

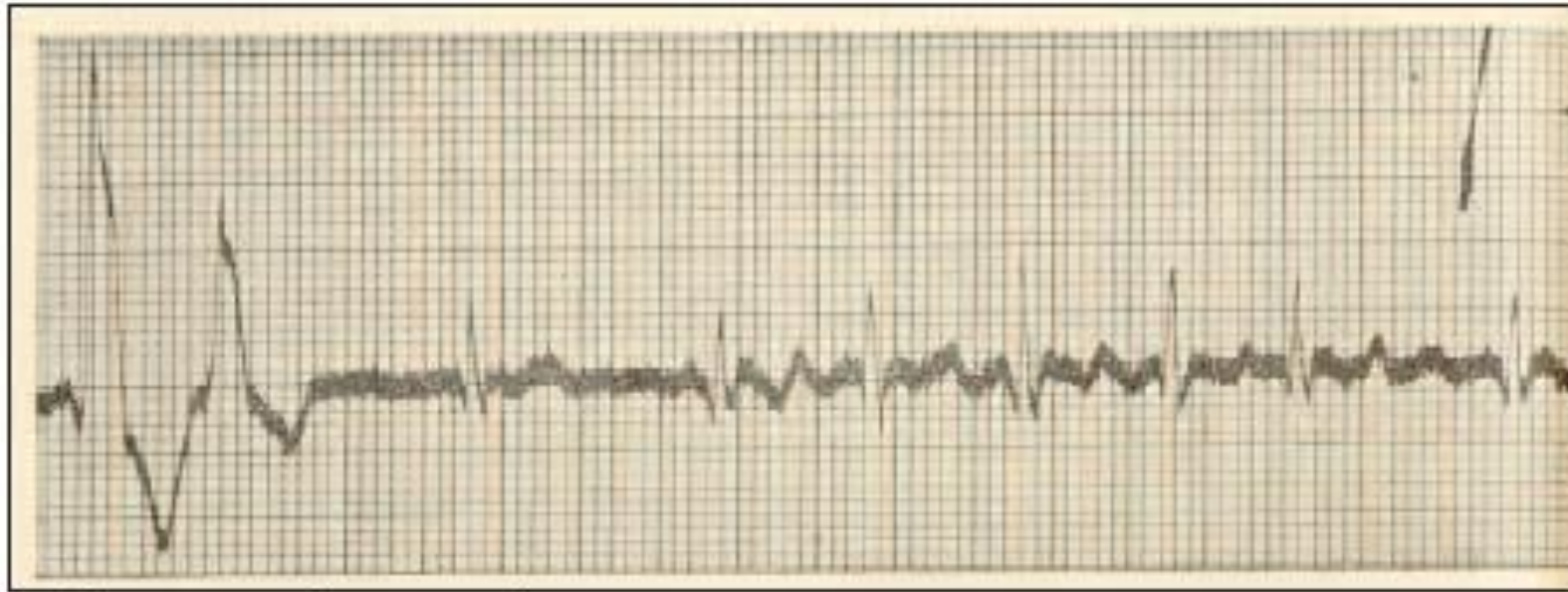
# Fibrillazione atriale: vecchia malattia con giovane storia

**VITTORIO PENGO**  
**UNIVERSITÀ DI PADOVA**  
**FONDAZIONE ARIANNA BOLOGNA**

# Atrial Fibrillation

Atrial fibrillation (AF) is a supraventricular arrhythmia characterized electrocardiographically by low-amplitude baseline oscillations (fibrillatory or f waves) and an irregularly irregular ventricular rhythm.

The f waves have a rate of 300 to 600 min and are variable in amplitude, shape,  
and timing.

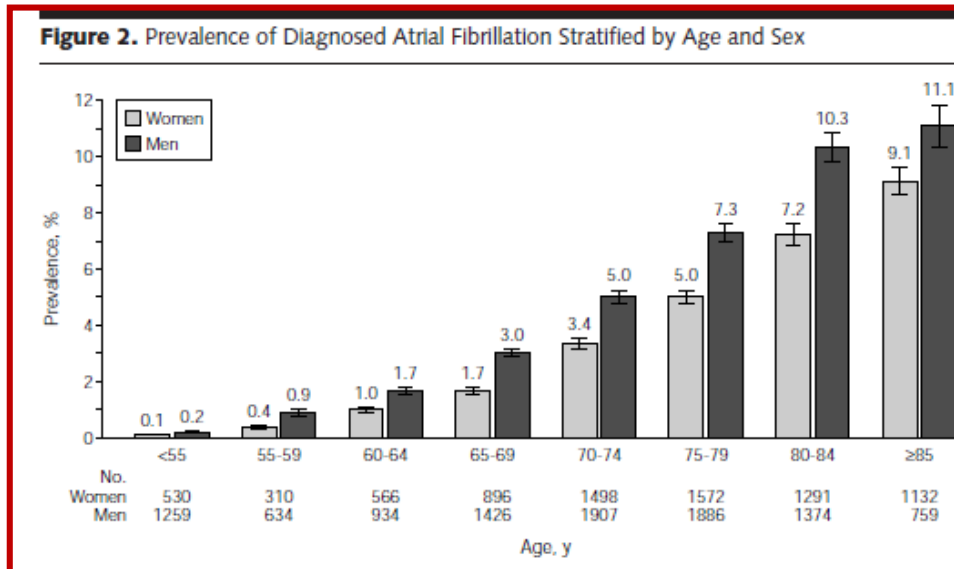


"Pulsus Inaequalis et Irregularis."

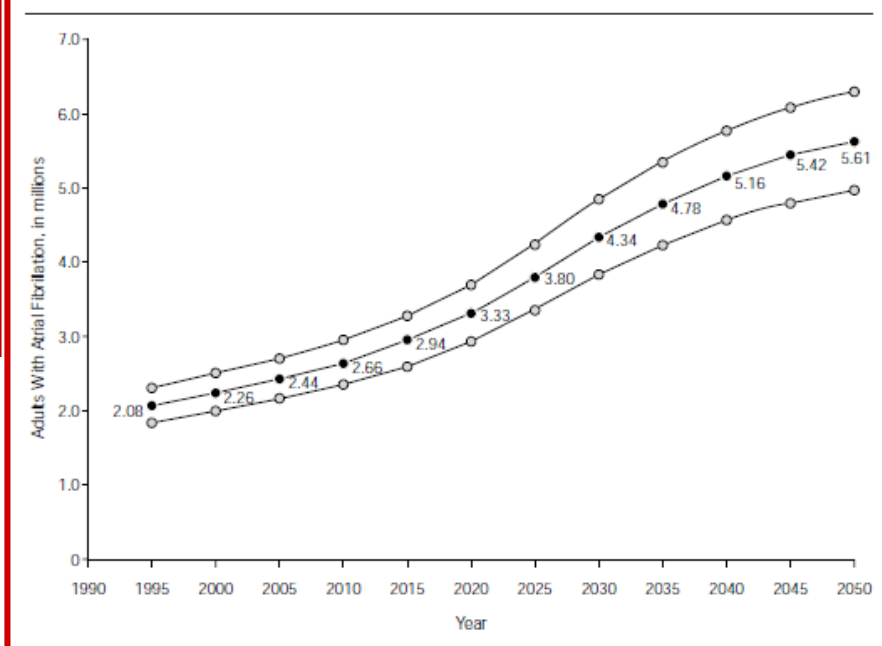
*Einthoven W*  
*Le télécardiogramme.*  
*Arch Int Physiol 1906;4:132-64.*

# EPIDEMIOLOGIA

- Most common arrhythmia in adults (1-2%)
- Rate and incidence increase with ageing aumentano



