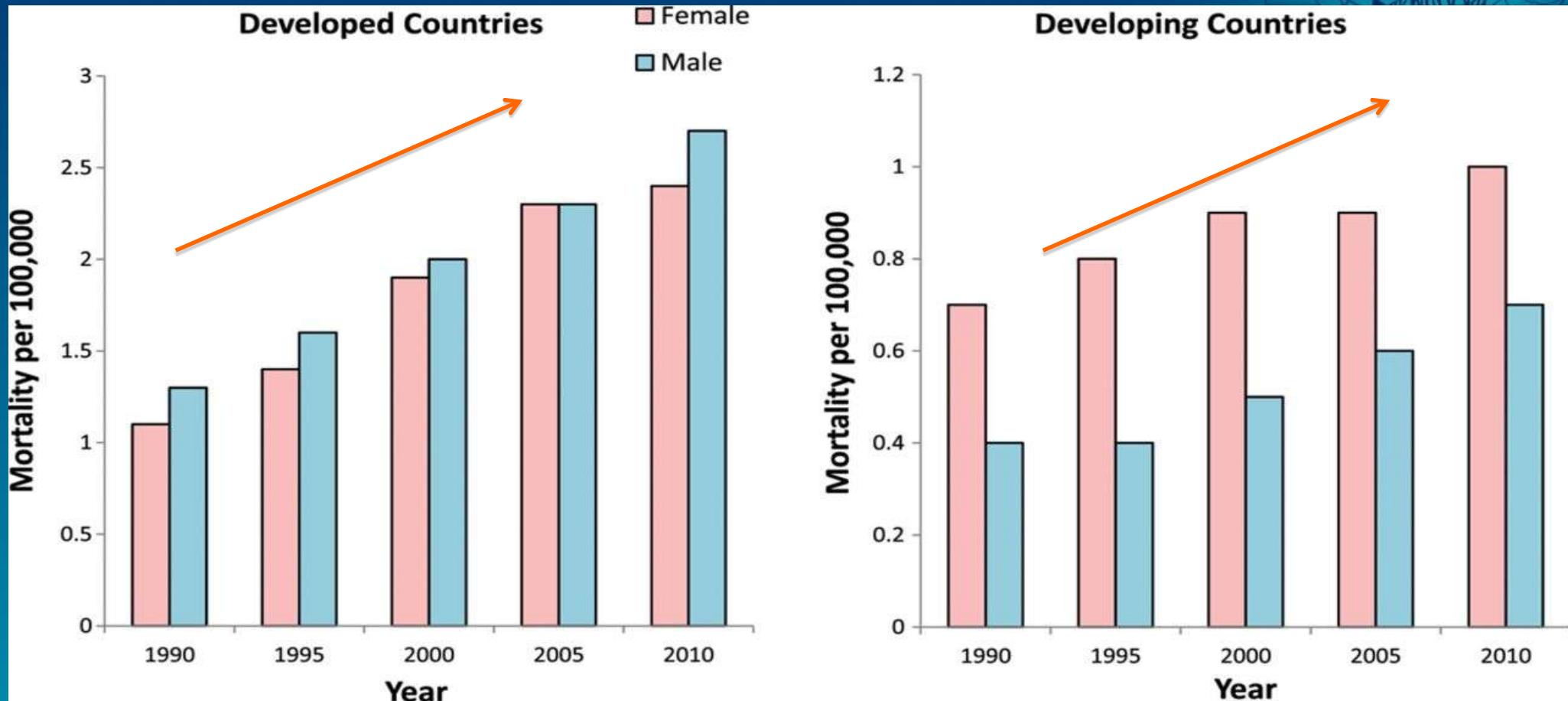
Sumeet S **Chugh**, Rasmus Havmoeller, Kumar Narayanan, David Singh, Michiel Rienstra, Emelia J. Benjamin, Richard F. Gillum, Young-Hoon Kim, John H. McAnulty, Zhi-Jie Zheng, Mohammad H. Forouzanfar, Mohsen Naghavi, George A. Mensah, Majid Ezzati, and Christopher J.L. Murray

