FIBRILLAZIONE ATRIALE E INSUFFICIENZA CARDIACA

Francesco Vetta MD PhD
Direttore U.O. Cardiologia
Ospedale Israelitico Roma

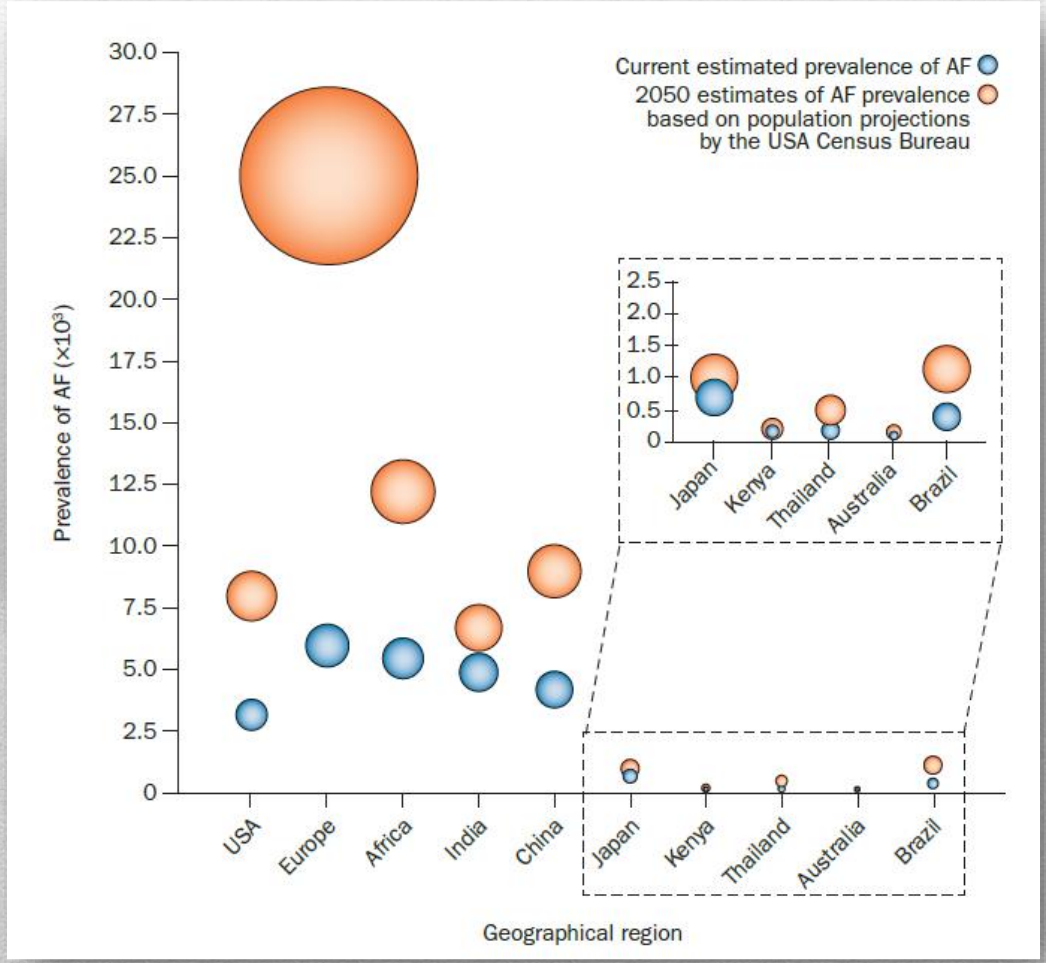
Global epidemiology of atrial fibrillation

Faisal Rahman, Gene F. Kwan and Emelia J. Benjamin

Nat. Rev. Cardiol. **11**, 639–654 (2014)

Key points

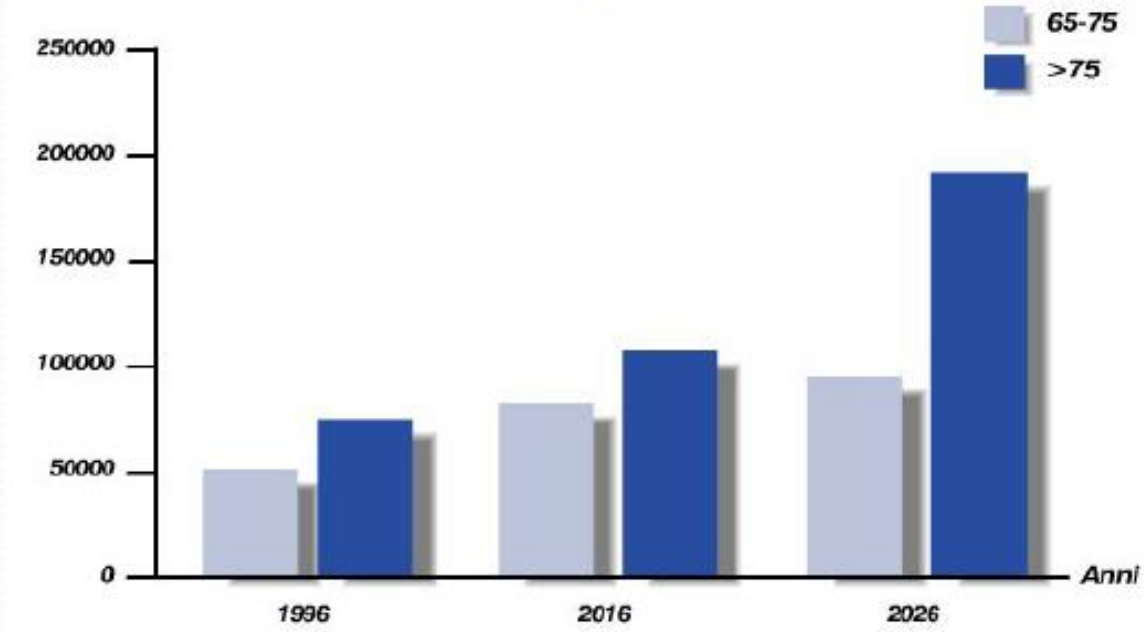
- Atrial fibrillation (AF) is a worldwide epidemic affecting approximately 33 million people, and its rising prevalence is expected to account for increasing clinical and public health costs
- Australia, Europe, and the USA have the highest reported prevalence of AF (1% in the adult population), but the prevalence of AF in low-income and middle-income countries is probably underestimated
- AF is associated with an increased risk of myocardial infarction, heart failure, stroke, dementia, and chronic kidney disease, as well as increased mortality
- Treatment of patients with AF is inadequate: <50% of those at high thromboembolic risk receive anticoagulation therapy worldwide
- The dearth of data on the prevalence, lifetime risk, prognosis, prevention, treatment, and economic implications of AF in many regions around the world remains to be addressed



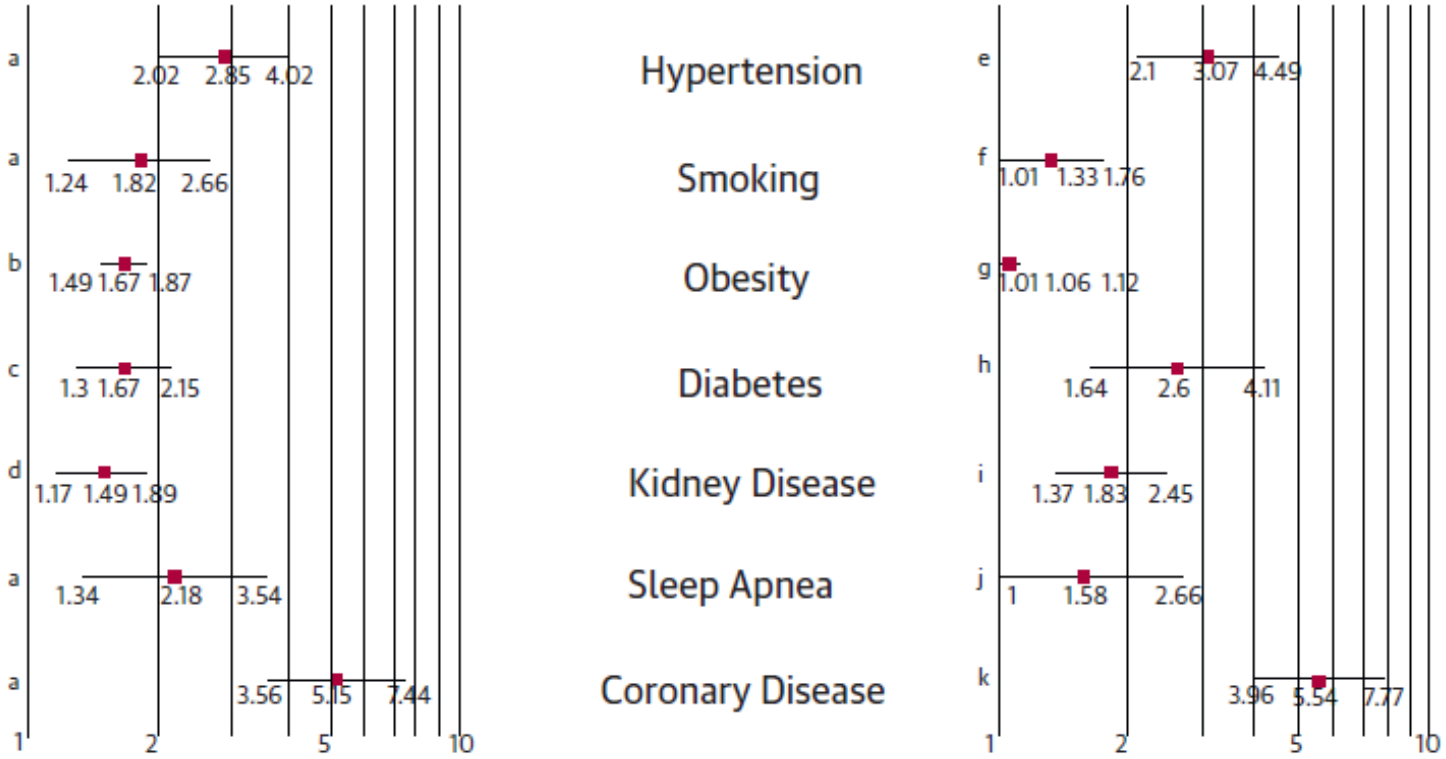
A Public Health Crisis: Heart Failure Hospitalizations have Tripled in 25 Years

- Più di **1.500.000** pazienti affetti da SC*
- **170.000** nuovi casi ogni anno*
- **500** ricoveri/giorno dovuti a SC*
- Incremento del **40%** del numero di ricoveri negli ultimi 5 anni*
- Incidenza aumenta all'aumentare della classe d'età del paziente
- Numero di persone affette da SC raddoppia entro il 2030*

Proiezione prevalenza SC



HR OF INCIDENT AF AND HF ACCORDING TO SHARED RISK FACTORS



Compromissione del riempimento Diastolico:

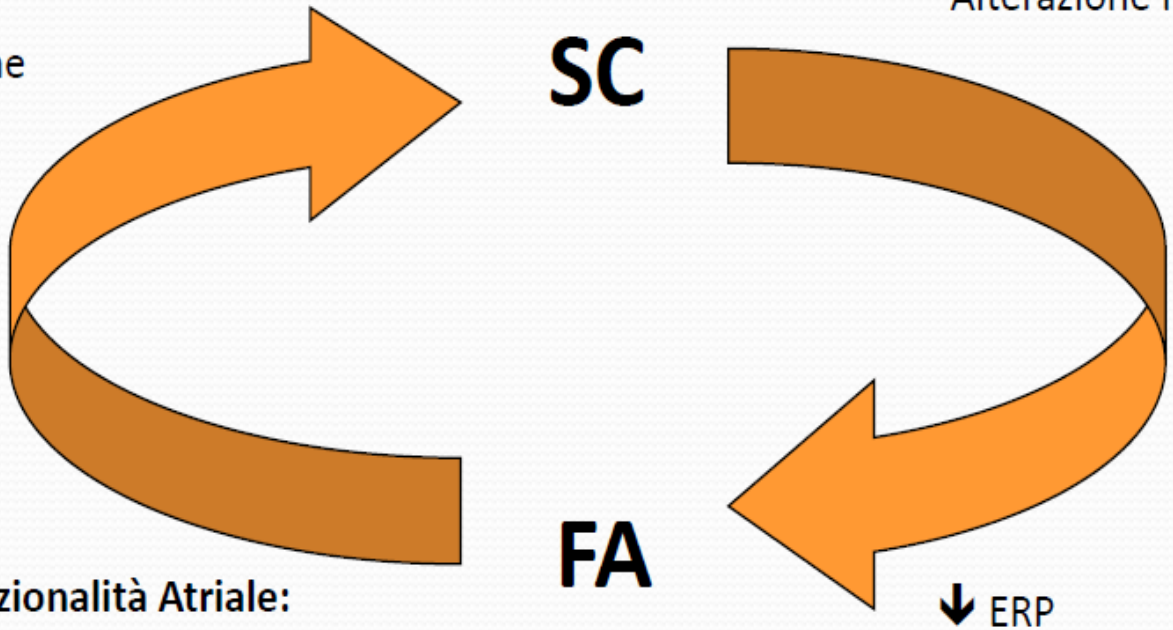
- ↓ Stroke Volume
- ↓ Cardiac Output
- ↑ LVEDP
- ↑ Catecolamine

Dilatazione Atriale

Ipertrofia Atriale

- ↑ Pressione Atriale

Alterazione Neuro-Ormonale



Perdita della Funzionalità Atriale:

- Frequenza Cardiaca non fisiologica
- Risposta Ventricolare Irregolare
- Perdita del Sincronismo A-V

- ↓ ERP
- ↓ Velocità di Conduzione
- ↑ Refrattarietà
- ↑ Attività Ectopica

Combined AF and HF: Epidemiological and Prognostic Implications

Ferreira JP Int J Mol Sci 2015; 16: 3133-47

In HF trials: AF prevalence = 13 – 41%

In AF trials: HF prevalence = 30 – 65%

The frequency of HF preceding AF = AF preceding HF

HF + AF = + 33% in mortality

Atrial Fibrillation Begets Heart Failure and Vice Versa

Temporal Associations and Differences in Preserved Versus Reduced Ejection Fraction

(*Circulation*. 2016;133:484-492.

