



# Preliminary Results of the ACTIVE I Trial

# Background and Rationale

Elevated BP is one of the strongest risk factors for development of AF

Stroke and HF related to elevated BP are common complications of AF

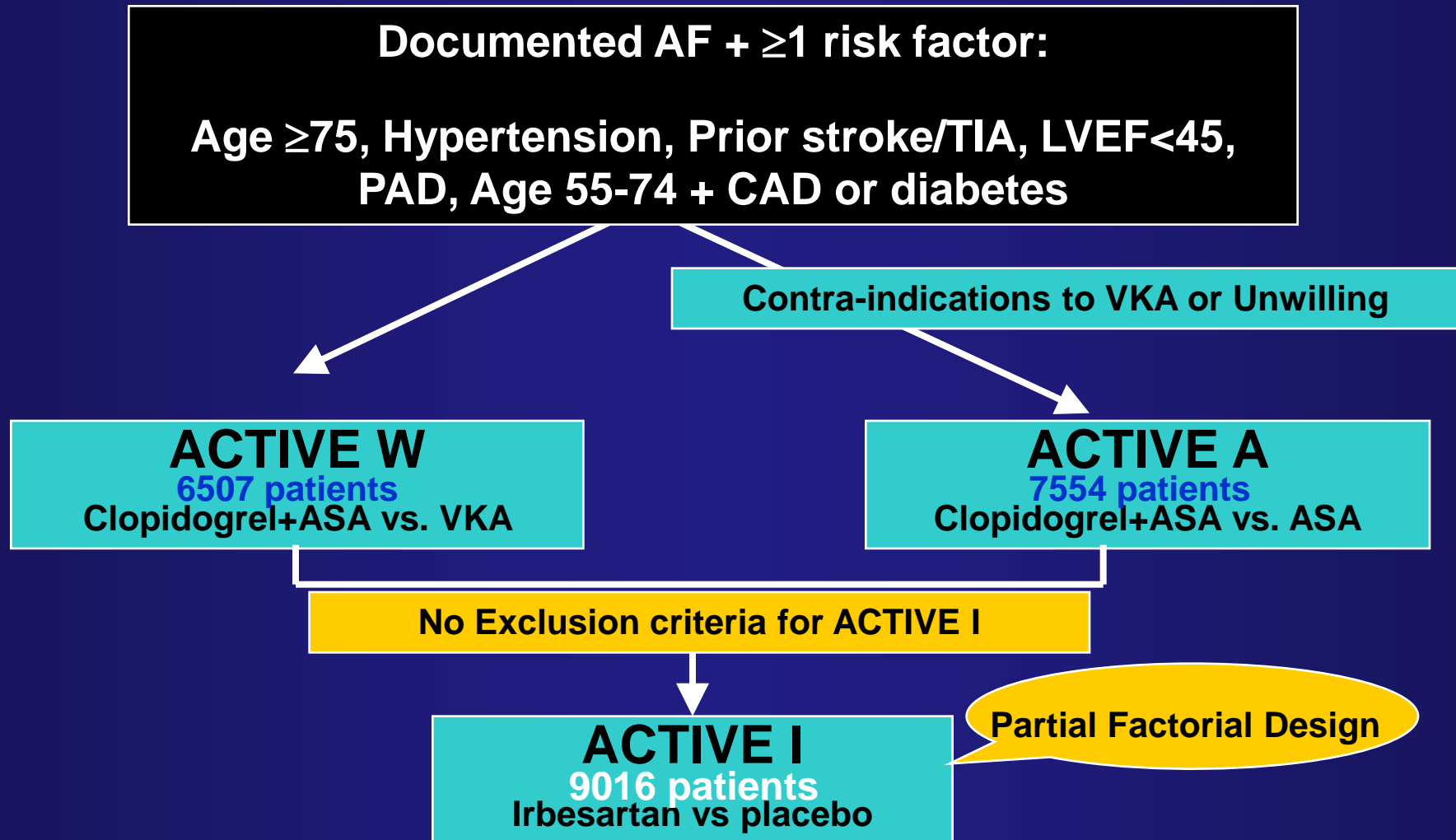
Blockade of the RAAS in patients with AF has not been studied in large studies

Most research in AF has been focused on reducing stroke and other embolic events even though HF occurs more frequently in AF patients

## Opportunity:

While studying VKA and dual antiplatelet therapy in the ACTIVE W & A trials, we also randomized patients to an ARB (Irbesartan/ placebo) to test the hypothesis that blockade of the RAAS and blood pressure lowering would reduce Stroke, MI and Vascular Death and Hospitalization for Heart Failure.

