The role of Irbesartan on the Development and Recurrence of Atrial Fibrillation in Hypertension

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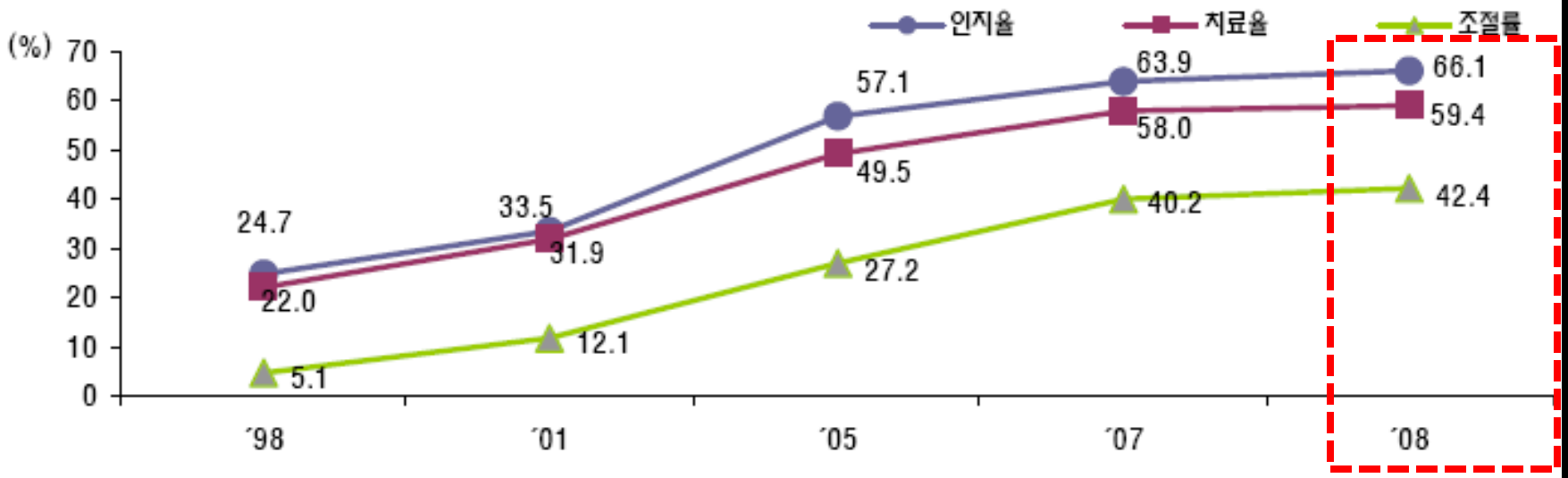
Contents

Hypertension Control in Korea

그림 37. 고혈압 관리현황

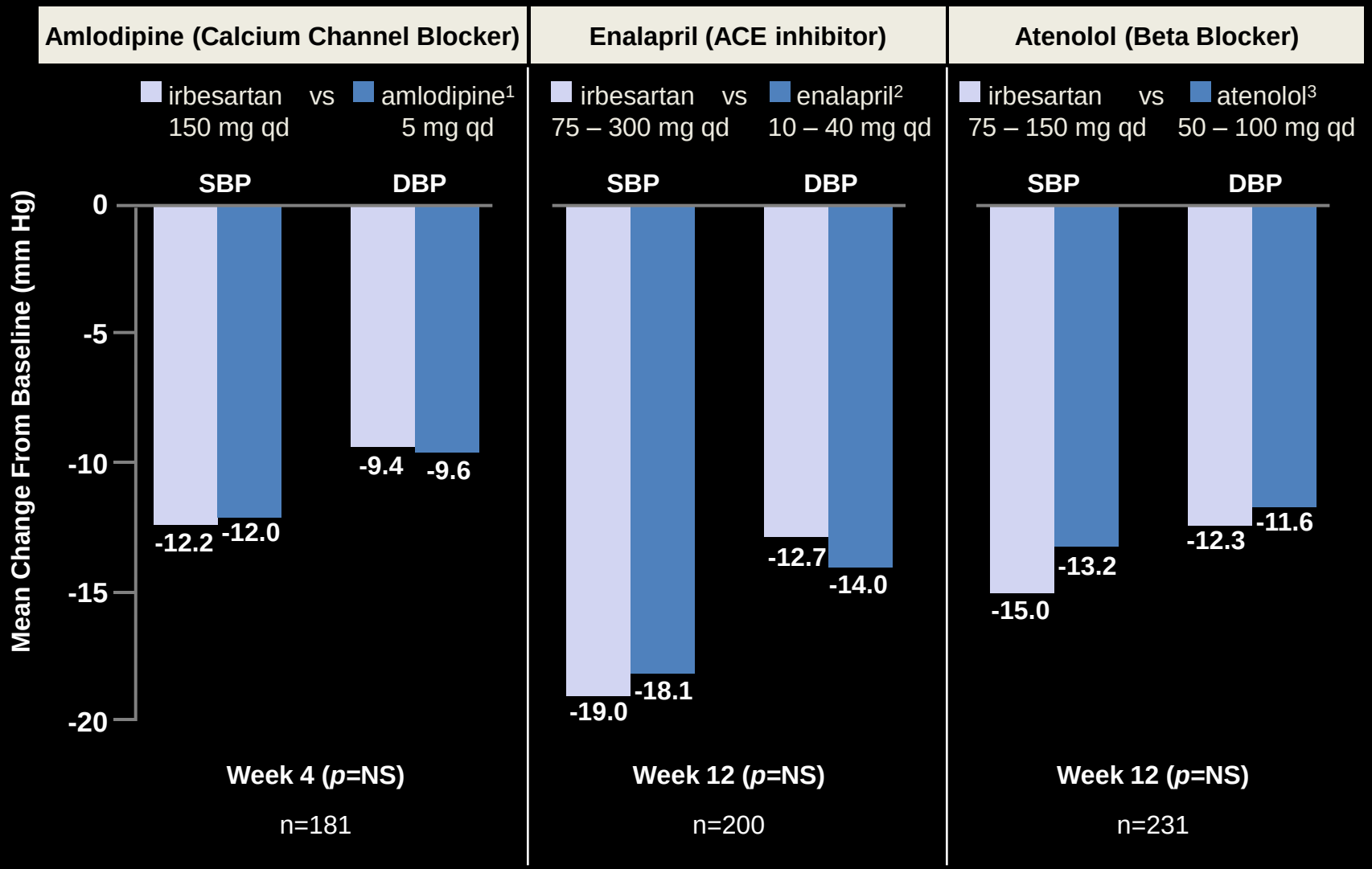


※인지율 : 고혈압 유병자중 의사로부터 고혈압 진단을 받은 분율, 만30세이상
치료율 : 고혈압 유병자중 혈압강하제를 한달에 20일 이상 복용한 분율, 만30세이상
조절률(유병자기준) : 고혈압 유병자중 수축기혈압 140mmHg 미만이면서 이완기혈압 90mmHg 미만인 분율, 만30세이상
※2005년 고혈압추정인구(2005년 추계인구×2005년 고혈압 유병률)로 연령표준화

고혈압 조절율은 꾸준히 증가하고 있으나, 여전히 개선이 요구된다.

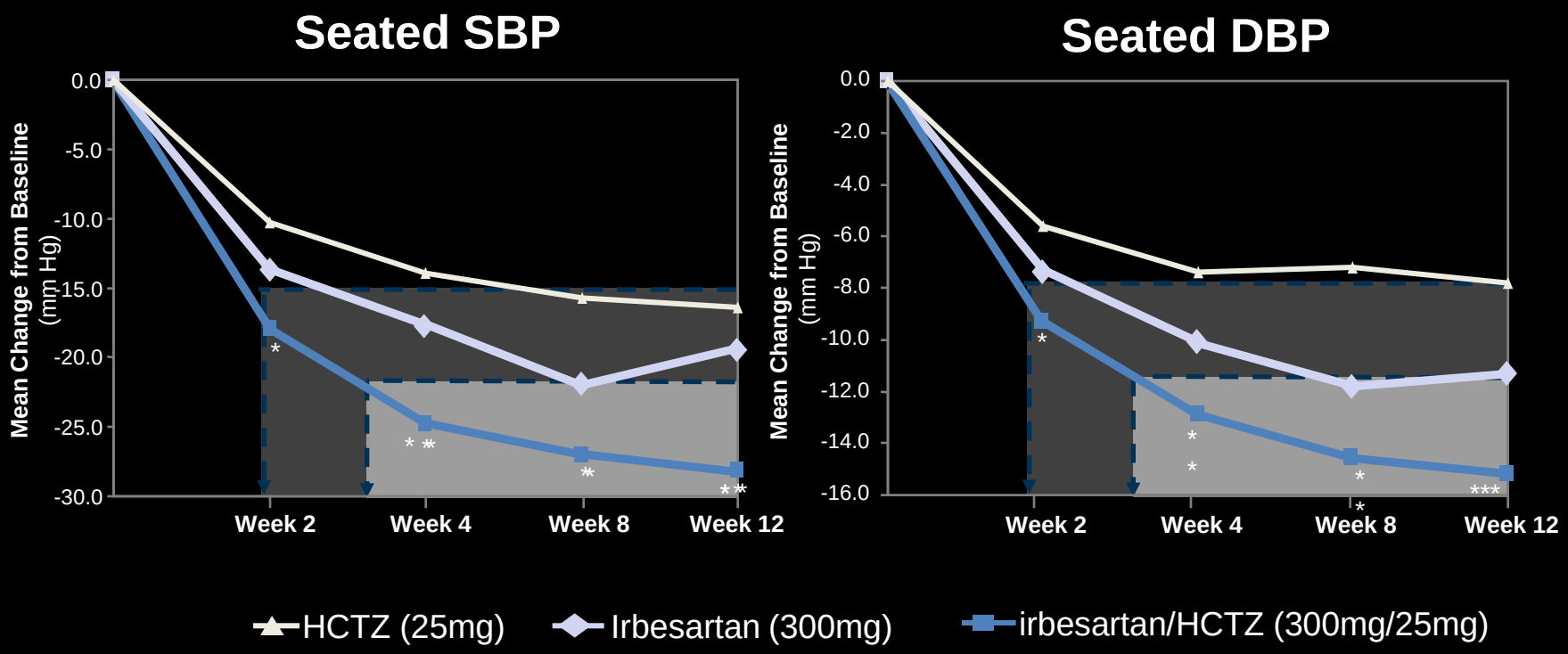
2008 국민건강통계 p51

BP lowering efficacy of irbesartan



1. Neutel J *et al. JRAAS* 2005; 6:84-89.
2. Mimran A *et al*. *J Hum Hypertens* 1998;12:203-208.
3. Stumpe KO *et al*. *Blood Press* 1998;7:31-37.

Irbesartan in mono- or combination



*P<0.0001 vs HCTZ; P<0.01 vs irbesartan
**P<0.0001 vs HCTZ; P<0.0001 vs irbesartan

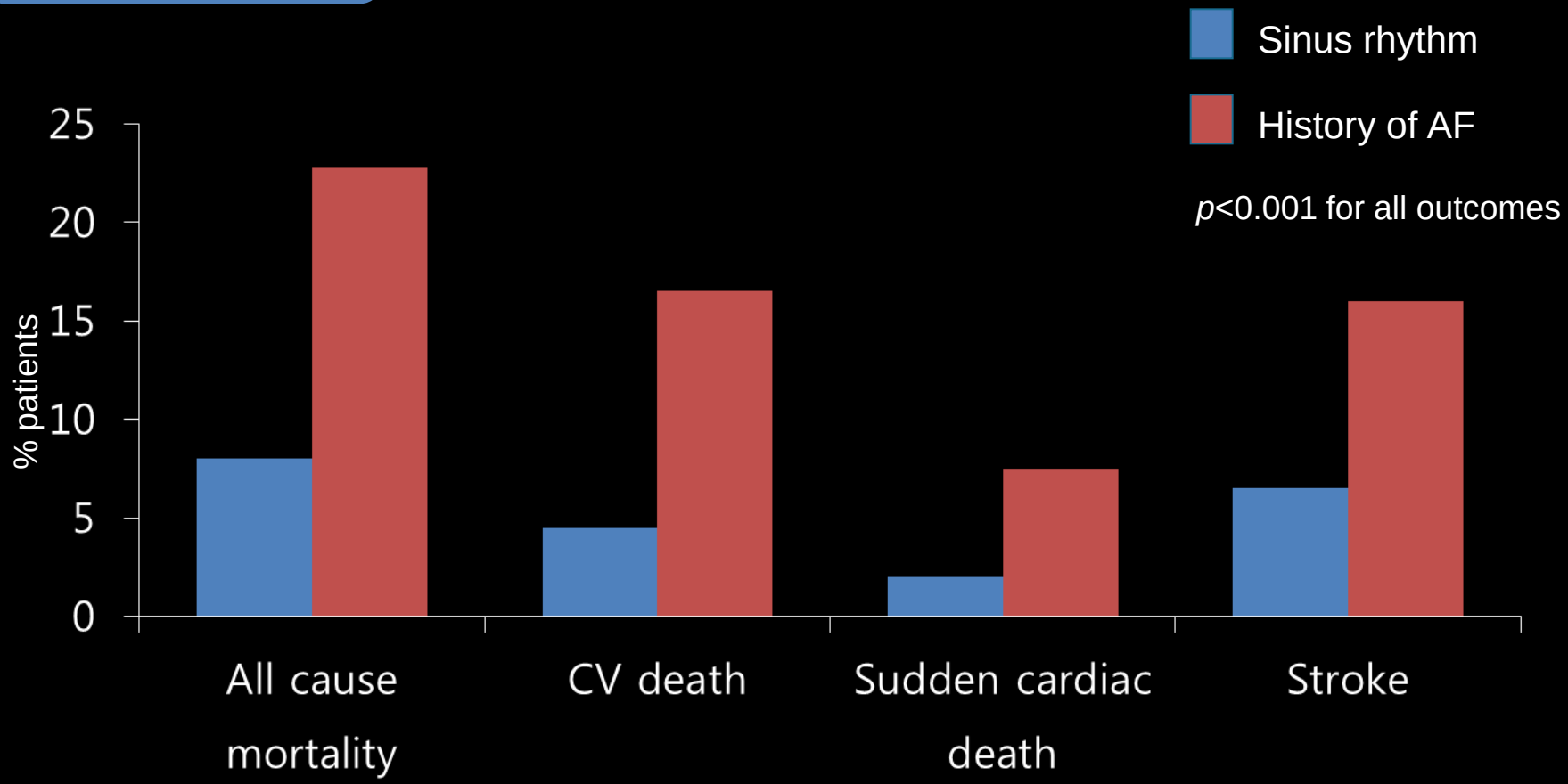
*P<0.0001 vs HCTZ; P<0.05 vs irbesartan
**P<0.0001 vs HCTZ; P<0.01 vs irbesartan
***P<0.0001 vs HCTZ; P<0.0001 vs irbesartan

