AF a risk factor or a risk marker: does it matter for therapy? - Drugs

Andrea Sarkozy
University Hospital of Antwerp
Belgium

EUROPEAN Heart Rhythm ASSOCIATION
A Registered Branch of the ESC

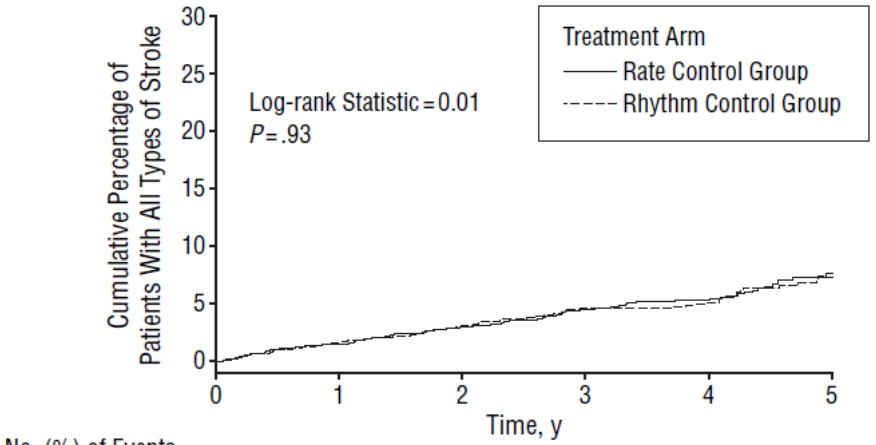
EUROPEAN SOCIETY OF CARDIOLOGY®

AF risk factor or risk marker for stroke; does it matter for drug therapy?

- Pharmacological rate vs. rhythm control
- Antiarrhythmic drugs
- Upstream therapy
- Global treatment of modifiable CV risk factors

Pharmacological rate vs. rhythm control

Pharmacological Rate vs rhythm control AFFIRM study



No. (%) of Events

Rate Control Group	2027, 1	1905, 31 (1.6)	1789, 59 (3)	1286, 83 (4.5)	745, 94 (5.5)	224, 105 (7.4)
Rhythm Control Group	2033, 0	1903, 34 (1.7)	1761, 62 (3.2)	1273, 85 (4.7)	749, 90 (5.2)	242, 104 (7.8)

Table 3. Anticoagulation Therapy and Sinus Rhythm at the Time of Stroke*

Variable	Total	Rate Control Group	Sinus Rhythm Control Group	*P* Value†
		Patients Who Had Ischemic Strokes		
Warfarin sodium use/INR at time of stroke	**152**	75	77	.79
Not receiving warfarin therapy	**69** (45.4)	25 (33.3)	44 (57.1)	.01
Receiving warfarin therapy				
INR <2.0	**44** (28.9)	27 (36.0)	17 (22.1)	
INR ≥2.0	**39** (25.7)	23 (30.7)	16 (20.8)	
Rhythm at time of stroke	**128**	61	67	<.001
AF	**67** (52.3)	42 (68.9)	25 (37.3)	
Sinus rhythm	**61** (47.7)	19 (31.1)	42 (62.7)	