Rajalakshmi Santhanakrishnan, MBBS; Na Wang, MA; Martin G. Larson, SD; Jared W. Magnani, MD, MSc; David D. McManus, MD; Steven A. Lubitz, MD, MPH; Patrick T. Ellinor, MD, PhD; Susan Cheng, MD; Ramachandran S. Vasan, MD; Douglas S. Lee, MD, PhD; Thomas J. Wang, MD; Daniel Levy, MD; Emelia J. Benjamin, MD, ScM; Jennifer E. Ho, MD

Table 4. Concomitant AF and HF as Predictors of All-Cause Mortality

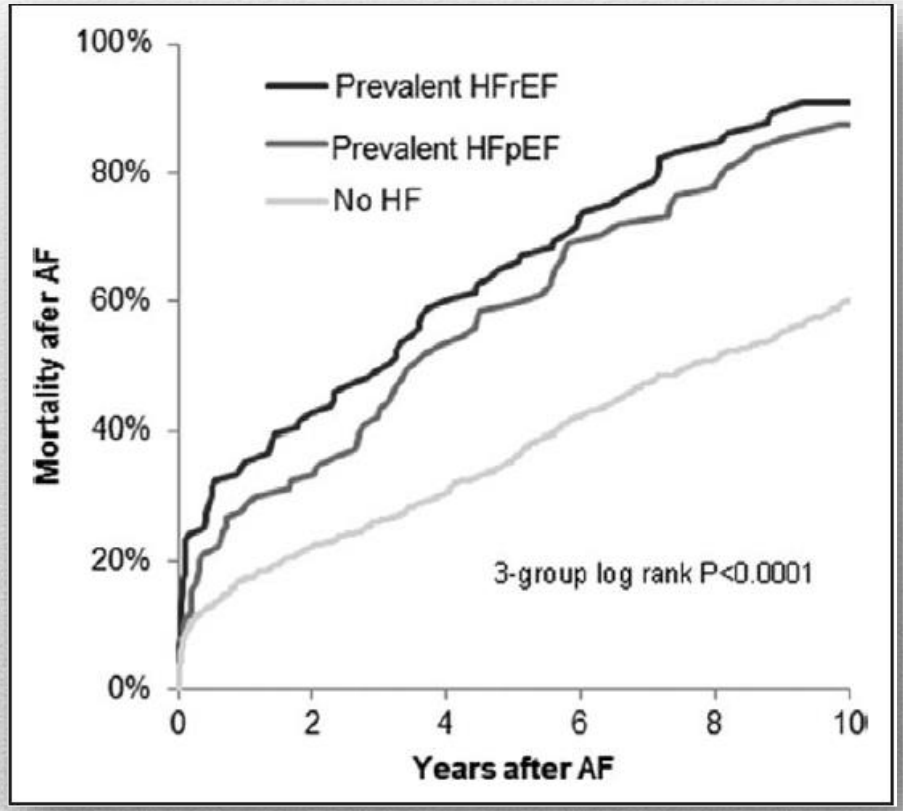
		Age and Sex Adjusted		Multivariable Adjusted	
Outcome	Predictor	HR (95% CI)†	*P* Value	HR (95% CI)†	*P* Value
Mortality after new HF (n=598)	Prevalent AF	1.18 (0.98–1.42)	0.09	1.25 (1.04–1.51)	0.02
	Interim AF	1.88 (1.50–2.35)	<0.0001	1.89 (1.51–2.38)	<0.0001
Mortality after new HFpEF (n=221)	Prevalent AF	1.23 (0.90–1.68)	0.19	1.33 (0.97–1.83)	0.08
	Interim AF	1.66 (1.15–2.39)	0.007	1.58 (1.08–2.30)	0.02
Mortality after new HFrEF (n=289)	Prevalent AF	1.19 (0.91–1.56)	0.2	1.18 (0.90–1.56)	0.23
	Interim AF	2.03 (1.47–2.80)	<0.0001	2.02 (1.46–2.79)	<0.0001
Mortality after new AF (n=683)	Prevalent HFpEF	1.85 (1.43–2.40)	<0.0001	1.83 (1.41–2.37)	<0.0001
	Prevalent HFrEF	2.77 (2.18–3.51)	<0.0001	2.72 (2.12–3.48)	<0.0001
	Prevalent HFpEF vs HFrEF	0.67 (0.49–0.92)	0.01	0.67 (0.48–0.94)	0.02
	Interim HFpEF	2.11 (1.57–2.83)	<0.0001	2.31 (1.72–3.11)	<0.0001
	Interim HFrEF	2.43 (1.82–3.24)	<0.0001	2.36 (1.76–3.16)	<0.0001
	Interim HFpEF vs HFrEF	0.87 (0.59–1.26)	0.46	0.98 (0.67–1.43)	0.91

Treatment of Patients With Atrial Fibrillation and Heart Failure With Reduced Ejection Fraction

Circulation. 2017;135:1547–1563. DOI: 10.1161/CIRCULATIONAHA.116.026054

Atul Verma, MD
Jonathan M. Kalman, MBBS, PhD
David J. Callans, MD

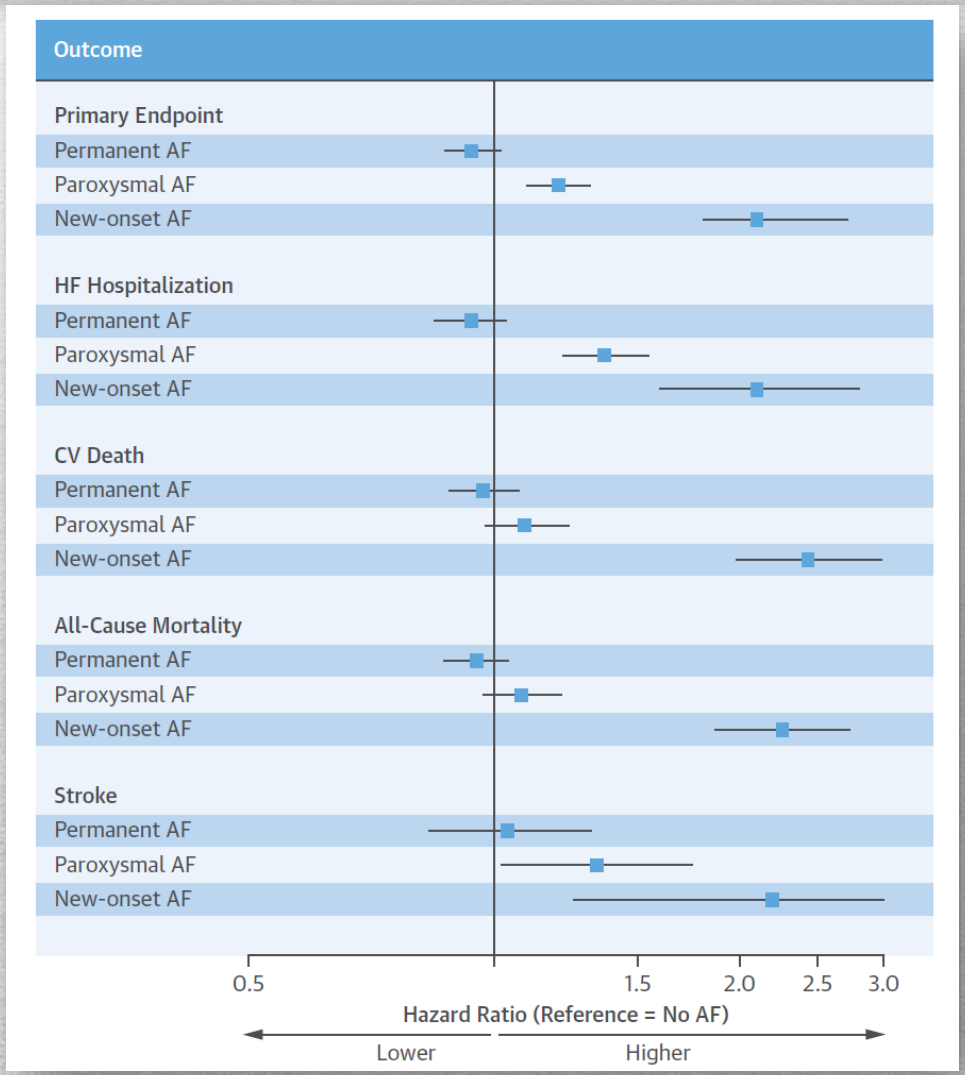
Incidence of all-cause mortality of new onset AF stratified by HF status



Type of Atrial Fibrillation and Outcomes in Patients With Heart Failure and Reduced Ejection Fraction

JACC VOL. 70, NO. 20, 2017
NOVEMBER 14/21, 2017:2490–500

Ulrik M. Mogensen, MD, PhD,[a,b] Pardeep S. Jhund, MBChB, PhD,[a] William T. Abraham, MD,[c] Akshay S. Desai, MD, MPH,[d] Kenneth Dickstein, MD, PhD,[e] Milton Packer, MD,[f] Jean L. Rouleau, MD,[g] Scott D. Solomon, MD,[d] Karl Swedberg, MD, PhD,[h,i] Michael R. Zile, MD,[j] Lars Køber, MD, DMSc,[b] John J.V. McMurray, MD,[a] on behalf of the PARADIGM-HF and ATMOSPHERE Investigators and Committees

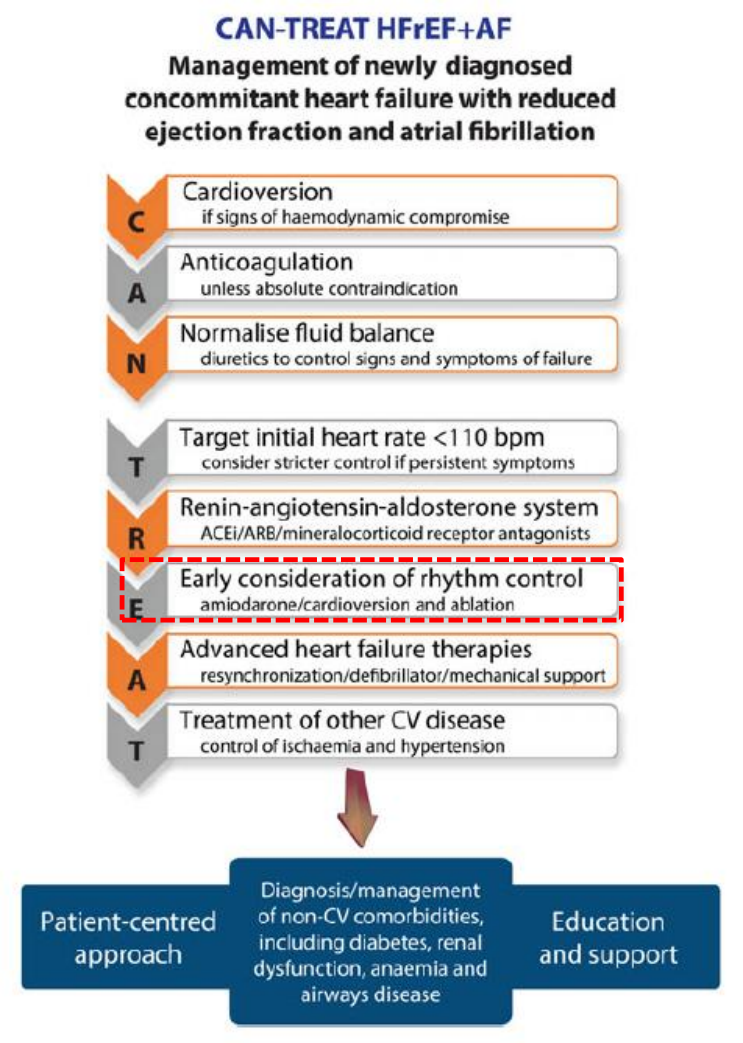


Controversies in cardiovascular medicine

Atrial fibrillation in heart failure: what should we do?