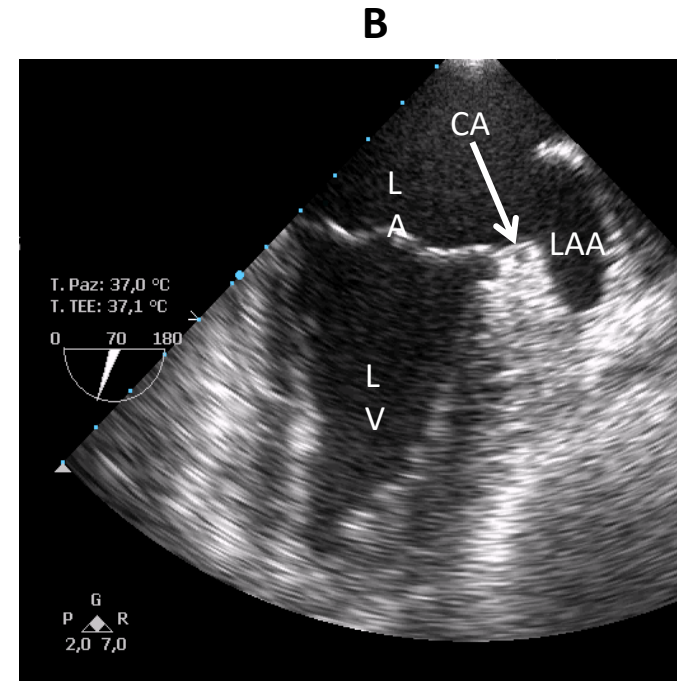
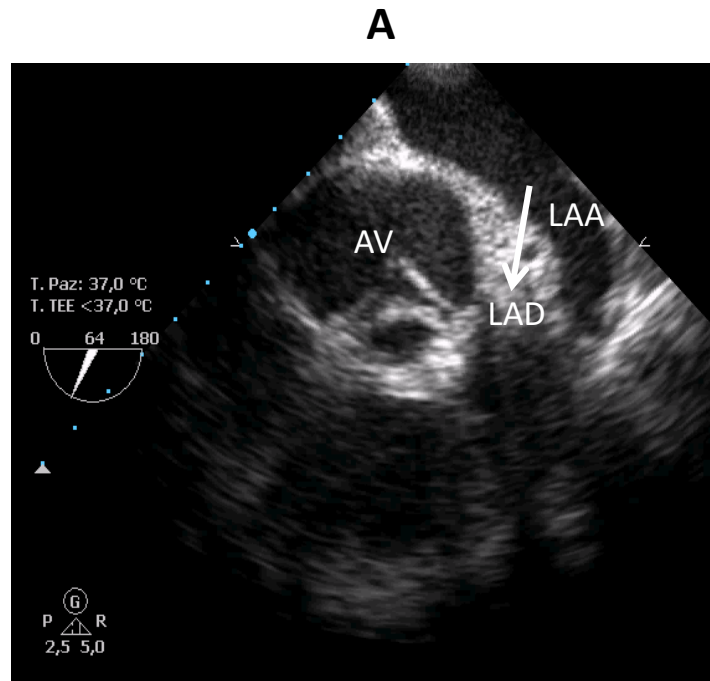
**Figure 3.** Projected Number of Adults With Atrial Fibrillation in the United States Between 1995 and 2050



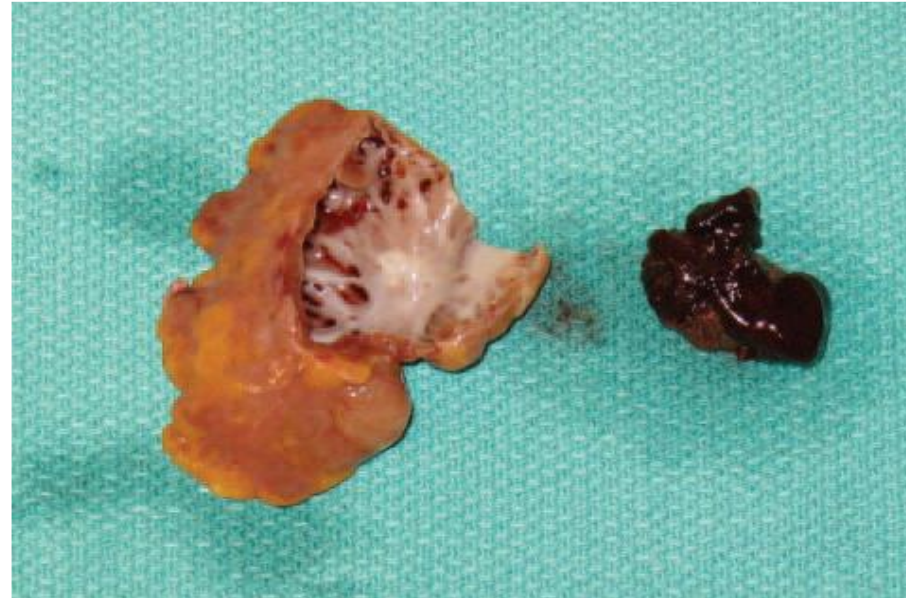
# Atrial Fibrillation: thrombosis burden

- AF is associated with an approximately fivefold increase in the risk for stroke and a two-fold increase in the risk for all-cause mortality.
- AF is also associated with the development of heart failure.