Sherman DG Arch intern Med 2005;165:1185

Pharmacological Rate vs rhythm control AF-CHF study

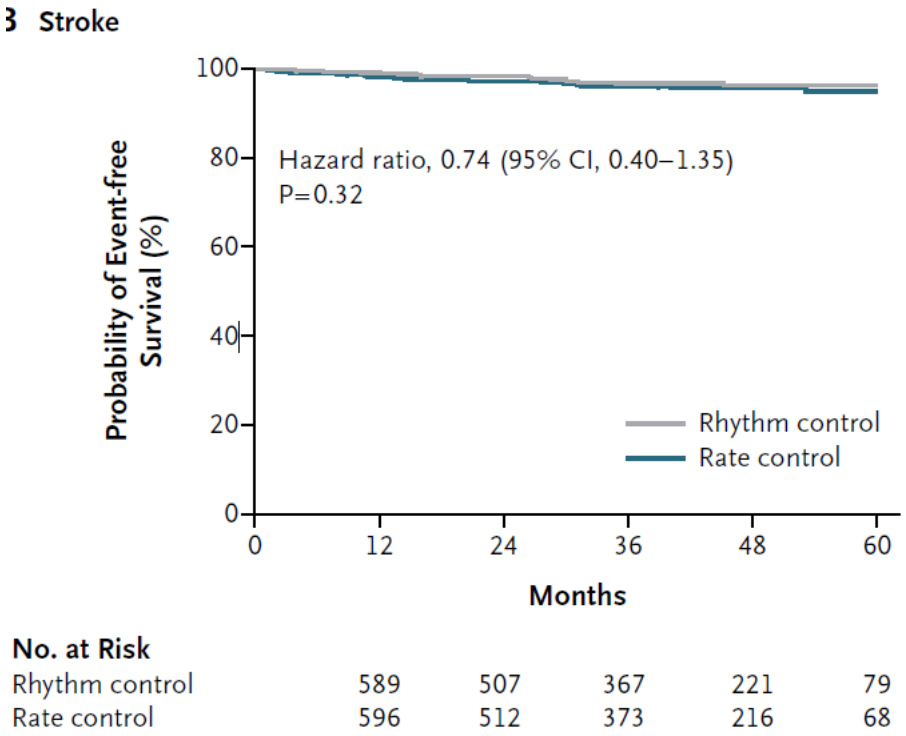


Table 2. Medical Therapy at 12 Months.*

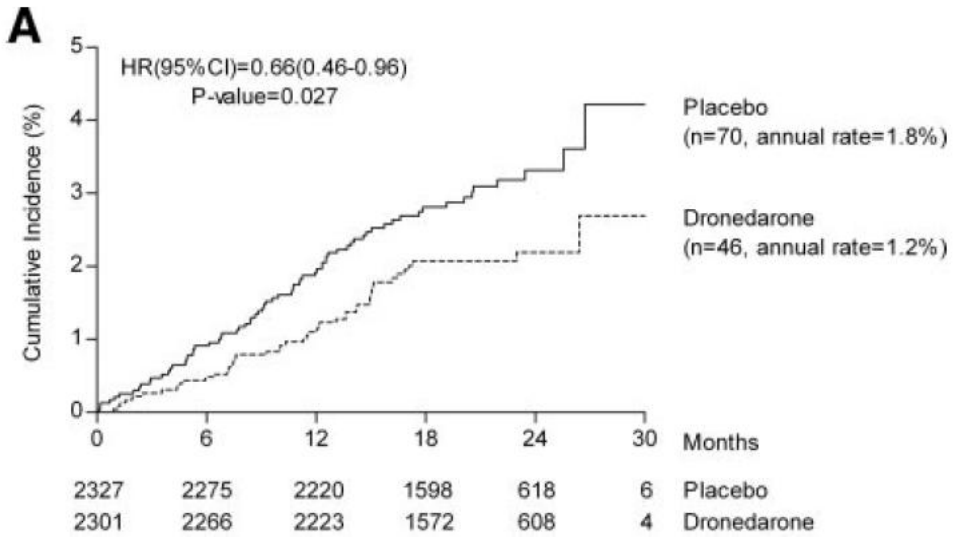
Drug	Rhythm-Control Group (N = 682)	Rate-Control Group (N = 694)	P Value
	percent		
Amiodarone	82	7	<0.001
Sotalol	2	<1	0.02
Dofetilide	<1	<1	0.62
Beta-blocker	80	88	<0.001
Digoxin	51	75	<0.001
Verapamil or diltiazem	2	3	0.10
ACE inhibitor	81	82	0.41
ARB	16	13	0.09
ACE inhibitor or ARB	94	94	0.57
Diuretic	80	82	0.37
Aldosterone antagonist	47	49	0.51
Oral anticoagulant	88	92	0.03
Aspirin	34	31	0.31
Lipid-lowering drug	44	46	0.61

- **58% of patients in the rhythm control group had at least one episode of recurrent AF**

Roy D New Eng J Med 2008;358:266

Antiarrhythmic drugs

Dronaderone – ATHENA trial

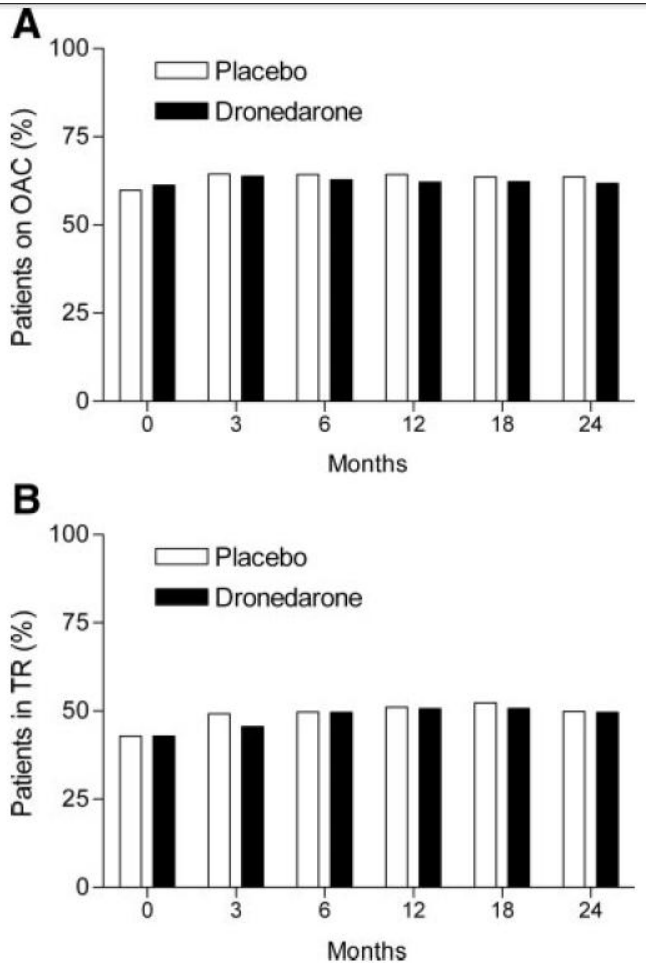


Connolly Circulation 2009;120:1174

Dronaderone – ATHENA trial

Table 1. Baseline Characteristics

	Placebo (n=2327)	Dronedarone (n=2301)
Age, mean (SD), y	72 (9)	72 (9)
Female gender, n (%)	1038 (45)	1131 (49)
AF/atrial flutter at baseline, n (%)	586 (25)	569 (25)
Mean baseline systolic BP (SD), mm Hg	134 (18)	135 (18)
History of CHF, n (%)	693 (30)	672 (29)
Hypertension, n (%)	1996 (86)	1999 (87)
Age ≥75 y, n (%)	978 (42)	947 (41)
Diabetes mellitus, n (%)	463 (20)	482 (21)
Prior stroke or TIA, n (%)	300 (13)	316 (14)
Mean $CHADS_2$ score (SD)	2.0 (1.1)	2.1 (1.1)
$CHADS_2$ 0–1, n (%)	846 (36)	793 (35)
$CHADS_2$ 2–3, n (%)	1234 (53)	1263 (55)
$CHADS_2$ 4–6, n (%)	247 (11)	245 (11)
$CHADS_2$ ≥2, n (%)	1481 (64)	1508 (66)
Baseline antithrombotic therapy, n (%)		
OAC only	1050 (45)	1055 (46)
OAC plus antiplatelet	334 (14)	348 (15)
Antiplatelet only	765 (33)	723 (31)
Neither OAC nor antiplatelet	178 (8)	175 (8)