European Heart Journal (2015) **36**, 3250–3257
doi:10.1093/eurheartj/ehv513

Dipak Kotecha[1,2*] and Jonathan P. Piccini[3]



Rhythm Control versus Rate Control for Atrial Fibrillation and Heart Failure

Atrial Fibrillation and Congestive Heart Failure Investigators

Table 3. Cause of Death.

Cause	Rhythm-Control Group (N=682)	Rate-Control Group (N=694)	P Value
	no. (%)		
Total deaths	217 (32)	228 (33)	0.68
Cardiovascular	182 (27)	175 (25)	0.53
Presumed arrhythmic cause	71 (10)	88 (13)	0.19
Congestive heart failure	73 (11)	57 (8)	0.11
Myocardial infarction	15 (2)	9 (1)	0.20
Stroke	9 (1)	11 (2)	0.68
Other	14 (2)	10 (1)	0.39
Noncardiovascular	35 (5)	53 (8)	0.06
Cancer	14 (2)	20 (3)	0.32
Renal failure	1 (<1)	2 (<1)	1.0
Trauma	0	1 (<1)	1.0
Sepsis	11 (2)	26 (4)	0.01
Other	9 (1)	4 (1)	0.15

Controversies in cardiovascular medicine

Atrial fibrillation in heart failure: what should we do?

European Heart Journal (2015) **36**, 3250–3257
doi:10.1093/eurheartj/ehv513

Dipak Kotecha[1,2*] and Jonathan P. Piccini[3]

Table 2 **Antiarrhythmic drug therapy for atrial fibrillation in heart failure**

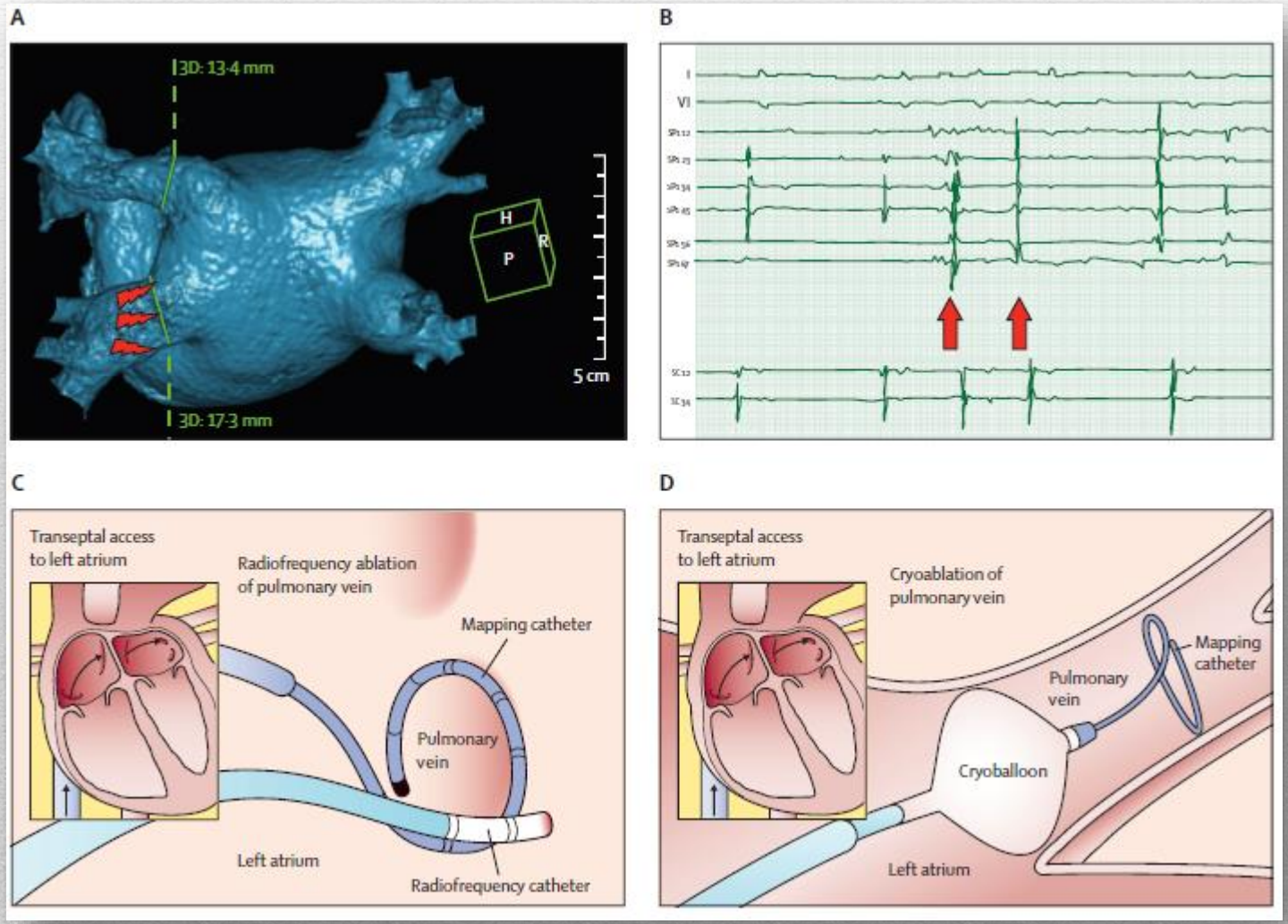
Guidelines	Agent	Class	Safety	Efficacy
Recommended	Amiodarone	Mixed channel blockade	Risks of toxicity, including thyroid, hepatic, pulmonary, and neurological.[78]	Superior efficacy for maintenance of sinus rhythm vs. placebo: odds ratio 0.15 (95% CI 0.10–0.22).[79]
	Dofetilide	III	Requires inpatient stay for loading. Risk of torsades 0.8–3.3%. Not approved in EU.	Lower risk of all-cause rehospitalization in patients with AF at baseline vs. placebo: relative risk 0.70 (95% CI 0.56–0.89).[80]
Caution required	Dronedarone	Mixed channel blockade	Increased mortality in patients with HF and permanent AF.[15,81]	Decreased risk of CV hospitalization or death in patients with AF and no recent HF decompensation vs. placebo: 0.76 (95% CI 0.69–0.84).[82]
	Sotalol	III	Concern for excess proarrhythmia in patients with acute myocardial infarction or LVEF $\leq$40%: relative risk 1.65 (95% CI 1.15–2.36) for all-cause mortality.[83a]	Sotalol was inferior to amiodarone in patients with AF (28% had NYHA class I/II HF).[84]
Contraindicated	Flecainide and Propafenone	I	Flecainide, encainide and moracizine increased mortality in patients with myocardial infarction.[85] Propafenone can precipitate decompensated HF, particularly in CYP 2D6 slow-metabolizers.	

[a]SWORD evaluated D-sotalol rather than D,L-sotalol.

Rhythm control in atrial fibrillation

Jonathan P Piccini, Laurent Fauchier

Lancet 2016; 388: 829–40

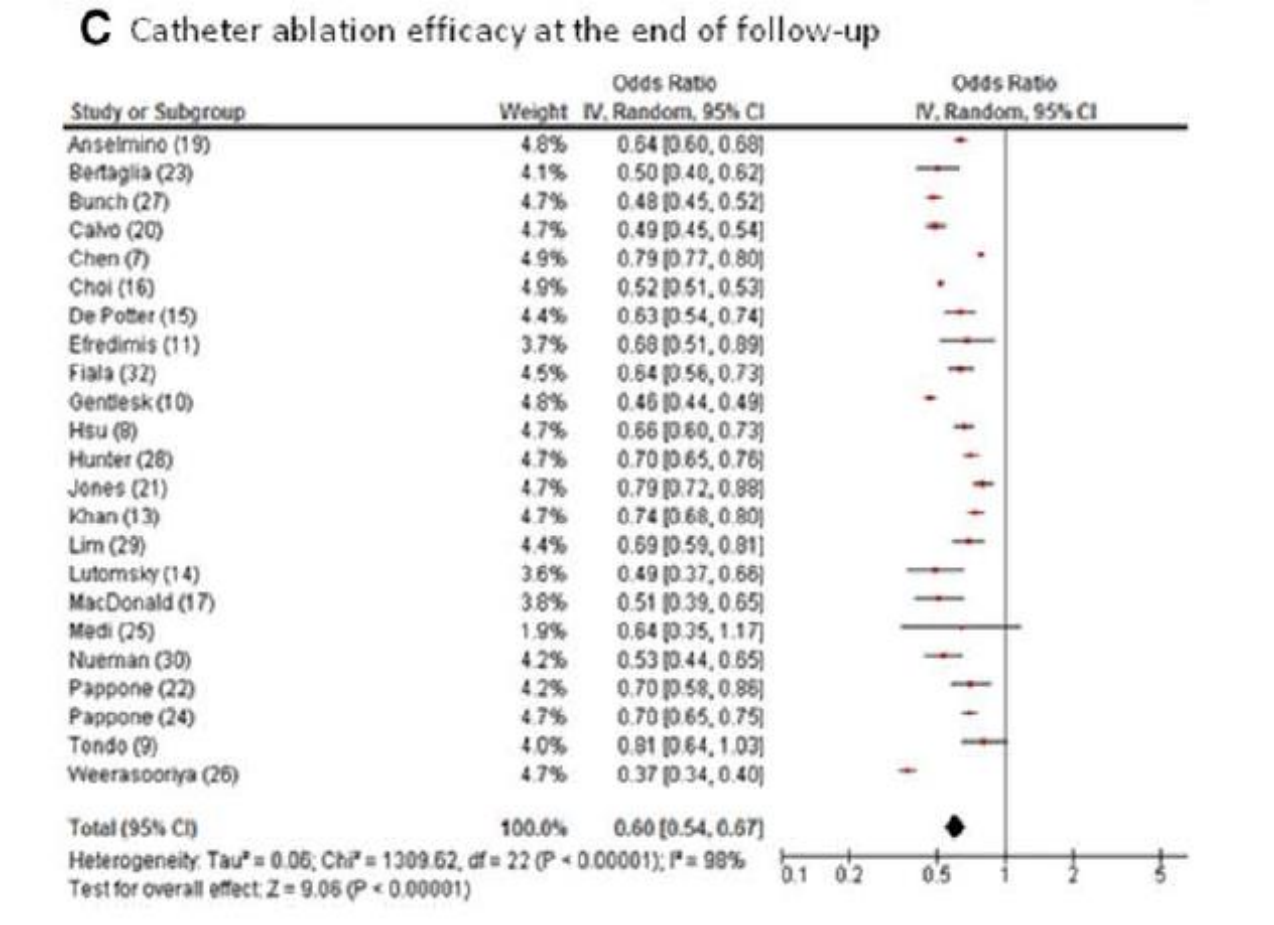


Catheter Ablation of Atrial Fibrillation in Patients With Left Ventricular Systolic Dysfunction

A Systematic Review and Meta-Analysis

Circ Arrhythm Electrophysiol **December 2014**

Matteo Anselmino, MD, PhD; Mario Matta, MD; Fabrizio D'Ascenzo, MD;