# ACTIVE Program – Three Trials



# Eligibility Criteria

## **Inclusion :**

Enrolled in ACTIVE-A or ACTIVE-W

Systolic BP  $\geq$  110 mm Hg

## **Exclusion :**

Already receiving an ARB, proven indication or previous intolerance

## **Primary Outcomes:**

- **Stroke, MI or vascular death**
- **Stroke, MI, vascular death + HF hospitalization**
- **Components**

# 9016 pts from 639 centers in 33 countries (99.5% complete followup)

ACTIVE

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Argentina	642*	Germany	744	Portugal	51
Australia	160	Greece	86	Russia	782*
Austria	20	Hong Kong	88	Singapore	51
Belgium	163	Hungary	206	South Africa	121
Brazil	680*	Israel	47	Spain	63
Canada	710	Italy	255	Sweden	153
Chile	212	Malaysia	44	Switzerland	11
Czech Republic	523*	Mexico	206	Taiwan	164
Denmark	30	Netherlands	223	Turkey	26
Finland	36	Norway	61	United Kingdom	234
France	124	Poland	1517	United States	583*

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# Baseline Characteristics

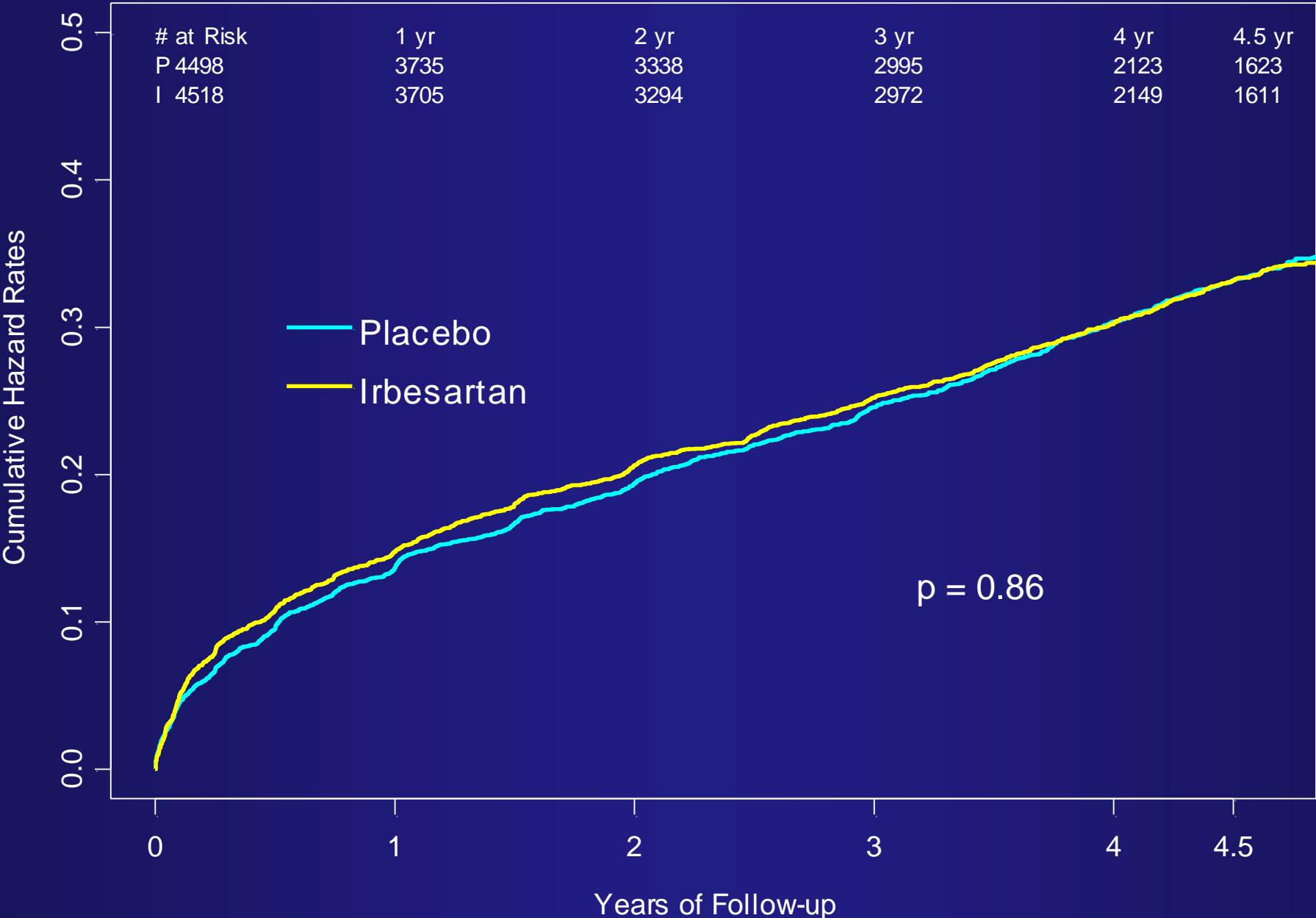
	<b>Irbesartan</b> (n = 4518)	<b>Placebo</b> (n = 4498)
<b>Age (mean)</b>	<b>69.5</b>	<b>69.6</b>
<b>% Female</b>	<b>39.2</b>	<b>39.3</b>
<b>AF - Permanent (%)</b>	<b>66.0</b>	<b>64.4</b>
<b>Paroxysmal (%)</b>	<b>19.6</b>	<b>20.5</b>
<b>Persistent (%)</b>	<b>14.3</b>	<b>14.9</b>
<b>Sinus Rhythm (%)</b>	<b>18.7</b>	<b>19.6</b>
<b>Heart Failure (%)</b>	<b>32.3</b>	<b>31.6</b>
<b>CHADS Risk Score</b>	<b>1.99</b>	<b>1.97</b>
<b>SBP/DBP</b>	<b>138/83</b>	<b>138/82</b>
<b>Heart Rate</b>	<b>75.3</b>	<b>74.9</b>

\* LV function data available in 4803 patients.