Dronaderone PALLAS Trial

Characteristic	Dronedarone (N=1619)	Placebo (N=1617)
Age		
Mean — yr	75.0±5.9	75.0±5.9
65 to <75 yr — no. (%)	783 (48.4)	779 (48.2)
≥75 yr — no. (%)	836 (51.6)	838 (51.8)
Male sex — no. (%)	1051 (64.9)	1040 (64.3)
Heart rate — bpm	77±16	78±16
Systolic blood pressure — mm Hg	133±17	133±17
Inclusion risk criteria — no. (%)		
Coronary artery disease	661 (40.8)	666 (41.2)
Symptomatic heart failure†	233 (14.4)	240 (14.8)
Left ventricular ejection fraction ≤40%	345 (21.3)	335 (20.7)
Previous stroke or transient ischemic attack	436 (26.9)	458 (28.3)
Peripheral arterial disease	187 (11.6)	213 (13.2)
Age ≥75 yr plus hypertension and diabetes	294 (18.2)	276 (17.1)
$CHADS_2$ score‡		
Mean	2.8±1.2	2.9±1.2
≥2 — no. (%)	1427 (88.1)	1444 (89.3)
Duration of permanent atrial fibrillation >2 yr — no. (%)	1119 (69.1)	1124 (69.5)
Heart failure — no. (%)		
No history	512 (31.6)	535 (33.1)
New York Heart Association class I	234 (14.5)	209 (12.9)
New York Heart Association class II	732 (45.2)	749 (46.3)
New York Heart Association class III	141 (8.7)	124 (7.7)
Other risk factors		
Previous myocardial infarction	392 (24.2)	420 (26.0)
Prior coronary-artery bypass grafting	236 (14.6)	206 (12.7)
Permanent pacemaker	229 (14.1)	218 (13.5)
Hypertension	1352 (83.5)	1385 (85.7)
Diabetes mellitus	573 (35.4)	598 (37.0)

* Plus–minus values are means ±SD. There were no significant differences between the two study groups.