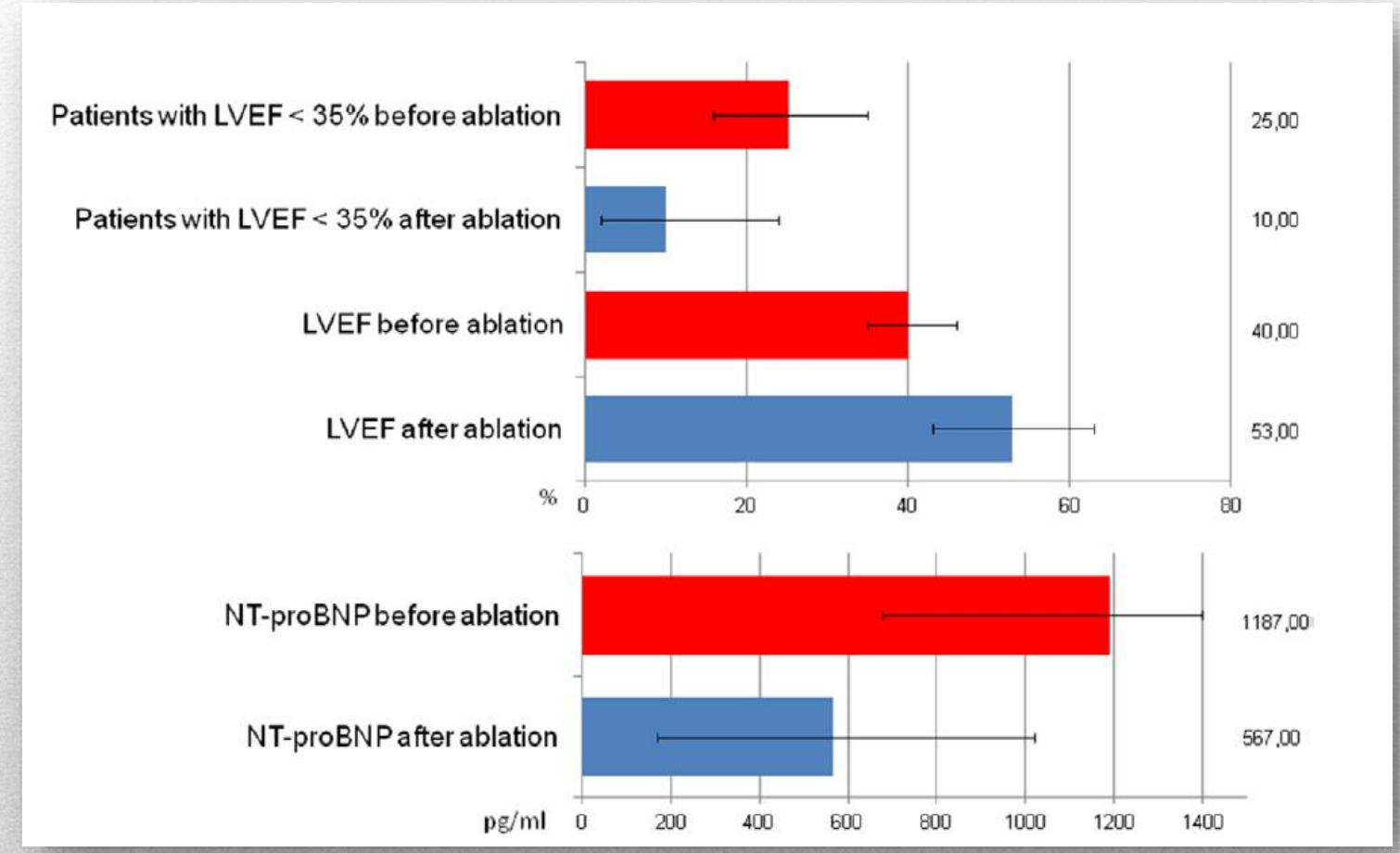


Catheter Ablation of Atrial Fibrillation in Patients With Left Ventricular Systolic Dysfunction

A Systematic Review and Meta-Analysis

Circ Arrhythm Electrophysiol **December 2014**

Matteo Anselmino, MD, PhD; Mario Matta, MD; Fabrizio D'Ascenzo, MD;



Rhythm control in atrial fibrillation

Jonathan P Piccini, Laurent Fauchier

Lancet 2016; 388: 829–40

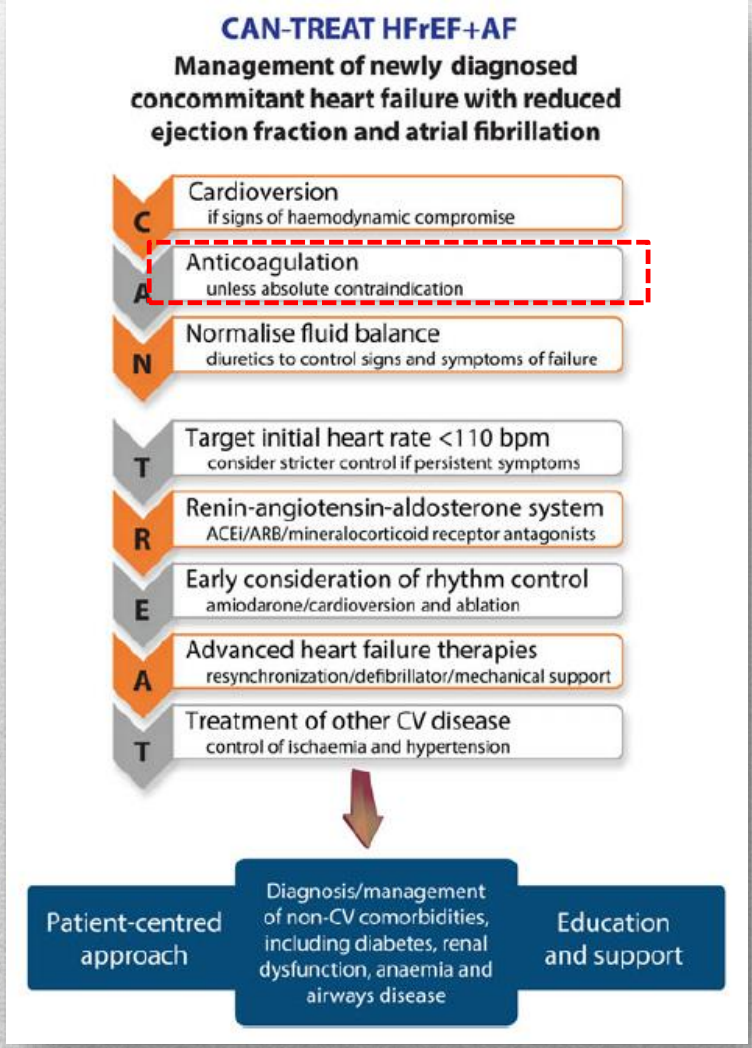
	Number of patients	Atrial fibrillation pattern	Age (years)	Ablation as a first-line therapy	Ablation method	Outcome: sinus rhythm at 1 year		
						Ablation	AAD	p value
Krittayaphong et al (2003)[54]	30	Paroxysmal, persistent	55 (45–65; ablation); 47 (32–62; AAD)	No	Radiofrequency, PVI with LA lines; with CTI ablation and RA lines	79%	40%	0·02
Wazni et al (RAAFT study; 2005)[55]	70	Mainly paroxysmal	53 (45–61; ablation); 54 (46–62; AAD)	Yes	Radiofrequency, PVI	87%	37%	<0·001
Stabile et al (CACAF study; 2006)[52]	245	Paroxysmal, persistent	62 (53–71; ablation); 62 (52–72; AAD)	No	Radiofrequency, PVI with LA lines; with or without CTI ablation	56%	9%	<0·001
Oral et al (2006)[56]	245	Persistent	57 (48–66)	No	Radiofrequency, CPVA	70%	4%	<0·001
Pappone et al (APAF study; 2006)[57]	198	Paroxysmal	55 (45–65; ablation); 57 (47–67; AAD)	No	Radiofrequency, CPVA with CTI ablation	86%	22%	<0·001
Jais et al (A4 study; 2008)[58]	112	Paroxysmal	51 (40–62)	No	Radiofrequency, PVI with or without LA lines; with or without CTI ablation	89%	23%	<0·001
Forleo et al (2008)[59]	70	Paroxysmal, persistent	63 (54–72; ablation); 65 (59–71; AAD)	No	Radiofrequency, PVI with or without LA lines; with or without CTI ablation	80%	43%	0·001
Wilber et al (Thermocool study; 2010)[60]	167	Paroxysmal	56 (ablation); 56 (AAD)	No	Radiofrequency, PVI with or without LA lines with or without CFAEs; with or without CTI ablation with or without RA lines	66%	16%	<0·001
Cosedis Nielsen et al (MANTRA-PAF study; 2012)[23,51]	294	Paroxysmal	56 (ablation); 54 (AAD)	Yes	Radiofrequency, circumferential PVI with voltage abatement	85%	71%	0·01
Packer et al (STOP-AF study; 2013)[61]	245	Paroxysmal	57 (ablation); 56 (AAD)	No	Cryoablation, PVI; with or without LA lines	69·9%	7·3%	<0·001
Morillo et al (RAAFT2 study; 2014)[50]	127	Mainly paroxysmal	56 (ablation); 54 (AAD)	Yes	Radiofrequency, circumferential PVI with electrical isolation	45%	28%	0·02
Mont et al (SARA study; 2014)[53]	146	Persistent	55 (ablation); 55 (AAD)	No	Radiofrequency, PVI with or without LA lines with or without CFAEs	70%	44%	0·002
Di Biase et al (AATAC study; 2016)[79]	203	Persistent with heart failure, LVEF <40%, ICD	62 (ablation); 60 (AAD)	No	Radiofrequency, PVI with or without LA posterior wall isolation with or without LA lines with or without CFAEs with or without SVC isolation	70%	34%	<0·001

Controversies in cardiovascular medicine

Atrial fibrillation in heart failure: what should we do?

European Heart Journal (2015) **36**, 3250–3257
doi:10.1093/eurheartj/ehv513

Dipak Kotecha[1,2*] and Jonathan P. Piccini[3]

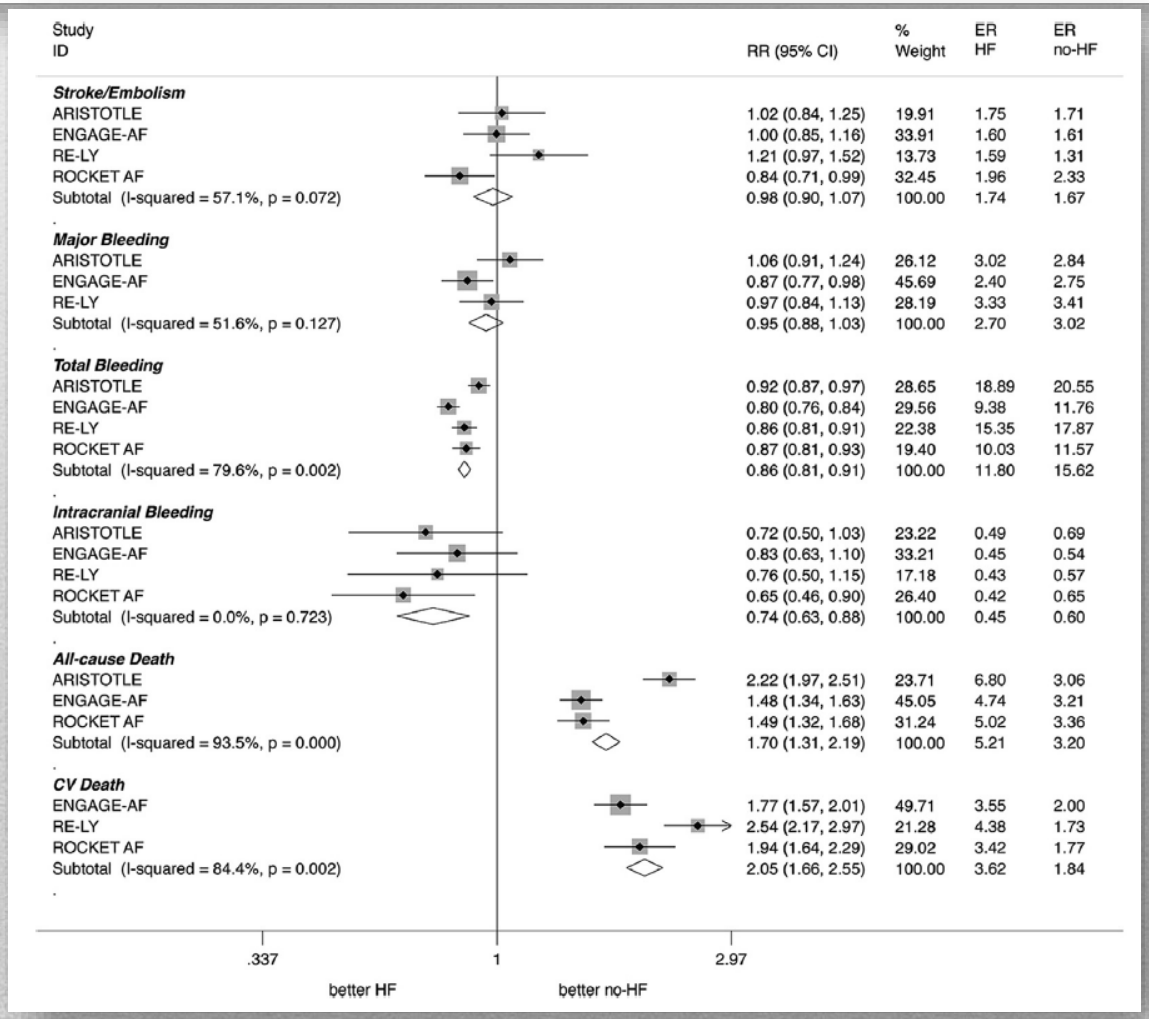


Efficacy and Safety of Novel Oral Anticoagulants in Patients With Atrial Fibrillation and Heart Failure