# Medications at Baseline

	Irbesartan (n = 4518) %	Placebo (n = 4498) %
<b>ACE-I</b>	<b>60.2</b>	<b>60.6</b>
<b>Beta-blockers</b>	<b>54.4</b>	<b>54.6</b>
<b>Diuretic</b>	<b>54.3</b>	<b>54.1</b>
<b>Calcium Channel Blocker</b>	<b>27.0</b>	<b>27.2</b>
<b>Alpha Blocker/Vasodilator</b>	<b>11.9</b>	<b>11.1</b>
<b>Aspirin</b>	<b>58.7</b>	<b>59.3</b>
<b>Vitamin K Antagonist</b>	<b>38.1</b>	<b>37.6</b>
<b>Antiarrhythmics</b>	<b>22.7</b>	<b>23.1</b>
<b>Digoxin</b>	<b>35.1</b>	<b>34.7</b>

# Permanent Discontinuation of Study Drug



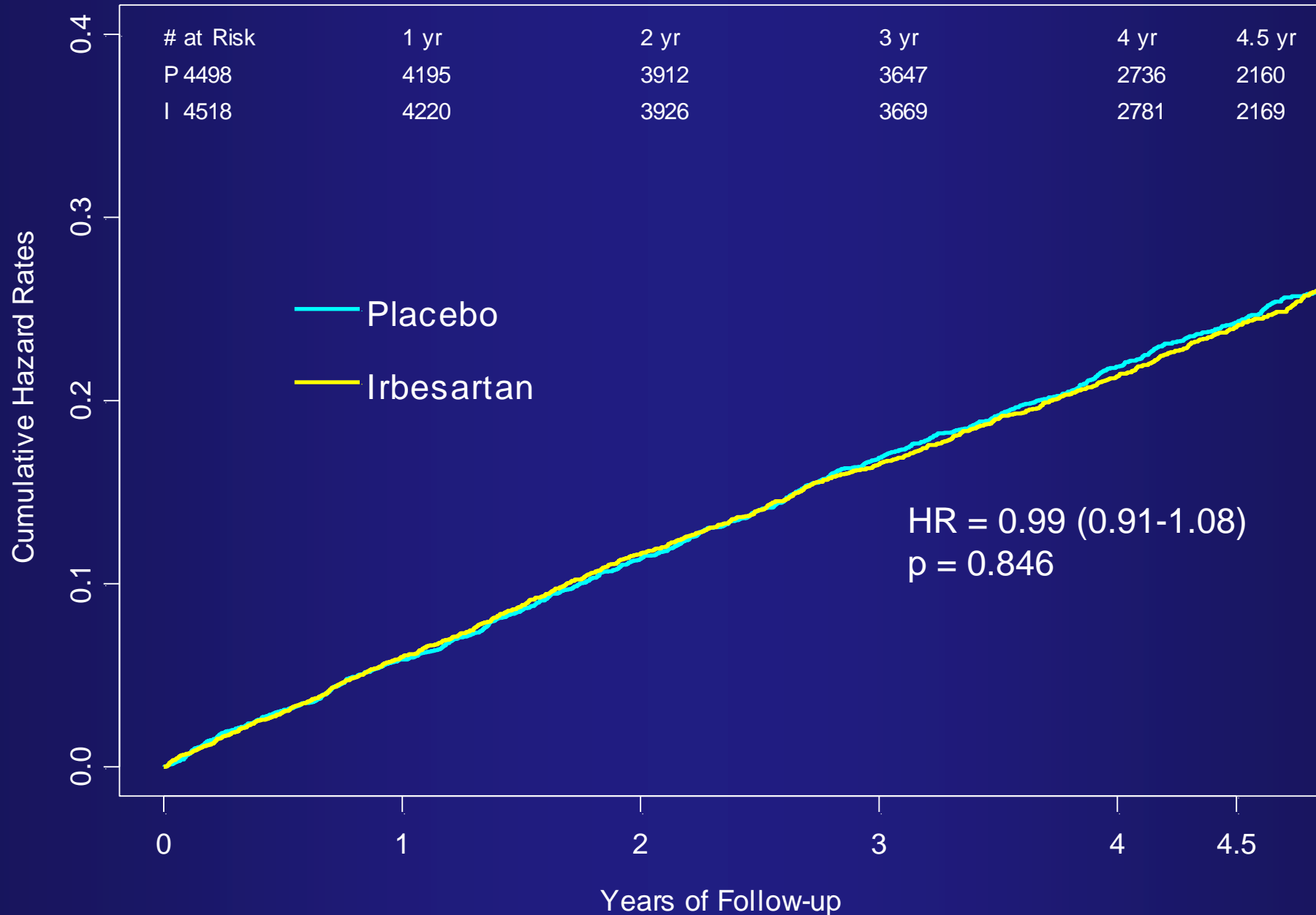
# In Trial Blood Pressure Changes from Baseline

	<b>Irbesartan</b> (n = 4518)	<b>Placebo</b> (n = 4498)	<b>Differences</b>
<b>Baseline</b>			
<b>Systolic BP</b>	<b>138.3</b>	<b>138.2</b>	
<b>Diastolic BP</b>	<b>82.6</b>	<b>82.2</b>	
<b>Change in SBP</b>	<b>- 6.84</b>	<b>- 3.93</b>	<b>- 2.91</b>
<b>Change in DBP</b>	<b>- 4.51</b>	<b>- 2.63</b>	<b>- 1.88</b>