Connolly New Eng J Med 2011;365:2268

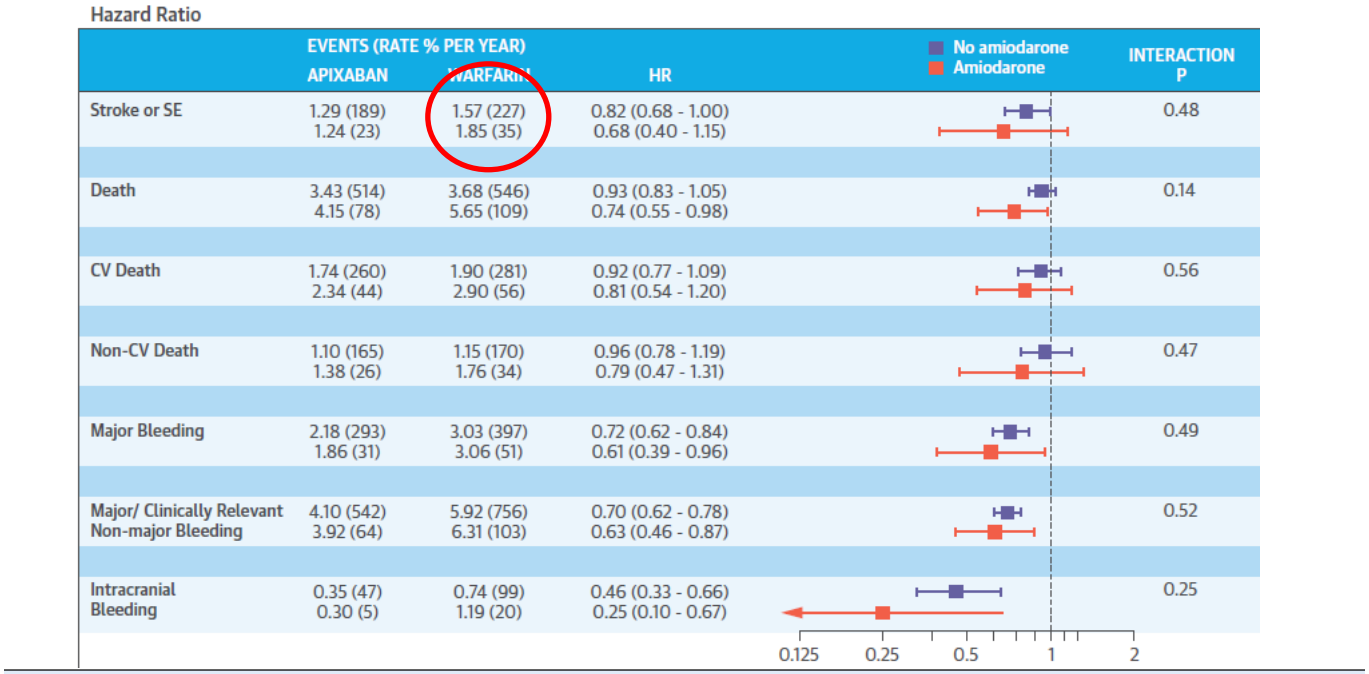
Dronaderone PALLAS Trial

Outcome	Dronedarone		Placebo		Hazard Ratio (95% CI)†	P Value
	No. of Events	Rate/100 Patient-Yr	No. of Events	Rate/100 Patient-Yr		
First coprimary outcome	43	8.2	19	3.6	2.29 (1.34–3.94)	0.002
Second coprimary outcome	127	25.3	67	12.9	1.95 (1.45–2.62)	<0.001
Death						
From any cause	25	4.7	13	2.4	1.94 (0.99–3.79)	0.049
From cardiovascular causes	21	4.0	10	1.9	2.11 (1.00–4.49)	0.046
From arrhythmia	13	2.5	4	0.8	3.26 (1.06–10.0)	0.03
Stroke						
Any‡	23	4.4	10	1.9	2.32 (1.11–4.88)	0.02
Ischemic	18	3.4	9	1.7	2.01 (0.90–4.48)	0.08
Systemic embolism	1	0.2	0	0.0	NA	NA
Myocardial infarction or unstable angina	15	2.9	8	1.5	1.89 (0.80–4.45)	0.14
Myocardial infarction	3	0.6	2	0.4	1.54 (0.26–9.21)	0.63
Unplanned hospitalization for cardiovascular causes	113	22.5	59	11.4	1.97 (1.44–2.70)	<0.001
Hospitalization for heart failure	43	8.3	24	4.6	1.81 (1.10–2.99)	0.02
Heart-failure episode or hospitalization§	115	23.2	55	10.7	2.16 (1.57–2.98)	<0.001

* The first coprimary outcome was a composite of stroke, myocardial infarction, systemic embolism, or death from cardiovascular causes. The second coprimary outcome was a composite of unplanned hospitalization for cardiovascular causes or death. NA denotes not applicable.

Connolly New Eng J Med 2011;365:2268

Amiodarone – ARISTOTLE study



CENTRAL ILLUSTRATION **Patient Outcomes by Amiodarone Use at Randomization**

Event rates and hazard ratios (HRs) comparing apixaban to warfarin by amiodarone use at randomization. CV = cardiovascular; SE = systemic embolism.

- **2051 pts on amiodarone younger, more CHF, less diabetes and previous stroke**
- **Amiodarone stroke/SE rate: 1.58% vs. 1.19 % without amiodarone (p=0.03)**
- **TTR Warfarin + Amiodarone 56.5% vs. warfarin 63%, p<0.0001**

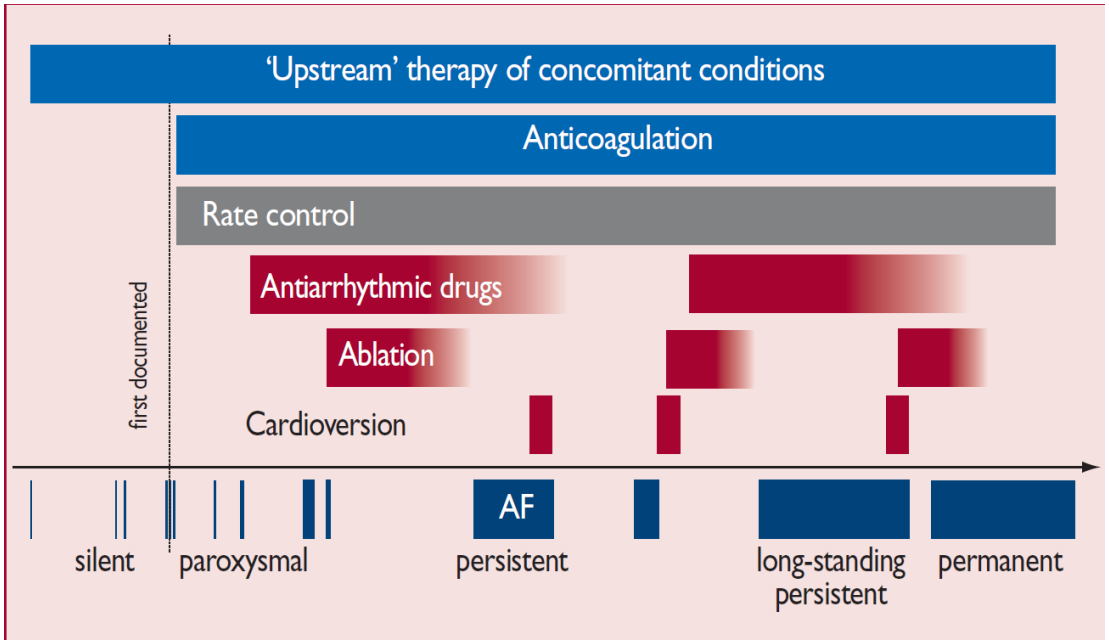
Flaker J Am Col Cardiol 2014;64:1541

EUROPEAN Heart Rhythm ASSOCIATION

EUROPEAN SOCIETY OF CARDIOLOGY®

Upstream therapy

Upstream therapy



- **Modifying atrial substrate to reduce susceptibility to (primary prevention) or progression of AF (secondary prevention) through antifibrotic, antioxidative, antiinflamatory antiarrhythmic effect**