Neutel *et al*, J Hum Hypert 2008 Apr: 22(4):266 – 74

2. Hypertension as a risk factor of Atrial Fibrillation

Patients with Hypertension and new onset AF Have Higher Rates of CV and All-cause Mortality

LIFE



Wachtell K, et al. J Am Coll Cardiol. 2005;45:705-711

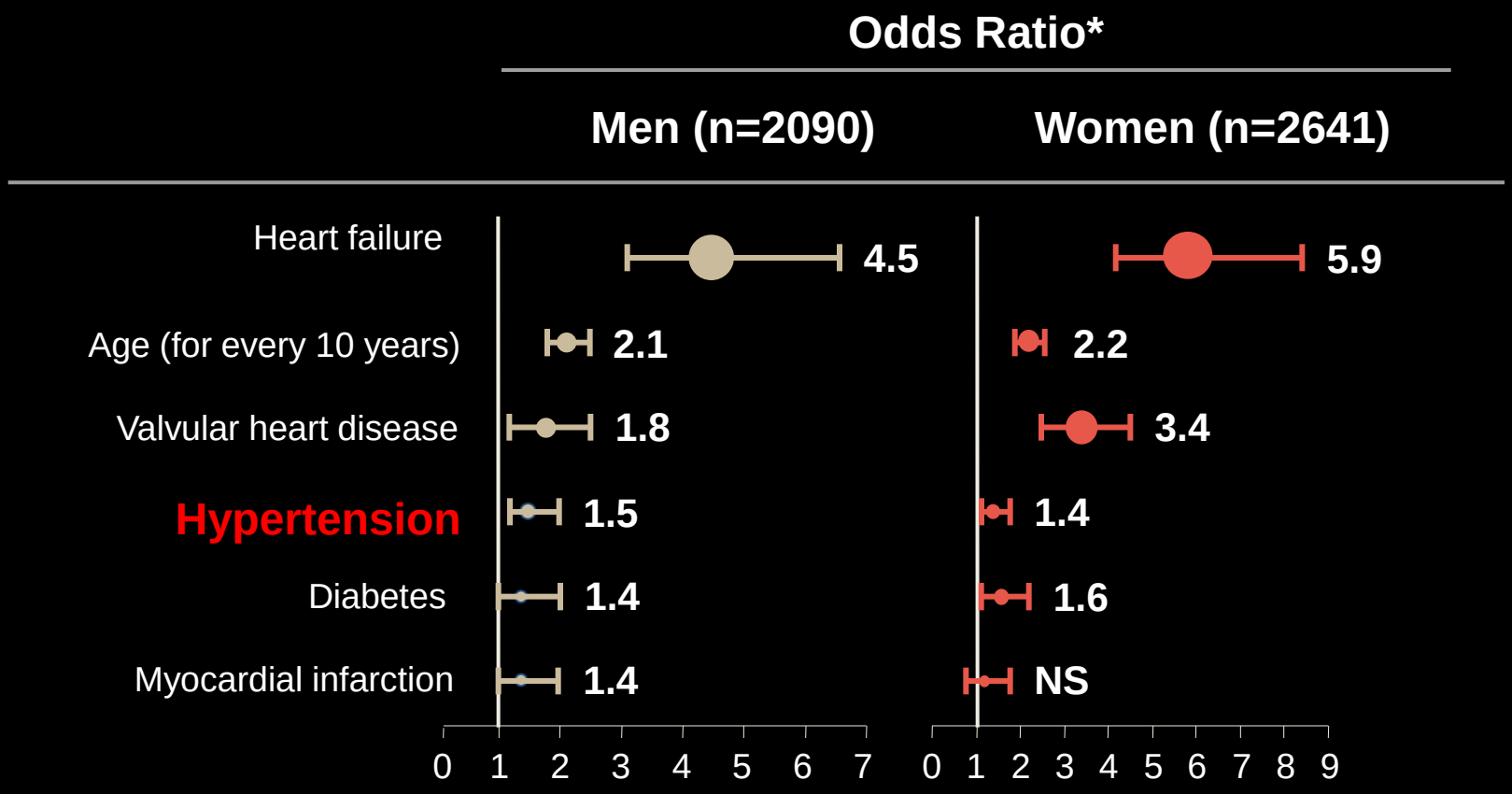
AF Worsens the Prognosis of Patients with Comorbidities

Patients with new onset AF	Events	Risk
Hypertension[1] • n=8851 • Follow-up: 4.8 ± 1years	Cardiovascular events	X 1.88
	Fatal and non-fatal stroke	X 3
	Hospitalisation for heart failure	X 5
CHF[2] • n=1470 • Follow-up: 5.6 years	Mortality in men	X 1.6
	Mortality in women	X 2.7
MI[3] • n= 17944 • Follow-up: 4 years	In-hospital mortality	X 1.98
	Long-term mortality (4 years)	X 1.78

1. Adapted from Wachtell K, *et al. J Am Coll Cardiol*. 2005;45:712–719.
2. Adapted from Wang *et al. Circulation* 2003;107:2920–2925.
3. Adapted from Pizzetti F, *et al. Heart*. 2001;86:527–532.

Hypertension is an Independent Risk Factor for AF

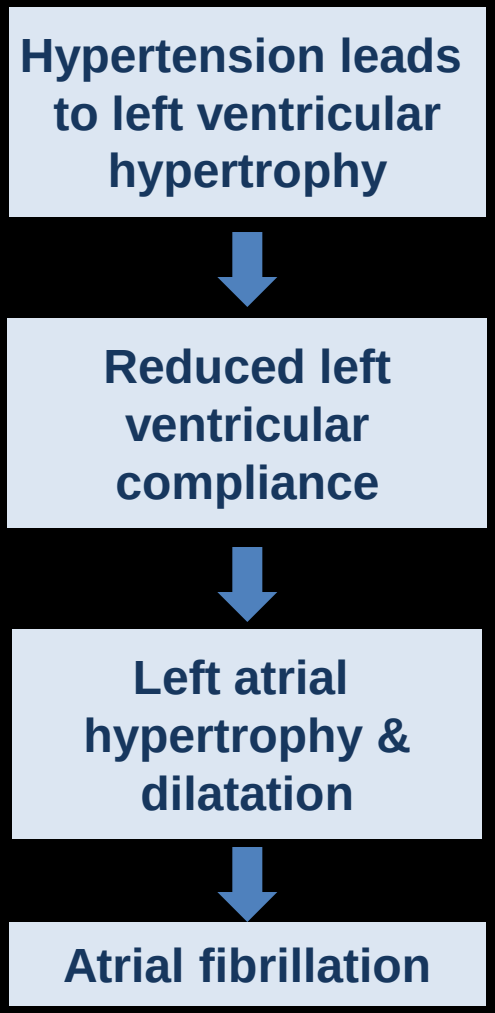
Framingham



*2-year pooled logistic regression.

Benjamin EJ, *et al. JAMA*. 1994;271:840-844.

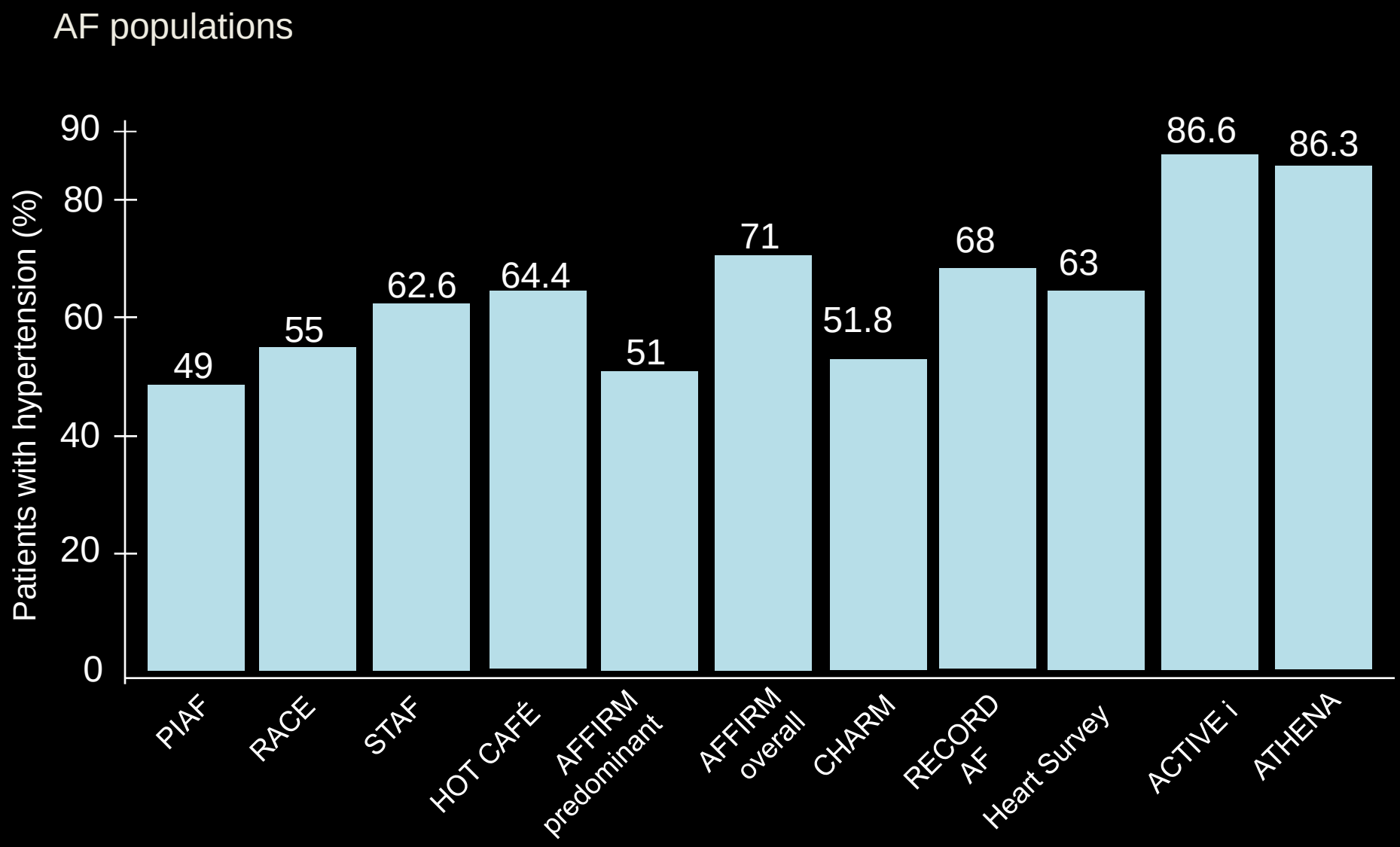
Hypertension is a key risk factor for AF



1. Hypertension increases the risk of developing AF by 80% and is present in almost 50% of AF patients[1–3]
2. Hypertension is responsible for 14% of AF cases[4]
3. Hypertension increases the risk of stroke in AF by 90% compared to AF patients without hypertension[4]
4. Hypertension is the commonest co-morbidity with AF

1. Wolf PA et al. Stroke 1991; 22: 983-988.
2. Wolf PA et al. Arch Intern Med 1987; 147: 1561-1564.
3. Kannel. Am J Cardiol 1998; 82: 2N-9N.
4. AF Investigators. Arch Intern Med 1994; 154: 1449-1457.

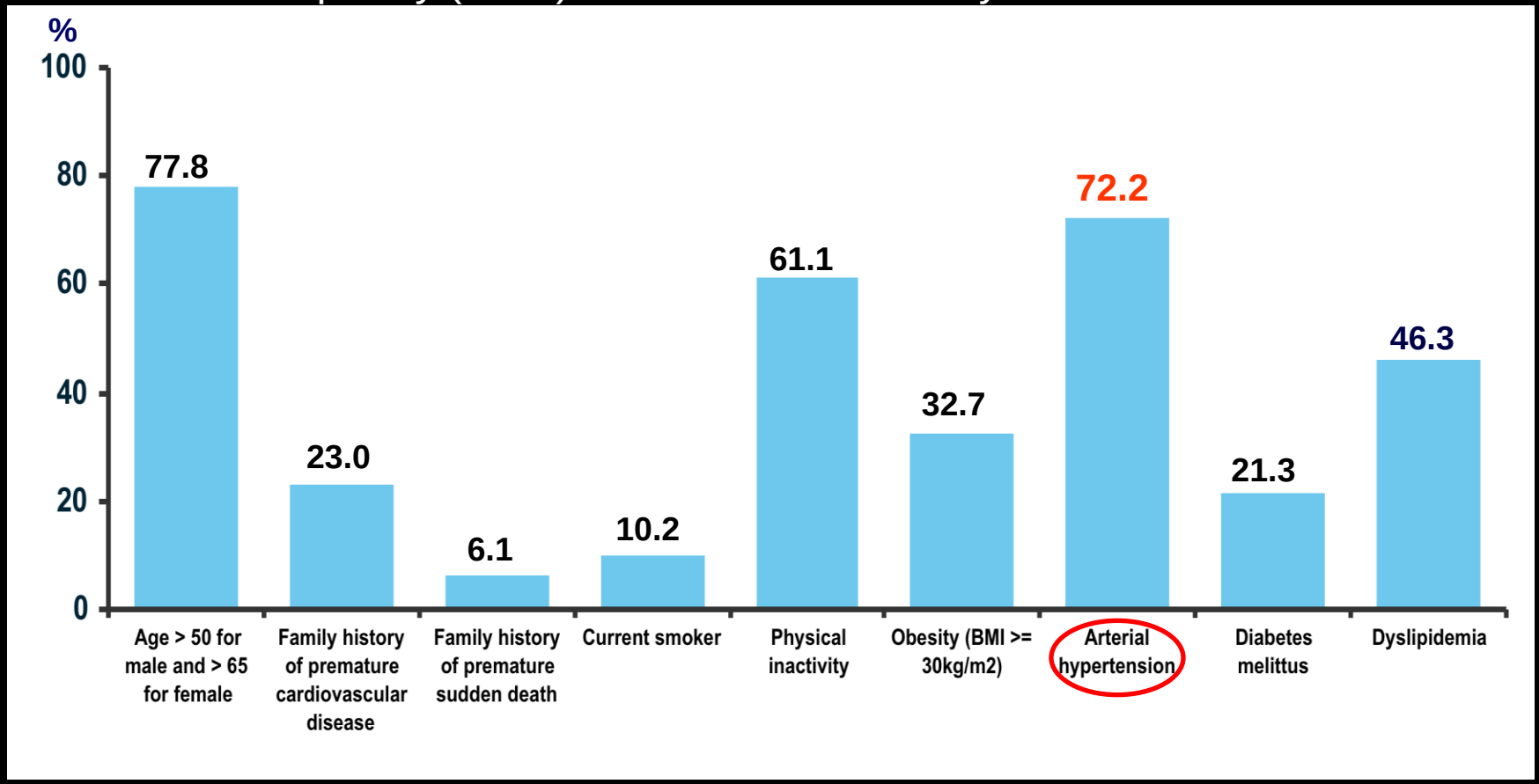
Prevalence of hypertension in AF patients