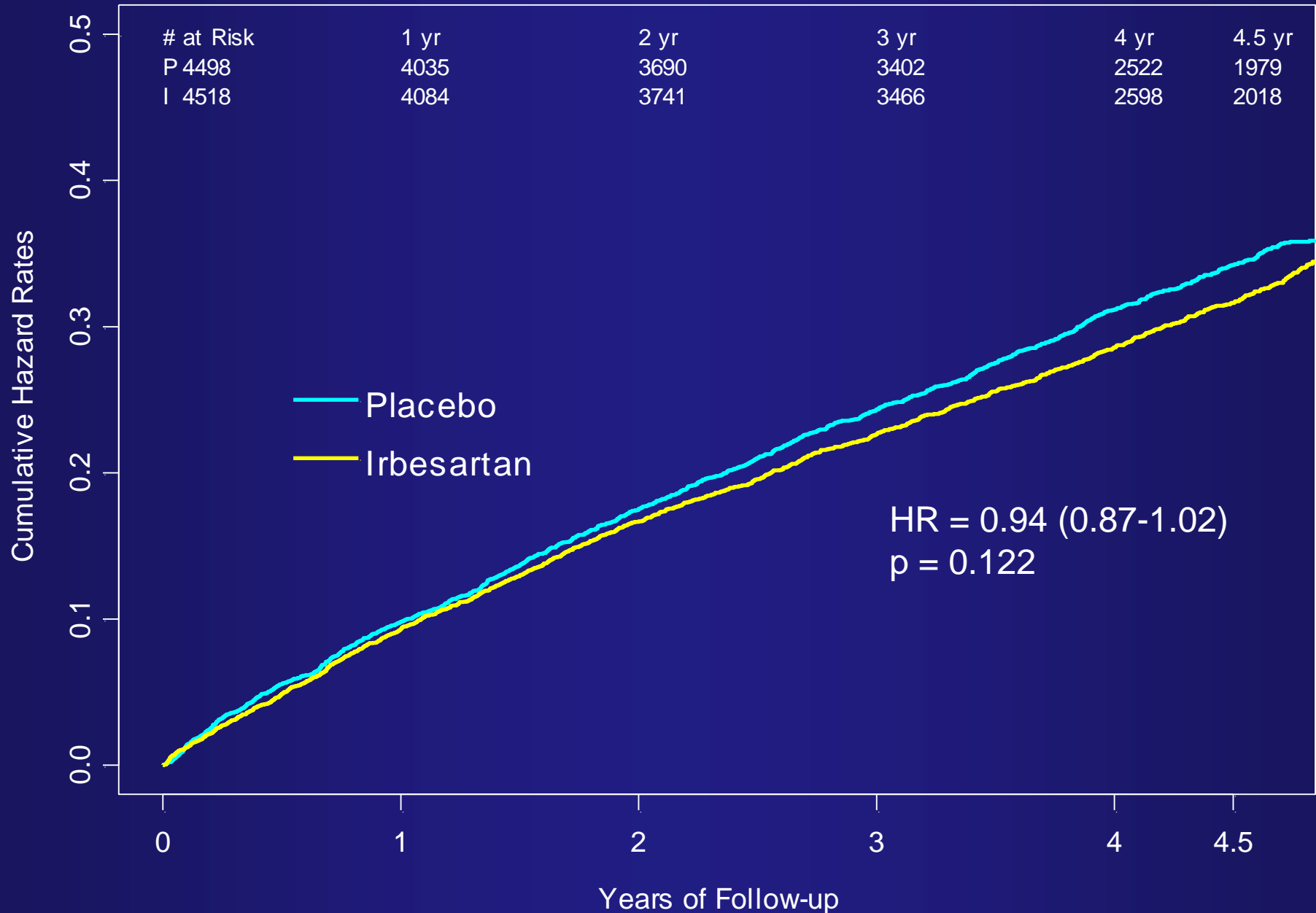
# Non-Study BP Lowering Drugs at 2yrs

	<b>Irbesartan</b> (n = 4518) %	<b>Placebo</b> (n = 4498) %
<b>None</b>	<b>10.7</b>	<b>7.7</b>
<b>1 - 2 BP Lowering Drugs</b>	<b>55.3</b>	<b>53.2</b>
<b>≥ 3 BP Lowering Drugs</b>	<b>34.1</b>	<b>39.1</b>
<b>Mean Number of BP Lowering Drugs</b>	<b>2.00</b>	<b>2.15</b>