- **ACE inhibitors/ARBs, Statins, N-3 polyunsaturated fatty acids**

Camm Eur Heart J 2010, January Circulation 2014,130:199

Upstream therapy

Recommendations for primary prevention of AF with 'upstream' therapy

Recommendations	Class[a]	Level[b]	Ref.[c]
ACEIs and ARBs should be considered for prevention of new-onset AF in patients with heart failure and reduced ejection fraction.	IIa	A	145–149
ACEIs and ARBs should be considered for prevention of new-onset AF in patients with hypertension, particularly with left ventricular hypertrophy.	IIa	B	147, 150, 151
Statins should be considered for prevention of new-onset AF after coronary artery bypass grafting, isolated or in combination with valvular interventions.	IIa	B	161, 162
Statins may be considered for prevention of new-onset AF in patients with underlying heart disease, particularly heart failure.	IIb	B	164, 165
Upstream therapies with ACEIs, ARBs, and statins are not recommended for primary prevention of AF in patients without cardiovascular disease.	III	C	

Recommendations for secondary prevention of AF with 'upstream' therapy

Recommendations	Class[a]	Level[b]	Ref.[c]
Pre-treatment with ACEIs and ARBs may be considered in patients with recurrent AF undergoing electrical cardioversion *and* receiving antiarrhythmic drug therapy.	IIb	B	145–147, 152–153
ARBs or ACEIs may be useful for prevention of recurrent paroxysmal AF or in patients with persistent AF in the absence of significant structural heart disease if these agents are indicated for other reasons (e.g. hypertension).	IIb	B	145, 155–156

Camm Eur Heart J 2010

Global treatment concept of modifiable CV risk factors

ARREST-AF study

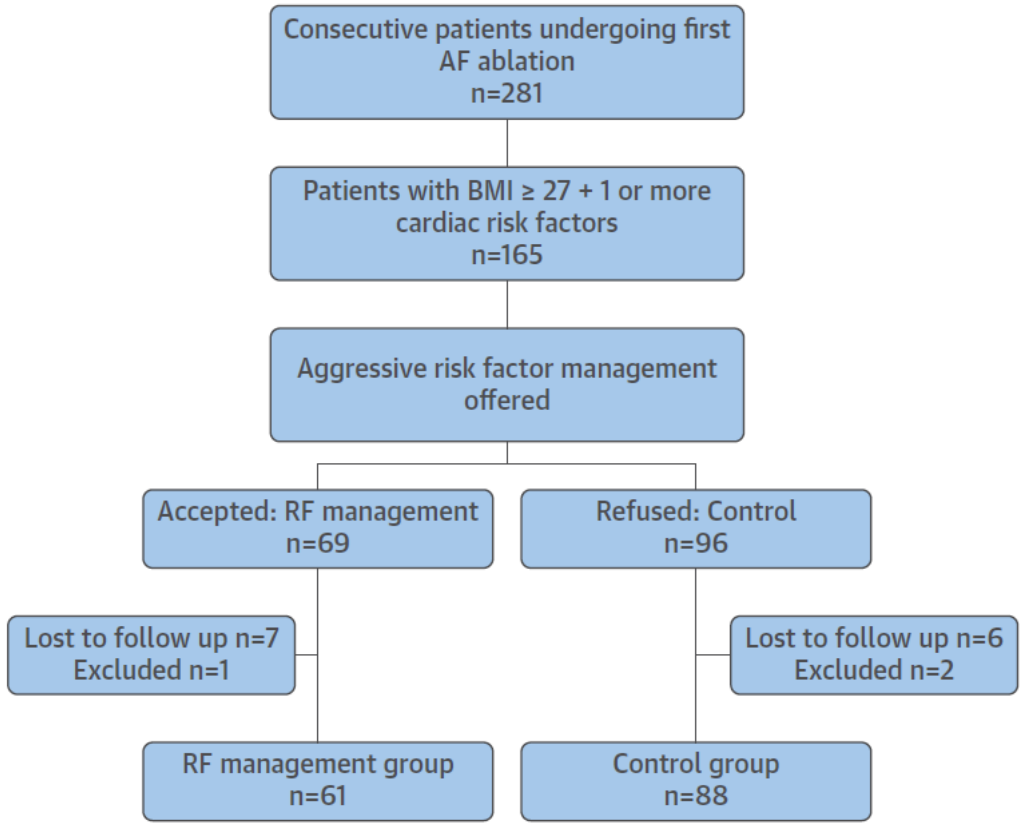


FIGURE 1 Patient Selection

RFM

- BP control: 80%<130/80 Hgmm
- Weight control: BMI<25
- Lipid control: LDL<100 mg/dl + TG + HDL
- Glycemic control: HbA1c<7%
- Sleep disorder management: AHI>30 or 20 HTN: CPAP
- Smoking cessation
- Alcohol (<30g/week)

