# The role of calcium channel blockers in high risk hypertension

Professor D G Beevers
Department of Medicine
City Hospital, Birmingham

29th September 2005

# Calcium channel blockers

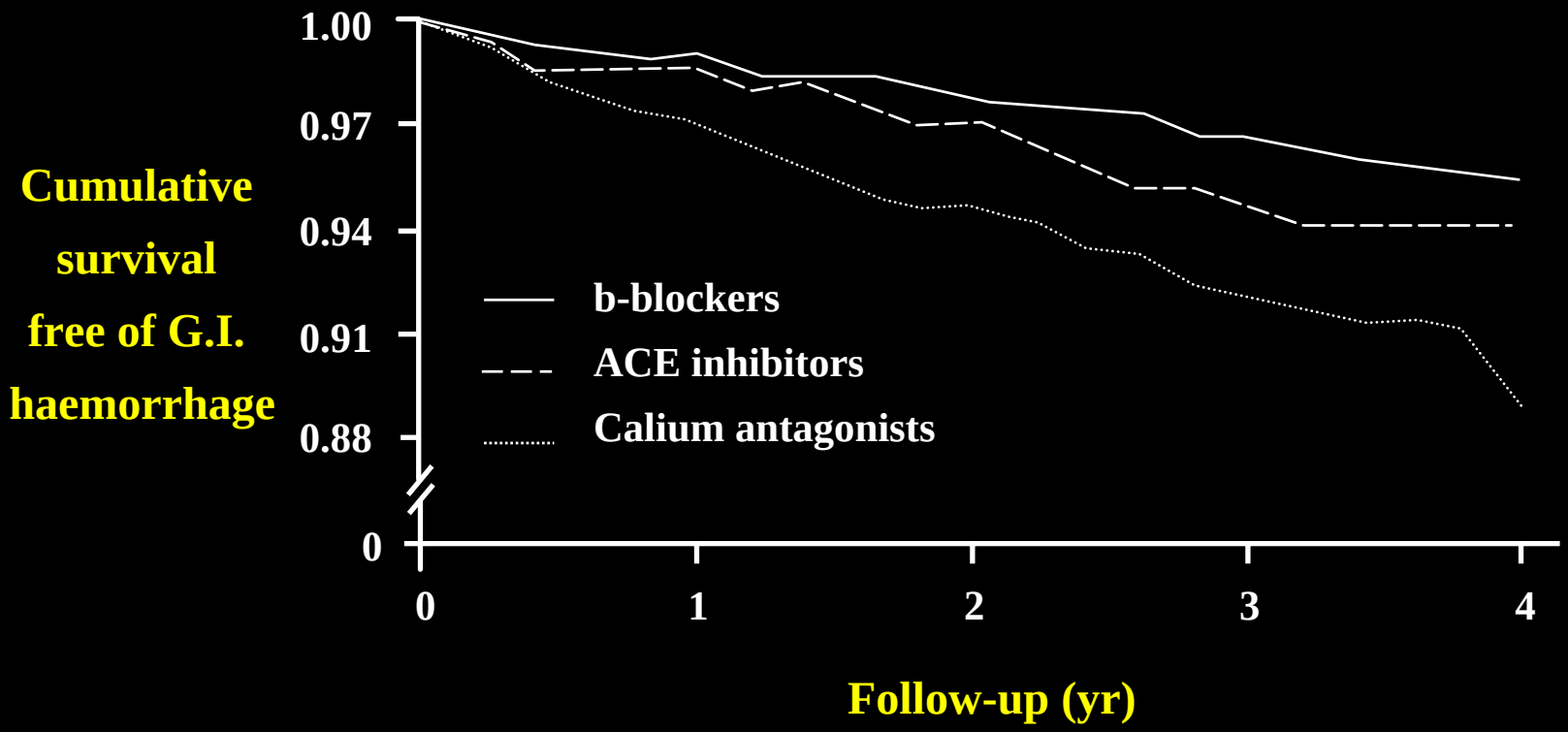
- 1978. CCBs mainly used for angina and arrhythmias (verapamil). Anti-hypertensive properties under-recognised.
- 1986. Nifedepine found to be of no value in post-infarct patients (Wilcox).
- Verapamil and diltiazem shown to be effective in some post-infarct patients.
- 1995. Anxieties about the safety of CCBs (Furberg).
- 1997. Syst-Eur, Syst-China.
- 2002. ALLHAT
- 2004. VALUE.
- 2005. ASCOT-BPLA.