# Stroke/MI/Vascular Death



# Stroke/MI/Vascular Death + HF Hosp



# Primary Outcomes

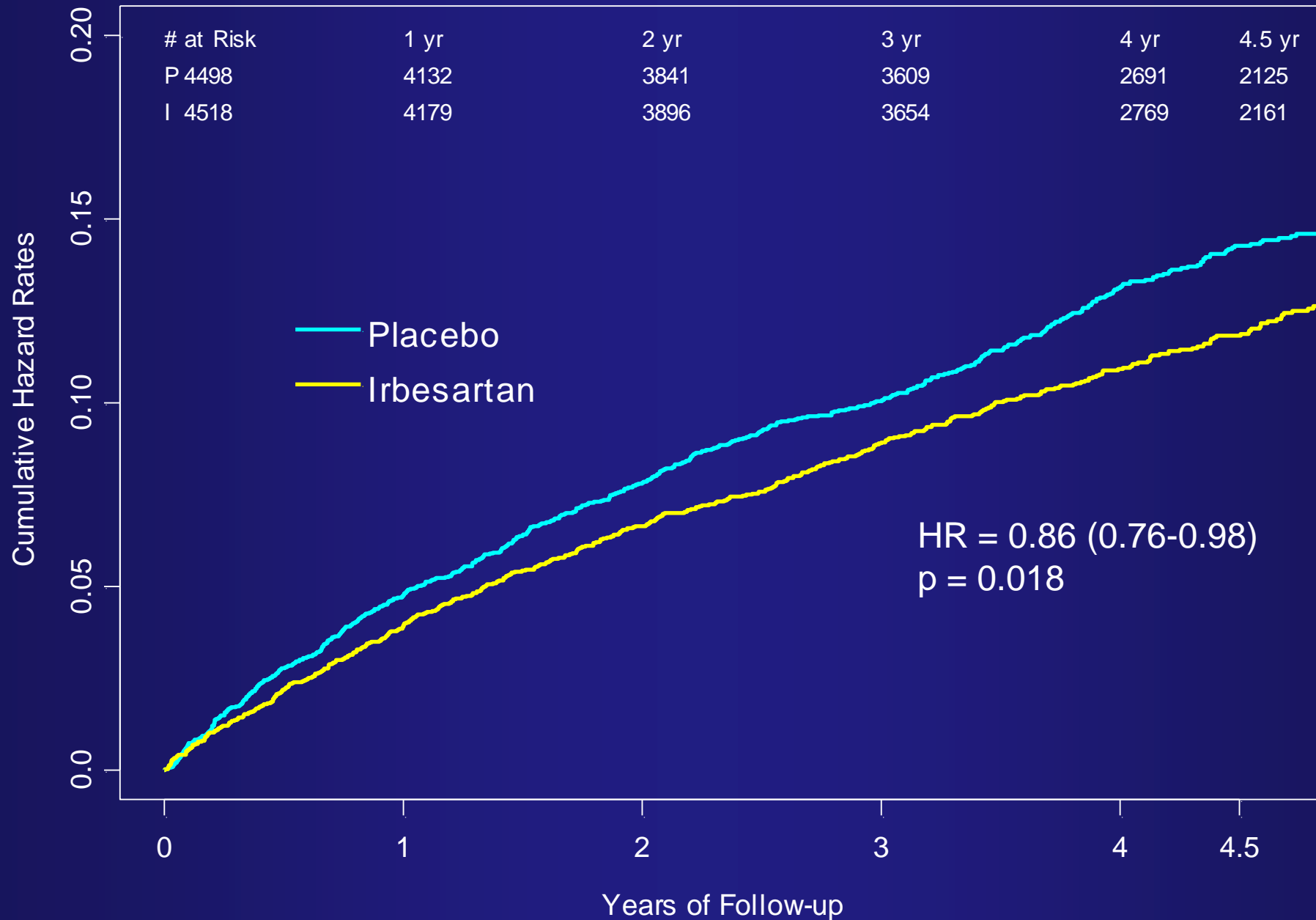
	Irbesartan (4518 pts)		Placebo (4498 pts)		Hazard Ratio	95% CI	p value
	n	%/yr	n	%/yr			
<b>Stroke/MI/Vascular Death</b>							
First event	963	5.4	963	5.4	0.99	0.91-1.08	0.846
Recurrent events*	1100	24.3	1122	24.9	0.97	0.89-1.07	0.579
<b>Stroke/MI/Vascular Death + HF Hosp</b>							
First event	1236	7.3	1291	7.7	0.94	0.87-1.02	0.122
Recurrent events*	1791	39.6	1992	44.3	0.89	0.82-0.98	0.016

\* Proportional means model.

# Components of the Primary Outcomes

	Irbesartan (4518 pts)		Placebo (4498 pts)		Hazard Ratio	95% CI	p value
	n	%/yr	n	%/yr			
Stroke	380	2.1	411	2.3	0.92	0.80-1.05	0.213
MI	143	0.8	135	0.7	1.05	0.83-1.33	0.675
Vascular Death	666	3.6	646	3.5	1.02	0.92-1.14	0.674
Hospitalization for HF	482	2.7	551	3.2	0.86	0.76-0.98	0.018