1. Hohnloser SH, *et al*. *Lancet*. 2000; 356:1789-94 ; 2. Carlsson J, et al. *J Am Coll Cardiol*. 2003; 41:1690-6.
2. Wyse DG, *et al*. *N Engl J Med*. 2002; 347:1825-33 ; 3. Van Gelder IC, *et al*. *Am Heart J.* 2006; 152:420-6.
4. Opolski Chest 2004;126;476 ; 5. Robby N, et al. Eurheartj. 2006;27:953-942 ; 6. S. H. Hohnloser et al. N Engl J Med 360;668-678)

High prevalence of concomitant CV risk factors in AF patients in the Realize AF

- An international (26 countries) large scale (more than 10,000 Pts) contemporary (2010) cross-sectional survey



RealiseAF
Real life global survey evaluating patients with Atrial Fibrillation

HTN is associated with AF

Population Surveys[1]

Risk Factor	CH study (all AF)	CH study (new AF)	Framingham study	Manitoba follow-up study	Rotterdam study/ Goteborg study
Age	1.03	1.05 (1.03-1.08)	2.1 (1.8-2.5)	-	1.1 (1.07-1.16)[R]
HTN	1.39	1.11 (1.05-1.18)	1.5 (1.2-2.0)	1.42 (1.10-1.84)	1.33 (1.07-1.65)[G]
CHF	2.67	1.51 (1.17-1.97)	4.5 (3.1-6.6)	3.37 (2.29-4.96)	6.7 (5.17-8.87)[G]
CAD/MI	-	1.48 (1.13-1.95)	1.4 (1.0-2.0)	3.62 (2.59-5.07)	-
VHD	3.27	2.42 (1.62-3.60)	1.8 (1.2-2.5)	3.15 (1.99-5.0)	-
Diabetes	-	1.08 (1.03-1.13)	1.4 (0.9-2.4)	-	-
Smoking	-	-	1.1 (0.8-1.5)	-	-
BMI	-	-	1.03 (0.99-1.06)	1.28 (1.02-1.62)	1.04 (1.03-1.06)[G]

CH study: Cardiovascular Health study; HTN; Hypertension; CHF: Congestive Heart Failure;
CAD/MI: Coronary Heart Disease/Myocardial Infarction; VHD: Valvular Heart Disease; BMI: Body Mass Index
[R]: Rotterdam study; [G]: Goteborg study

1. Savelieva I & Camm AJ. *J Intern Med* 2001;250:369-372.

Pathophysiological link between HTN and AF

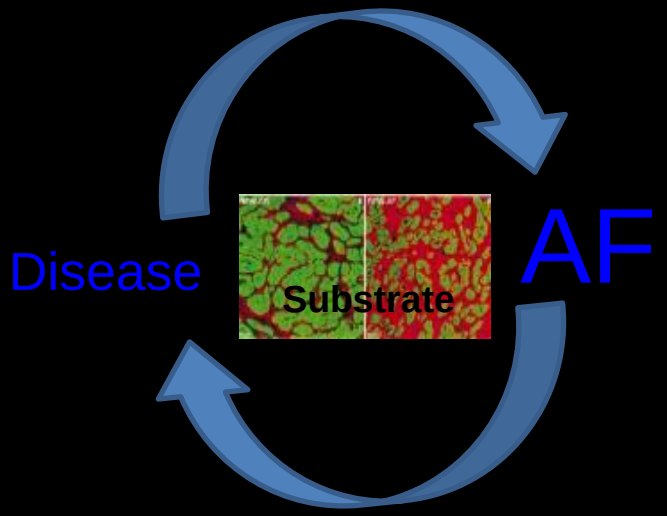
- Hypertension and AF have several pathophysiological features in common[1]
  - Inflammation
  - Both are pre-thrombotic states
  - Diastolic dysfunction of hypertension leads to atrial stretch and dilatation
  - Both are associated with activation of the renin-angiotensin aldosterone system (RAAS)

1. Boos CJ & Lin GYH. J Hum Hypertens 2005; 19:855-859.

3. Upstream treatment of Atrial Fibrillation

“Upstream” therapies in AF

Therapies	Possible Target
ACE inhibitors, ARBs, Aldosterone antagonists	Hypertension Heart failure Direct effects (anti-fibrotic, antiarrhythmic?)
Statins	Coronary artery disease Systemic atherosclerosis Direct effects (anti-inflammatory, antioxidant)
Corticosteroids	Anti-inflammatory effects
n-3 PUFA (fish oil)	Lipid-lowering effects Direct antiarrhythmic effects
Beta blockers	Reduction of BP, CHF MI, etc. Direct antiarrhythmic effects

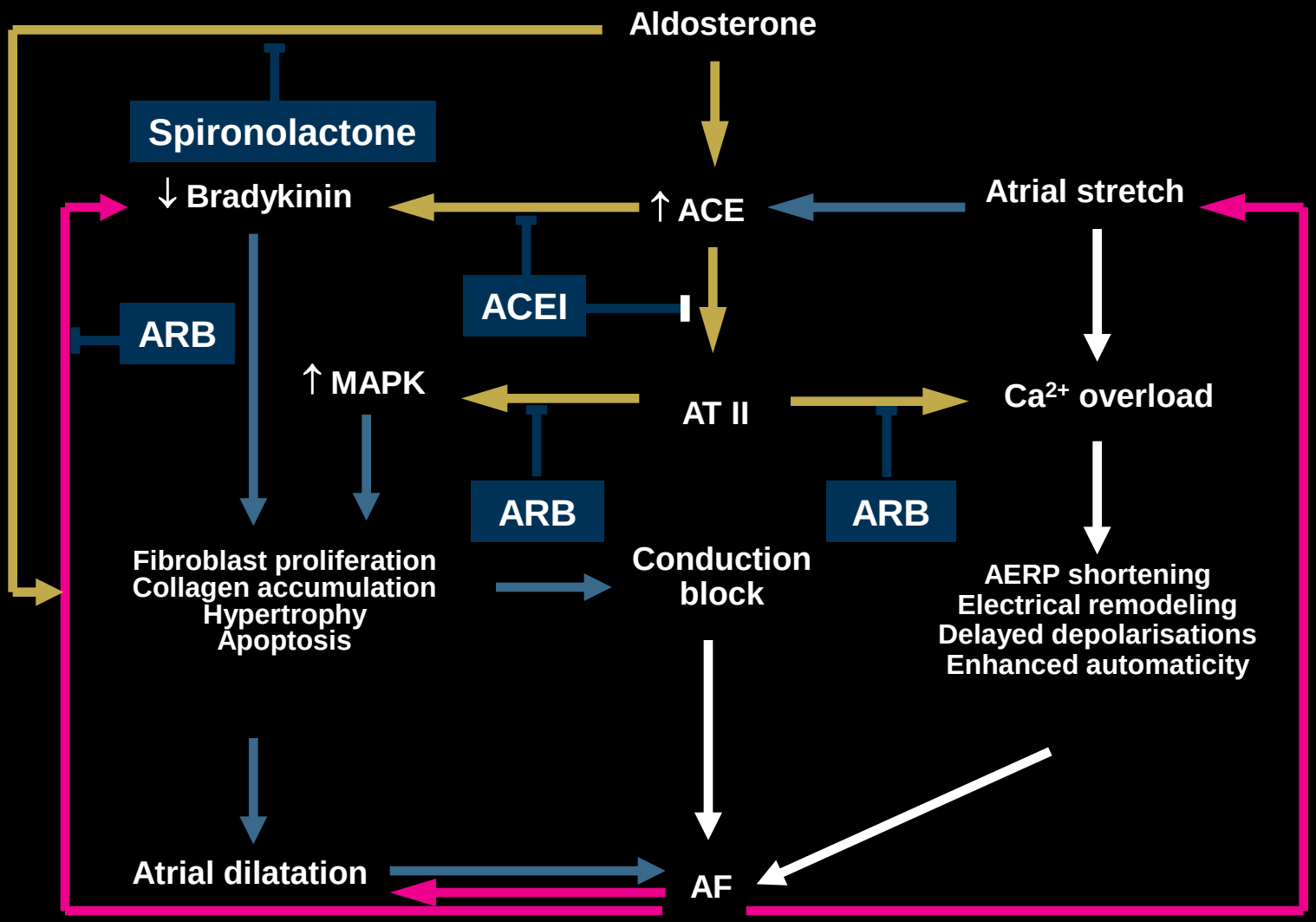


The RAAS in AF

- RAAS is involved in pathophysiology of AF[1]
  - Mediates structural remodelling of the atrium
  - Associated with pro-antiarrythmic effects
- Studies suggest that modulation of the RAAS may be an effective treatment for AF[1]
  - ACE inhibitors (ACEIs)
  - Angiotensin receptor blockers (ARBs)

1. Healy J et al. J Am Coll Cardiol 2005; 45(11):1832-1839.

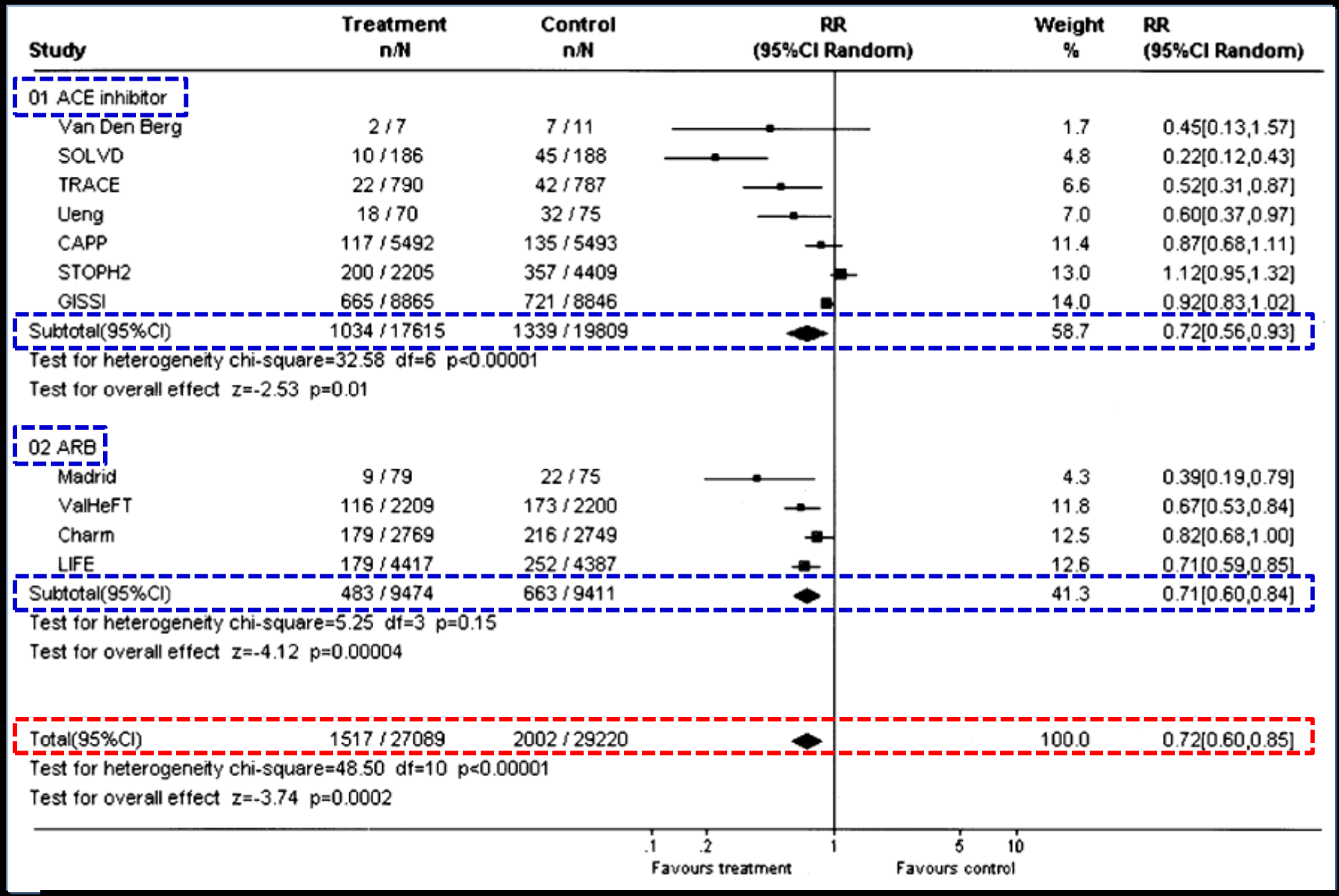
Angiotensin II in pathophysiology of Atrial Fibrillation



MAPK = mitogen-activated protein kinase
AERP = atrial effective refractory period

Dilaveris P et al. *Curr Drug Targets Cardiovasc Haematol Disord* 2005; 5:387-403

Prevention of AF with ACEi and ARB: a meta-analysis.



- 11 studies (47,457 patients)
- CHF: 4 studies; 10,314 pts
- MI: 2 studies; 10,441 pts
- HTN: 3 studies; 26,403 pts
- AF: 2 studies; 299 pts

J Am Coll Cardiol. 2005 Jun 7;45(11):1832-9.