# Transesophageal Echocardiography

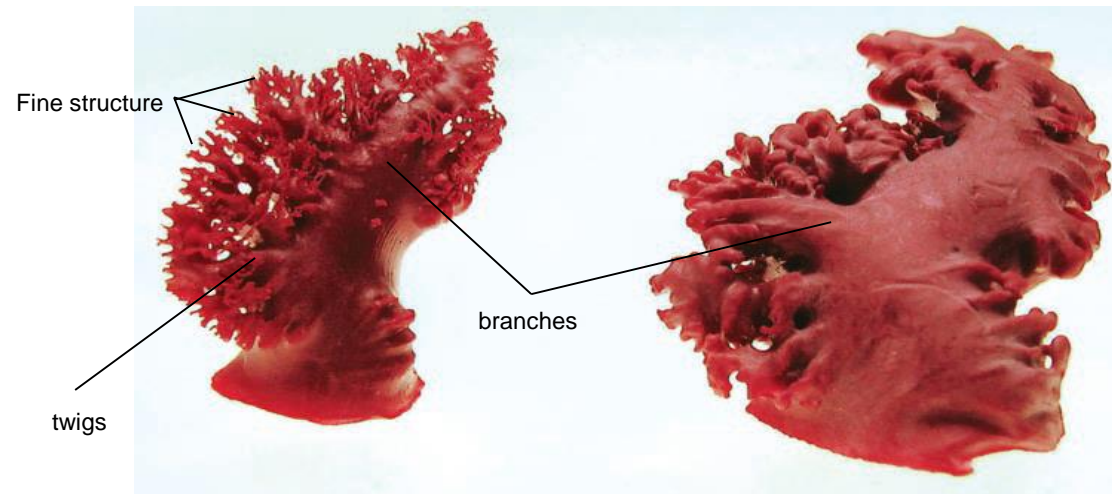


Excised left atrial appendage with thrombus extracted from within



*Circulation* 2009;120:1927-1932

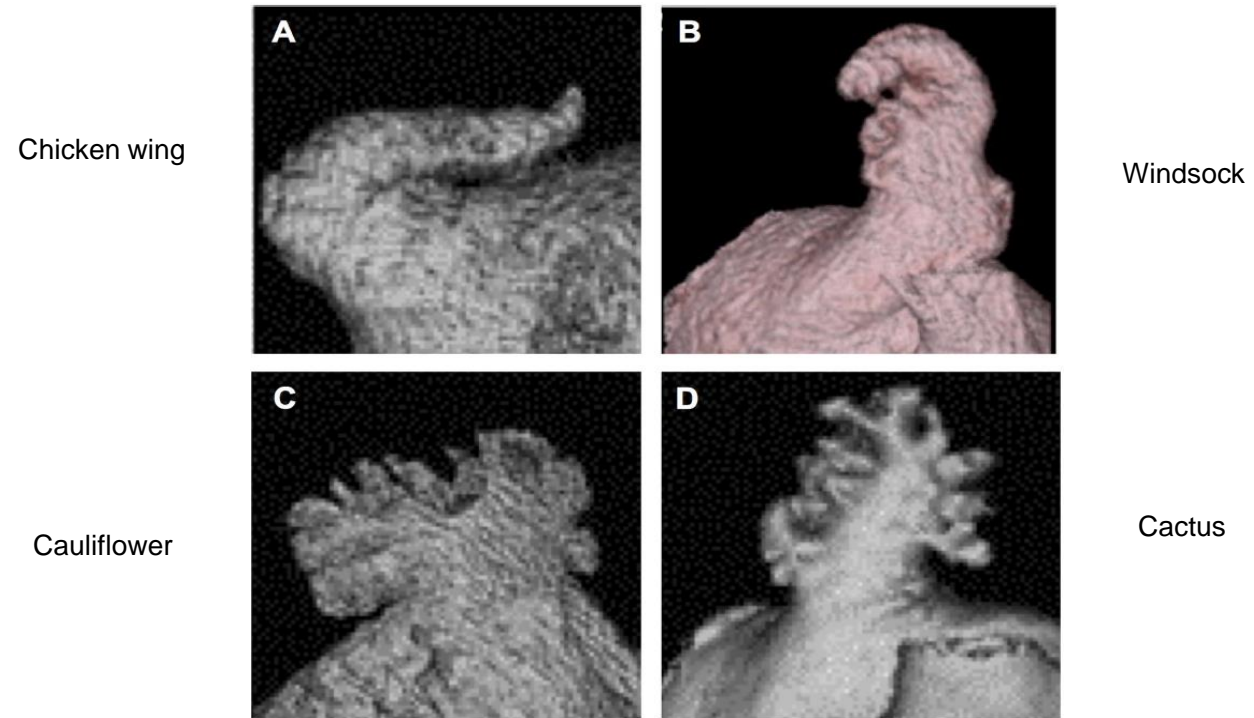
## LAA casts



Postmortem LAA casts. The cast on the left side is from a 52-year-old man who had antemortem sinus rhythm. The cast on the right side is from a 76-year-old woman who had antemortem atrial fibrillation.



Morfology classification of LAA and different risk of thrombus formation



# Prevention of thrombus formation

# **Atrial fibrillation--a review of course and prognosis.**

Petersen P, Godtfredsen J.

Acta Med Scand. 1984;216(1):5-9.

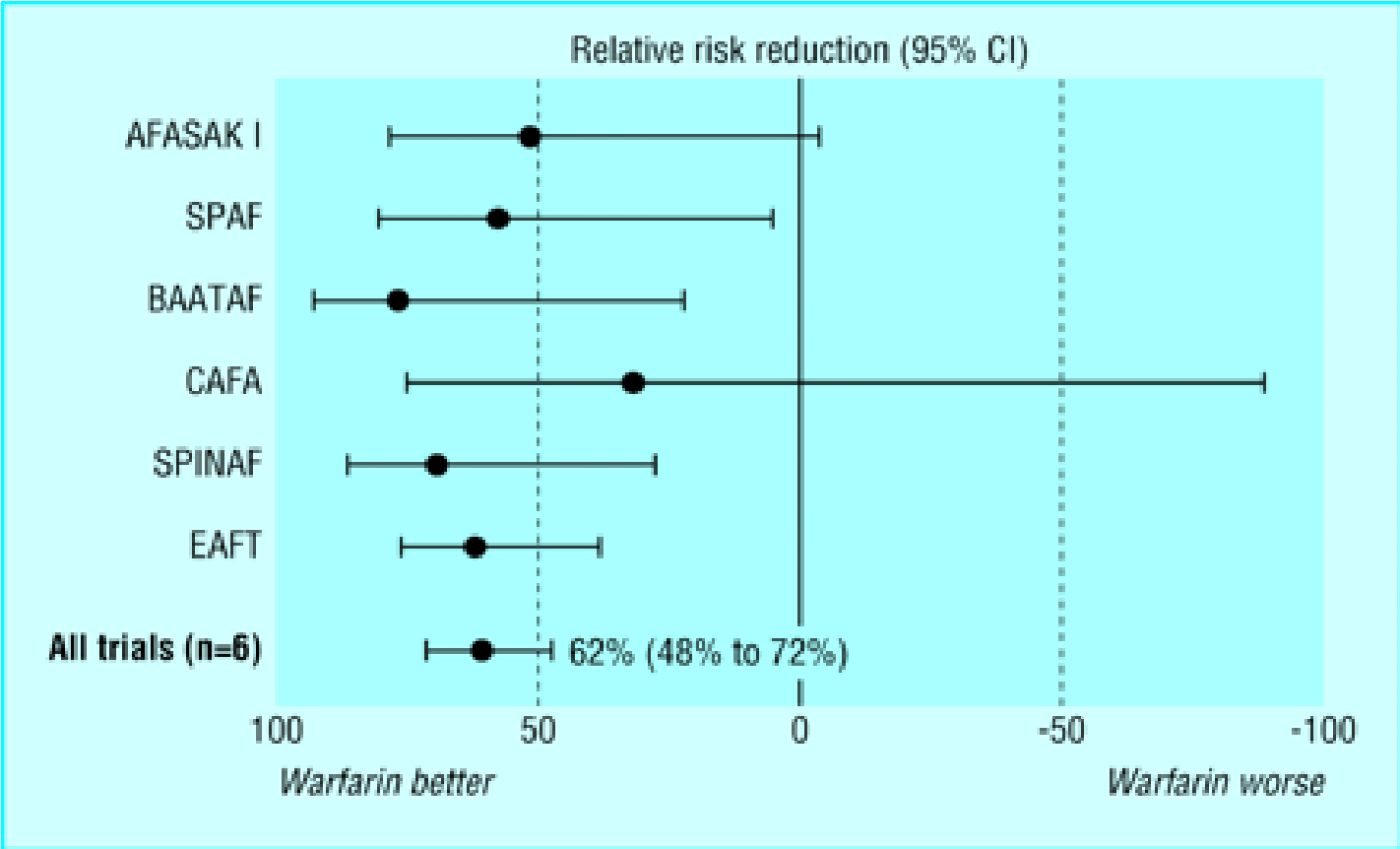
## **Abstract**

Four recent major studies concerning the prognosis in atrial fibrillation (AF) are reviewed. The one-year mortality ranged from 16.0 to 0.2%, highest in elderly, hospitalized patients with chronic AF and lowest in young individuals with paroxysmal AF without other heart disease. The recognized clinical impression that the prognosis in AF is determined by age, type of AF and clinical status is thus confirmed. In three studies, however, the prognosis in lone atrial fibrillation seemed to be poorer than previously thought.

**The overall rate of thromboembolic complications in AF was about 25% in several studies.**

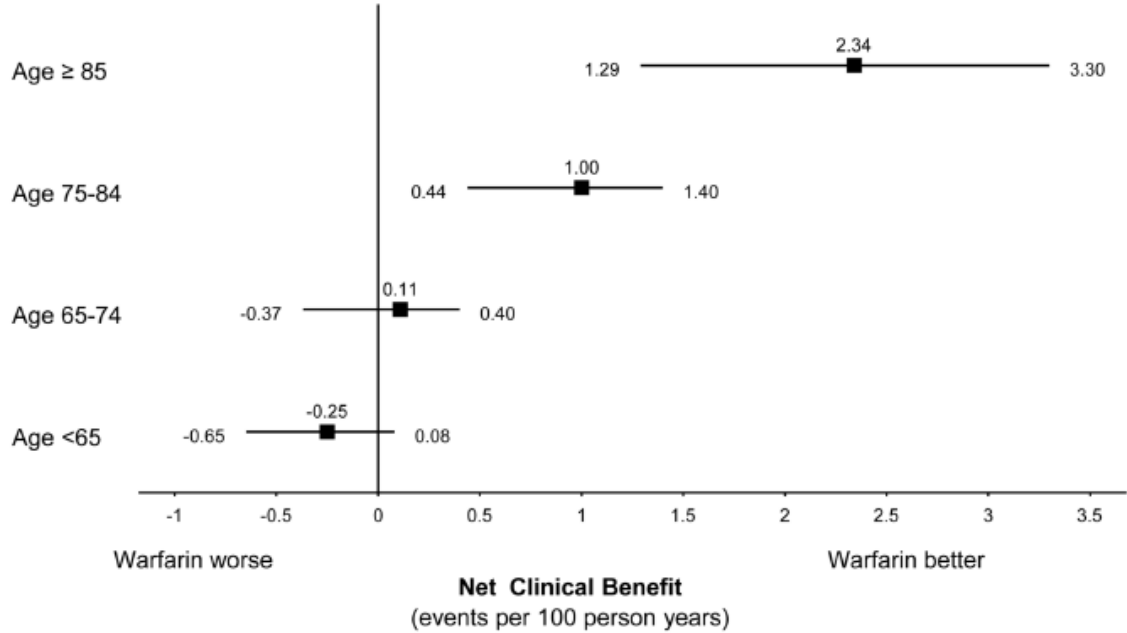
**The effectiveness of coumarin drugs in the prophylaxis of these complications is not proved, and the time has come to subject them to more careful clinical investigation.**