Pathak J Am Coll Cardiol 2014:64:2222

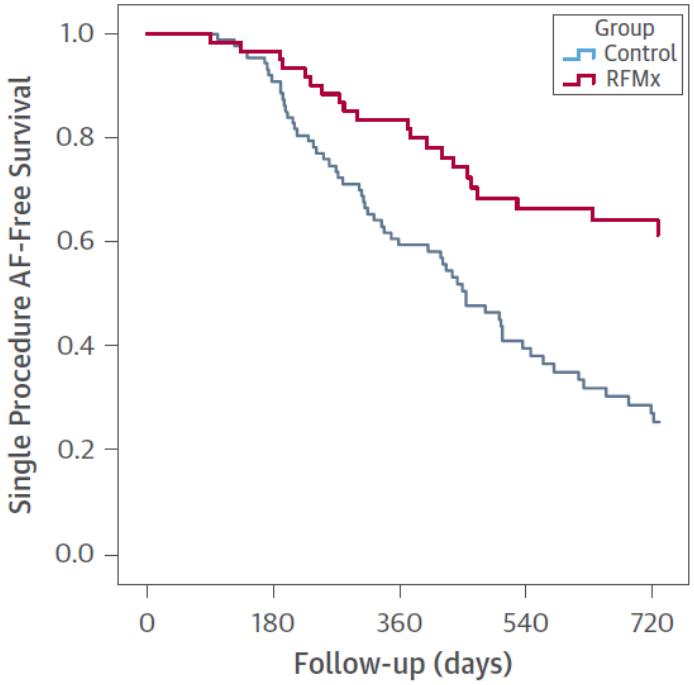
ARREST-AF study

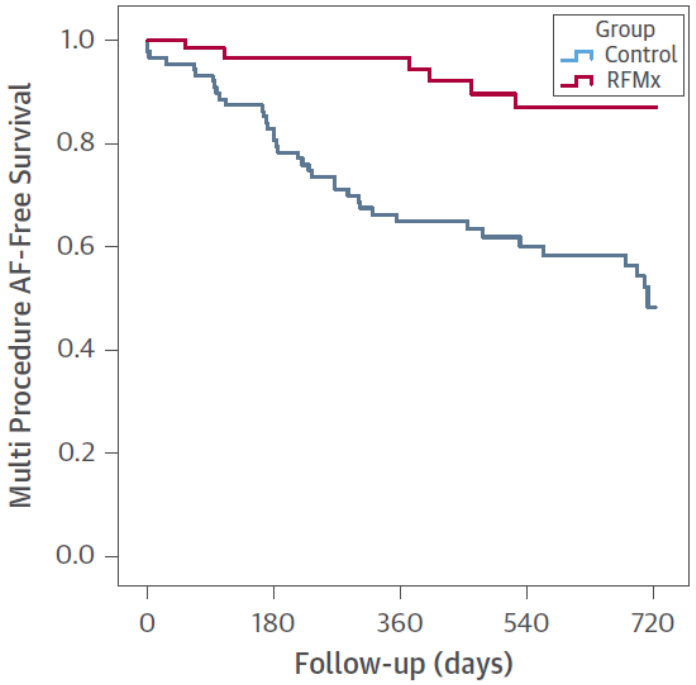
TABLE 2 Risk Factor, Echocardiographic, and AF Severity Changes

	Control Group (n = 88)			RFM Group (n = 61)			
	Baseline	Follow-Up‡	p Value*	Baseline	Follow-Up‡	p Value*	p Value†
Risk factors							
Weight, kg	96.6 ± 16.8	95.8 ± 17.6	0.13	100.7 ± 17.6	87.5 ± 14.9	<0.001	0.002
BMI, kg/m^2	32.1 ± 4.7	31.8 ± 4.9	0.12	33.5 ± 4.6	29.1 ± 3.9	<0.001	<0.001
Mean SBP, mm Hg	158.7 ± 21.3	138.2 ± 18.0	<0.001	160.8 ± 20.3	126.8 ± 12.8	<0.001	0.006
DM with HbA_{1c} ≥7%, n	17	5		9	0		0.001
No. with AHI >30	54	46		32	16		<0.001
Medication use							
No. of antiarrhythmic agents	1.0 ± 0.2	0.7 ± 0.7	<0.001	1.1 ± 0.3	0.3 ± 0.6	<0.001	<0.001
No. of antihypertensive agents	1.6 ± 1.2	1.9 ± 1.3	0.2	1.5 ± 1.1	1.2 ± 0.9	0.04	<0.001
Echocardiographic measures							
LA volume index, ml/m^2	42.4 ± 10.4	39.5 ± 12.1	0.07	42.5 ± 12	30.4 ± 8.3	<0.001	0.001
LV septum, mm	11.0 ± 2.0	10.9 ± 0.19	0.047	12.0 ± 2.0	9.6 ± 0.17	<0.001	<0.001
LVIDd, cm	5.1 ± 0.7	5.1 ± 0.6	0.204	5.3 ± 0.5	4.9 ± 0.6	<0.001	0.047
LVEF, %	60 ± 10.1	61.1 ± 8	0.538	61.3 ± 10	62.6 ± 5.5	0.524	0.971
Atrial Fibrillation Severity Score							
AF frequency (1-10)	6.6 ± 1.1	3.2 ± 1.1	<0.001	6.8 ± 1.2	2.0 ± 0.9	<0.001	<0.001
AF duration (1.25-10)	6.7 ± 1.3	3.3 ± 1.3	<0.001	6.4 ± 1.6	2.1 ± 0.9	<0.001	0.001
AF episode severity (1-10)	6.9 ± 1.3	5.2 ± 1.9	<0.001	6.6 ± 1.5	3.3 ± 1.5	<0.001	<0.001
AF symptom subscale (0-35)	23.1 ± 3.7	13.3 ± 6.2	<0.001	22 ± 5.2	7.1 ± 4.6	<0.001	<0.001
Global well-being (1-10)	2.5 ± 0.9	5.7 ± 2.0	<0.001	2.4 ± 0.9	7.6 ± 1.7	<0.001	<0.001