ARBs in AF guidelines

- Common ACC/AHA/ESC guidelines (2006)[1]
  - "The role of treatment with inhibitors of the RAAS in long term maintenance of sinus rhythm in patients at risk of developing recurrent AF requires clarification in randomised trials before this approach can be taken"

- ESC guidelines (2010)[2]
  - Evidence for 'upstream' therapy for prevention of atrial remodelling still remains controversial.
  - ACEi and ARB should be considered for prevention of new-onset AF in patients with HF and reduced EF.
  - ACEi and ARB should be considered for prevention of new-onset AF in patients with HTN, particuraly with LVH

1. Fuster et al. Europace 2006; 8:651-745.
2. Europace. 2010 Oct;12(10):1360-420.

Upstream therapy for AF (2010 ESC guideline)

For primary prevention of AF

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

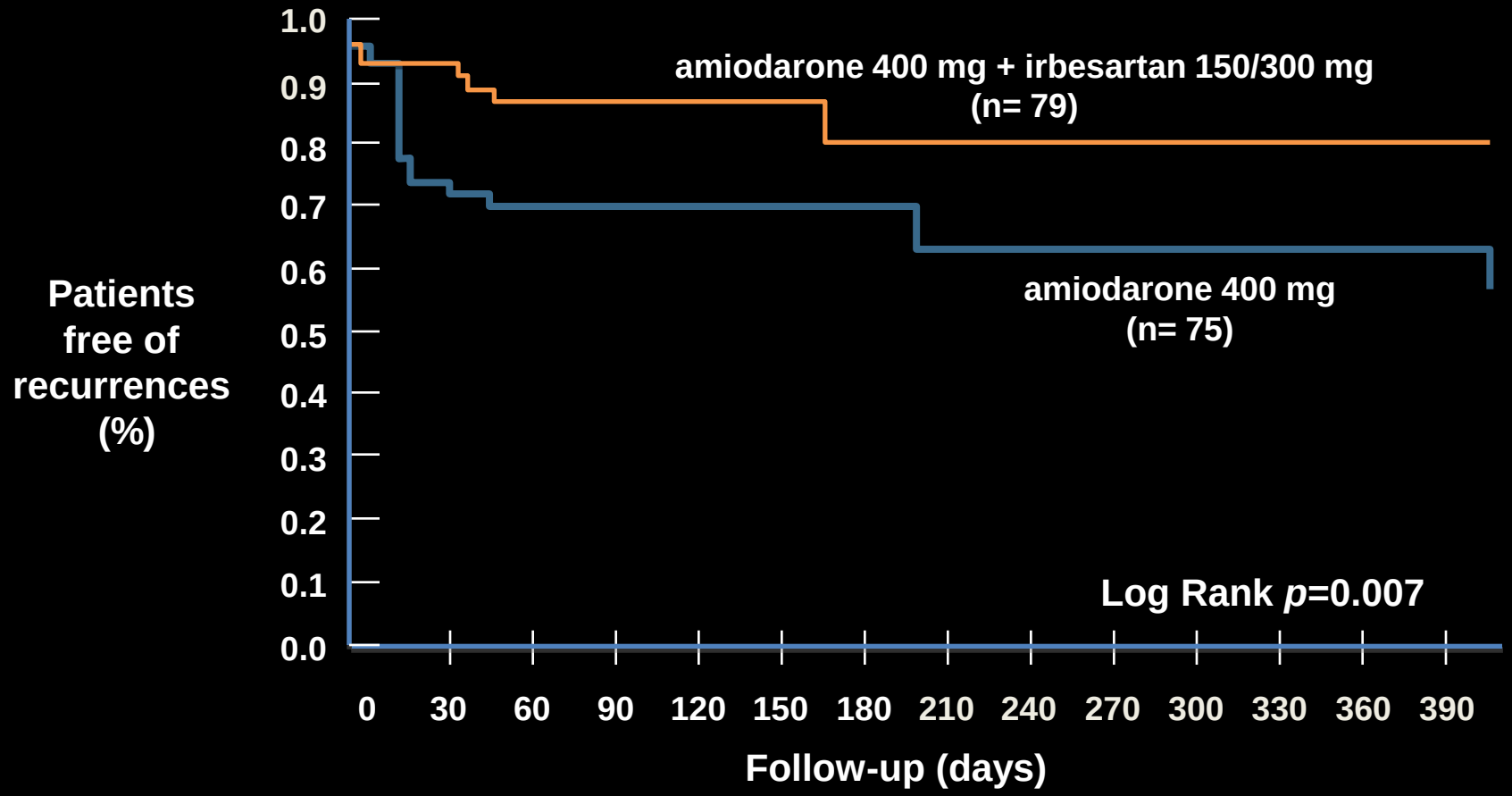
For secondary prevention of AF

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

4. Irbesartan & Atrial Fibrillation

- MADRID
- ACTIVE-I
- Recent Studies on role of Irbesartan in treatment of AF

Addition of irbesartan to amiodarone in reducing recurrence of atrial fibrillation (AF)



n=186

Inclusion criteria: Patients with persistent AF >7days

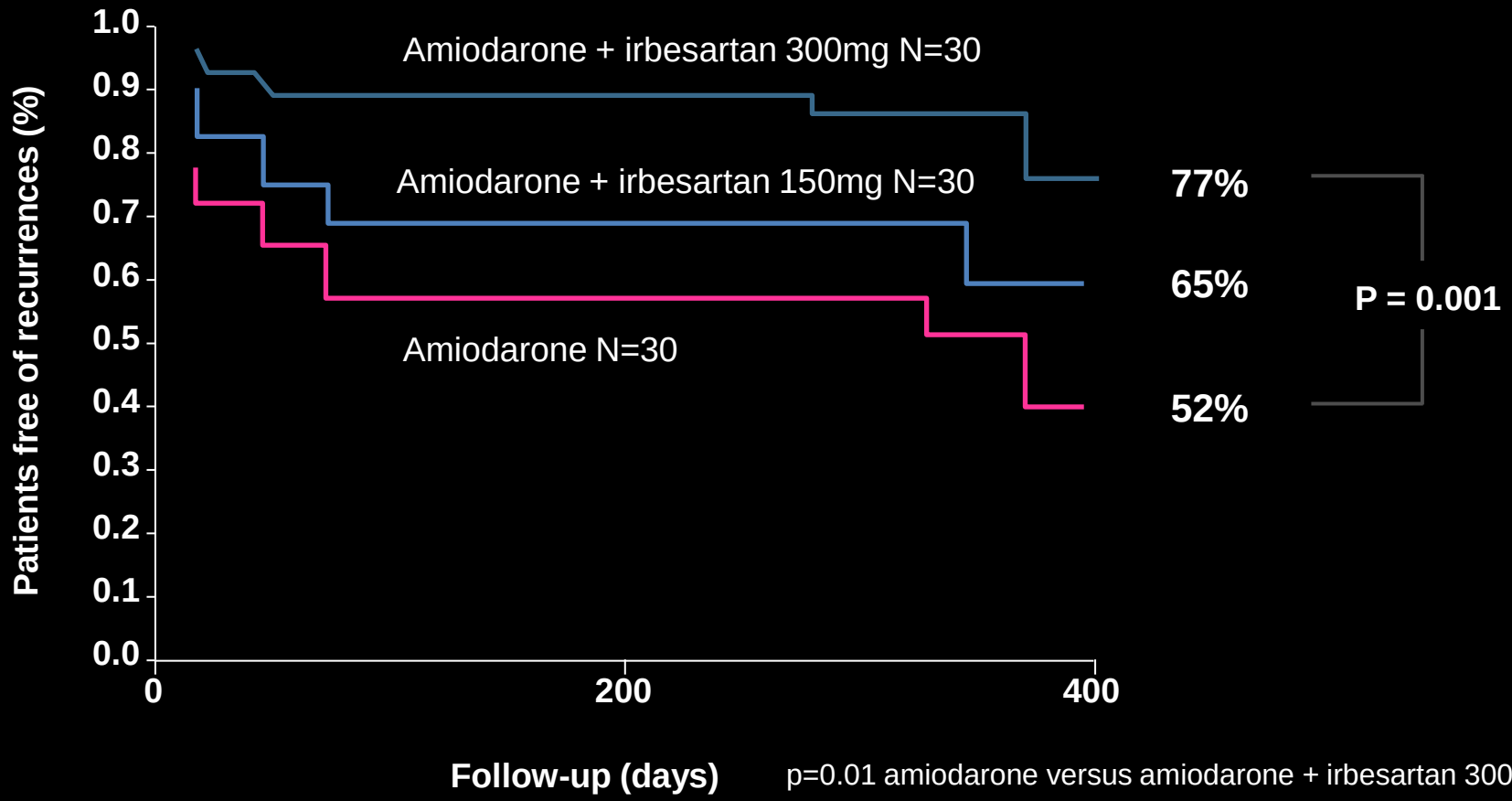
Design: open-label randomised study

Primary endpoint: the length of time to first recurrence of AF

Safety was similar in both groups

Madrid AH et al. *Circulation* 2002; 106: 331–336.

Prevention of recurrences in patients with lone AF

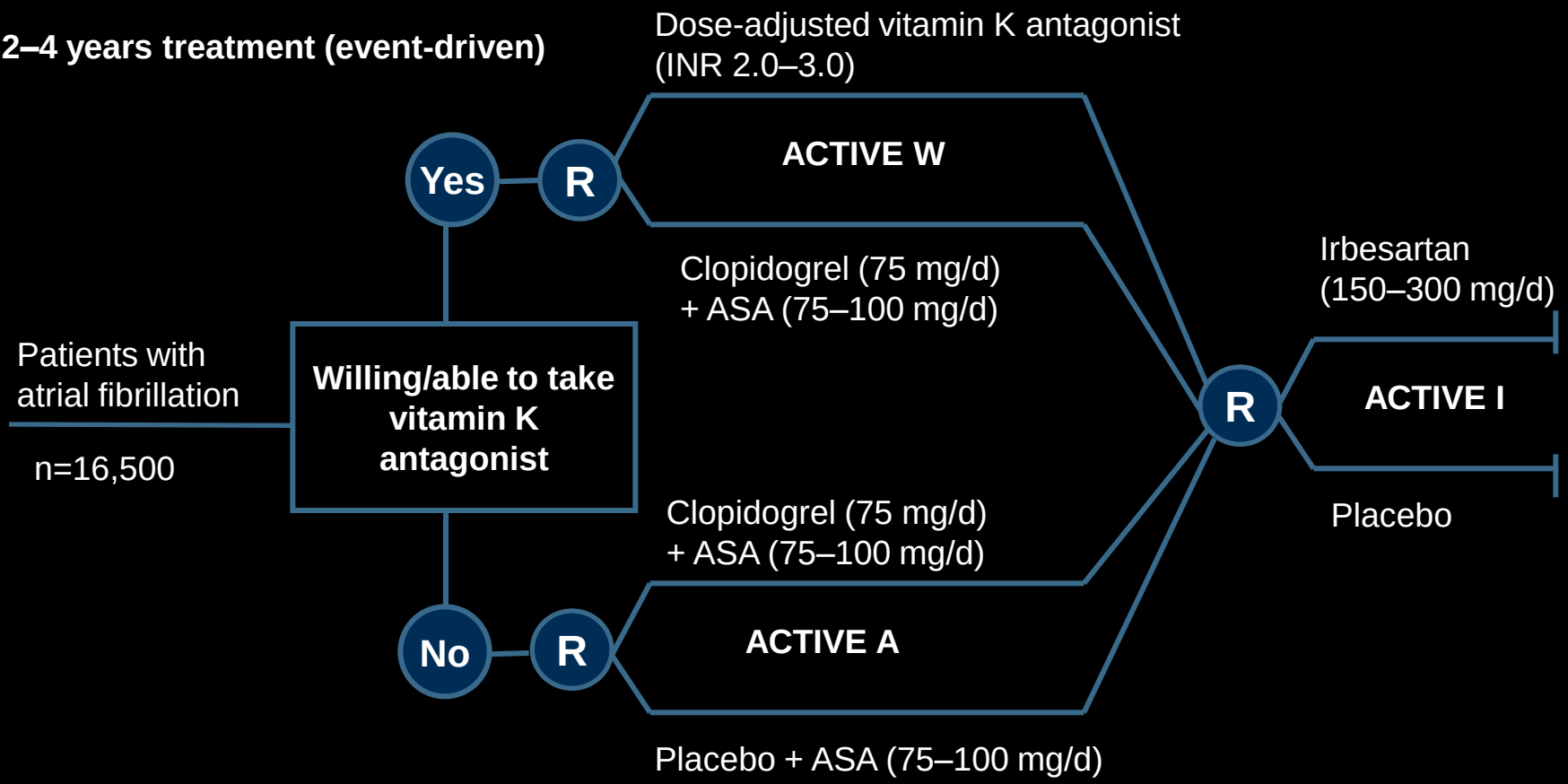


p=0.01 amiodarone versus amiodarone + irbesartan 300mg

- n=90
- Primary endpoint: the length of time to first recurrence of AF
- persistent Af for >7 days
- f/u: median 220 days

Madrid AH et al. *JRAAS* 2004; 5: 114–20.

ACTIVE: Design



ACTIVE-I Inclusion criteria: SBP≥ 100 mm Hg

Primary endpoint:

Time to first vascular event (stroke, myocardial infarction, vascular death)

The ACTIVE Steering Committee. Am Heart J 2006; 151:1187-93

Baseline Characteristics of the Patients

Variables	Irbesartan (n=4518)	Placebo (n=4498)
Age (yr)	69.5±9.7	69.6±9.7
Blood Pressure (mmHg)		
Systolic	138.3±17.6	138.2±17.2
Diastolic	82.6±11.5	82.2±11.1
Heart rate (beats/min)	75.3±14.4	74.9±14.4
$CHADS_2$ score	2.0±1.1	2.0±1.07
Male sex	2745 (60.8)	2730 (60.7)
Type of atrial fibrillation (%)		
Permanent	2982 (66.0)	2898 (64.4)
Paroxysmal	886 (19.6)	921 (20.5)
Persistent	644 (14.3)	668 (14.9)
Missing data	6 (0.1)	11 (0.2)
Sinus rhythm at randomization	847 (18.7)	883 (19.6)

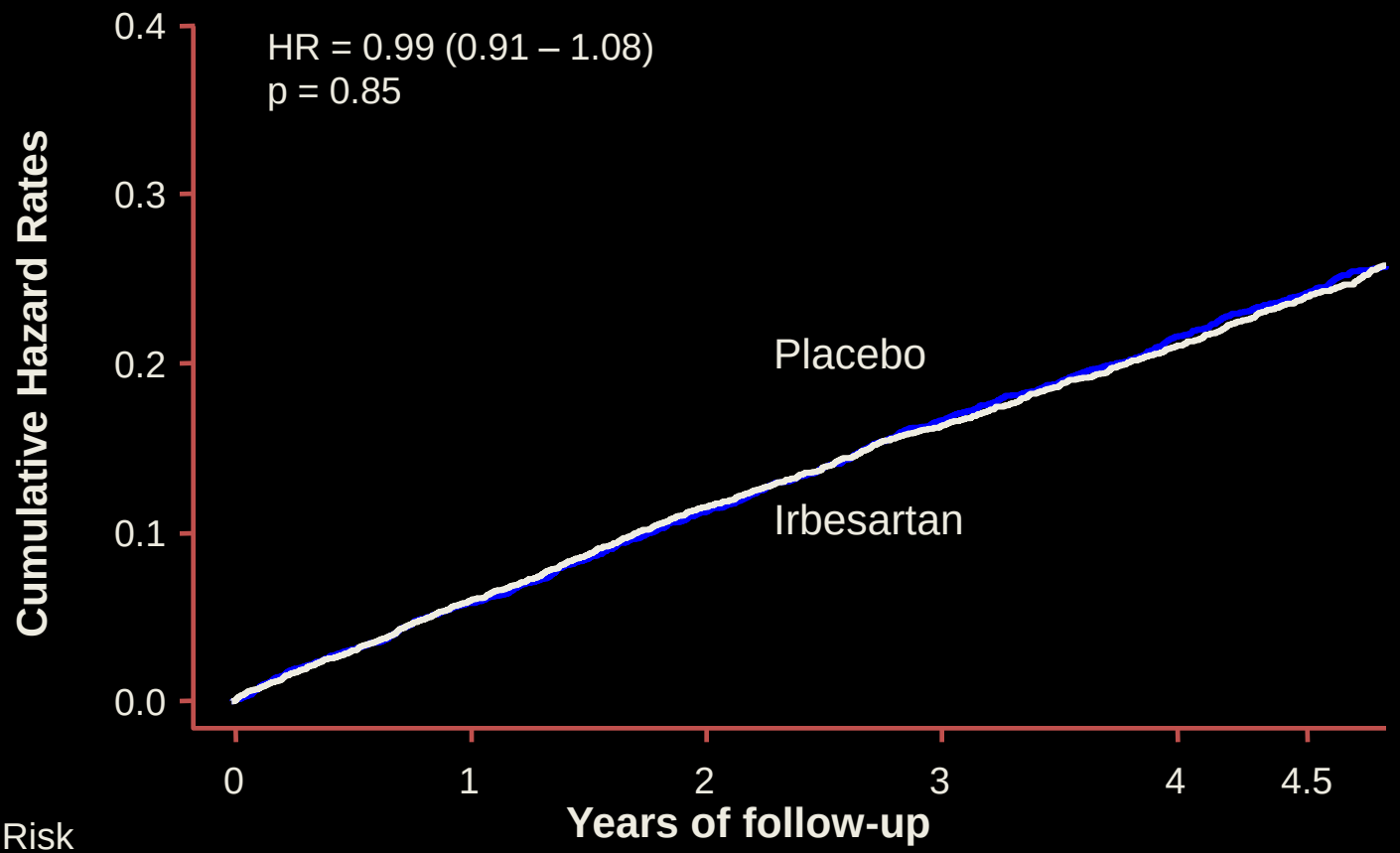
N Engl J Med. 2011 Mar 10;364(10):928-38.