# Calcium Channel Blockers - ? Hazards

Heart attack
Cancer
Suicide
GI haemorrhage
Stroke
Surgical haemorrhage

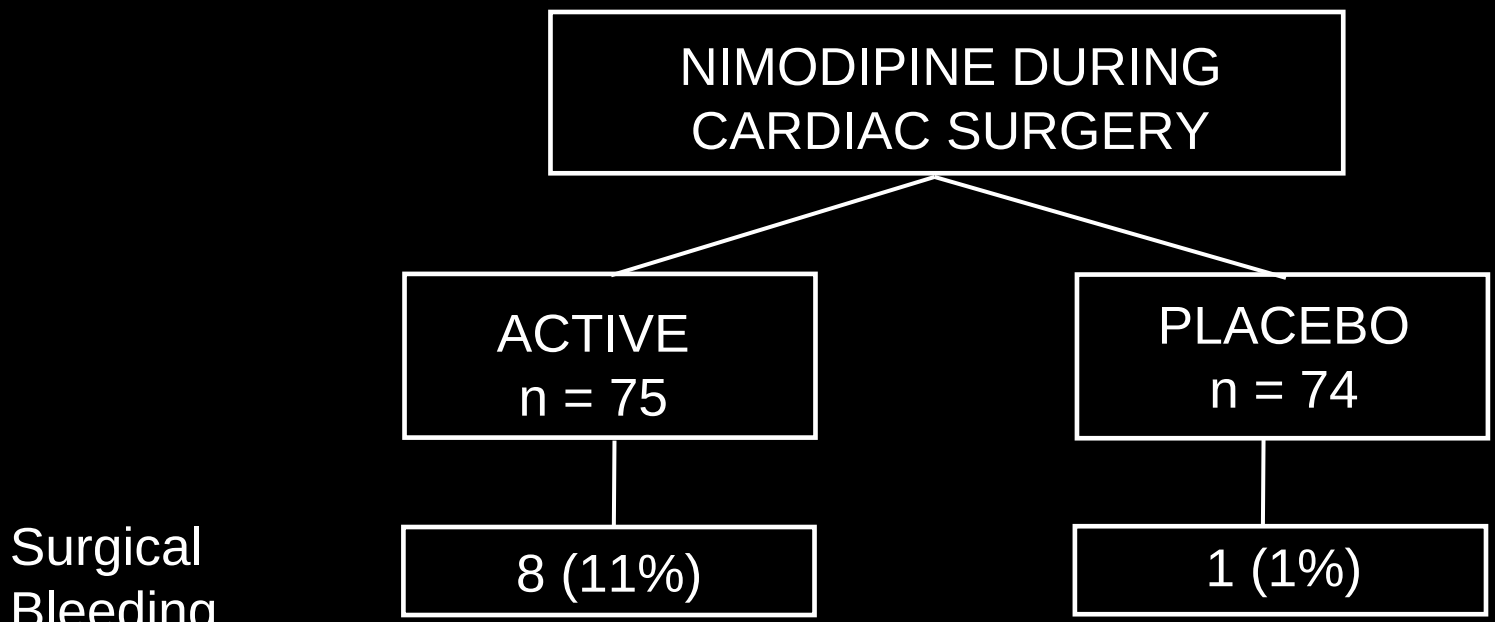
# Risk of Gastrointestinal Haemorrhage With Calcium Antagonists In Hypertensive Persons Over 67 Years Old

Pahor et al. Lancet 1996;347:1061-5



# Surgical Bleeding: Unexpected effect of a Calcium Antagonist

Wagenknecht, Furberg et al . Brit Med J 1995; 310: 776-7.