Meta-analysis comparing warfarin with placebo (six trials)



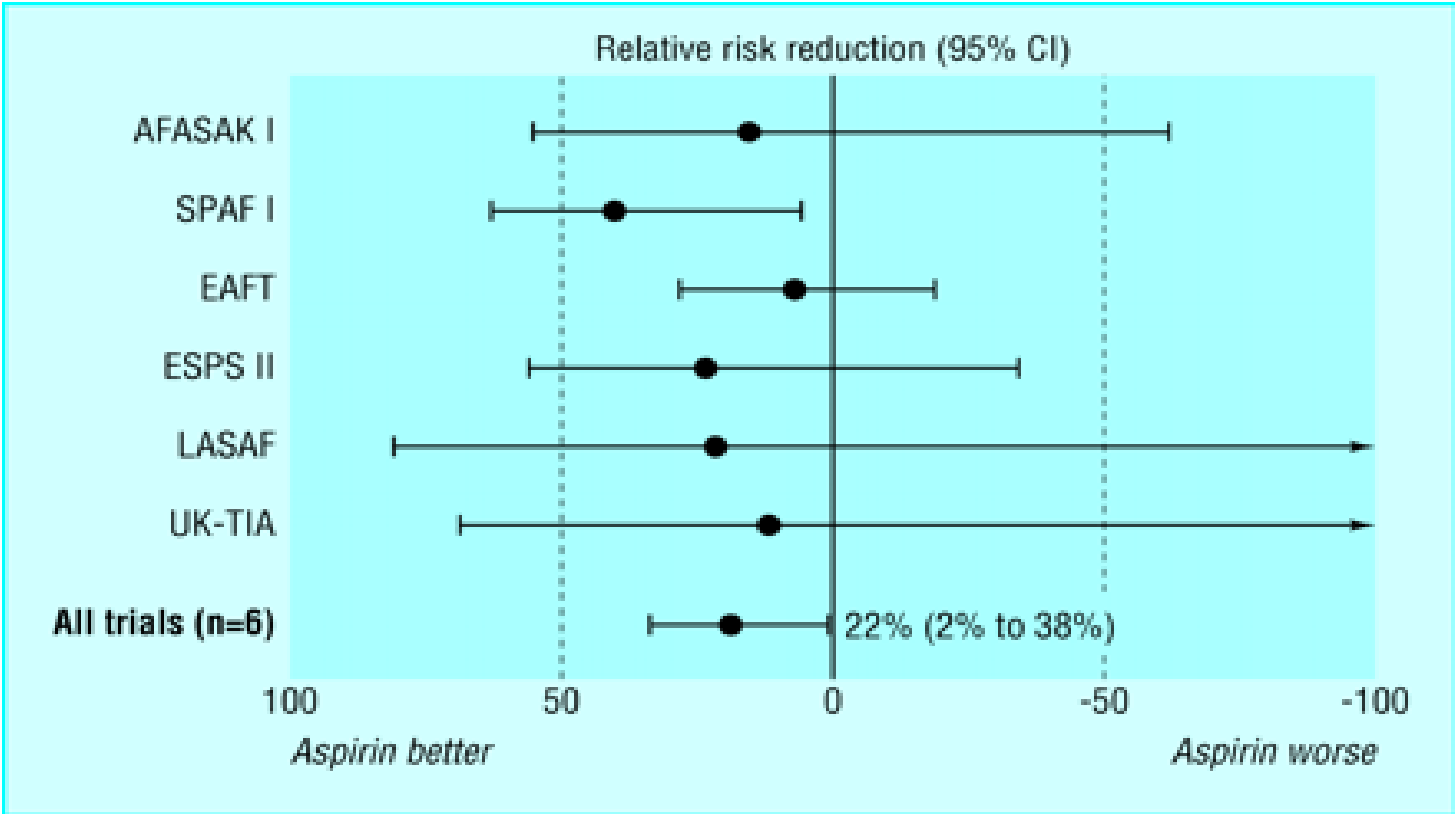
Hart RG, Ann Intern Med 1999

# Net clinical benefit of warfarin in the elderly patients



Singer DE Ann Intern Med. 2009;151:297-305.

# Mata-analysis comparing aspirin with placebo (five trials)



Hart RG, Ann Intern Med 1999

# Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial

*Jonathan Mant, FD Richard Hobbs, Kate Fletcher, Andrea Roalfe, David Fitzmaurice, Gregory YH Lip, Ellen Murray, on behalf of the BAFTA investigators\* and the Midland Research Practices Network (MidReC)\**

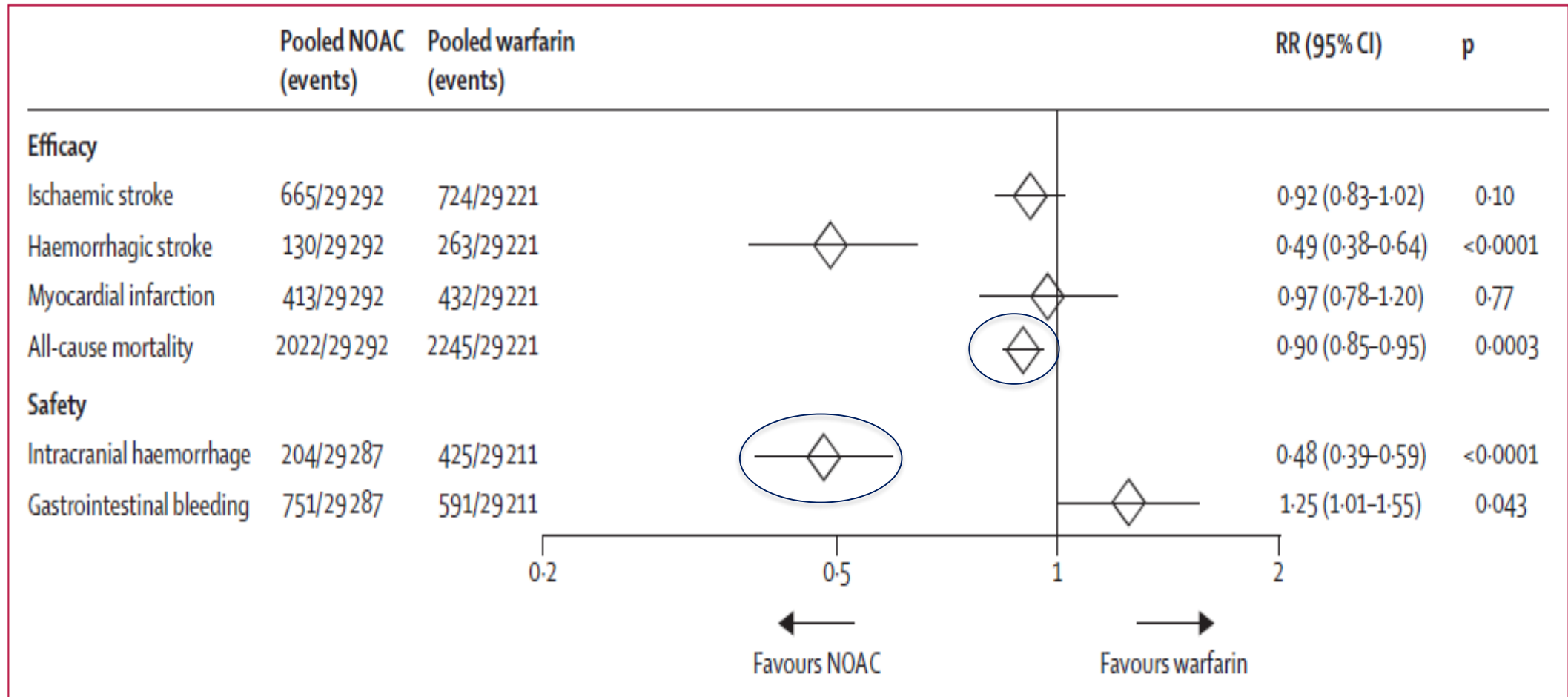
Lancet 2007; 370: 493–503

# Summary

- Do not use aspirin for stroke prevention in AF
- Warfarin is especially beneficial in elderly patients with AF