A Meta-Analysis

JACC: HEART FAILURE VOL. 4, NO. 11, 2016
NOVEMBER 2016:870–80

Gianluigi Savarese, MD,[a,b] Robert P. Giugliano, MD, SM,[c] Giuseppe M.C. Rosano, MD, PhD,[d,e] John McMurray, MD,[f] Giulia Magnani, MD,[c] Gerasimos Filippatos, MD, PhD,[g] Santo Dellegrottaglie, MD, PhD,[h,i] Lars H. Lund, MD, PhD,[b] Bruno Trimarco, MD, PhD,[a] Pasquale Perrone-Filardi, MD, PhD[a]



Efficacy and Safety of Novel Oral Anticoagulants in Patients With Atrial Fibrillation and Heart Failure

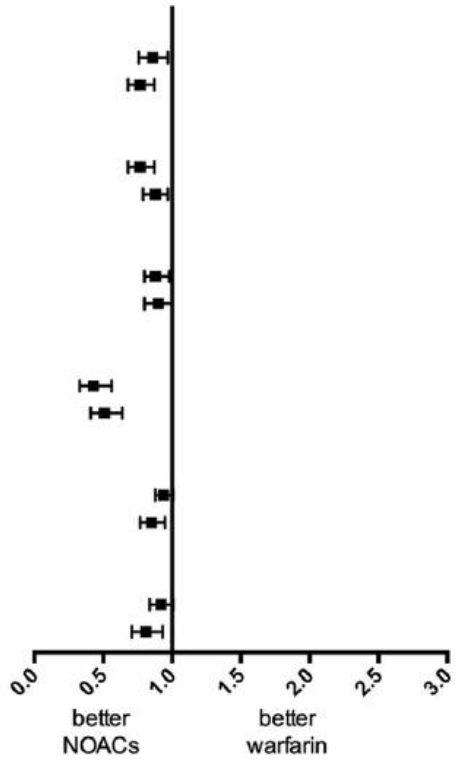
A Meta-Analysis

JACC: HEART FAILURE VOL. 4, NO. 11, 2016
NOVEMBER 2016:870–80

Gianluigi Savarese, MD,[a,b] Robert P. Giugliano, MD, SM,[c] Giuseppe M.C. Rosano, MD, PhD,[d,e] John McMurray, MD,[f] Giulia Magnani, MD,[c] Gerasimos Filippatos, MD, PhD,[g] Santo Dellegrottaglie, MD, PhD,[h,i] Lars H. Lund, MD, PhD,[b] Bruno Trimarco, MD, PhD,[a] Pasquale Perrone-Filardi, MD, PhD[a]

DOACS in HF vs no HF pts

Outcome	ER NOACs	ER Warfarin	RR (95% CI)	p for interaction
Stroke/Embolism				
HF	1.60	1.87	0.86 (0.76, 0.97)	0.23
no HF	1.45	1.88	0.77 (0.68, 0.87)	
Major Bleeding				
HF	2.35	3.06	0.77 (0.68, 0.87)	0.09
no HF	2.83	3.22	0.88 (0.79, 0.97)	
Total Bleeding				
HF	11.11	12.50	0.88 (0.80, 0.98)	0.99
no HF	14.66	16.57	0.90 (0.80, 1.00)	
Intracranial Bleeding				
HF	0.27	0.63	0.43 (0.33, 0.56)	0.32
no HF	0.41	0.80	0.51 (0.41, 0.64)	
All-cause Death				
HF	5.05	5.37	0.94 (0.88, 1.01)	0.13
no HF	2.94	3.45	0.85 (0.77, 0.95)	
CV Death				
HF	3.47	3.77	0.92 (0.84, 1.01)	0.11
no HF	1.64	2.03	0.81 (0.71, 0.93)	



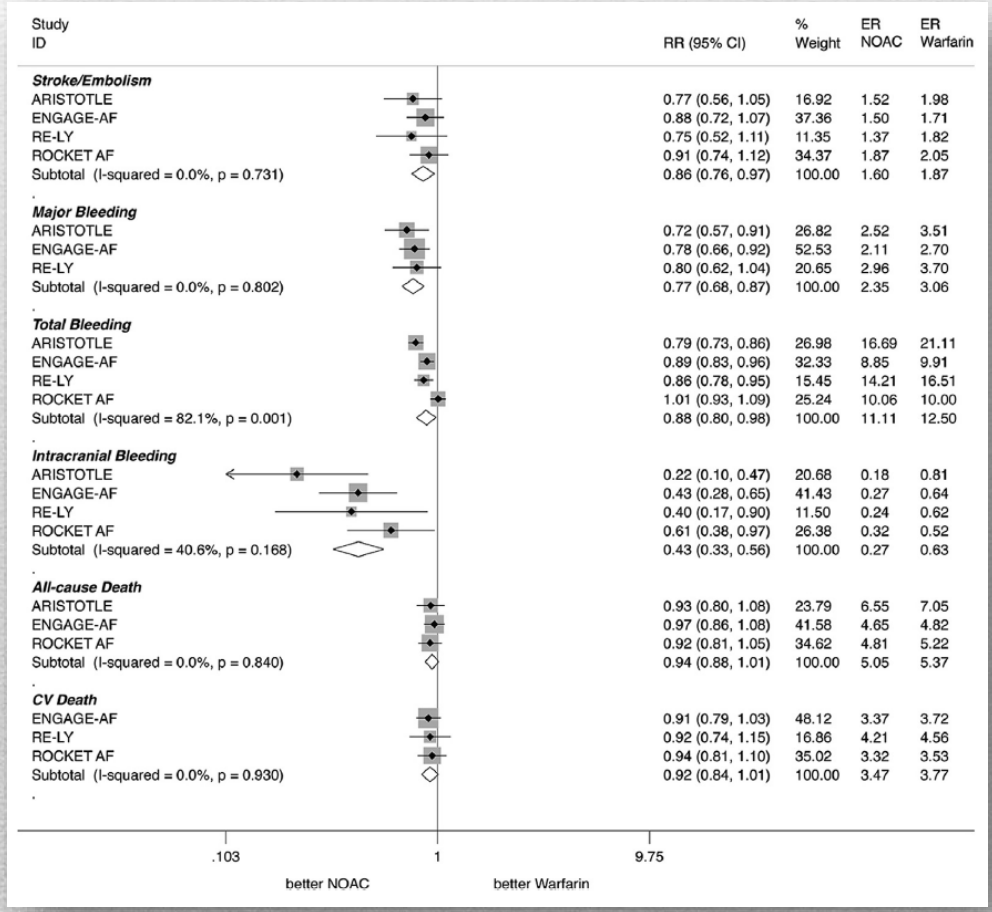
Efficacy and Safety of Novel Oral Anticoagulants in Patients With Atrial Fibrillation and Heart Failure

A Meta-Analysis

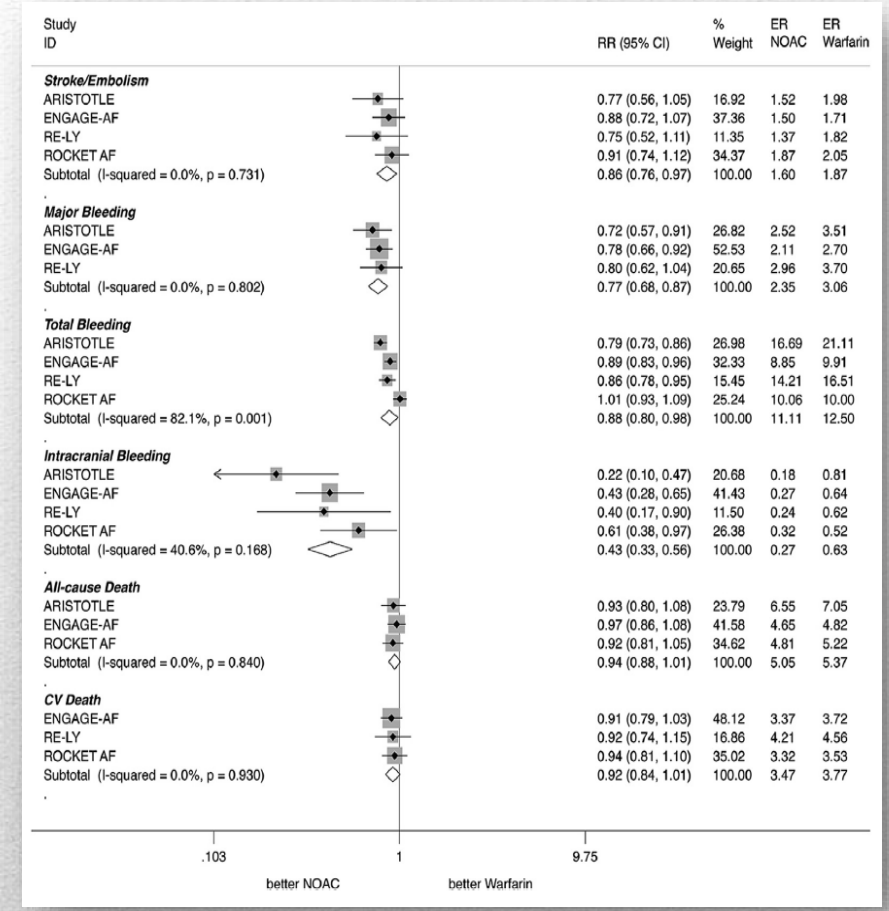
JACC: HEART FAILURE VOL. 4, NO. 11, 2016
NOVEMBER 2016:870–80

Gianluigi Savarese, MD,[a,b] Robert P. Giugliano, MD, SM,[c] Giuseppe M.C. Rosano, MD, PhD,[d,e] John McMurray, MD,[f] Giulia Magnani, MD,[c] Gerasimos Filippatos, MD, PhD,[g] Santo Dellegrottaglie, MD, PhD,[h,i] Lars H. Lund, MD, PhD,[b] Bruno Trimarco, MD, PhD,[a] Pasquale Perrone-Filardi, MD, PhD[a]