Circulation 2014; 129: 837-847

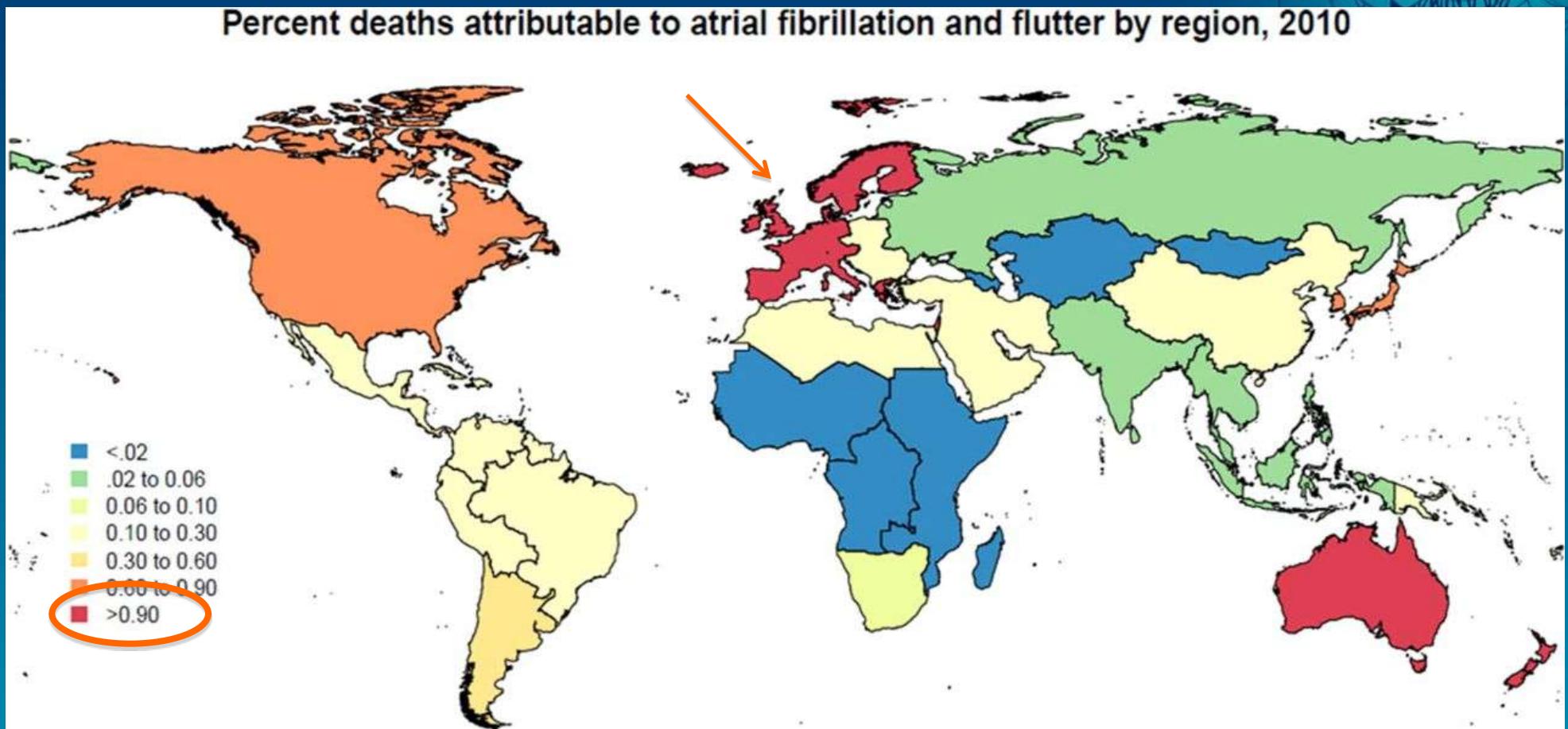
Mortality associated with atrial fibrillation: 1990 to 2010



Mortality associated with atrial fibrillation (AF) stratified by sex and type of region (developed vs developing).



Proportion of global deaths associated with atrial fibrillation in 2010.