# Non-vitamin K antagonist Oral Anticoagulants





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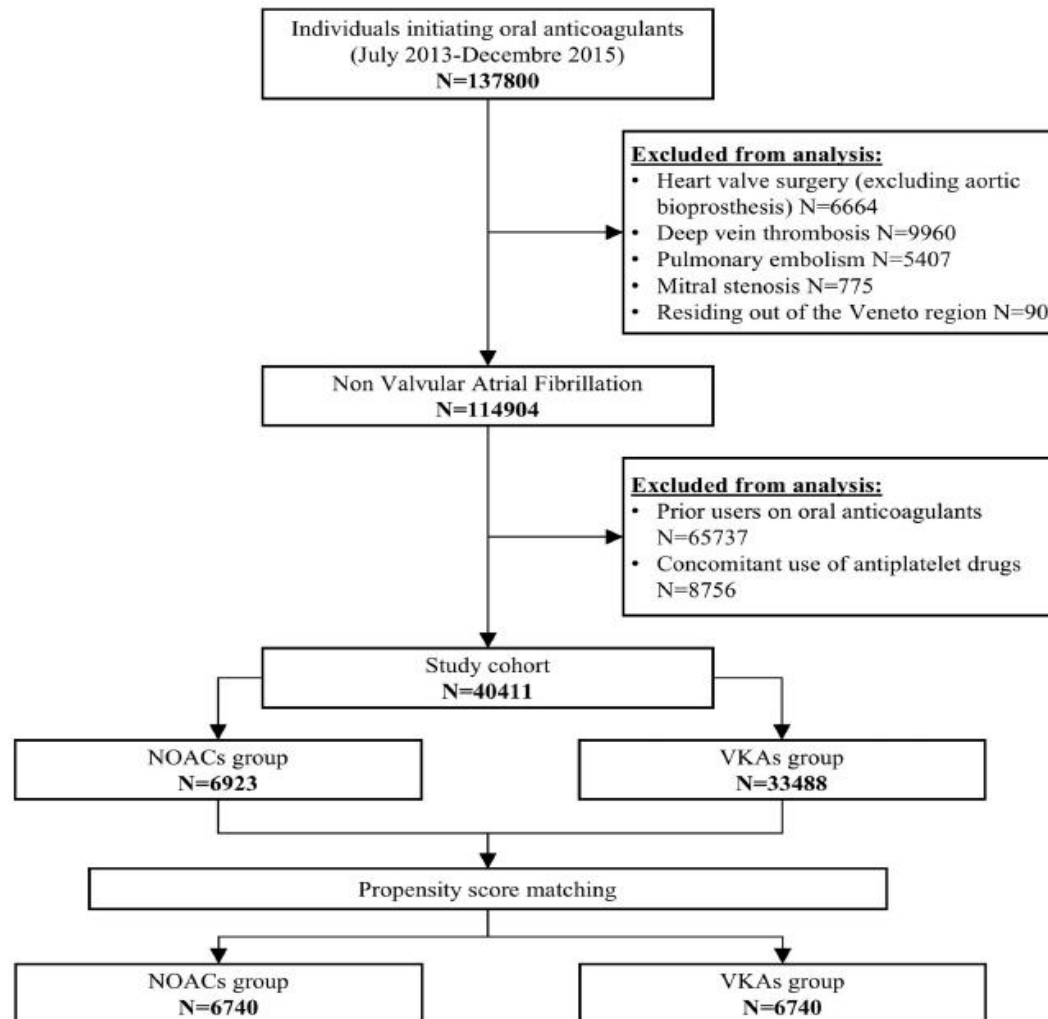


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Effectiveness and safety of oral anticoagulation with non-vitamin K  
antagonists compared to well-managed vitamin K antagonists in  
naïve patients with non-valvular atrial fibrillation:  
Propensity score matched cohort study

Gentian Denas , Nicola Gennaro , Eliana Ferroni , Ugo Fedeli , Mario Saugo, Giacomo Zoppellaro ,  
Seena Padayattil Jose, Giorgio Costa, Maria Chiara Corti, Margherita Andretta, Vittorio Pengo,\*  
a Cardiology Clinic, Department of Cardiac, Thoracic and Vascular Sciences, Padua University Hospital  
b Epidemiological Department (SER), Veneto Region, Padua, Italy  
c Unified Pharmaceutical Coordination Centre (CRUF), Veneto Region, Venice, Italy

*Int J Cardiol. 2017 Dec 15;249:198-203*

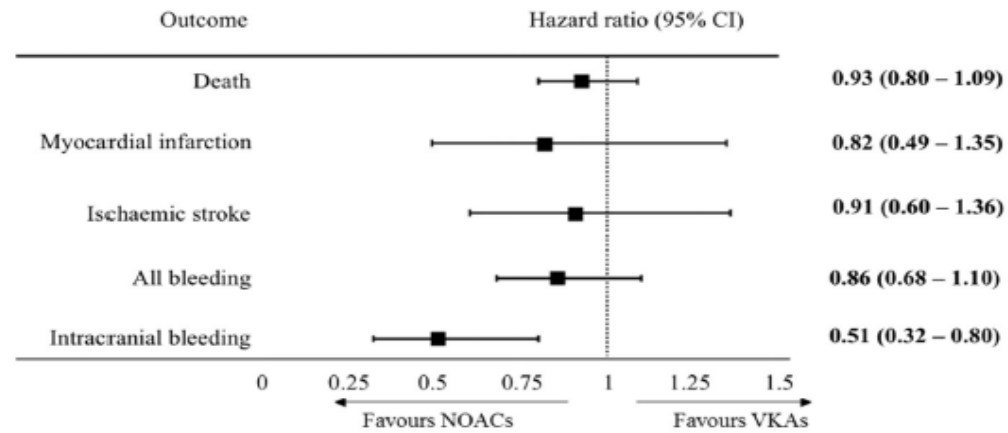


Baseline demographics and clinical characteristics of study subjects treated with NOACs or VKAs (propensity score 1:1 match).

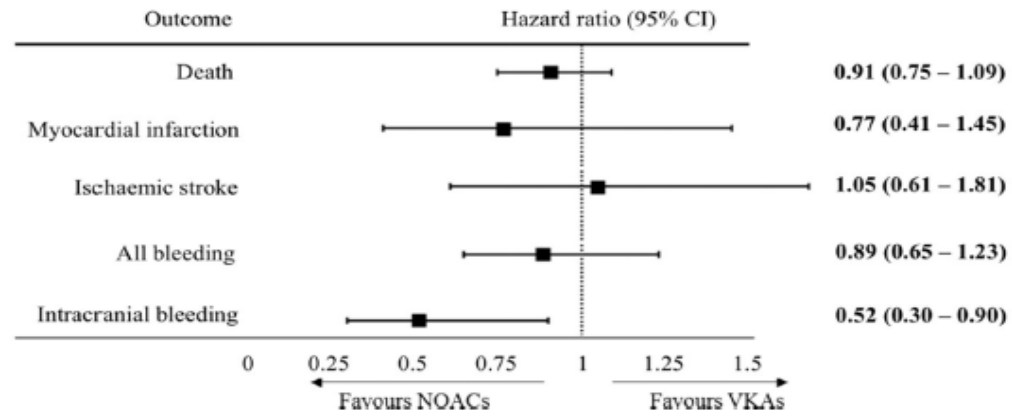
	All study subjects			Propensity score-matched		
	NOAC (n = 6923)	VKA (n = 33,488)	P value	NOAC (n = 6740)	VKA (n = 6740)	P value
Subjects no.	6923	33,488		6740	6740	
Gender						
Male	47.3%	52.2%	<0.001	47.9%	48.2%	0.809
Female	52.7%	47.8%		52.1%	51.8%	
Age: mean (SE)	75.3 (0.14)	74.3 (0.06)	<0.001	75.2	75.1	0.491
Age groups						
<65 yrs	14.8%	15.8%	<0.001	15.1%	15.1%	0.987
65–74 yrs	24.5%	26.8%		24.7%	24.6%	
75–84 yrs	39.3%	41.0%		39.5%	39.5%	
85 + yrs	21.3%	16.4%		20.7%	20.8%	
Risk scores at baseline						
CHA <sub>2</sub> DS <sub>2</sub> VASc mean (SD)	3.23 (1.45)	3.05 (1.42)	<0.001	3.20 (1.45)	3.19 (1.45)	0.7
HAS-BED mean (SD)	2.36 (1.10)	2.19 (1.03)	<0.001	2.33 (1.09)	2.32 (1.09)	0.12
Comorbidities						
Congestive heart failure	9.8%	11.5%	<0.001	9.9%	10.1%	0.646
Hypertension	73.0%	73.1%	0.812	72.8%	72.3%	0.512
Stroke/TIA/thromboembolism	22.5%	9.9%	<0.001	20.5%	20.1%	0.492
Myocardial infarction	2.2%	2.3%	0.808	2.2%	2.3%	0.485
Peripheral artery disease	1.4%	1.8%	0.046	1.5%	1.4%	0.512
Diabetes	16.2%	17.6%	<0.001	16.1%	16.6%	0.456
Cancer	9.4%	9.5%	0.652	9.4%	9.5%	0.791
Chronic renal disease	2.5%	4.3%	<0.001	2.6%	2.7%	0.591
Chronic liver disease	1.4%	1.3%	0.390	1.4%	1.3%	0.501
History of bleeding	3.5%	2.1%	<0.001	3.1%	3.1%	0.961