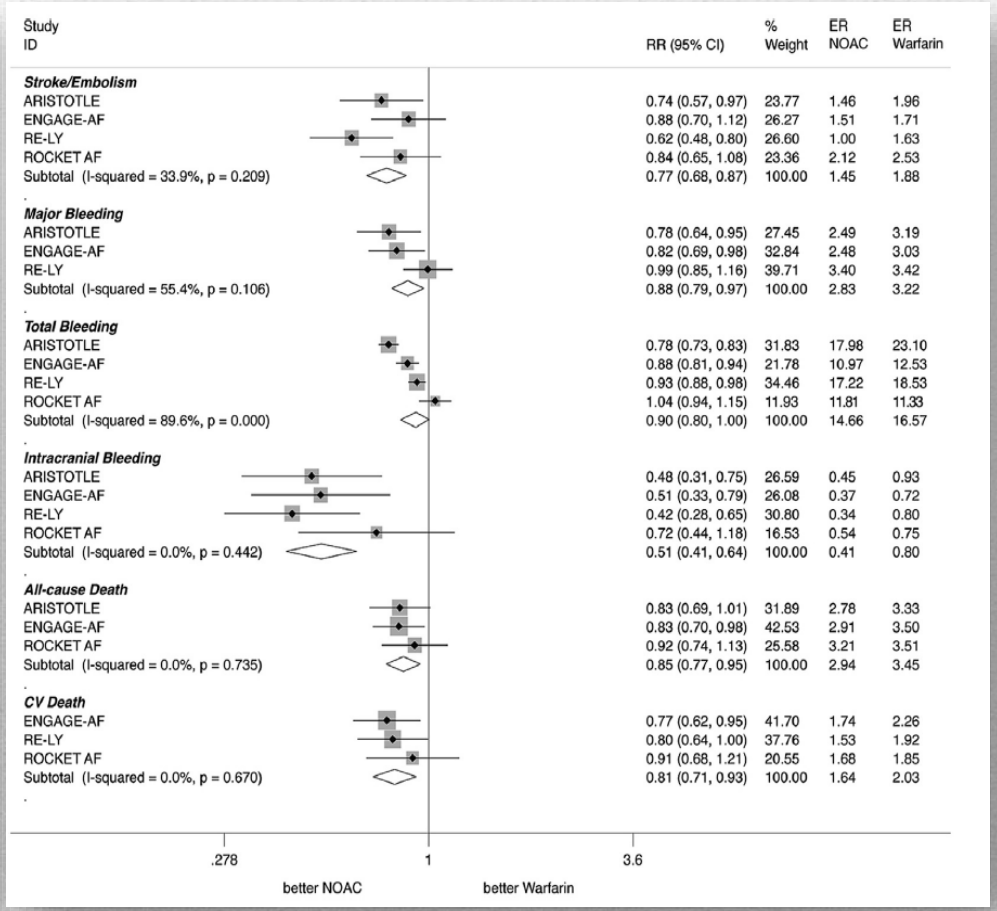
DOACS in HF pts



DOACS in HF pts



DOACS in no HF pts



Efficacy and Safety of Novel Oral Anticoagulants in Patients With Atrial Fibrillation and Heart Failure

A Meta-Analysis

JACC: HEART FAILURE VOL. 4, NO. 11, 2016
NOVEMBER 2016:870–80

Gianluigi Savarese, MD,[a,b] Robert P. Giugliano, MD, SM,[c] Giuseppe M.C. Rosano, MD, PhD,[d,e] John McMurray, MD,[f] Giulia Magnani, MD,[c] Gerasimos Filippatos, MD, PhD,[g] Santo Dellegrottaglie, MD, PhD,[h,i] Lars H. Lund, MD, PhD,[b] Bruno Trimarco, MD, PhD,[a] Pasquale Perrone-Filardi, MD, PhD[a]

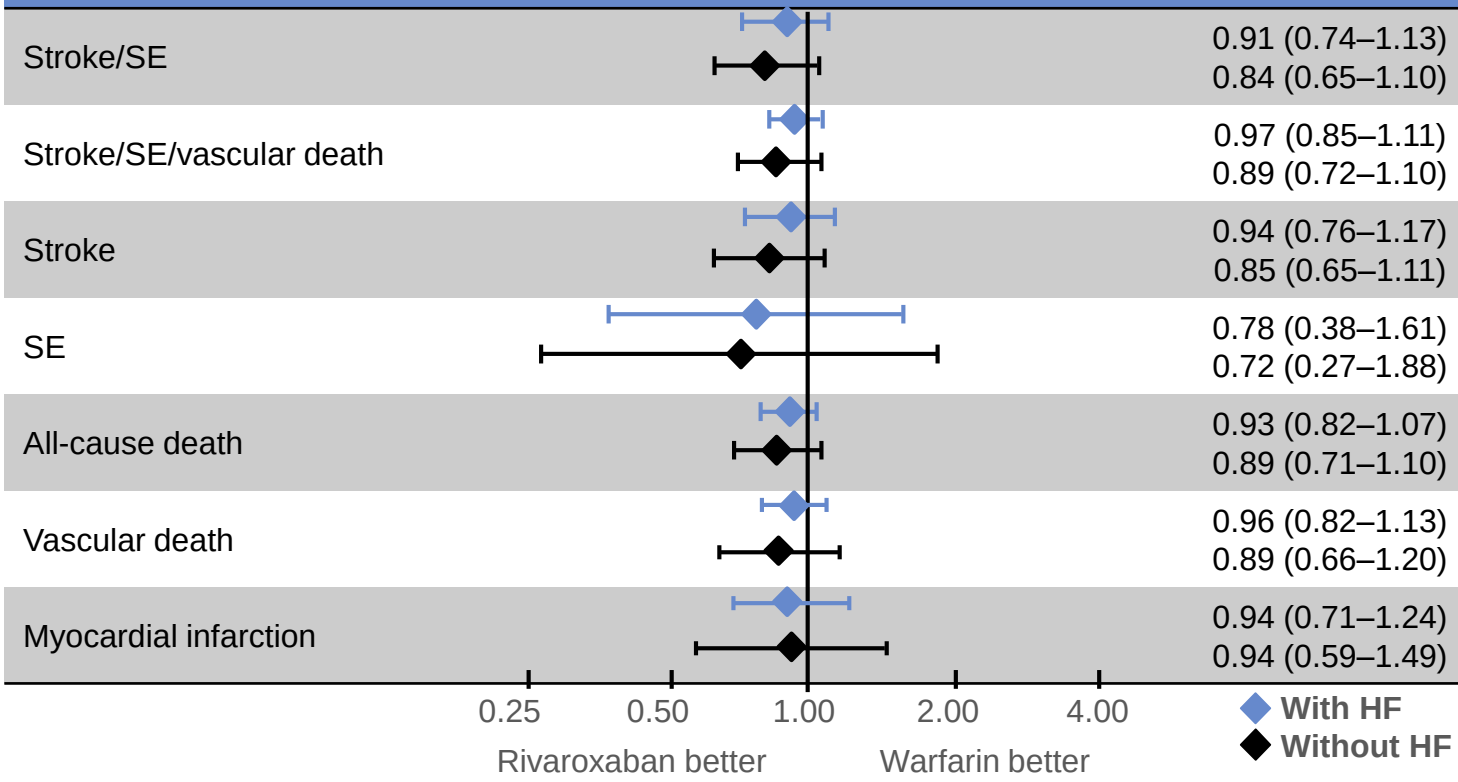
TABLE 1 Baseline Characteristics of Trials Included in the Analysis

	ARISTOTLE		ENGAGE AF		RE-LY		ROCKET AF		TOTAL		HF vs. No HF
	HF	No HF	HF	No HF	HF	No HF	HF	No HF	HF	No HF	p Value
Year	2013		2015		2013		2013				
Treatment	Apixaban 5 mg twice daily		Edoxaban 60 mg once daily		Dabigatran 150 mg twice daily		Rivaroxaban 20 mg once daily				
FUP, yrs	1.5		2.8		2.0		1.94		NA		NA
Patients, %	5,943	8,728	8,145	5,926	3,263	8,835	9,033	5,138	26,384	28,627	NA
Females, %	33	35	38	38	34	39	39	40	36	38	<0.01
Age, yrs	69	71	70	75	68	73	72	74	70	73	0.03
$CHADS_2$	2.46	1.88	3.00	2.60	2.65	2.00	3.70	3.15	2.95	2.41	0.22
Hypertension, %	83	90	94	93	75	80	93	86	86	87	<0.01
Diabetes, %	26	25	31	44	27	22	42	35	31	31	1.00
Prior MI/CAD, %	22	11	15	8	32	26	22	10	23	14	<0.01
NYHA functional classes I-II, %	57	NA	78	NA	NA	NA	69	NA	68	NA	NA
NYHA functional classes III-IV, %	23	NA	22	NA	NA	NA	31	NA	25	NA	NA
Aspirin, %	33	30	31	29	NA	NA	31	25	32	28	<0.01
Detsky quality score	100%		100%		95%		100%		100%		NA
Definition of HF	Symptomatic congestive HF within 3 months with reduced or preserved ejection fraction		Current presence or history of HF class C or D according to the AHA/ACC definition*		Presence of NYHA class II or higher HF symptoms within 6 months in patients with history of previous admission for HF		Left ventricular ejection <40%		NA	NA	NA

ROCKET AF
Subanalysis heart failure – Results

Efficacy endpoints by treatment and HF

Outcome	Hazard ratio (95% CI)	p-value (interaction)
Stroke/SE	0.91 (0.74–1.13) 0.84 (0.65–1.10)	0.62
Stroke/SE/vascular death	0.97 (0.85–1.11) 0.89 (0.72–1.10)	0.52
Stroke	0.94 (0.76–1.17) 0.85 (0.65–1.11)	0.57
SE	0.78 (0.38–1.61) 0.72 (0.27–1.88)	0.88
All-cause death	0.93 (0.82–1.07) 0.89 (0.71–1.10)	0.68
Vascular death	0.96 (0.82–1.13) 0.89 (0.66–1.20)	0.64
Myocardial infarction	0.94 (0.71–1.24) 0.94 (0.59–1.49)	0.99

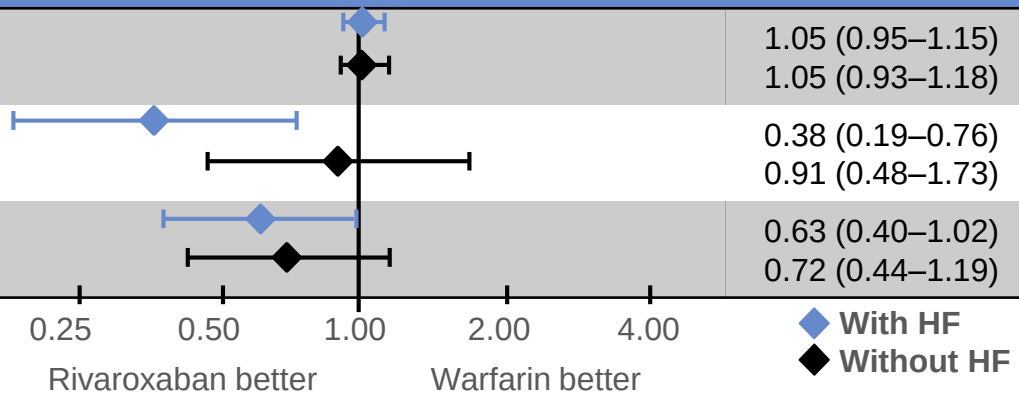


Van Diepen S *et al. Circ Heart Fail* 2013;6(4): 740–747

ROCKET AF
Subanalysis heart failure – Results

Safety endpoints by treatment and HF

Outcome	Hazard ratio (95% CI)	p-value (interaction)
Major or NMCR bleeding	1.05 (0.95–1.15) 1.05 (0.93–1.18)	0.99
Haemorrhagic stroke	0.38 (0.19–0.76) 0.91 (0.48–1.73)	0.067
Intracranial haemorrhage	0.63 (0.40–1.02) 0.72 (0.44–1.19)	0.71