Considerazioni



- ✓ La FA è una condizione clinica molto diffusa e la mortalità legata a questa patologia è in crescita
- ✓ Se la FA è la responsabile diretta di morte, allora l'uso di terapie per sopprimere la FA - pittosto che l'uso di terapie per prevenirne i sintomi – è da preferire

Criteri di Hillis x stabilire una causalità



- ✓ Forza dell'associazione
- ✓ Consistenza dell'associazione
- ✓ Gradiente biologico
- ✓ Plausibilità biologica
- ✓ Evidenza sperimentale

Incident AF & Overall Mortality



HR = 1.5 – 2.0

Andersson T et al. Eur Heart J 2013;34:1061-1067



	Smoking			No smoking	
	HR† (95% CI)	p value		HR† (95% CI)	p value
All-cause mortality	1.74 (1.37 to 2.22)	<0.001		1.40 (1.13 to 1.74)	0.002
CVD mortality	1.62 (1.11 to 2.35)	0.01		1.21 (0.90 to 1.62)	0.21
CHD mortality	2.55 (1.45 to 4.50)	0.001		1.24 (0.86 to 1.80)	0.25
Stroke mortality	0.81 (0.41 to 1.61)	0.55		0.96 (0.49 to 1.87)	0.90
Cancer mortality	1.46 (0.95 to 2.24)	0.08		1.53 (0.98 to 2.39)	0.06
Lung cancer	3.39‡ (0.43 to 26.4)	0.24		2.29‡ (1.08 to 4.86)	0.03
Respiratory mortality	3.26 (1.56 to 6.81)	0.002		2.39 (1.15 to 4.97)	0.02

Criteri di Hillis x stabilire una causalità



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Table I Studies examining the relationship between atrial fibrillation and all-cause mortality

Study	Cohort	Adjusted relative risk of death (95% CI)		
Andersson ¹	272 186 incident AF vs. 544 344 controls	<65 years: F 2.15 (1.99–2.32) M 1.76 (1.69–1.84)	65–74 years: F 1.72 (1.67–1.78) M 1.36 (1.33–1.40)	75–85 years: F 1.44 (1.42–1.46) M 1.24 (1.22–1.26)
Ruigómez ⁶	1035 chronic AF vs. 5000 controls		F 2.8 (2.2–3.6) M 2.3 (1.8–3.0)	
Benjamin ⁷	621 incident AF vs. 1242 controls		F 1.5 (1.2–1.8) ^a M 1.1 (0.9–1.4) ^a	
Conen ⁸	1011 incident AF vs. 33 711 controls		F 1.70 (1.30–2.22)	
Haywood ⁹	334 prevalent AF vs. 30,370 controls		2.01 (1.68–2.41)	
Stewart ¹⁰	100 prevalent AF vs. 15 306 controls		F 2.2 (1.5–3.2) M 1.5 (1.2–2.2)	
Miyasaka ¹¹	4618 incident AF vs. general population		2.08 (2.01–2.16)	

AF, atrial fibrillation; CI, confidence interval; F, female; M, male

^aOdds ratio of death by pooled logistic regression amongst those surviving at least 30 days after AF diagnosis.

Considerazione



Nonostante l'aggiustamento per le comorbidità,
tutti gli studi finora eseguiti sono stati osservazionali
e come tali ovviamente non hanno tenuto conto di fattori
potenzialmente confondenti non misurati, quali fibrosi
miocardica, uso di digossina, obesità, apnea notturna
ostruttiva, controllo dell'ipertensione, aderenza del paziente
alla terapia dell'insufficienza cardiaca, ecc.

Criteri di Hillis x stabilire una causalità



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Atrial Fibrillation Patterns and Risks of Subsequent Stroke, Heart Failure, or Death in the Community

Steven A. Lubitz, MD, MPH; Carlee Moser, PhD; Lisa Sullivan, PhD; Michiel Rienstra, MD, PhD; João D. Fontes, MD; Mark L. Villalon, MD; Manju Pai, MD; David D. McManus, MD, ScM; Renate B. Schnabel, MD, MSc; Jared W. Magnani, MD, MSc; Xiaoyan Yin, PhD; Daniel Levy, MD; Michael J. Pencina, PhD; Martin G. Larson, ScD; Patrick T. Ellinor, MD, PhD;* Emelia J. Benjamin, MD, ScM*

J Am Heart Assoc 2013; doi: 10.1161/JAHA.113000126

Table 2. Association Between Early AF Patterns and Death, Heart Failure, and Stroke Among Individuals With Incident AF