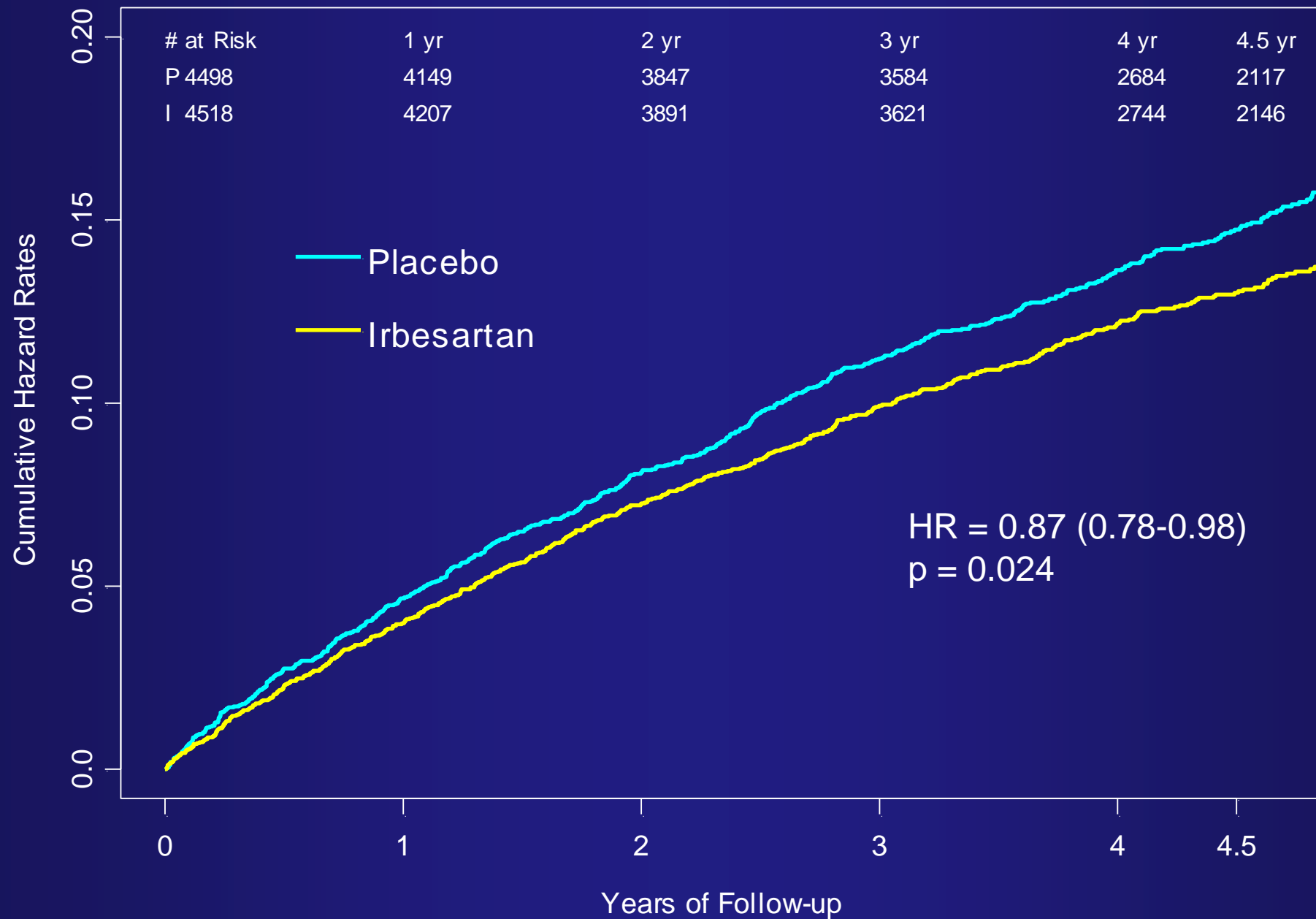
# Heart Failure Hospitalization



# Stroke and other Thromboembolic Events

	Irbesartan (4518 pts)		Placebo (4498 pts)		Hazard Ratio	95% CI	p- value
	n	%/yr	n	%/yr			
Stroke	380	2.1	411	2.3	0.92	0.80-1.05	0.213
TIA	130	0.7	150	0.8	0.86	0.68-1.09	0.208
Non CNS Embolism	49	0.3	65	0.4	0.74	0.51-1.07	0.114
Stroke/TIA/Non CNS Emb	518	2.9	585	3.4	0.87	0.78-0.98	0.024