Pathak J Am Coll Cardiol 2014:64:2222

ARREST-AF study





Time (days)	0	180	360	540	730
RFM	61	59	48	33	27
Control	88	79	51	28	16

0	180	360	540	730
61	55	46	32	25
88	72	51	36	23

FIGURE 3 Outcomes of AF Ablation

Pathak J Am Coll Cardiol 2014:64:2222

Current underuse of CVR prevention therapies

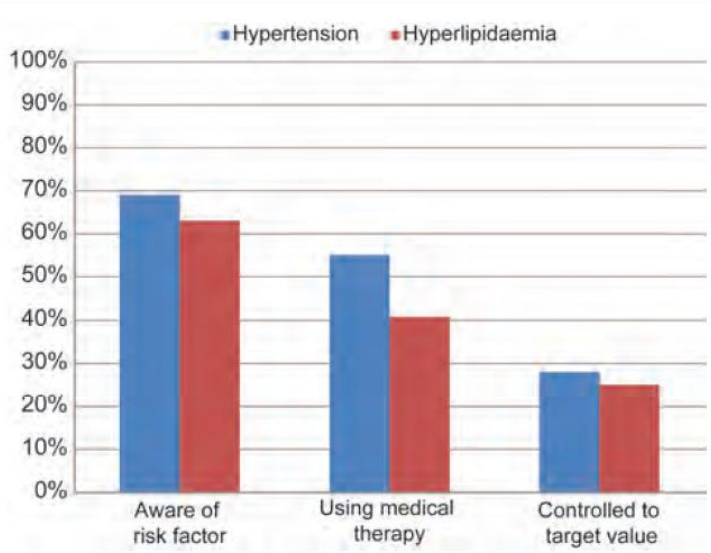
European Heart Journal (2013) **34**, 1262–1269
doi:10.1093/eurheartj/ehs481

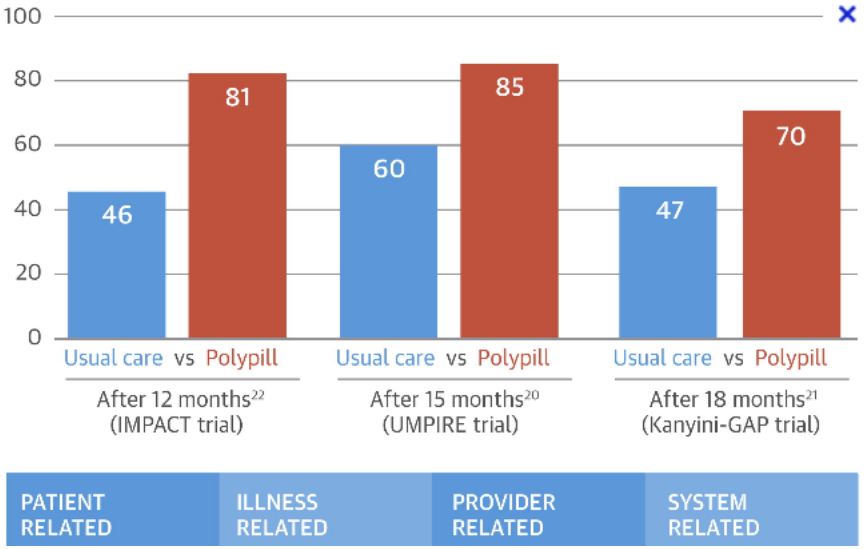
REVIEW

Controversies in cardiovascular medicine

Why are we failing to implement effective therapies in cardiovascular disease?

Robby Nieuwlaat[1,2]*, Jon-David Schwalm[2,3], Rasha Khatib[2], and Salim Yusuf[2,3]





Castellano J Am Coll Cardiol 2014:64:613

Polypill concept

European Heart Journal (2014) **35**, 353–364
doi:10.1093/eurheartj/eht407

REVIEW

Controversies in cardiovascular medicine

Combination pharmacotherapy to prevent cardiovascular disease: present status and challenges

Working Group on the Summit on Combination Therapy for CVD†

Table 2 Estimated relative risk reductions in cardiovascular disease with a combination pill based on impact on risk factors from four trials

	Parallel-group RCTs									Crossover RCT		
	Half standard-dose Polycap (based on TIPS-1)			Standard-dose Polycap (based on TIPS-1 and TIPS-2)			PILL collaborative group			Wald 2012[b]		
	Risk factor Reduction	eRRR in events		Risk factor Reduction	eRRR in events		Risk factor Reduction	eRRR in events		Risk factor Reduction	eRRR in events	
		CHD	Stroke		CHD	Stroke		CHD	Stroke		CHD	Stroke
LDL-C(mg/dL)	−27.0	27%	8%	−33.6	33%	10%	−30.9	35%	23%	−54.1	54%	16%
DBP(mmHg)	−5.6	24%	33%	−7.3	32%	43%	−5.3	22%	41%	−9.8	42%	58%
LDL-C and BP	NA	44%	33%	NA	54%	49%	NA	NA	NA	NA	NA	NA
Aspirin only[a]	NA	32%	16%	NA	32%	16%	NA	20%	17%	NA	32%	16%
LDL-C and BP and Aspirin (e.g. secondary prevention)		62%	48%		69%	57%		60%	56%		72%	64%

Combination-pill constituents: TIPS-1 (half standard-dose Polycap) = aspirin 100 mg, simvastatin 20 mg, ramipril 5 mg, hydrochlorothiazide 12.5 mg, atenolol 50 mg; TIPS-2 (standard-dose Polycap) = aspirin 200 mg, simvastatin 40 mg, ramipril 10 mg, hydrochlorothiazide 25.mg, atenolol 100 mg; PILL collaborative polypill = aspirin 75 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg, simvastatin 20 mg; Wald 2012 = amlodipine 2.5 mg, losartan 25 mg, hydrochlorothiazide 12.5 mg, simvastatin 40 mg.

TIPS, The Indian Polycap Study; PILL, Programme to Improve Life and Longevity; LDL-C, LDL cholesterol; DBP, diastolic blood pressure; eRRR, estimated relative risk reduction.