	AF Without 2-Year Recurrence	Recurrent AF	Sustained AF					
Total number with specific pattern	63	162	207					
Primary outcome								
Death								
No. of events/person-years	29/431	87/678	141/852					
Adjustment		HR (95% CI)	P	HR (95% CI)	P			
Age and sex	Referent	1.91 (1.25 to 2.90)	0.003	1.99 (1.33 to 2.97)	<0.001			
Multivariable*	Referent	2.04 (1.27 to 3.29)	0.003	2.36 (1.49 to 3.75)	<0.001			
Secondary outcomes								
Heart failure								
No. of events/person-years	12/360	29/401	29/595					
Adjustment		HR (95% CI)	P	HR (95% CI)	P			
Age and sex	Referent	2.08 (1.06 to 4.07)	0.03	1.08 (0.54 to 2.13)	0.84			
Multivariable†	Referent	2.53 (1.19 to 5.38)	0.02	1.23 (0.56 to 2.67)	0.61			
Stroke								
No. of events/person-years	9/352	24/570	22/621					
Adjustment		HR (95% CI)	P	HR (95% CI)	P			
Age and sex	Referent	1.52 (0.70 to 3.27)	0.29	1.15 (0.53 to 2.50)	0.73			
Multivariable*	Referent	1.84 (0.77 to 4.38)	0.17	1.32 (0.55 to 3.18)	0.54			



Risk of Death and Cardiovascular Events in Initially Healthy Women With New-Onset Atrial Fibrillation

David Conen, MD, MPH; Claudia U. Chae, MD, MPH; Robert J. Glynn, ScD; Usha B. Tedrow, MD, MSc; Brendan M. Everett, MD, MPH; Julie E. Buring, ScD; Christine M. Albert, MD, MPH

JAMA. 2011; 305: 2080-2087



Table 4. Risk of Death Among Women With New-Onset Paroxysmal AF **FU = 15.4 years**

Outcome	No Paroxysmal AF (n = 34 066) ^a	Incident Paroxysmal AF (n = 656)
All-cause mortality (n = 1567)		
Events	1539	28
Incidence rate (95% CI) ^b	3.0 (2.9-3.2)	7.2 (4.5-9.8)
Hazard ratio (95% CI)		
Age-adjusted model (n = 34 722)	1 [Reference]	1.52 (1.04-2.22)
Multivariable-adjusted model 1 (n = 33 840) ^c	1 [Reference]	1.44 (0.98-2.11)
Multivariable-adjusted model 2 (n = 33 840) ^d	1 [Reference]	1.18 (0.80-1.73)

Criteri di Hillis x stabilire una causalità



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Plausibili meccanismi di morte in pz con FA

- ✓ Stroke / Eventi Tromboembolici
- ✓ Peggioramento Scompenso Cardiaco

Considerazioni



- ✓ Lo Stroke è responsabile solo di una minoranza di tutte le morti nei pazienti con FA
- ✓ Nello studio AF-CHF il trattamento della FA mediante controllo del ritmo non ha ridotto la mortalità per scompenso cardiaco