Baseline Characteristics of the Patients

Use of medication at baseline (%)	Irbesartan (n=4518)	Placebo (n=4498)
Aspirin	2652 (58.7)	2666 (59.3)
Oral anticoagulant	1721 (38.1)	1692 (37.6)
ACE inhibitor	2720 (60.2)	2724 (60.6)
Angiotension-receptor blocker	232 (5.1)	211 (4.7)
Beta-blocker	2458 (54.4)	2455 (54.6)
Digoxin	1586 (35.1)	1562 (34.7)
Calcium-channel blocker	1220 (27.0)	1225 (27.2)
Diuretic	2453 (54.3)	2432 (54.1)
Antiarrhythmic drug	1025 (22.7)	1041 (23.1)

N Engl J Med. 2011 Mar 10;364(10):928-38.

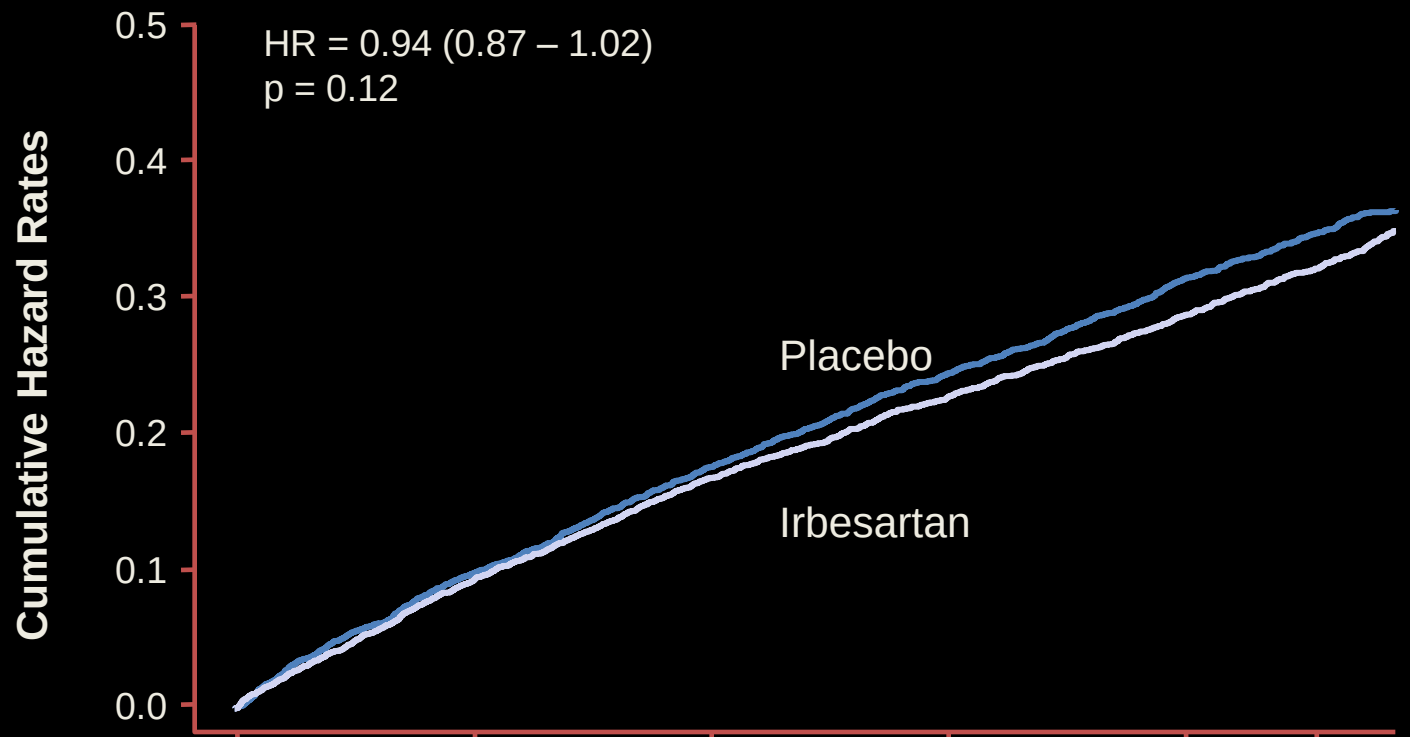
Primary Outcome: Stroke/MI/Vascular Death



# at Risk						
P	4498	4195	3912	3647	2737	2160
I	4518	4220	3926	3669	2781	2170

N Engl J Med. 2011 Mar 10;364(10):928-38.

Stroke/MI/Vascular Death + HF Hosp



# at Risk						
P	4498	4035	3690	3402	2523	1979
I	4518	4084	3741	3466	2598	2019

N Engl J Med. 2011 Mar 10;364(10):928-38.

Stroke / Hosp. for Heart failure

	Irbesartan (4518 pts)		Placebo (4498 pts)		Hazard Ratio	95% CI	p-value
	n	%/yr	n	%/yr			
Stroke	379	2.1	411	2.3	0.91	0.79-1.05	0.20
TIA	130	0.7	150	0.8	0.86	0.68-1.09	0.21
Non CNS Embolism	47	0.3	64	0.3	0.72	0.50-1.05	0.09
Stroke/TIA/Non CNS Emb	515	2.9	584	3.3	0.87	0.77-0.98	0.02
Hospitalization for heart failure	482	2.7	551	3.2	0.86	0.76-0.98	0.02

N Engl J Med. 2011 Mar 10;364(10):928-38.

Clinical Implications for Patients with AF shown from ACTIVE-I

- In the patients with hypertension and AF
  - High risk for HF and stroke

- ACTIVE-I is the first and largest morbidity and mortality trial specifically designed to assess the role for irbesartan in reducing the risk of vascular events in patients with AF.

- Irbesartan for hypertension and AF patients
  - Better maintenance after sinus conversion (MADRID)
  - Reduces HF incidence and its hospitalization (ACTIVE I, by 14%)
  - Reduces stroke, TIA and Non-CNS embolism (ACTIVE I, by 13%)

Role of irbesartan in prevention of post-coronary artery bypass graft atrial fibrillation

Table III. Odds of post-coronary artery bypass graft (CABG) atrial fibrillation associated with irbesartan use

Model 1[a]	Model 2[b]	Model 3[c]
OR (95% CI) p-value	OR (95% CI) p-value	OR (95% CI) p-value
0.23 (0.06, 0.87) 0.030	0.25 (0.06, 0.99) 0.049	0.20 (0.04, 0.94) 0.042

a Model 1: unadjusted.

b Model 2: model 1 + age, sex.

c Model 3: model 2 + diabetes mellitus, LVEF (≤55 vs >55), left main disease, aortic clamping time, bypass time, left atrial diameter, pre-CABG β-blocker, ACE inhibitor and statin use.

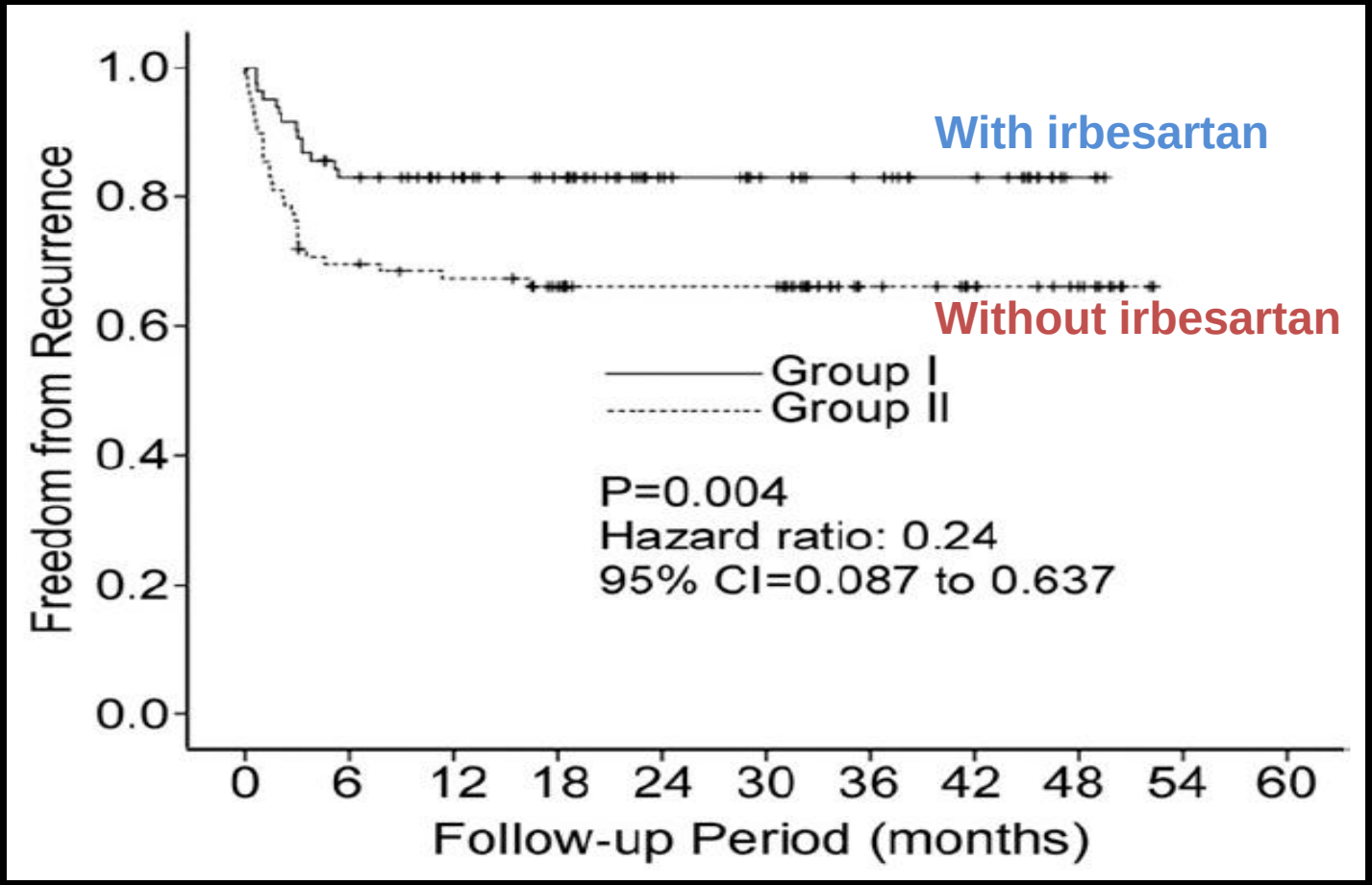
ACE = angiotensin-converting enzyme; **CI** = confidence interval; **LVEF** = left ventricular ejection fraction; **OR** = odds ratio.

Conclusion

Pretreatment with irbesartan tends to have a significant protective effect against the occurrence of AF during the post-operative period in patients undergoing CABG.

Am J Cardiovasc Drugs. 2011 May 27

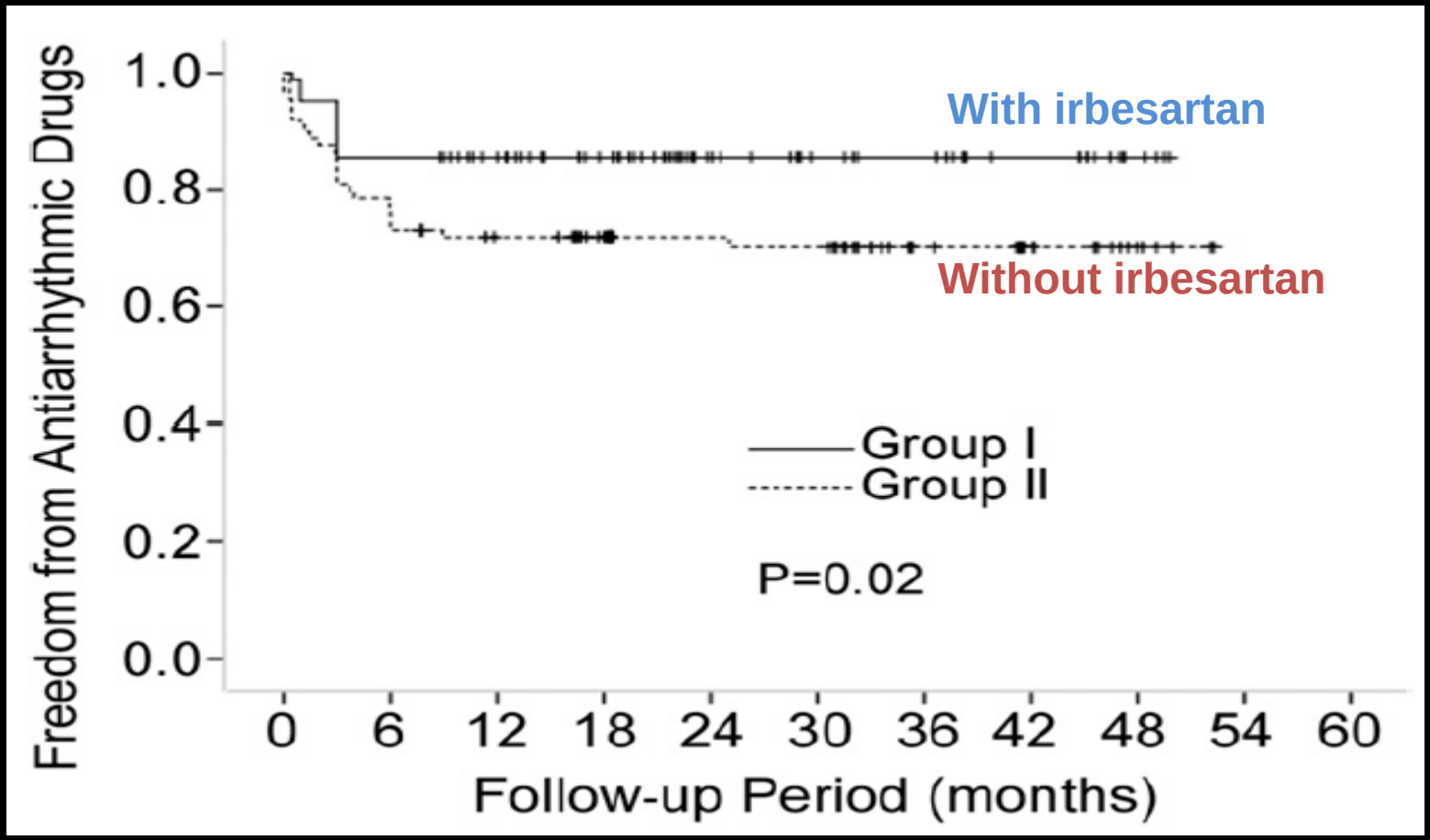
Patients with Irbesartan had a significantly lower rate of recurrent arrhythmia



- 83 patients with long-lasting persistent AF underwent minimally invasive ablation

Ann Thorac Surg. 2011 Apr;91(4):1183-9.