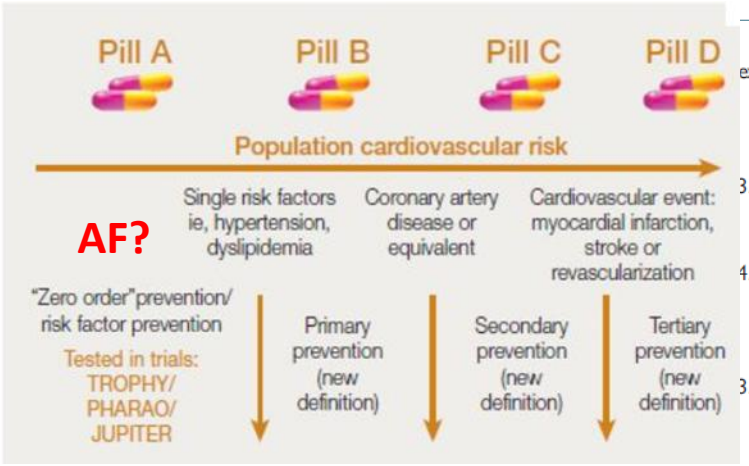
[a]As projected by Wald and Law, which is higher than that observed in the antithrombotic trialists meta-analyses.

[b]Participants had already received the medications for a prolonged period prior to randomization, due to high CVD risk and had higher baseline LDL-C and BP levels than other studies. Therefore, the data are not comparable.

Polypill concept

On-going studies (results not yet published)

Kanyini-GAP/ ACTRN12608000583347/ Ref.[55,64]	$n = 623/\geq 18$ years with CVD or 5-year CVD risk ≥15% among indigenous and non-indigenous people in Australia	Open-label RCT of choice of formulations vs. usual care months	expected in
FOCUS/ NCT01321255/Ref.[53]	$n = 1340/\geq 40$ years post- myocardial infarction patients in Argentina, Brazil, Italy, Paraguay, Spain	RCT of polypill vs. individual component drugs/9 month	3.
IMPACT/ ACTRN12606000067572/ Ref.[56]	$n = 513/\geq 18$–79 years with CVD or 5-year CVD risk ≥15% in indigenous Maori and non-indigenous people in New Zealand	Open-label RCT of choice of polypill formulations vs. us 12–30 months	4.
TEMPUS/ ISRCTN36672232/Ref.[54]	$n = 75$ (target)/≥18 years with CVD or 5-year CVD risk ≥10% in the Netherlands	PROBE crossover trial of eve morning polypill vs. individ components with 6–8 wee treatment	3.



Studies Assessing Impact on Cardiovascular Events

On-going Studies (Results not yet published)

HOPE-3/ NCT00468923[50]	$n = 12{,}705$/Men ≥55 years and women ≥60 years with at least 1 CV risk factor and with average BP and cholesterol levels in 22 countries.	2 × 2 factorial design rosuvastatin vs. placebo and candesartan/ hydrochlorothiazide vs. placebo/6 years	Fixed dose candesartan 16 mg and hydrochlorothiazide 12.5 mg or placebo with rosuvastatin 10 mg or placebo	Completed recruitment. Results expected in 2016.
TIPS-3/ NCT01646437[51]	$n = >5500$ (target)/Men ≥55 years and women ≥ 60 years with an INTERHEART risk score of ≥10 in India, Philippines, Canada, China, Brazil, Argentina, Chile, and Columbia	2 × 2 × 2 factorial of polypill vs. placebo; 75 mg aspirin vs. placebo; vitamin D (60 000 IU monthly) vs. placebo/5 years	Hydrochlorothiazide 25 mg, atenolol 100 mg, ramipril 10 mg, simvastatin 40 mg	Expected completion 2018
PolyIran/ NCT01271985[58]	$n = 7000$ (target)/50–79 years and enrolled in the Golestan Cohort Study in Iran	Open cluster RCT of polypill and minimal care vs. minimal care alone vs. usual primary care/5 years	Aspirin 81 mg, enalapril 5 mg (or valsartan 40 mg), atorvastatin 20 mg and hydrochlorothiazide 12.5 mg	Expected completion 2018
HOPE-4/ NCT01826019[57]	$n = 190$ communities and 9500 participants (target)/≥50 years with HT or history of CV risk factors in Colombia, Malaysia, Philippines, India, Argentina, South Africa, Tanzania, and Rwanda.	Cluster RCT with NPHW intervention of education and lifestyle counselling; three polypill formulations; treatment supporters/ text-messaging vs. usual care/6 years	Standard dose of simvastatin (40 mg), Atenolol (100 mg), Ramipril (10 mg), hydrochlorothiazide (25 mg) with and without ASA (100 mg) as well as half-dose of this formulation with and without ASA (100 mg)	Recruitment to pilot hypertension phase to start in 2014.

Yusuf Eur Heart J 2014:35:353

Conclusions

- **Rhythm control, antiarrhythmic drugs and upstream therapy with ACE/ARB, statins and fish oil does not substantially decrease the risk of stroke in AF**

- **Aggressive global treatment of the modifiable CV risk factors is currently the most important pharmacological therapy to reduce AF burden in each patient at risk of or with AF**
  - **Target BP:<140/90 Hgmm, HgA_{1c}<7%, LDL<100 mg/dl in each AF patient should be ensured (+weight, sleep disorder and lifestyle management)**
  - **Further studies should confirm the effect of these therapies on stroke incidence and AF recurrence but it does seem to matter**

- **Polypill concept for primary and secondary prevention of stroke in patients with (and without) AF and with or without CVR risk factors although controversial, is emerging**