Table 4. Causes of Death in the RE-LY Trial

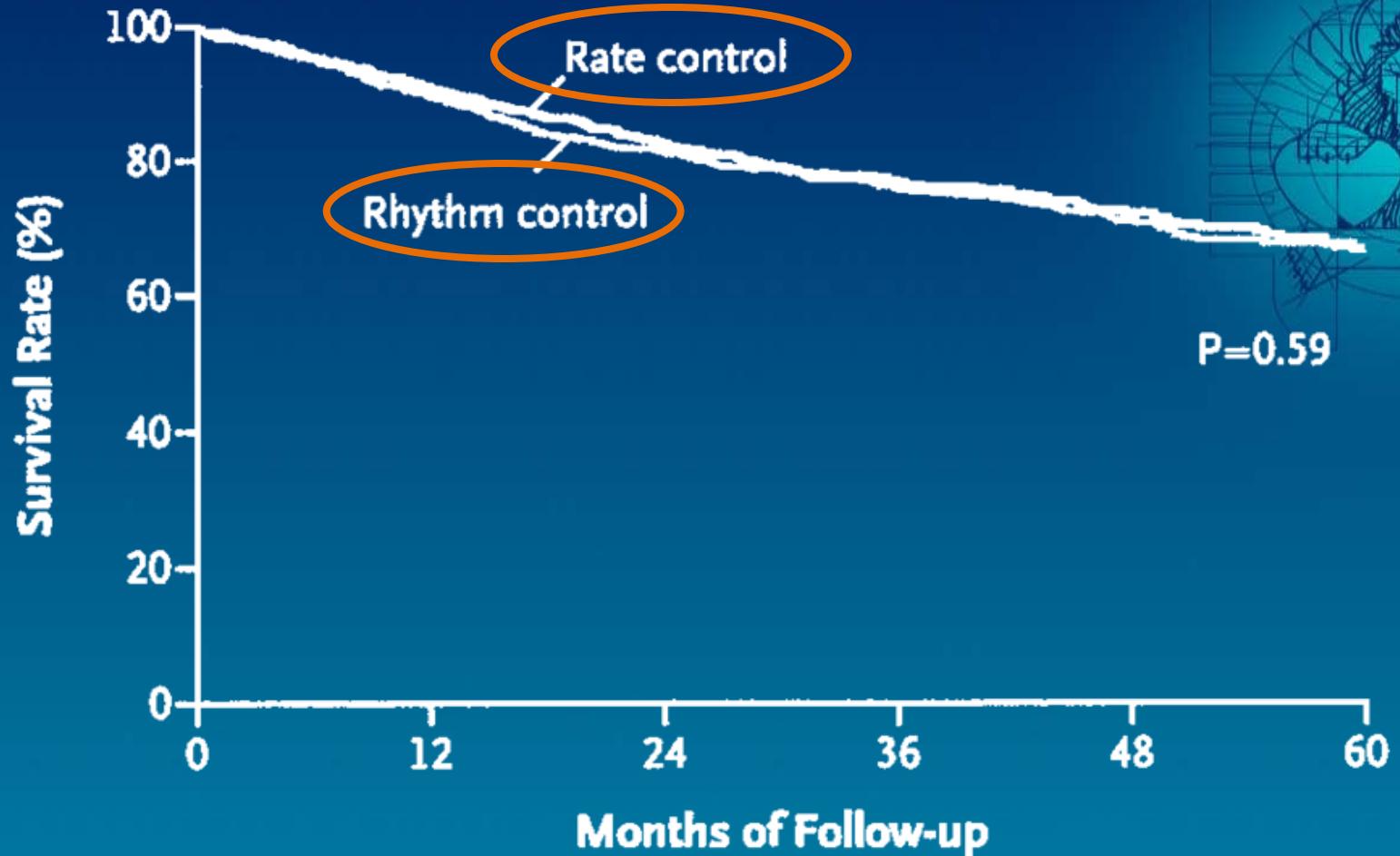
Causes of Death in RE-LY	n	%
Total	1371	100.00
Cardiovascular death	842	61.41
Cardiac	512	37.35
Sudden cardiac death	305	22.25
Progressive heart failure	207	15.10
Vascular	139	10.14
Stroke/peripheral embolism	96	7.00
Hemorrhage	39	2.84
Pulmonary embolism	4	0.29
Other/unknown	191	13.93
Noncardiovascular death	491	35.81
Cancer	191	13.93
Respiratory failure	79	5.76
Trauma	12	0.88
Infection	61	4.45
Other	148	10.80
Undetermined death	38	2.77

RE-LY indicates Randomized Evaluation of Long-Term Anticoagulant Therapy.

Considerazioni



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- ✓ Nello studio AF-CHF il trattamento della FA mediante controllo del ritmo non ha ridotto la mortalità per scompenso cardiaco



No. at Risk

Rhythm control	593	514	378	228	82
Rate control	604	521	381	219	69

Death from cardiovascular cause (primary endpoint)

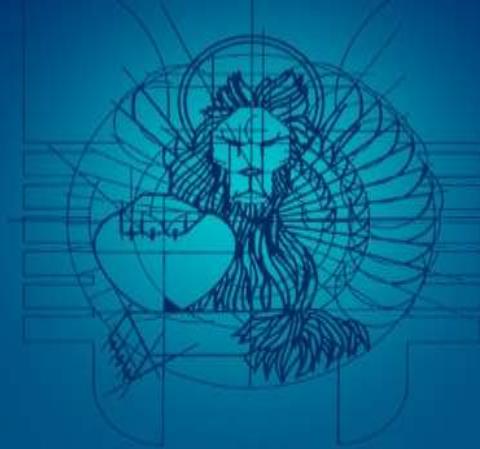
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Trials Clinici Randomizzati