NOACs: pazienti più vecchi, più femmine, CHADSVASC più alto soprattutto per pregresso stroke, Più storia di sanguinamenti, meno scompenso cardiaco, meno insufficienza renale

**As treated analysis: stratification by propensity score**



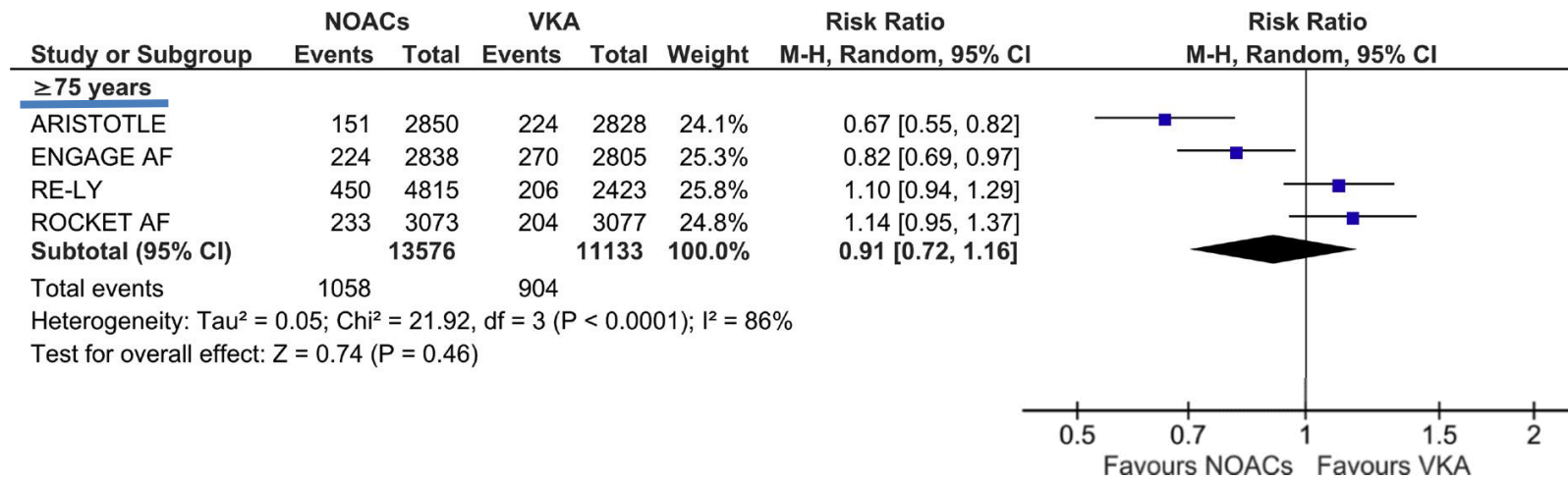
**As treated analysis: one-to-one matching by propensity score**



# Conclusioni

- I NOACs vengono preferenzialmente prescritti a pazienti più anziani con pregresso stroke e storia di sanguinamenti (sono ritenuti più sicuri)
- I risultati sia della analisi *intention to treat* (efficacia in termini di salute pubblica) che quella *as treated* (efficacia in base alla aderenza) sono favorevoli ai NOACs nonostante il buon controllo dell'anticoagulazione nel gruppo warfarin.

## Major bleeding in elderly patients (≥75) with NVAF enrolled in registration studies

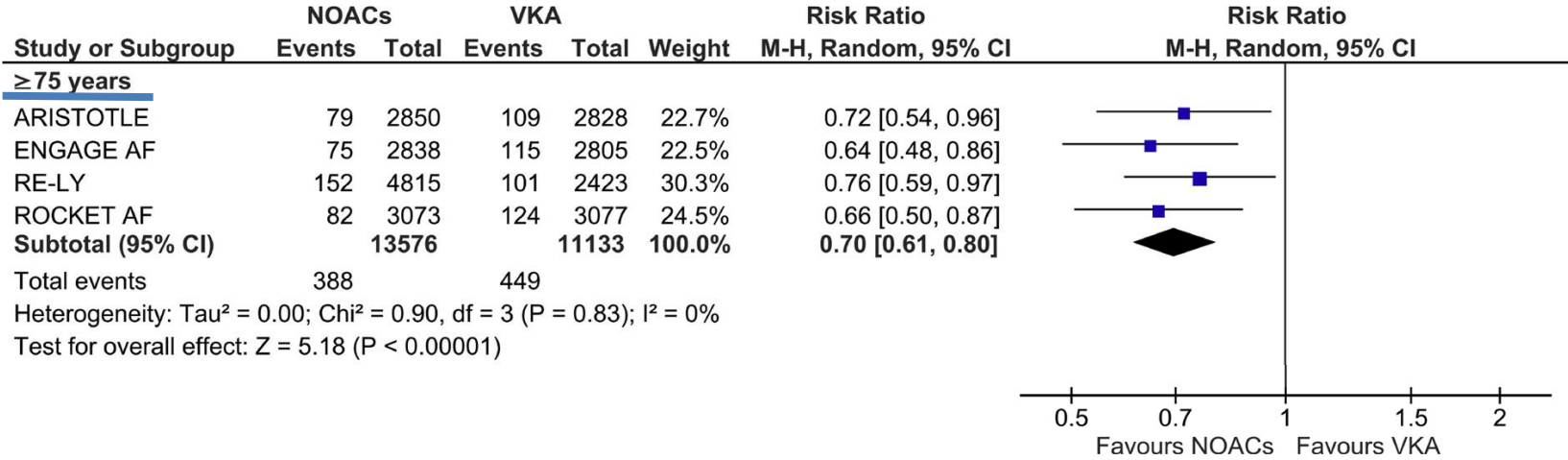


# Efficacy and safety of edoxaban according to age classes





# Stroke and systemic embolism in elderly (≥75) pts with NVAF enrolled in registration studies





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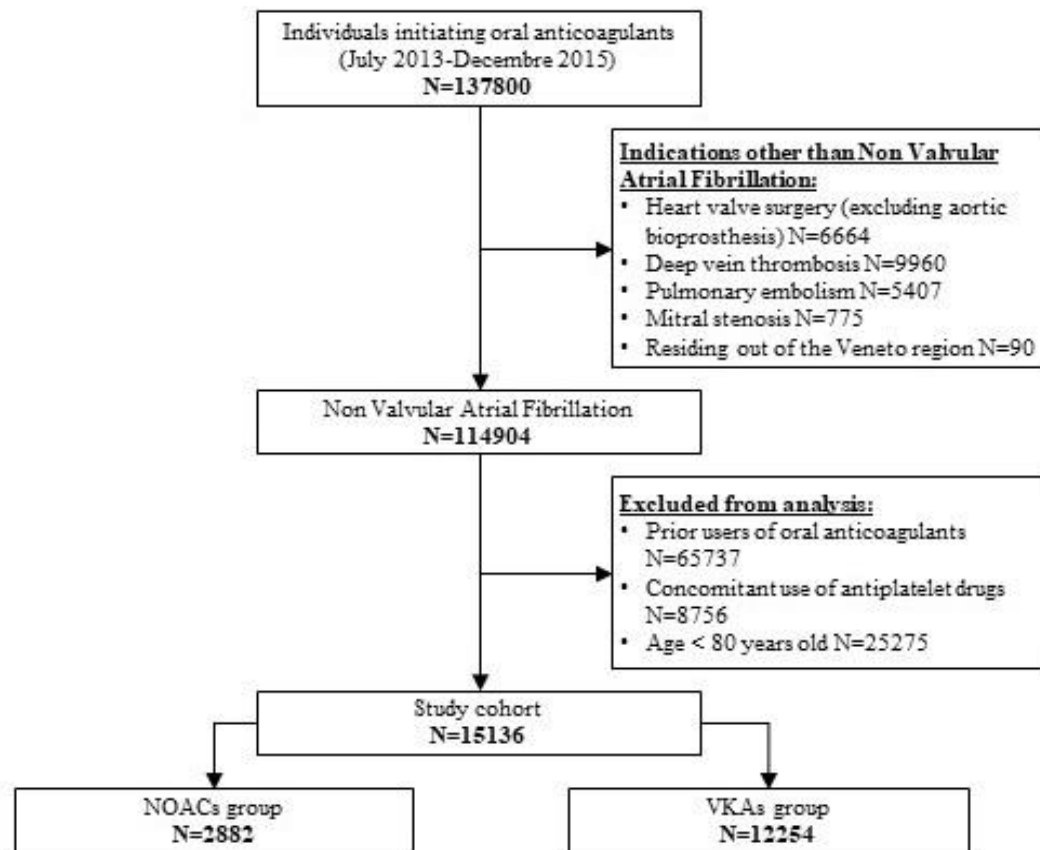