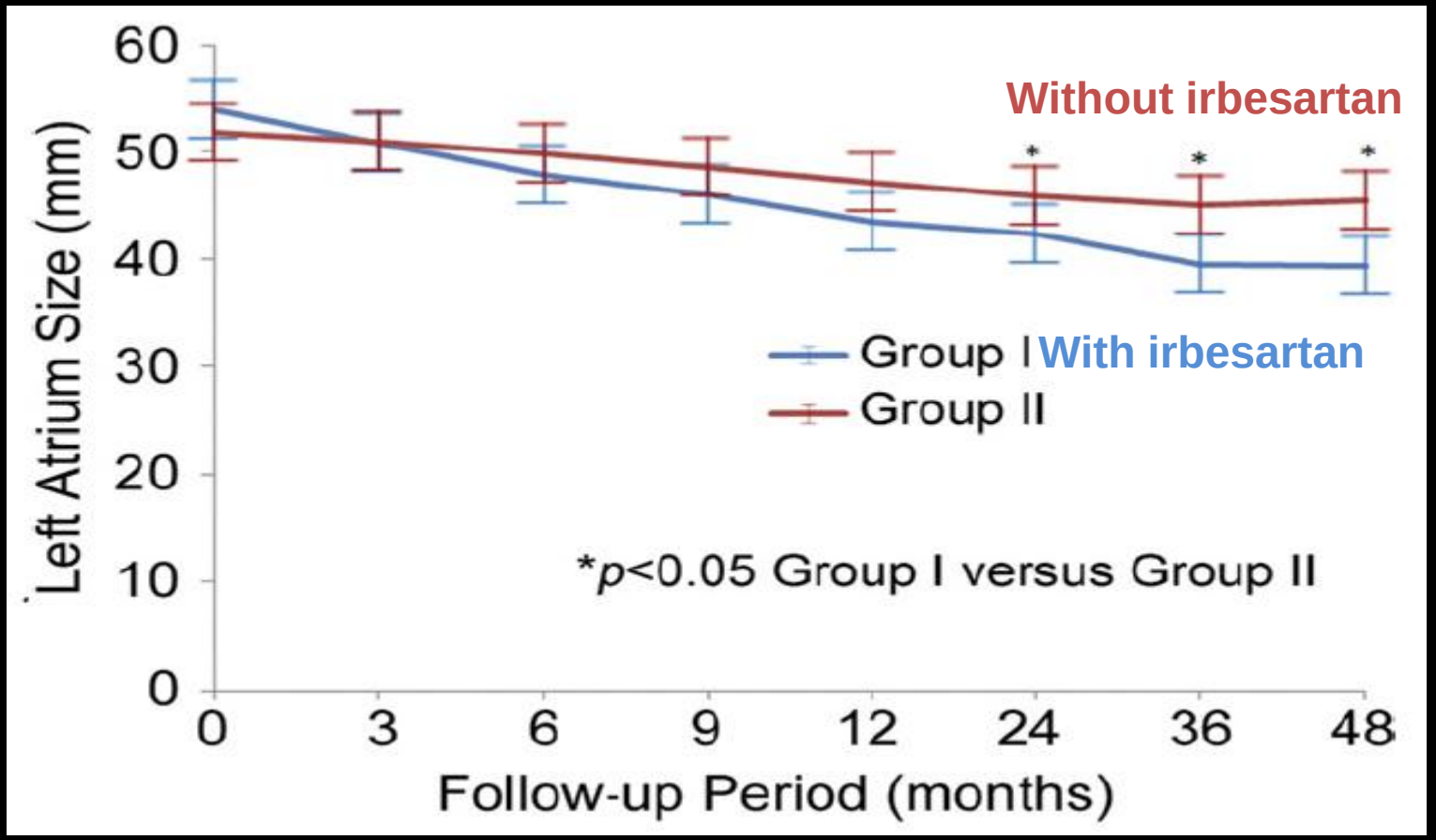
Patients treated with irbesartan had a significantly lower rate of use of antiarrhythmic drugs



- 83 patients with long-lasting persistent AF underwent minimally invasive ablation

Ann Thorac Surg. 2011 Apr;91(4):1183-9.

Mean left atrial size of patients treated with Irbesartan was less that of patients without irbesartan



Conclusion

Patients who were additionally treated with irbesartan had a significantly lower rate of AF recurrence than patients who were treated with ablation alone, maybe through suppression of atrial structural remodeling.

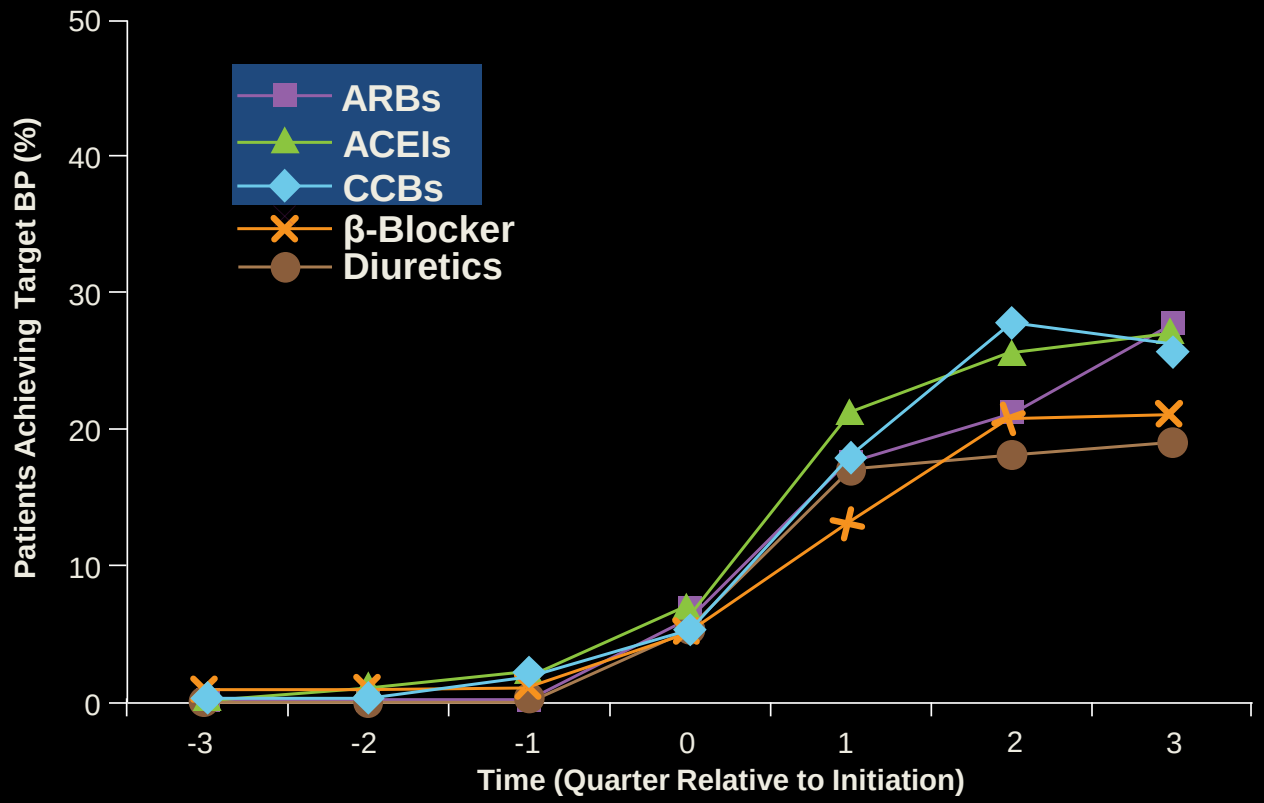
Ann Thorac Surg. 2011 Apr;91(4):1183-9.

5. Irbesartan in real-life practice

Irbesartan in Real-life practice

(South Western Ontario Primary Care Database Study)

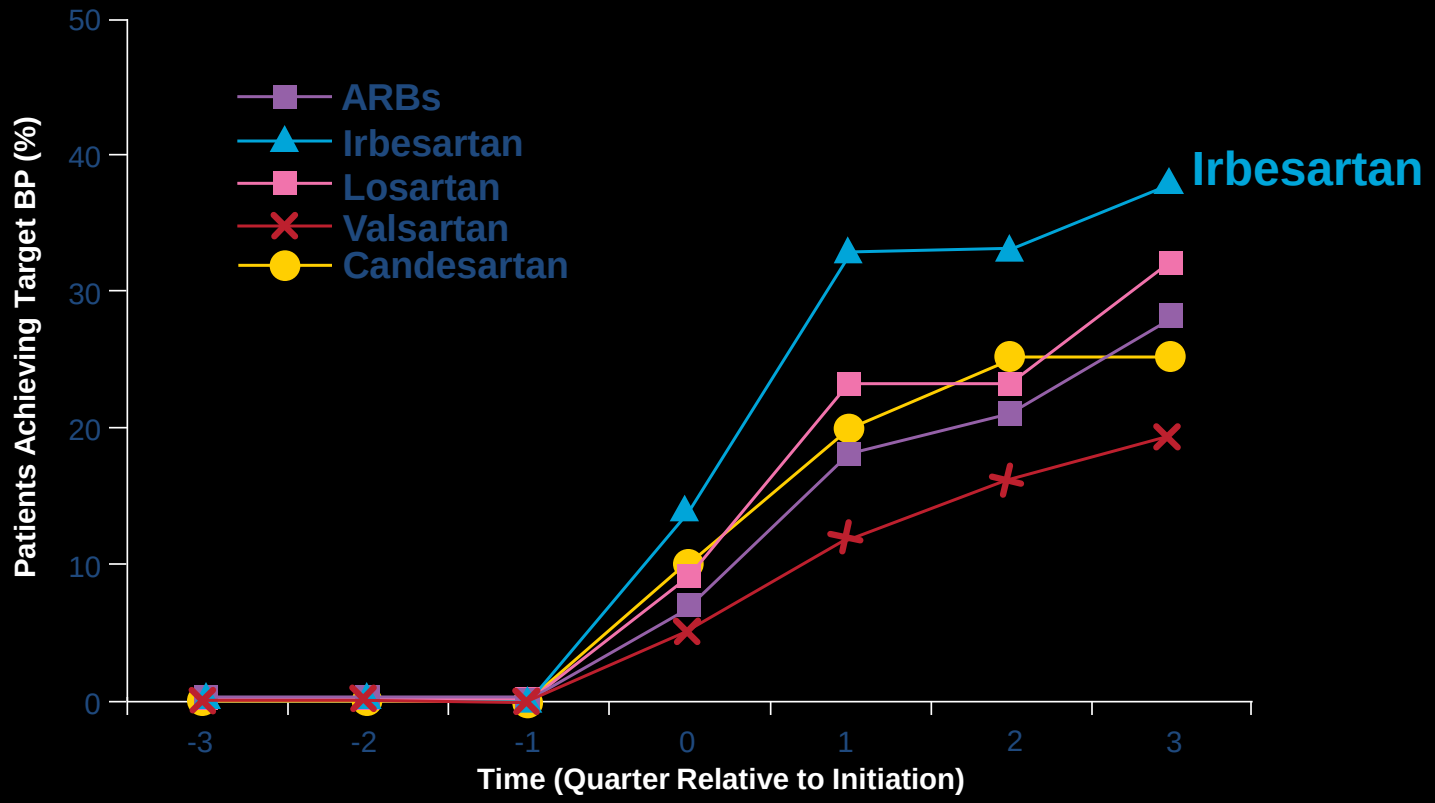
BP goal attainment rates were higher in ARB therapy



P = NS for ARBs vs ACEIs and vs CCBs
P = 0.002 for ARBs vs β-blockers
P = 0.001 for ARBs vs diuretics

Clin Ther. 2011 Sep;33(9):1190-1203
R Petrella. European Cardiology, 2010; 6(3):33-8