**rappresentano il supporto più forte
all'ipotesi di causalità**



AF Randomized Trials / Rhythm Control vs Rate Control



- ✓ PIAF, Lancet 2000
- ✓ AFFIRM, N Engl J Med 2002
- ✓ RACE, N Engl J Med 2002
- ✓ STAF, JACC 2003
- ✓ HOT- CAFE, Chest 2004
- ✓ AF-CHF, N Engl J Med 2008
- ✓ J-RHYTHM, Circ J 2009

Trial	Rate vs Rhythm Trials		Mean Follow-up	Sinus rhythm (%)	Warfarin (%)	Thrombo-embolic complications %	Mortality %
	n	Age, y					
PIAF	12m						
Rate control	125	61		10	100	NR	1.6
Rhythm control	127	60		56	100	NR	1.6
AFFIRM	42m						
Rate control	2027	70		35	85	6	21
Rhythm control	2033	70		63	70	7.5	24
RACE	27m						
Rate control	256	68		10	96-99	5.5	17
Rhythm control	266	68		39	86-99	7.9	13
STAF	22m						
Rate control	100	65		0	NR	0.6	5.0
Rhythm control	100	66		NR	NR	3.1	2.5
Hot Cafe	20m						
Rate control	101	61		NR	74	1	1.0
Rhythm control	104	60		63.5	NR	2.9	2.9
AF-CHF	37m						
Rate control	694	67		30-41	92	4	33
Rhythm control	682	66		73	88	3	32
J-RHYTHM	19m						
Rate control	404	64.5		44	59	2.9	0.7
Rhythm control	419	65		73	60	2.3	1.0

Modified from Falk, RH. *Circulation* (2005) 111: 3141



Relationships Between Sinus Rhythm, Treatment, and Survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study

The AFFIRM Investigators*

Circulation 2004; 109: 1509-13

TABLE 3. Covariates Significantly Associated With Survival Results With Echocardiographic Data Excluded

Covariate	P	HR	Lower	Upper	HR: 99% Confidence Limits
Age at enrollment*	<0.0001	1.06	1.04	1.08	
Coronary artery disease	<0.0001	1.65	1.31	2.07	
Congestive heart failure	<0.0001	1.83	1.45	2.32	
Diabetes	<0.0001	1.56	1.22	2.00	
Stroke or transient ischemic attack	<0.0001	1.54	1.17	2.05	
Smoking	<0.0001	1.75	1.29	2.39	
First episode of atrial fibrillation	0.0067	1.27	1.01	1.58	
Sinus rhythm	<0.0001	0.54	0.42	0.70	
Warfarin use	<0.0001	0.47	0.36	0.61	
Digoxin use	<0.0001	1.50	1.18	1.89	
Rhythm-control drug use	0.0005	1.41	1.10	1.83	

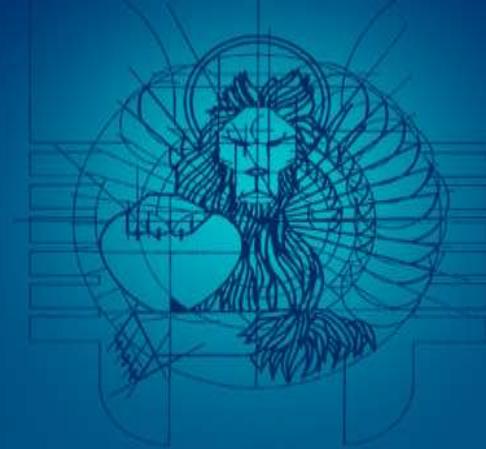
Table 2 Modified Hill criteria² for establishing causality

Criterion	Evidence to support AF causing excess mortality
Strength of association	Moderate
Consistency of association	Strong
Biological gradient	Moderate
Biological plausibility	Moderate
Experimental evidence	Against

AF, atrial fibrillation.

Conclusioni

Evidenze consistenti indicano che la FA è associata ad un' aumentata mortalità, ma quanto questo sia dovuto a un effetto diretto della FA e quanto, invece, sia causato dalle numerose comorbidità rimane ancora un puzzle da risolvere



Clinical approach to atrial fibrillation