Van Diepen S *et al. Circ Heart Fail* 2013;6(4): 740–747

Oral Anticoagulant Agents in Patients With Atrial Fibrillation and Heart Failure

Does Heart Failure Status Influence Efficacy and Safety?*

Faiez Zannad, MD, PhD, João Pedro Ferreira, MD, PhD

JACC: HEART FAILURE VOL. 4, NO. 11, 2016
NOVEMBER 2016:881–4

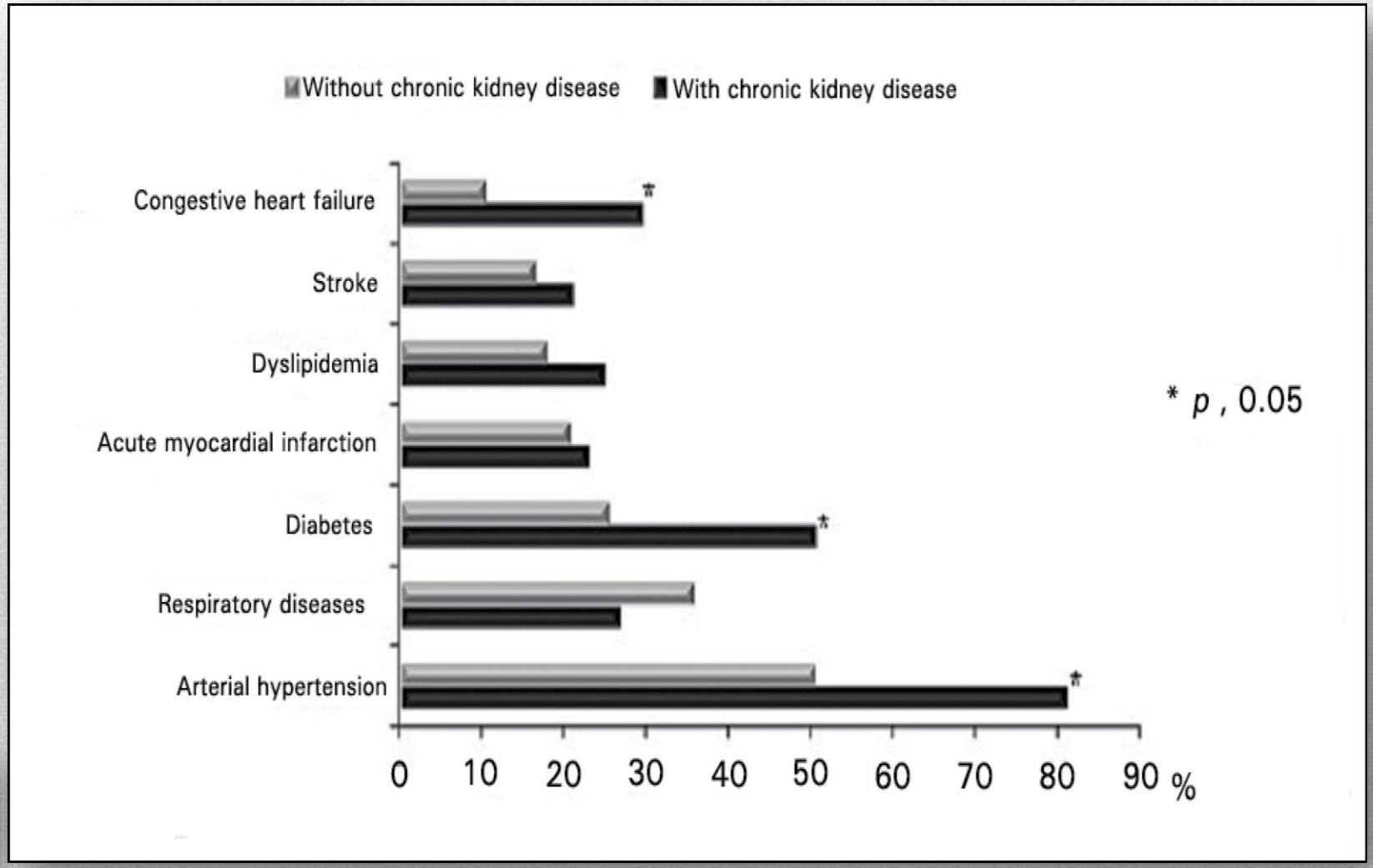
Trial	HF Definition	HHF Endpoints	HF Stratification	Severe Renal Impairment	Potential for Improvement
RE-LY	NYHA class ≥II LVEF	No	No	Excluded	• HF etiology • HF treatment
ROCKET-HF	HF history LVEF <40%	No	No	Excluded	• Volume status • Loop diuretic dose
ENGAGE AF–TIMI 48	HF history NYHA class	No	No	Excluded	• Previous HF hospitalizations • IV loop diuretic agents during index hospitalization
ARISTOTLE	HF history LVEF <40%	No	No	Excluded	• Natriuretic peptide levels • Concomitant antiplatelet agents

Review Article

Heart Failure in Patients with Chronic Kidney Disease: A Systematic Integrative Review

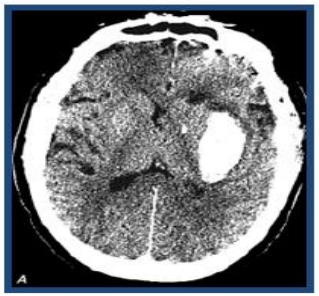
BioMed Research International
Volume 2014, Article ID 937398, 21 pages
http://dx.doi.org/10.1155/2014/937398

Liviu Segall, Ionut Nistor, and Adrian Covic

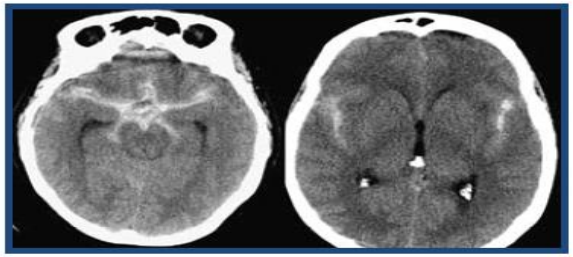


Cerebrovascular Disease: Stroke Subtype

Hemorrhagic stroke (17%)

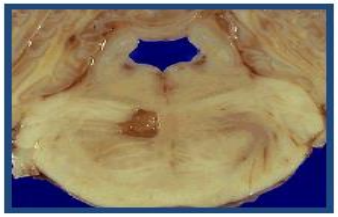


Intracerebral hemorrhage (59%)



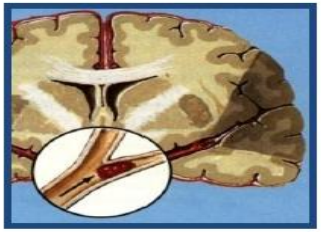
SAH (41%)

Ischemic stroke (83%)



Lacunar small vessel disease (25%)

Atherothrombotic disease (20-25%)



Embolism (20%)

Cryptogenic (30%)

Albers GW et al. Chest. 1998;114:683S-698S.
Rosamond WD et al. Stroke. 1999;30:736-743.

AF accounts for 15% of strokes
HF accounts for 9% of strokes

STATE-OF-THE-ART PAPER

Antiplatelet and Anticoagulant Agents in Heart Failure

Current Status and Future Perspectives

Paul A. Gurbel, MD, Udaya S. Tantry, PhD

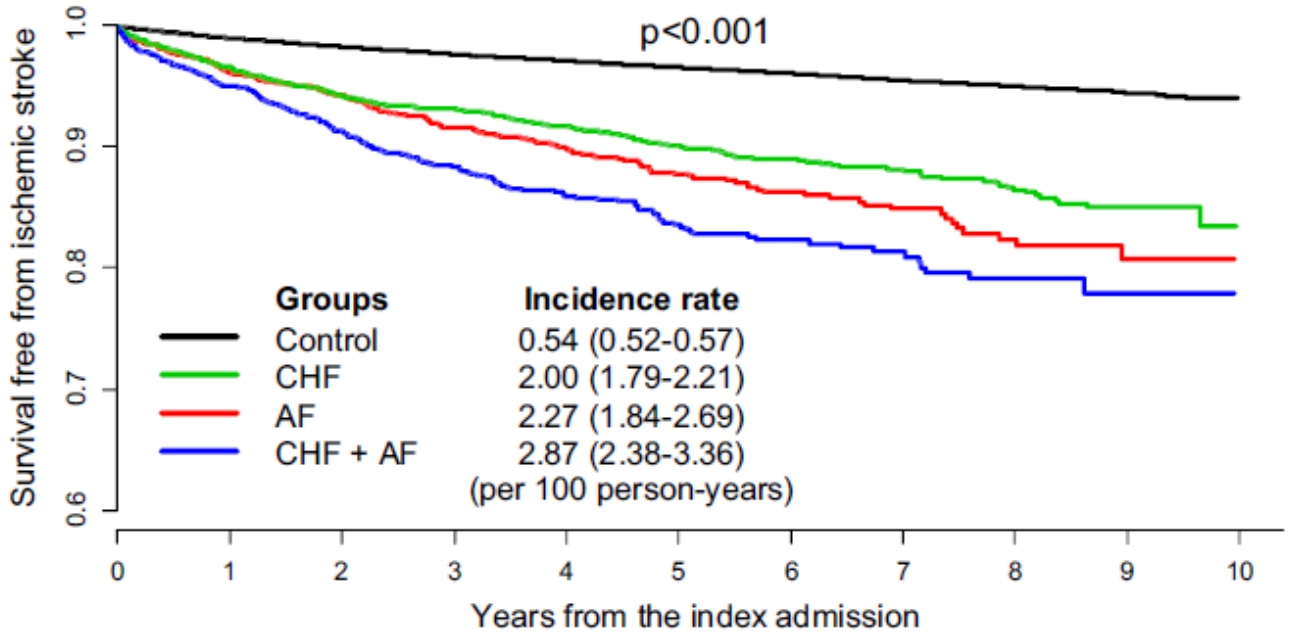
Baltimore, Maryland

J Am Coll Cardiol HF 2014;2:1–14

Risk of stroke in congestive heart failure with and without atrial fibrillation

International Journal of Cardiology 248 (2017) 182–187

Si-Hyuck Kang [a,1], Joonghee Kim [b,1], Jin Joo Park [a], Il-Young Oh [a], Chang-Hwan Yoon [a], Hee-Jun Kim [c], Kyuseok Kim [b,*], Dong-Ju Choi [a,*]

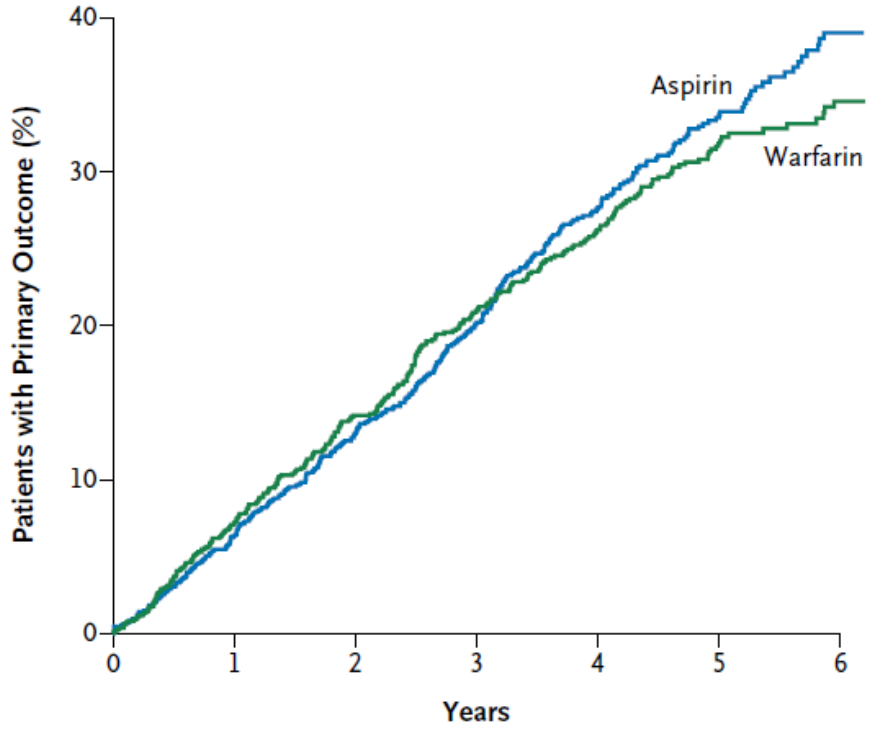


Patient number at risk

Control	90,277	73,689	52,171	33,255	17,865	4,919
CHF	4,533	2,947	1,879	1,129	582	170
AF	1,187	776	490	297	161	41
HF + AF	1,213	752	459	281	136	43

Warfarin and Aspirin in Patients with Heart Failure and Sinus Rhythm

The investigators in the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) Study Group are



No. at Risk							
Aspirin	1163	1073	860	658	508	329	94
Warfarin	1142	1049	852	653	525	363	115