# Stroke/TIA/Non CNS Embolism



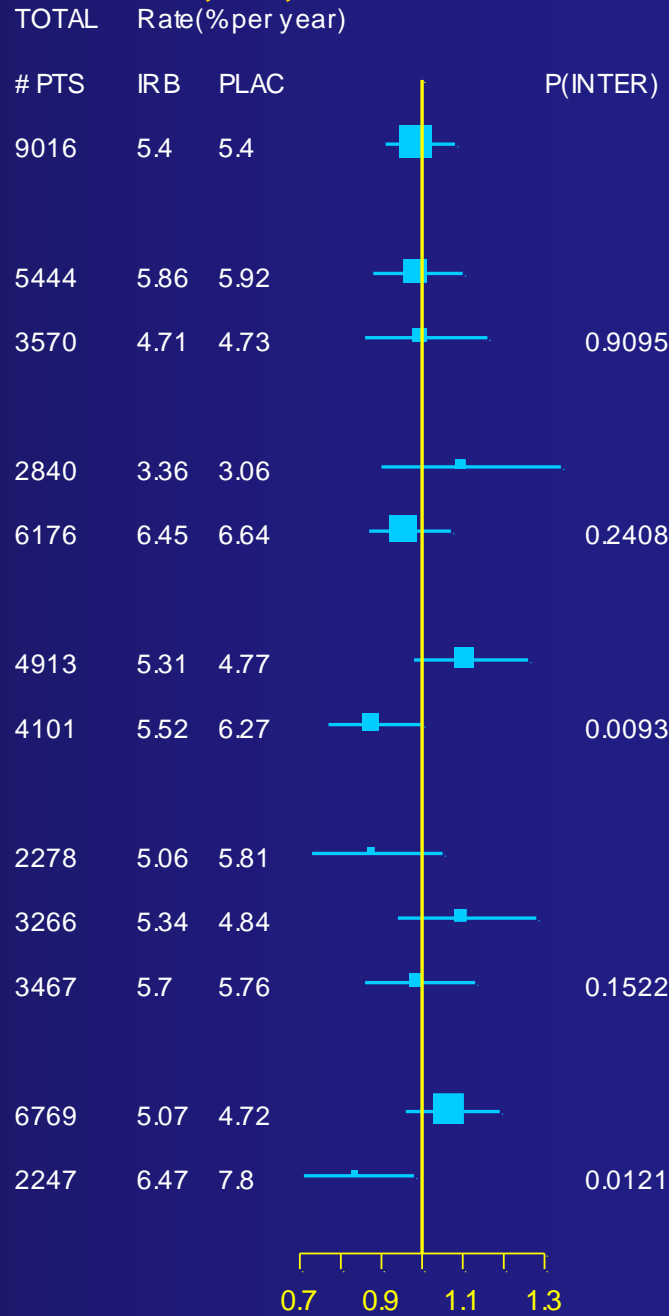
# Hospitalization for CV Reasons

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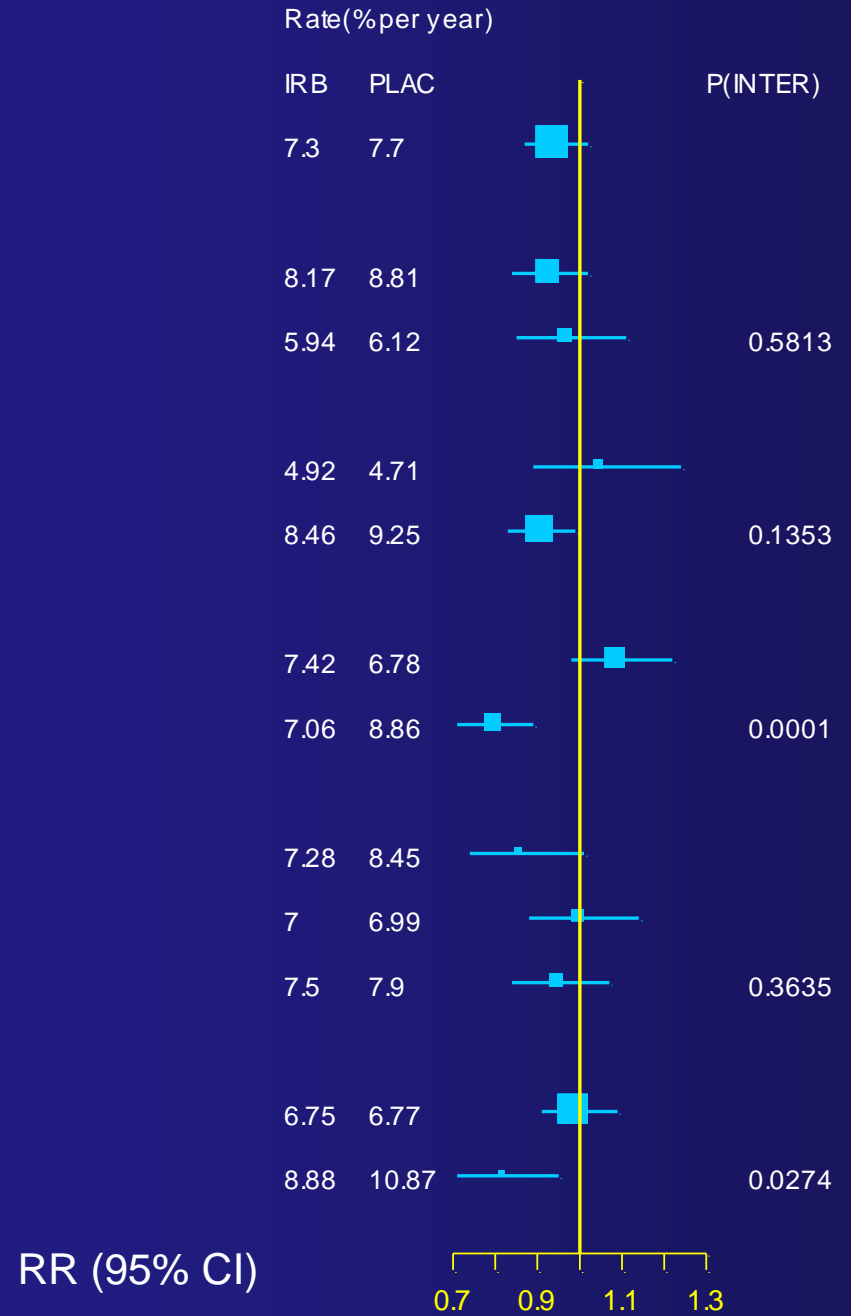
	<b>Irbesartan (n = 4518)</b>	<b>Placebo (n = 4498)</b>	<b>Difference</b>	<b>p value</b>
<b>No. of Hospital Admissions</b>	<b>3817</b>	<b>4059</b>	<b>-242</b>	<b>0.003</b>
<b>Mean days in Hospital</b>	<b>9.55</b>	<b>9.85</b>	<b>-0.3</b>	<b>0.253</b>
<b>Total Days in Hospital</b>	<b>36440</b>	<b>39971</b>	<b>-3531</b>	<b>0.0000</b>