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## Different safety profiles of oral anticoagulants in very elderly non-valvular atrial fibrillation patients. A retrospective propensity score matched cohort study.

Giacomo Zoppellaro, Luca Zanella, Gentian Denas , Nicola Gennaro , Eliana Ferroni , Ugo Fedeli ,  
Seena Padayattil Jose, Giorgio Costa, Maria Chiara Corti, Margherita Andretta, Vittorio Pengo,\*  
a Cardiology Clinic, Department of Cardiac, Thoracic and Vascular Sciences, Padua University Hospital  
b Epidemiological Department (SER), Veneto Region, Padua, Italy  
c Unified Pharmaceutical Coordination Centre (CRUF), Veneto Region, Venice, Italy

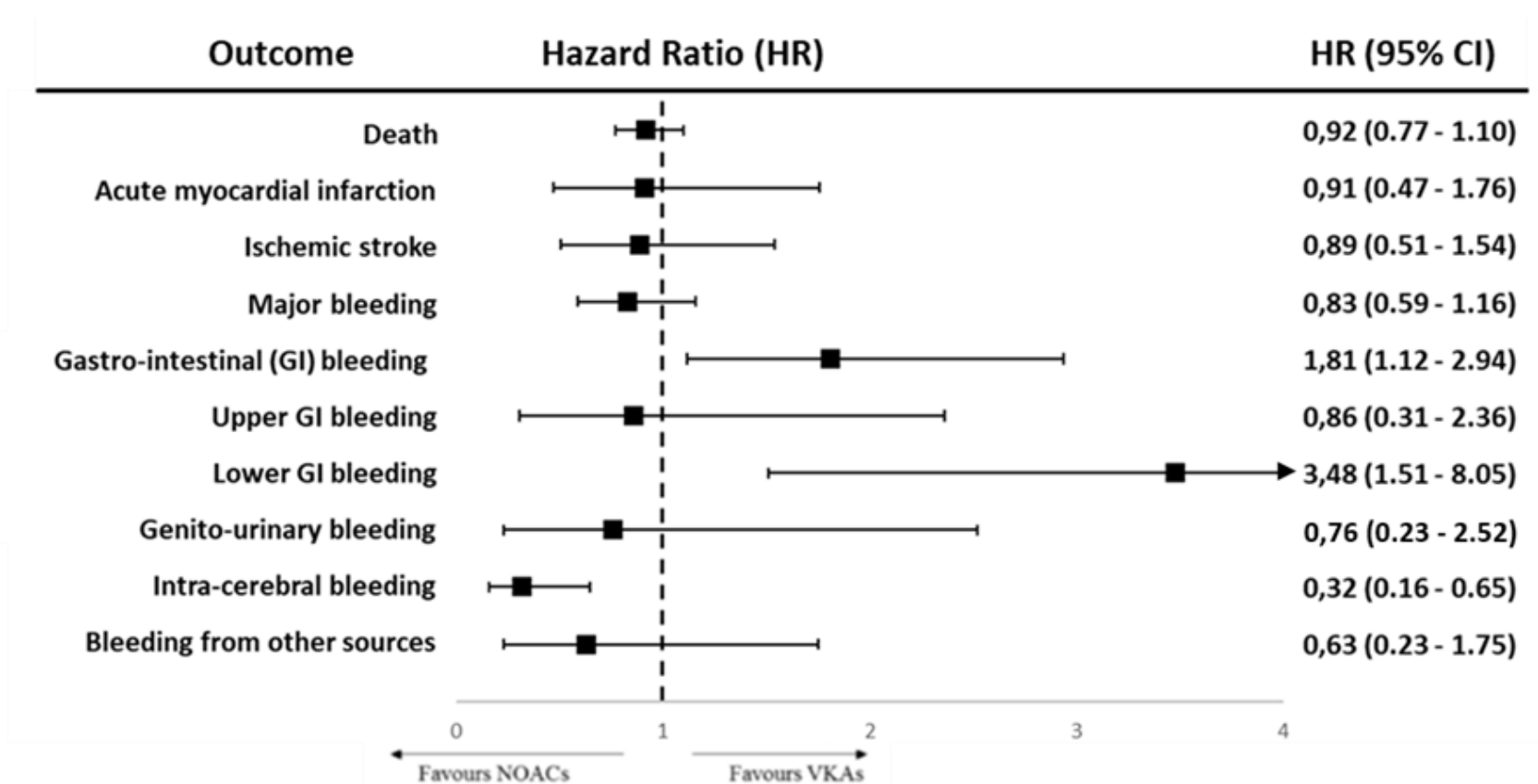
*Int J Cardiol. 2018 Aug 15;265:103-107*



Baseline demographics and clinical characteristics of study subjects treated with NOAC or VKA before application of propensity score AGE≥80

	NOACs (n=2 882)	VKAs (n=12 254)	p-value
Age class			
80 -84 years	48,8%	55,1%	p<0,001
≥85 years	51,2%	44,9%	
Gender			
Male	37,4%	40,9%	p<0,001
Female	62,6%	59,1%	
Comorbidities			
Congestive heart failure	15,0%	17,0%	p=0,009
Hypertension	81,0%	80,7%	p=0,721
Ictus/TIA/Thromboembolism	26,7%	13,3%	p<0,001
Myocardial Infarction	2,7%	2,9%	p=0,619
Peripheral artery disease	1,8%	2,2%	p=0,175
Diabetes	17,2%	18,3%	p=0,170
Cancer	9,8%	9,7%	p=0,835
Chronic renal disease	4,0%	6,2%	p<0,001
Chronic liver disease	1,1%	0,9%	p=0,285
History of bleeding	4,2%	2,7%	p<0,001
Risk scores at baseline			
CHA <sub>2</sub> DS <sub>2</sub> VASc, mean ± SD	4,33 ± 1,31	4,06 ± 1,19	p<0,001
2 - 3	27,8%	32,9%	p<0,001
4 - 5	51,1%	55,1%	
≥ 6	21,0%	12,0%	
HASBED, mean ± SD	2,72 ± 0,90	2,54±0,85	p<0,001

# As treated analysis



# Conclusioni

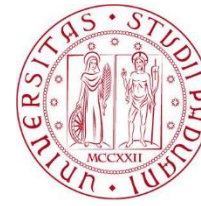
- Negli anziani sopra gli 80 anni si hanno più sanguinamenti intestinali con i NOAC
- Questi sanguinamenti avvengono preferenzialmente nel tratto intestinale terminale
- Si conferma la riduzione delle emorragie cerebrali con i NOAC

## Treat all elderly patients: which one might not be treated

- Active bleeding
- Life expectancy of 6 months or less
- Dementia where compliance can not be ensured by a caregiver
- Poor adherence



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## Real-world persistence with direct oral anticoagulants (DOACs) in naïve patients with non-valvular atrial fibrillation.