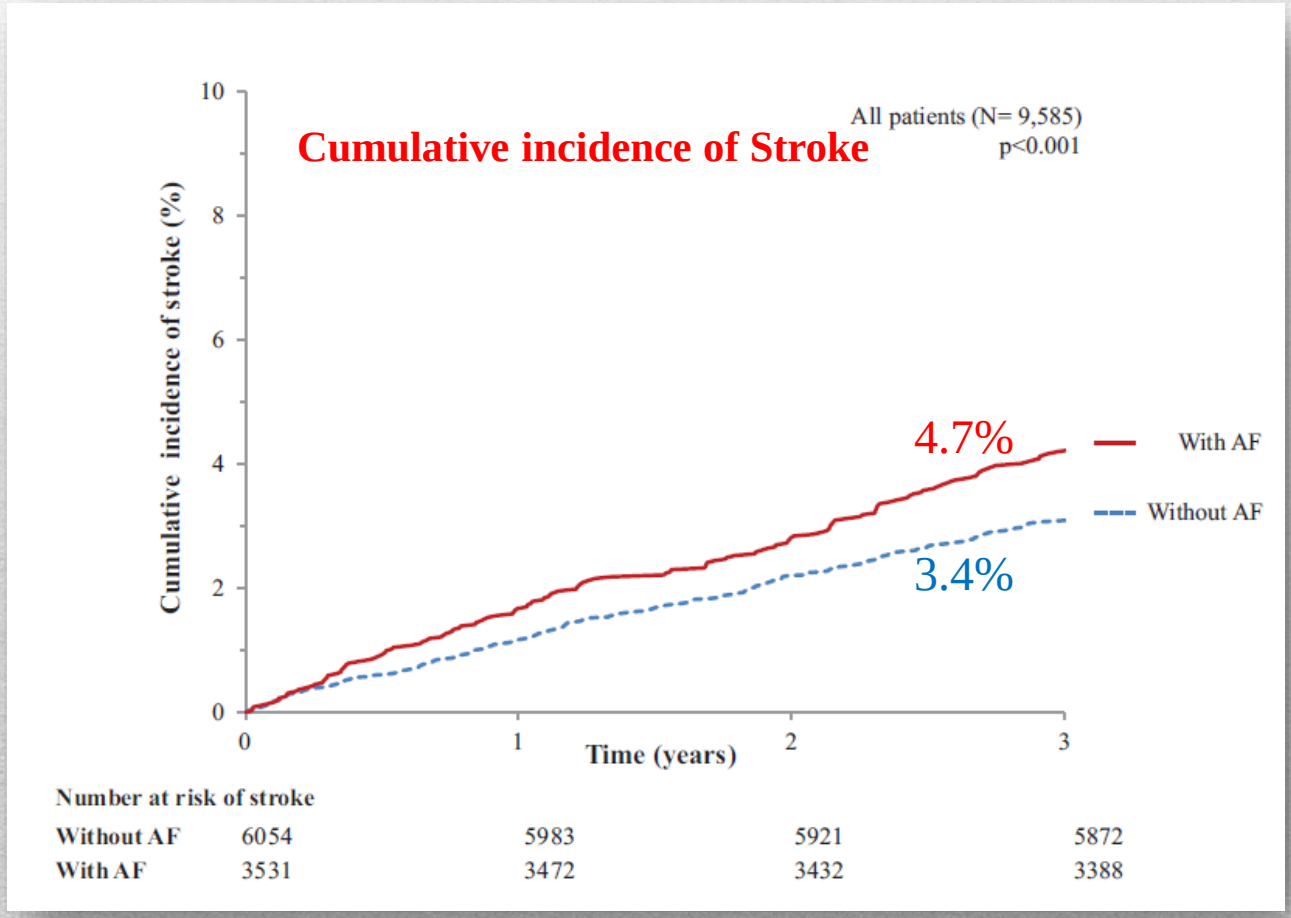
Figure 1. Cumulative Incidence of the Primary Outcome.

The primary outcome was the time to the first event in the composite end point of ischemic stroke, intracerebral hemorrhage, or death from any cause.

Risk of Stroke in Chronic Heart Failure Patients Without Atrial Fibrillation

Analysis of the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) Trials

Circulation. 2015;131:1486-1494.



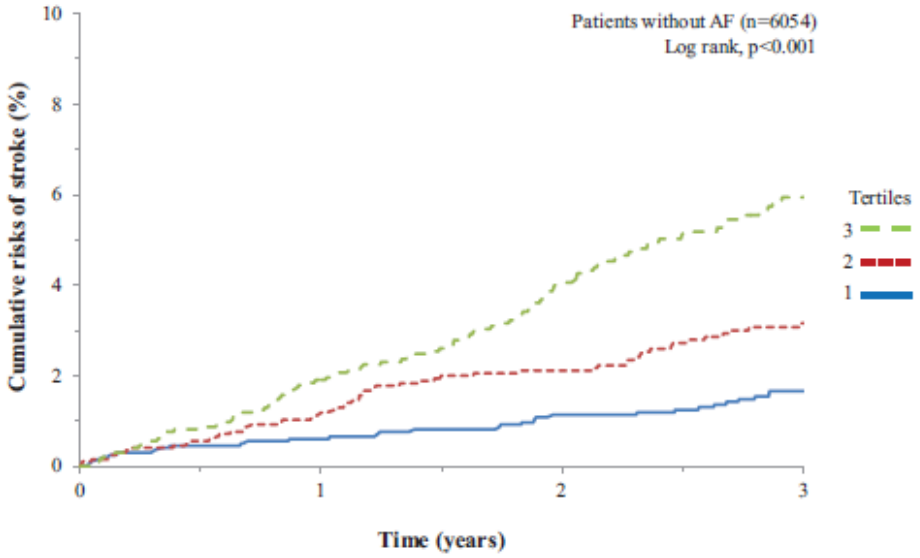
Risk of Stroke in Chronic Heart Failure Patients Without Atrial Fibrillation

Analysis of the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) Trials

Circulation. 2015;131:1486-1494.

Table 2. Best Clinical Model for Stroke Based on Forward Stepwise Cox Proportional Hazard Regression

Variables	Hazard Ratio	Lower 95% CI	Upper 95% CI	χ^2 Value	Coefficients	Standard Error	*P* Value
Age (per 10 y increase)	1.34	1.18	1.63	16.2	0.331	0.082	<0.001
NYHA class (NYHA III and IV)	1.60	1.21	2.12	10.8	0.472	0.143	0.001
Diabetes mellitus treated with insulin	1.87	1.22	2.88	8.1	0.626	0.220	0.004
BMI (per 5 kg/m^2 increase up to 30)	0.74	0.60	0.91	7.9	–0.301	0.107	0.005
Previous stroke	1.81	1.19	2.74	7.8	0.591	0.212	0.005



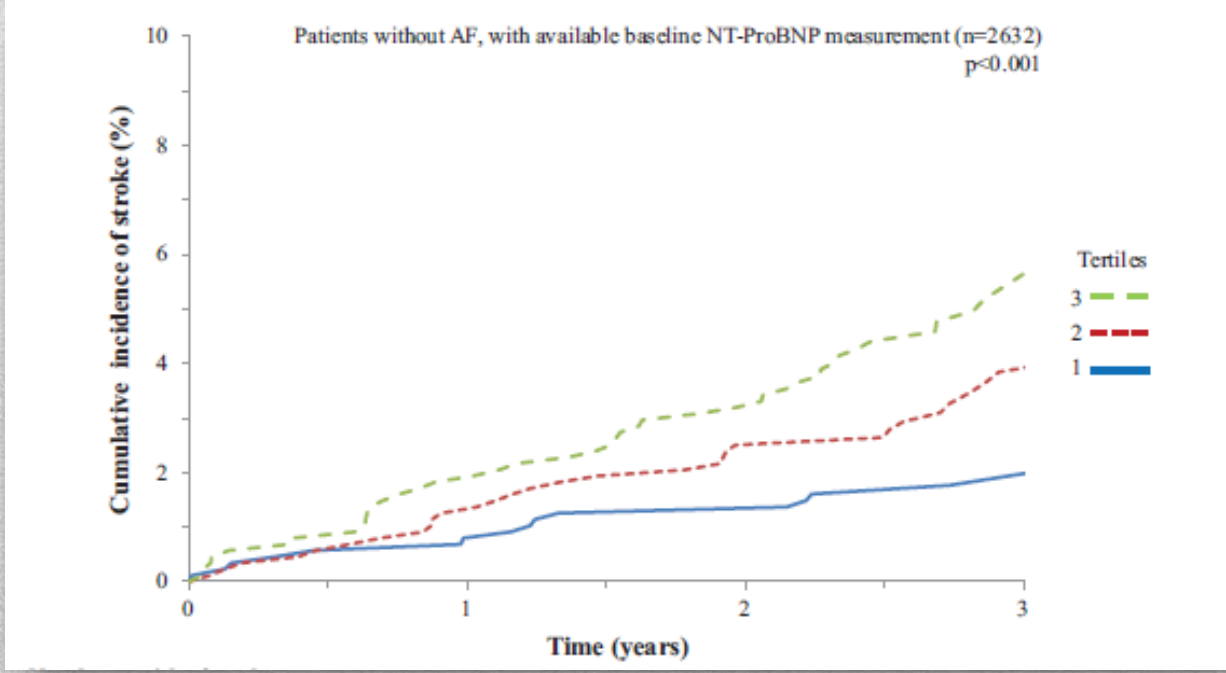
Risk of Stroke in Chronic Heart Failure Patients Without Atrial Fibrillation

Analysis of the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) Trials

Circulation. 2015;131:1486-1494.

Table 3. Final Model for Stroke Based on Forward Stepwise Cox Proportional Hazard Regression, Adding NT-proBNP to Independent Predictors Identified in Table 2 (n=2632)

Variables	Hazard Ratio	Lower 95% CI	Upper 95% CI	χ^2 Value	Coefficients	Standard Error	*P* Value
Log NT-ProBNP	1.32	1.11	1.57	10.4	0.280	0.087	0.001
Diabetes mellitus treated with insulin	2.09	1.19	3.70	6.5	0.739	0.290	0.011
Previous stroke	1.92	1.10	3.35	5.3	0.653	0.283	0.021



Risk of Stroke in Chronic Heart Failure Patients Without Atrial Fibrillation

Analysis of the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) Trials

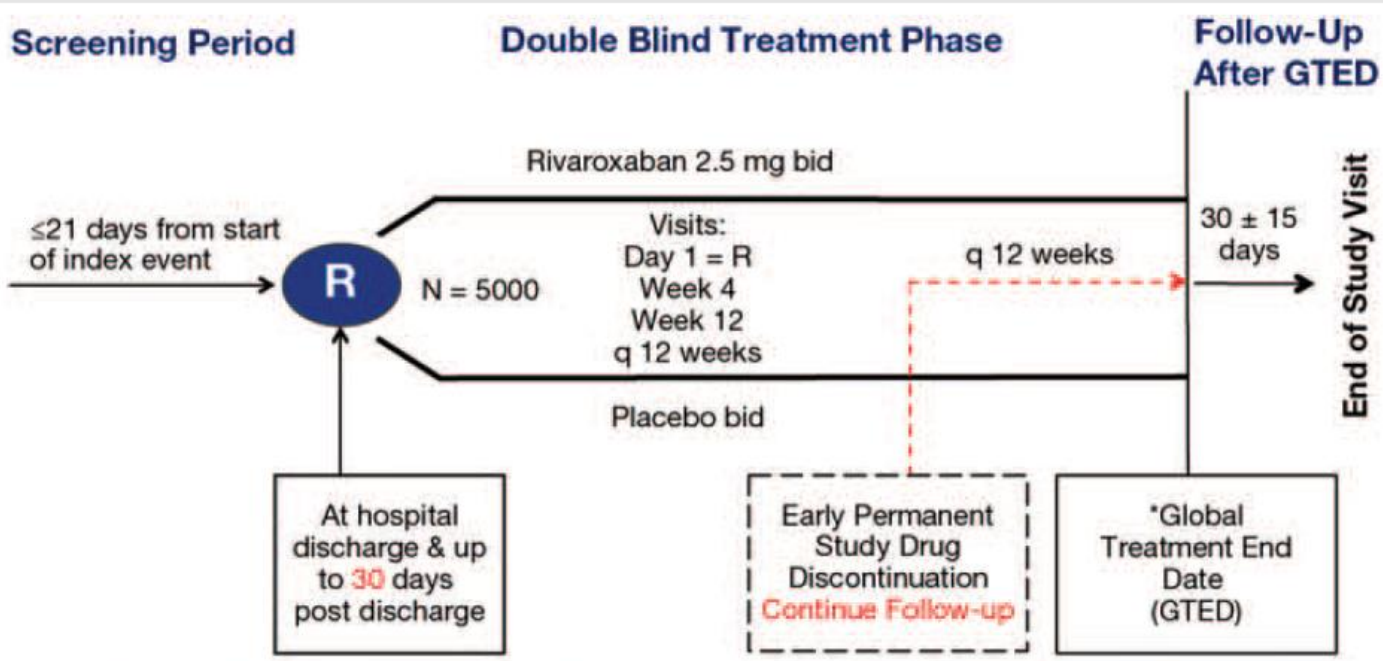
Circulation. 2015;131:1486-1494.

AF = 1.6% /year
No AF = 1.2% / year

No AF (upper tertile) = 2 % /year
AF no OAC = 2.2% / year

Rationale and design of a randomized, double-blind, event-driven, multicentre study comparing the efficacy and safety of oral rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an exacerbation of heart failure: the COMMANDER HF trial

European Journal of Heart Failure (2015)
doi:10.1002/ejhf.266



*Global Treatment End Date (GTED): date when targeted 984 primary outcome events are predicted to have occurred.