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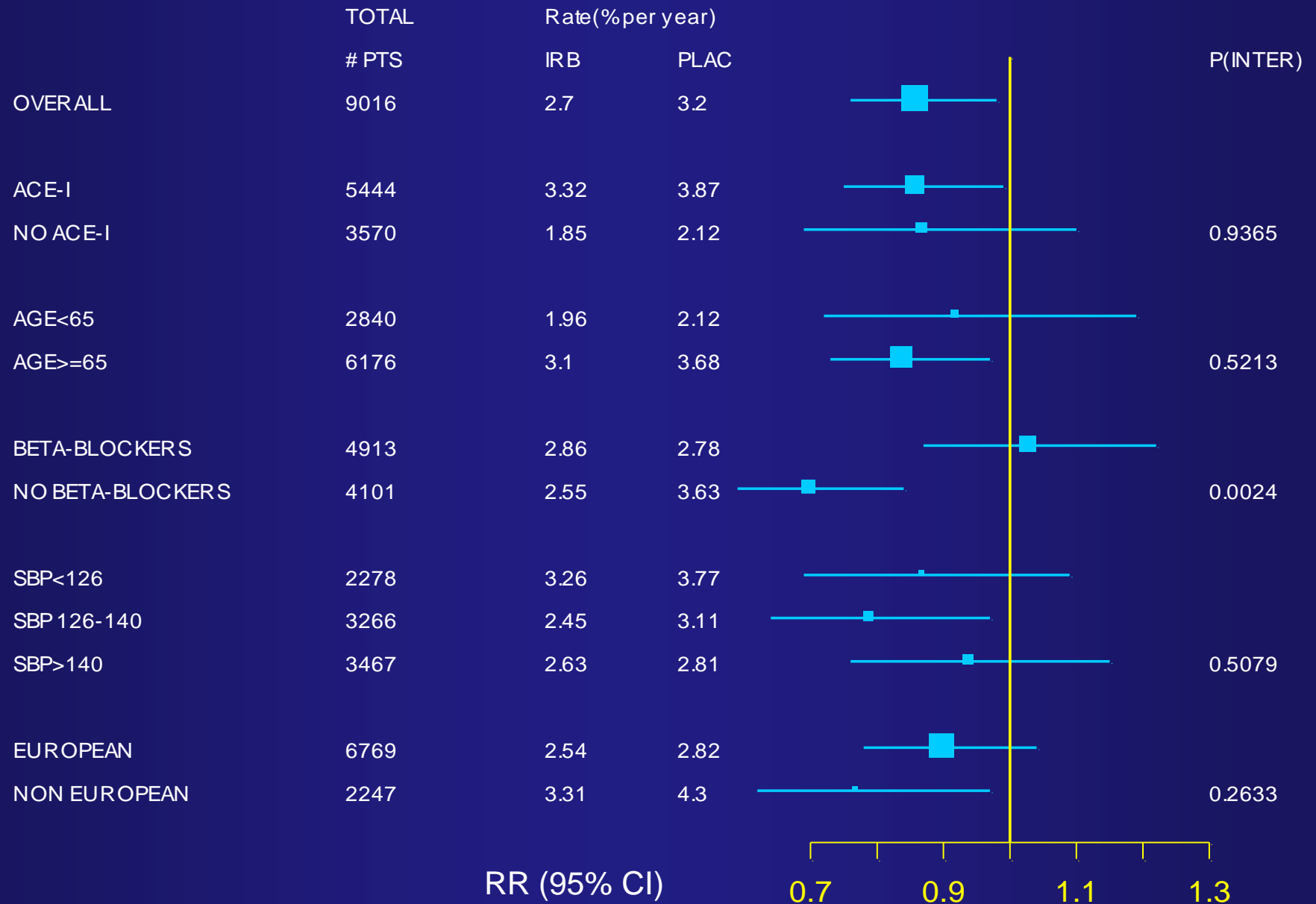
## Stroke, MI, Vascular Death



## HF Hosp, Stroke, MI, Vascular Death



# Hospitalization for Heart Failure



# Conclusions

1. In a normotensive population with AF, Irbesartan lowered BP by -3 / -2 mm Hg with:
  - a) No reduction of Stroke, MI or Vascular death
  - b) Significant reduction in heart failure by 14%
  - c) A 13% reduction in the composite of stroke, TIA and non-CNS embolism (not prespecified).
2. Significant reduction in recurrent events, resulting in a reduction in the no. of hospitalization days for CV reasons
3. Irbesartan is well tolerated.
4. Subgroup analyses indicated consistent and significant results, except an unexpected larger benefit in those not receiving a beta blocker compared to those on beta blockers.

# Clinical Implications for AF Patients

Given that hypertension is common in AF, and that Heart Failure is common (more frequent than stroke), it would be reasonable to lower BP with an ARB such as Irbesartan.

More aggressive BP lowering (with larger BP reductions) may reduce heart failure and perhaps cerebrovascular events and other embolic events to a greater degree.