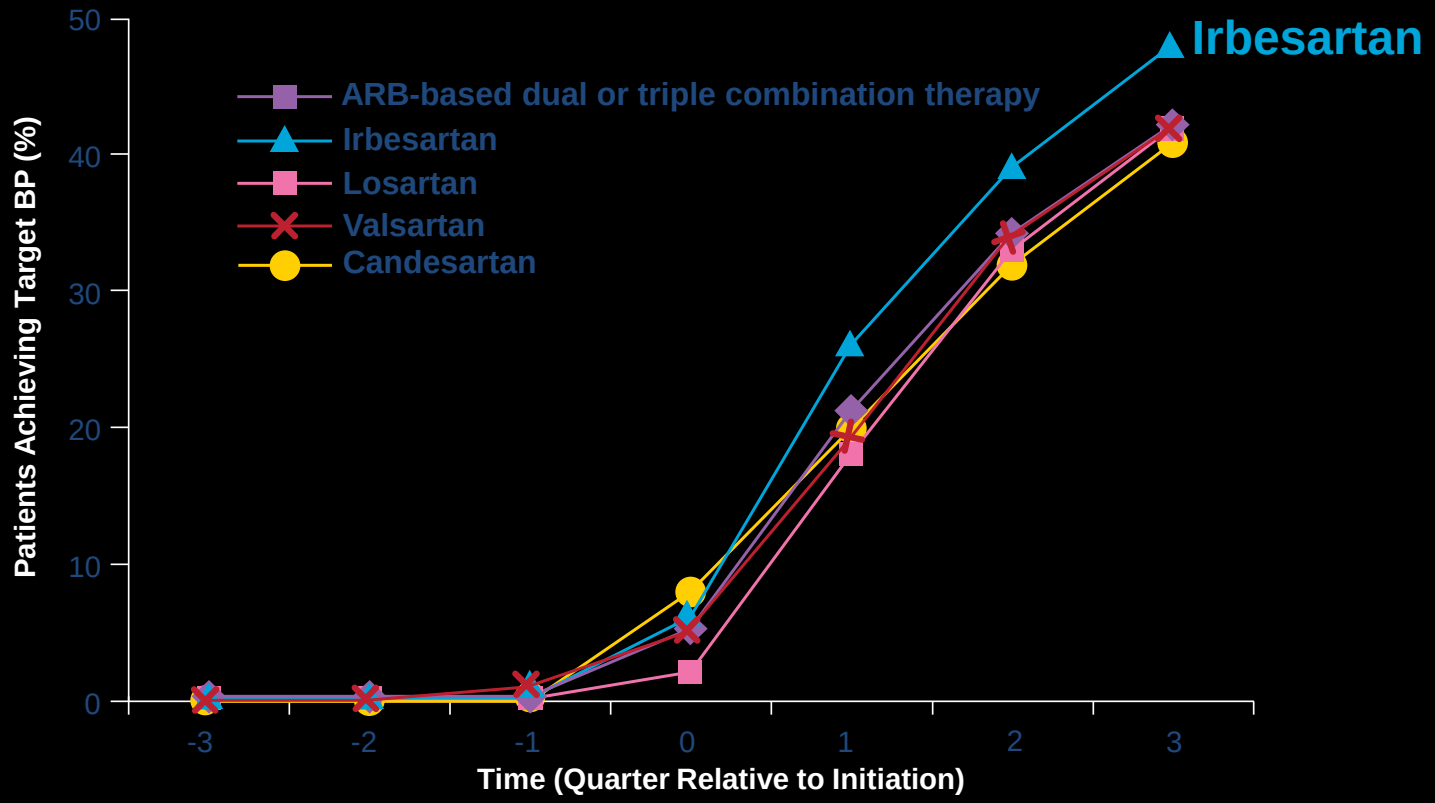
BP goal attainment rates were higher in irbesartan (in momotherapy)



P = 0.01 for irbesartan vs losartan
P = 0.001 for irbesartan vs valsartan
P = 0.001 for irbesartan vs candesartan

Clin Ther. 2011 Sep;33(9):1190-1203
R Petrella. European Cardiology, 2010; 6(3):33-8

BP goal attainment rates were higher in irbesartan (in combination therapy)



P = 0.001 for irbesartan vs losartan
P = 0.001 for irbesartan vs valsartan
P = 0.001 for irbesartan vs candesartan

Clin Ther. 2011 Sep;33(9):1190-1203
R Petrella. European Cardiology, 2010; 6(3):33-8

CV events with mono- and/or combination therapy including an ARB, ACEI, or CCB

	ARBs	ACEIs	CCBs
n	15,937	25,498	11,629
No. of CV events (%)	**688 (4.3)**	**1784 (7.0)**	**1279 (11.0)**
CV events (%)			
MI	1.0	1.5	2.7
CAD	1.3	1.9	2.8
CHF	0.6	1.1	1.5
Stroke	1.0	1.8	3.4
AF	0.2	0.2	0.1
PAD	0.1	0.1	0.2
TIA	0.1	0.3	0.3

CAD = coronary artery disease; CCB = calcium channel blocker; CHF = congestive heart failure; CV = cardiovascular; MI = myocardial infarction; PAD = peripheral artery disease; TIA = transient ischemic attack.

Clin Ther. 2011 Sep;33(9):1190-1203
R Petrella. European Cardiology, 2010; 6(3):33-8

CV events rate was lowest with irbesartan

	Irbesartan	Losartan	Valsartan	Candesartan
No. of patients	4974	3759	3008	2196
No. of CV events, %	149 (3.0; P < 0.02)	172 (4.6)	151 (5.0)	109 (5.0)
CV events, no.				
MI	38 (0.7)	31 (0.8)	43 (1.4)	23 (0.8)
CAD	51 (1.0)	59 (1.6)	40 (1.3)	35 (1.2)
CHF	22 (0.4)	21 (0.6)	26 (0.8)	16 (0.5)
Stroke	20 (0.4)	45 (1.2)	23 (0.7)	25 (1.1)
AF	7 (0.1)	8 (0.2)	5 (0.2)	2 (0.1)
PAD	4 (<0.1)	6 (0.2)	6 (0.2)	5 (0.2)
TIA	6 (0.1)	2 (<0.1)	8 (0.3)	3 (0.1)

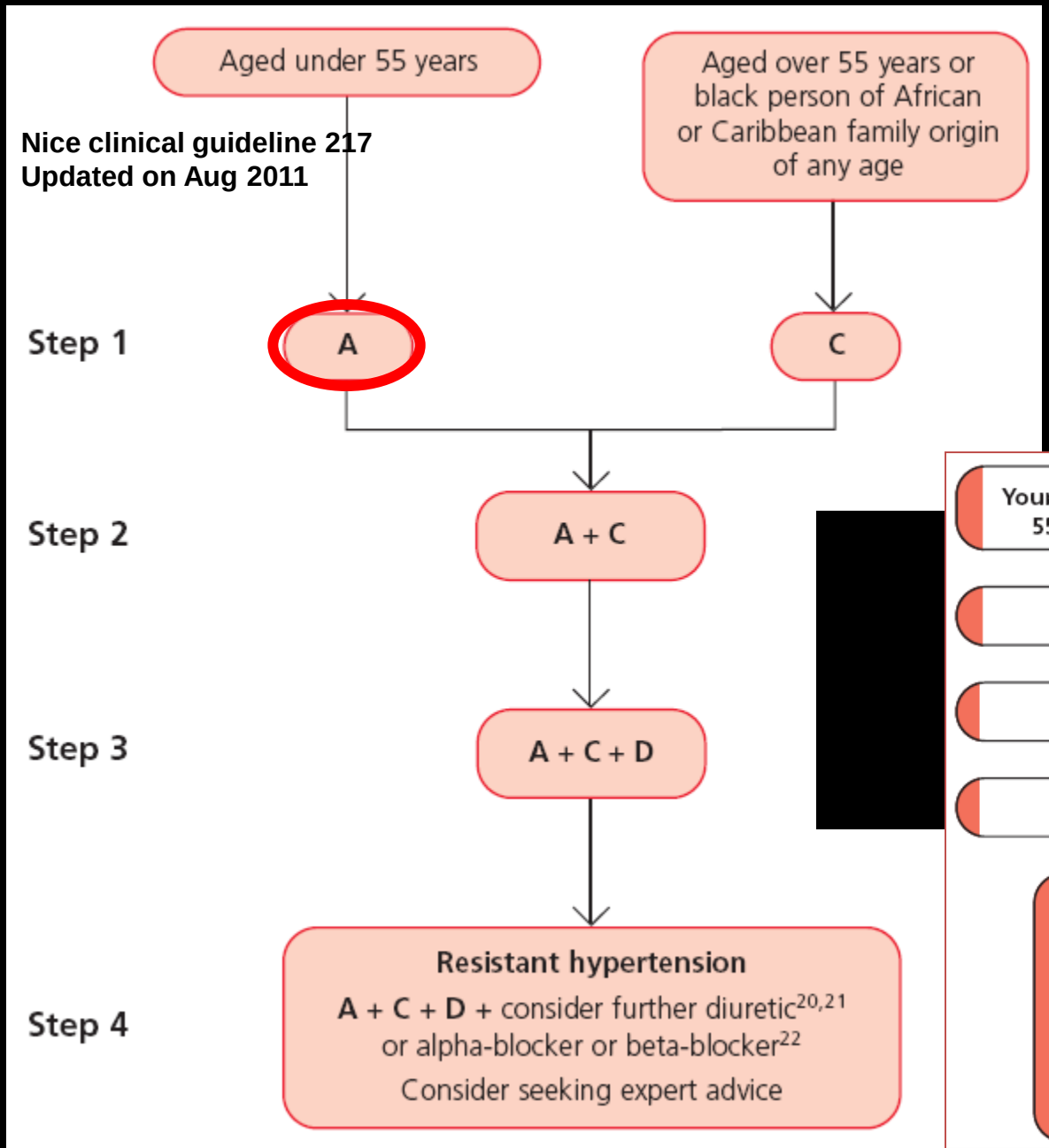
CAD = coronary artery disease; CCB = calcium channel blocker; CHF = congestive heart failure; CV = cardiovascular; MI = myocardial infarction; PAD = peripheral artery disease; TIA = transient ischemic attack.

Clin Ther. 2011 Sep;33(9):1190-1204
R Petrella. European Cardiology, 2010; 6(3):33-8

6. 2011 NICE recommendation

Summary of antihypertensive drug treatment

Nice clinical guideline 217
Updated on Aug 2011



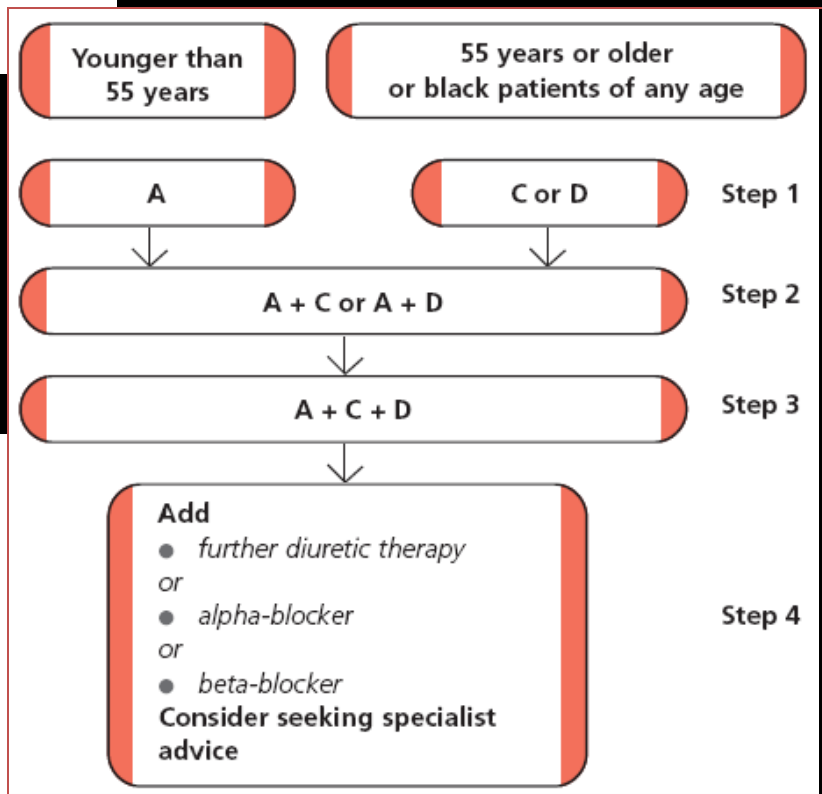
Key

A – ACE inhibitor or angiotensin II receptor blocker (ARB)[18]

C – Calcium-channel blocker (CCB)[19]

D – Thiazide-like diuretic

Cf) 2006 BHS guideline



Conclusions

- Hypertension is a major risk factor for Atrial Fibrillation and prevalence of AF is high in patients with CV co-morbidity.
- Irbesartan prevented AF recurrences in patients with long-tanding persistent AF & lone AF in dose-dependent effects.
- ACTIVE-I showed that in patients with AF, irbesartan did not reduce CV events, although showed some benefit in reducing HF hospitalizations, stroke, TIA and Non-CNS embolism.
- Pretreatment with irbesartan tends to have a significant protective effect against the occurrence of AF during the post-operative period in patients undergoing CABG.
- Irbesartan showed significantly lower rate of AF recurrence in patients treated with ablation.
- Irbesartan showed a superior BP lowering effect and reduced CV events in real-life practice.

Control rates of Hypertension remains poor

- 50% of patients with hypertension are known, 50% are treated and about 50% are finally controlled

Country	Study year	Age range	Control rate in treated hypertension
US	1999 – 2000	18 – 80+	53.10%
Canada	1986 – 1992	18 – 74	41.00%
Spain	1990	35 – 64	15.50%
England	1998	16 – 75	29.20%
Germany	1994 – 1995	25 – 74	33.60%
Greece	1997	18 – 90	49.50%
Japan	1980	30 – 74	55.7% (male)
			65.4% (female)
Mexico	1992 – 1993	20 – 69	21.80%
Venezuela	1996	20+	19.70%
Cuba	1998	15+	34.10%
Egypt	1991	25 – 95	33.50%
Turkey	1995	18+	19.80%
China	2000 – 2001	35 – 74	28.80%
Korea	**1990**	**30 – 70+**	**5.40%**
Taiwan	1993 – 1996	19+	18.00%

Expert Opin Pharmacother. 2009 Aug;10(11):1817-31.

Persistence with initial treatment in different studies

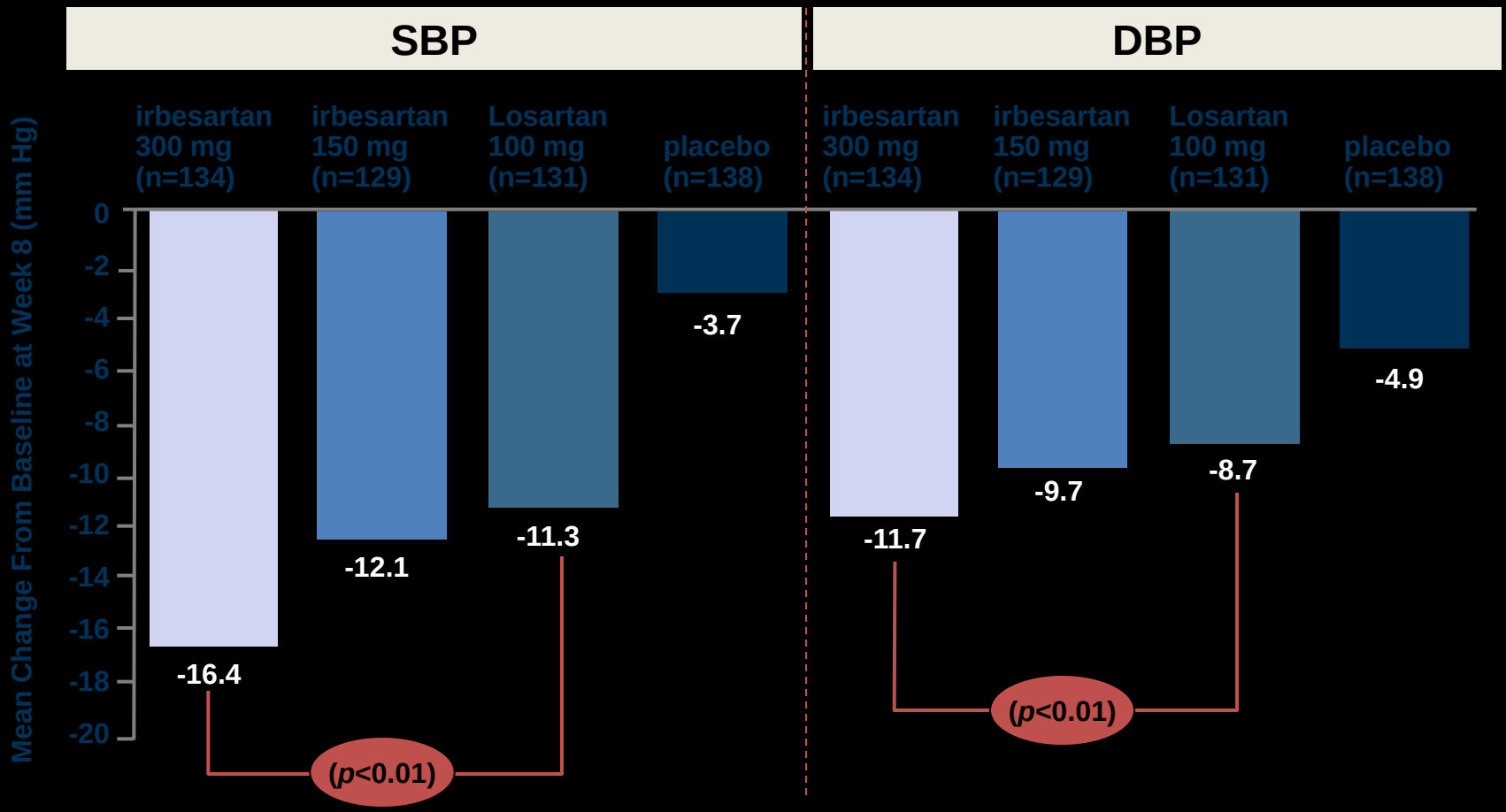
- Patients were more persistent on ARBs compared with other antihypertensive drugs including ACE-Is, CCBs, diuretics and BBs