Eliana Ferroni, Nicola Gennaro, Giorgio Costa, Ugo Fedeli, Gentian Denas, , Vittorio Pengo,  
Maria Chiara Corti

Epidemiological Department (SER), Veneto Region, Padua, Italy

Cardiology Clinic, Department of Cardiac, Thoracic and Vascular Sciences, Padua University  
Hospital

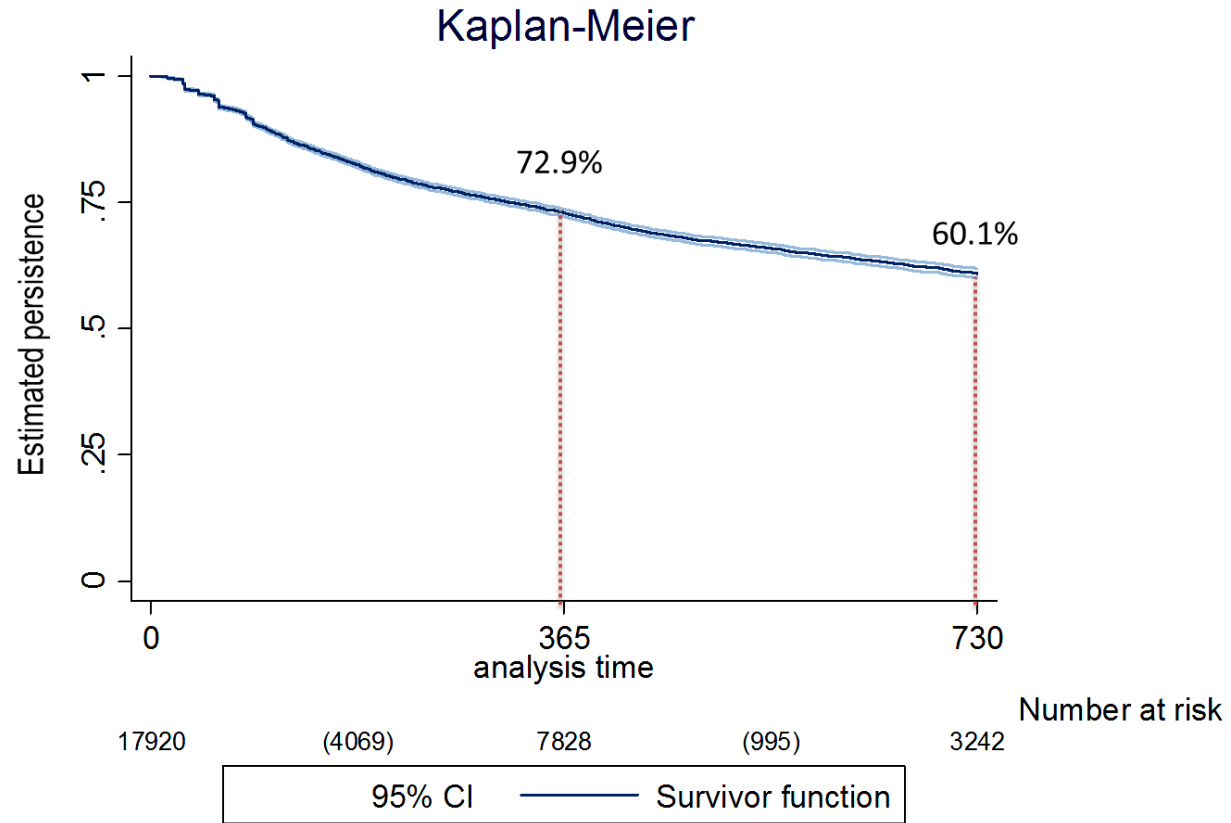
Unified Pharmaceutical Coordination Centre (CRUF), Veneto Region, Venice, Italy

*Int J Cardiol. 2019 Aug 1;288:72-75*



# Naive patients with NVAF (n. 17,920)

## Persistence rate for DOACs



## Predictors of medication persistence for DOACs.\*

Characteristics (Ref.)	HR	HR (95% CI)	Effect on the persistence of the ref. characteristic
<b>Demographics</b>			
Gender (Female)	1.10	(1.04 - 1.16)	Worsens persistence
Age (≤65 yrs)	2.12	(1.99 - 2.26)	Worsens persistence
<b>Other diseases</b>			
Hypertension	0.65	(0.62 - 0.69)	Improves persistence
Cancer	1.05	(0.96 - 1.15)	-
Diabetes	1.01	(0.93 - 1.08)	-
Renal disease	1.53	(1.31 - 1.80)	Worsens persistence
Stroke/TIA/Thromboembolism	0.76	(0.71 - 0.82)	Improves persistence
Acute Myocardial Infarction	0.76	(0.62 - 0.93)	Improves persistence
Bleeding	1.29	(1.12 - 1.50)	Worsens persistence

\*Stratified for Chronic Heart Failure

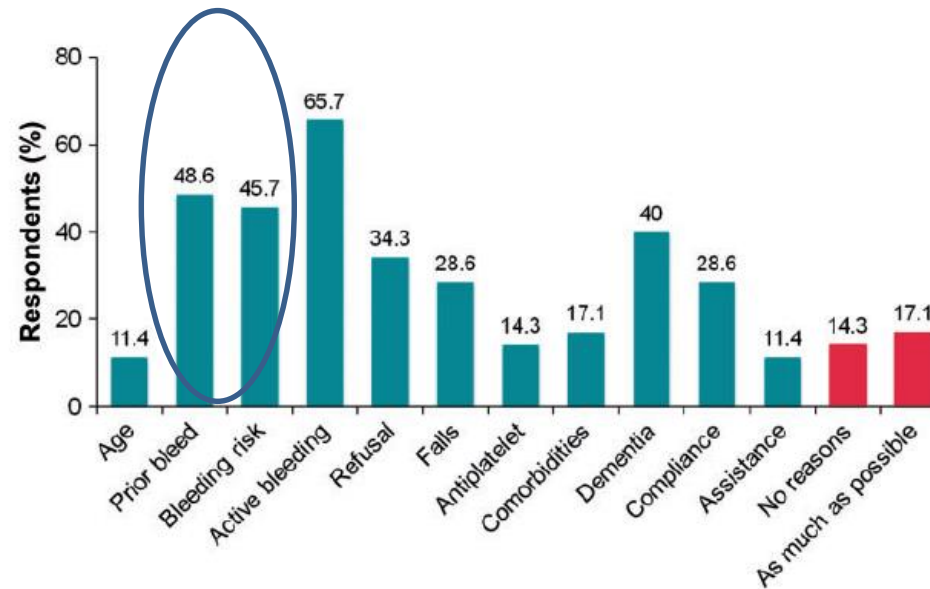
# CONCLUSIONI

- I nostri risultati mostrano che circa il 27% dei pazienti interrompe il trattamento con DOAC entro 12 mesi.
- Favoriscono la persistenza: Sesso maschile, l'età avanzata, storia di ictus / TIA / tromboembolia, sanguinamento precedente, ipertensione, malattia renale.
- Dovrebbero essere compiuti sforzi per migliorare la persistenza dei pazienti, attraverso una maggiore educazione dei pazienti e una migliore relazione paziente-medico.

# Frailty and oral anticoagulant prescription

<b>First author, Year</b>	<b>Perera, 2009</b>	<b>Nguyen, 2015</b>	<b>Lefebvre, 2015</b>
<b>Study design</b>	Prospective observational	Prospective observational	Cross-sectional
<b>Frailty instrument</b>	Edmonton Frail Scale	Edmonton Frail Scale	Clinical Frailty Scale
<b>Findings</b>	Frailty was associated with underprescription of OAC	Frailty was not associated with anticoagulation rates	Frailty was associated with underprescription of OAC

## Most important reasons not to prescribe an anticoagulant drug to a frail patient with atrial fibrillation.



## Key messages to minimize the risk of bleeding in elderly patients

### Issue

Use NOACs instead of Warfarin but check for GI disorders

Blood pressure control

Systematic evaluation of renal and hepatic function

Discontinuation of antiplatelet therapy if not strictly indicated

Use the appropriate dosage



## Factors to be taken into account

- Very elderly patients
- Frailty (ESCAPE)
- ↕
- Gastrointestinal diseases (angiodysplasia!)
- Polytherapy
- Hypertension
- Tendency to fall

Need for frequent clinical and laboratory follow up (Blood cell count, renal and liver function!!!!!!)