Study	Duration (months)	ARBs	ACE-Is	CCBs	BBs	Diuretics
Bloom	12	64%	58%§	50%	43%	38%
Conlin et al.	12	67.40%	60.7%*	54.1%*	45.6%*	20.8%*
Conlin et al.	48	50.90%	46.50%	40.7%‡	34.7%‡	16.4%‡
Hasford et al.	12	51.30%	42.00%	43.60%	49.70%	34.40%
Degli-Esposti et al.	12	41.70%	32.20%	26.70%	36.90%	25.90%
Erkens et al.	12	62.00%	59.70%	34.70%	35.00%	33.00%
Veronesi et al.	24	68.50%	64.50%	51.6%‡	44.8%‡	34.4%*
Hasford et al.	12	26.40%	28.20%	25.90%	25.80%	21.90%
Patel et al.	12	51.90%	48.00%	38.30%	40.30%	29.90%

*p < 0.01.
‡p < 0.05.
§p < 0.007 versus ACE-Is.

Bramlage & Hasford. Cardiovasc Diabetol 2009;8:18.

Irbesartan vs losartan



Kassler-Taub K *et al*. Am J Hypertens 1998;11:44 – 53

What's new in 2011 NICE

1. Diagnosing hypertension

• If the clinic BP is ≥140/90 mmHg, offer **ABPM** to confirm the diagnosis of HTN

→ Ensure that at least 2 measurements/hr are taken during the person's usual waking hrs (e.g. 08:00~22:00)

→ Use the average value of at least 14 measurements

→ The 2011 guidelines are the first in the world to formally recommend ABPM as a "key priority" in diagnosis of hypertension.

• **HBPM**

– For each BP recording, 2 consecutive measurements are taken at least **1 min apart** and with the person seated ***and***

– BP is recorded twice daily, ideally in the morning and evening ***and***

– BP recording continues for at least 4 days, ideally for 7 days.

Discard the measurements taken on the first day and use the average value of all the remaining measurements to confirm a diagnosis of HTN.

Nice clinical guideline 217
Updated on Aug 2011

Target BP

- < 80 yrs: 140/90 mmHg (clinic BP), 135/85 mmHg (ABPM or HBPM)
- ≥ 80 yrs: 150/90 mmHg (clinic BP), 145/85 mmHg (ABPM or HBPM)

- **Stage 1 HTN**
  - ≥140/90 mmHg (clinic BP) and subsequent ABPM daytime average or HBPM average BP is ≥135/85 mmHg
- **Stage 2 HTN**
  - ≥160/100 mmHg (clinic BP) and subsequent ABPM or HBPM is ≥150/95 mmHg
- **Stage 3 HTN**
  - ≥180 mmHg (clinic SBP) or ≥110 mmHg (clinic DBP)

Nice clinical guideline 217
Updated on Aug 2011

2. Initiating treatment

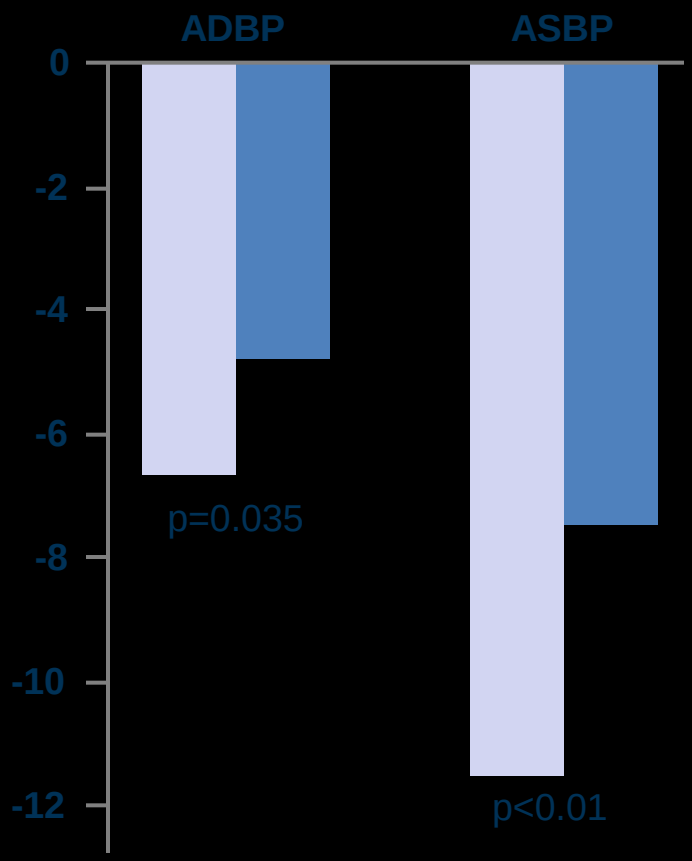
- Offer antihypertensive drug treatment to people (<80 yrs) with stage 1 HTN who have ≥1 of the following:
  - ✓ Target organ damage
  - ✓ Established CVD
  - ✓ Renal disease
  - ✓ Diabetes
  - ✓ A 10-yr CV risk equivalent to ≥ 20%
- Offer antihypertensive drug treatment to people of any age with stage 2 HTN
- For people (<40 yrs) with stage 1 HTN and no evidence of target organ damage, CVD, renal disease or diabetes, consider seeking specialist evaluation of secondary causes of HTN and a more detailed assessment of potential target organ damage. This is because 10-year CV risk assessments can underestimate the lifetime risk of CV events in these people.

3. Monitoring treatment

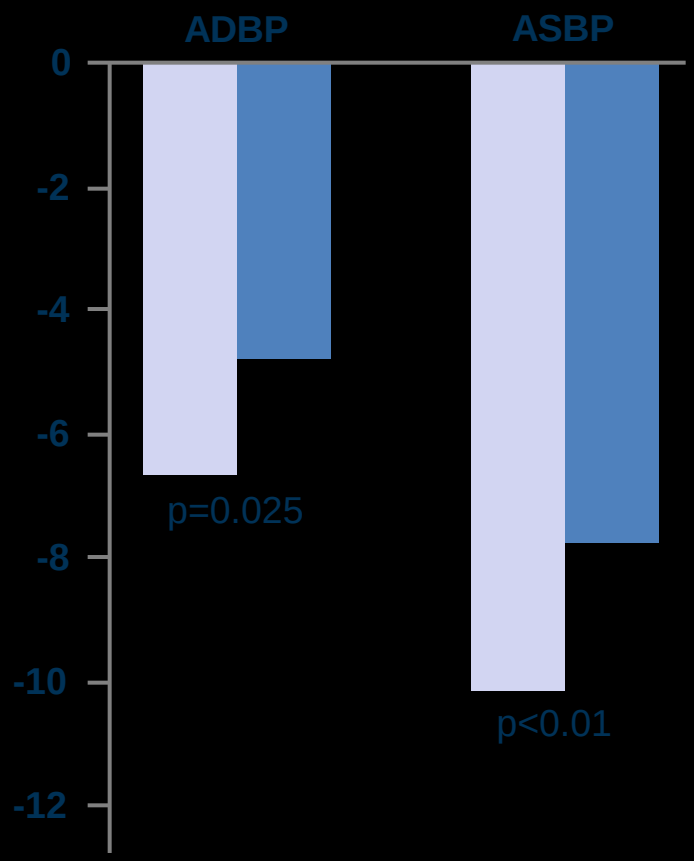
- For people identified as having a 'white-coat effect', consider **ABPM** or **HBPM**.

Nice clinical guideline 217
Updated on Aug 2011

Irbesartan vs valsartan



Mean change at trough from baseline



Mean 24h changes from baseline

irbesartan 150mg n=211

valsartan 80mg n=215

Mancia G, *et al. Blood Press Monit* 2002 ;7: 135 – 142.

Step 1~3 treatment

•Do not combine an ACEi with an ARB to treat HTN.

•If a CCB is not suitable, for example because of oedema or intolerance, or if there is evidence of HF or a high risk of HF, offer a thiazide-like diuretic

•If diuretic treatment is to be initiated or changed, offer a thiazide-like diuretic, such as chlortalidone (12.5-25.0 mg once daily) or indapamide (1.5 mg modified-release or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide

•For people who are already having treatment with bendroflumethiazide or hydrocholorothiazide and whose BP is stable and well controlled, continue treatment with the bendroflumethiazide or hydrocholorothiazide

Step 4 treatment

•For treatment of resistant HTN at step 4:

- Consider further diuretic therapy with low-dose spironolactone (25 mg once daily) if the blodd potassium level is ≤4.5 mmol/l. Use particular caution in people with a reduced eGFR because they have an increased risk of hyperkalaemia.
- Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is ≥4.5 mmol/l.

Irbesartan improves coronary microvascular function

- Three-month treatment with the ARB irbesartan for hypertensive patients without relevant arteriosclerosis and without significant left ventricular hypertrophy resulted in significant improvement in CFR as a marker of coronary microcirculatory function.

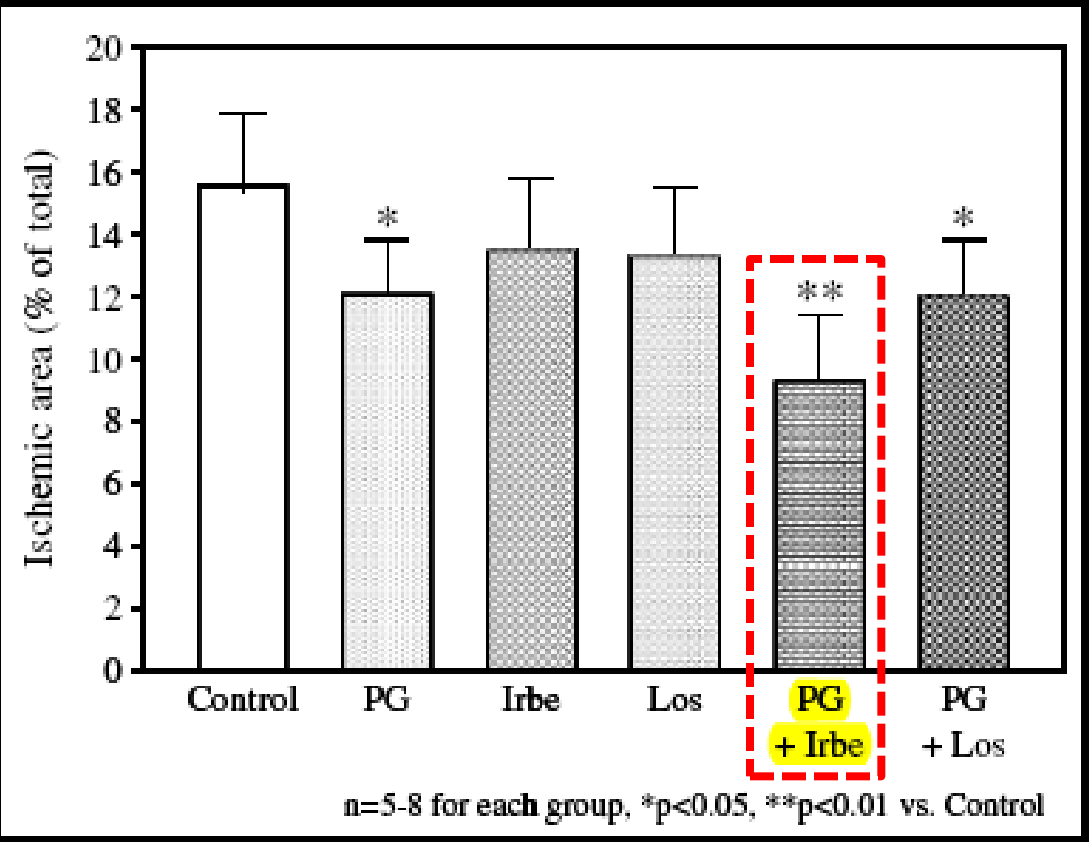
	Irbesartan (n=18)			Control (n=18)		
	Baseline	3 Month	P Value	Baseline	3 Month	P Value
SBP (mm Hg)	150±18	129±25	.001	145±23	147±22	ns
DBP (mm Hg)	88±11	81±12	.003	89±13	87±16	ns
IMT (mm)	1.06±.34	1.04±.30	.225	1.00±.46	.97±.52	ns
CFR	**2.87±.42**	**3.78±.32**	**.0001**	2.94±.61	3.06±.72	ns
LVMI (g/m^2)	135±35	131±37	ns	134±29	132±33	ns

- CFR, coronary flow velocity reserve
- DBP, diastolic 24-h ambulatory blood pressure
- SBP, systolic 24-h ambulatory blood pressure.
- IMT, intima-media thickness
- LVMI, left ventricular mass index
- ns, not significant

J Clin Hypertens (Greenwich). 2011 Mar;13(3):155-61.

Irbesartan attenuates ischemic brain damage

- Irbesartan, but not losartan, enhanced the inhibitory effect of propagermanium on ischemic brain damage



- C57BL/6J mice (8-weeks old, male)

→ 2 wks treatment of Irbesartan, losartan and propagermanium

→ cerebral ischemic damage was induced by permanent occlusion of the left middle cerebral artery (MCA) by electrocoagulation using a subtemporal approach

→ Mice were sacrificed 24 h after MCA occlusion

- Measurement of infarct volume

Biochem Biophys Res Commun. 2011 Jun 3;409(2):275-9.