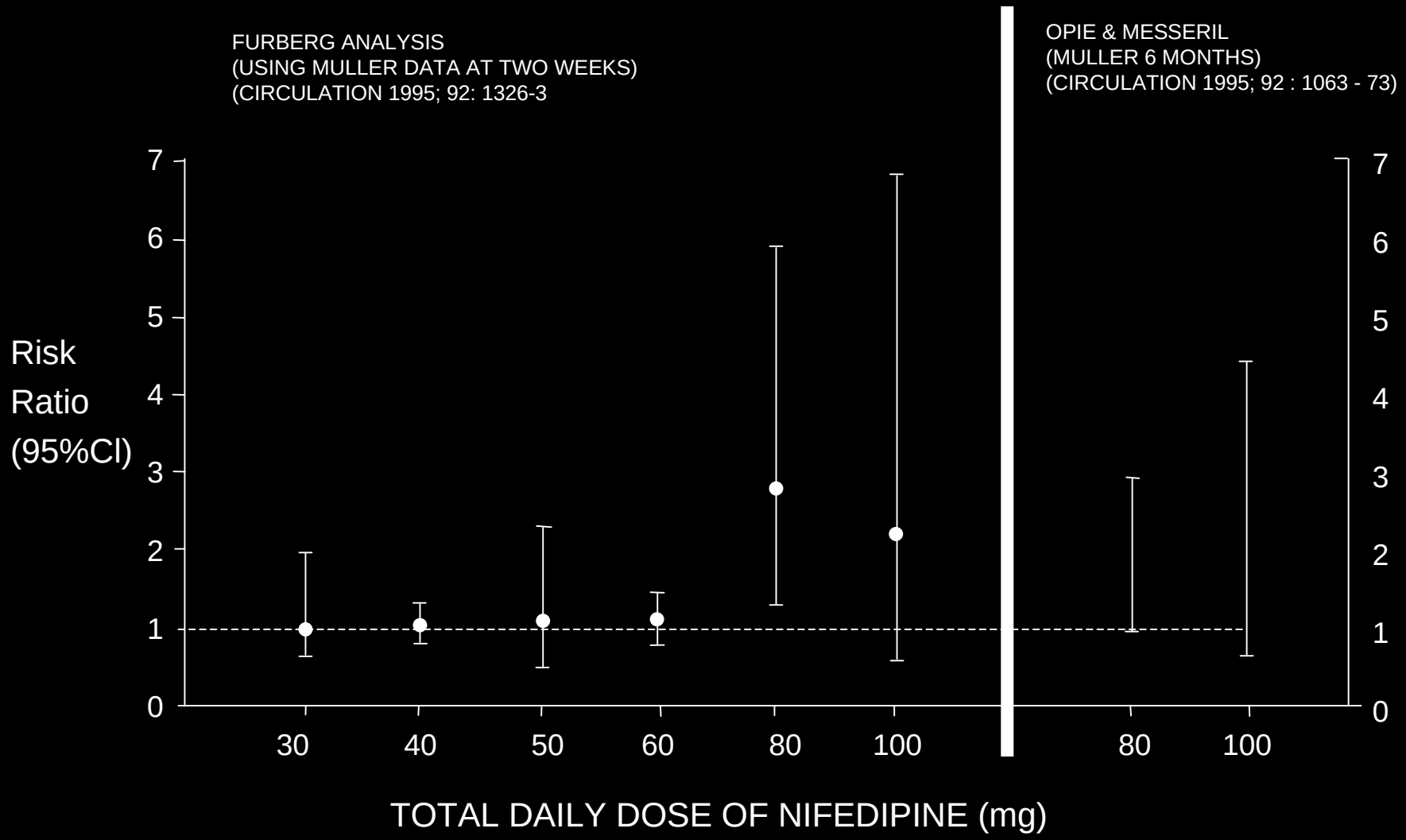
# Calcium channel blockers and cancer

Amer J Hypertens 1996; 9: 695-9.

| | Number on drug | Number of cancers | RR | 95% CI |
|---|---|---|---|---|
| Beta blockers | 424 | 28 | 1.0 | - |
| ACE inhibitors | 124 | 6 | 0.73 | 0.30-1.78 |
| Calcium blockers | 202 | 27 | 2.02 | 1.16-3.54 |
| Verapamil | 65 | 10 | 2.46 | 1.17-5.17 |
| Nifedepine | 61 | 10 | 2.34 | 1.09-5.03 |
| Diltiazem | 76 | 7 | 1.40 | 0.59-3.28 |

# Nifedipine in CHD

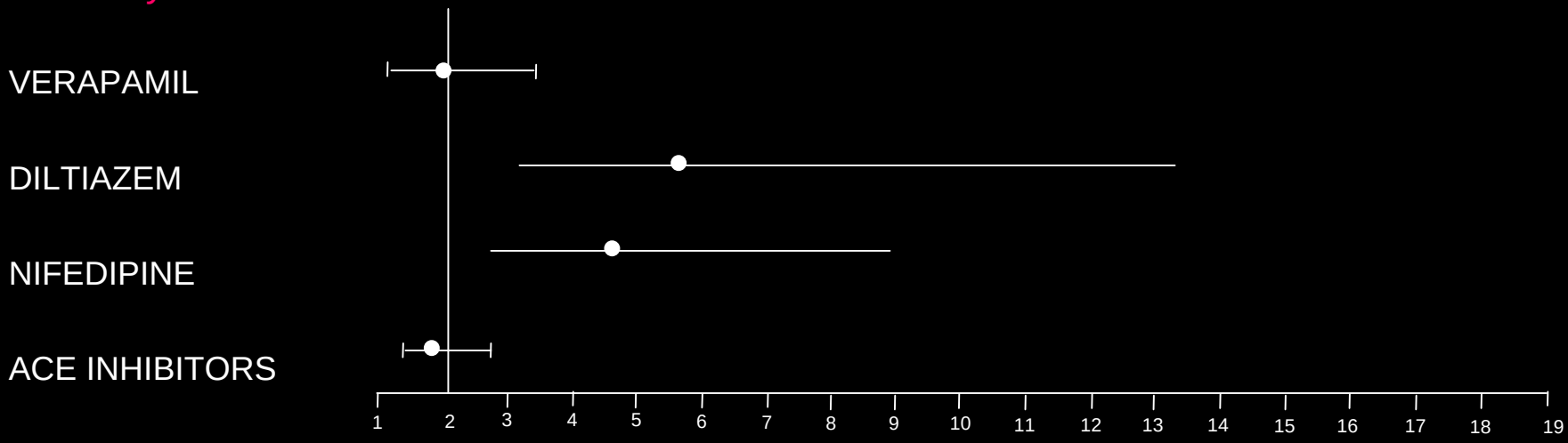
## Myocardial infarcts & unstable angina



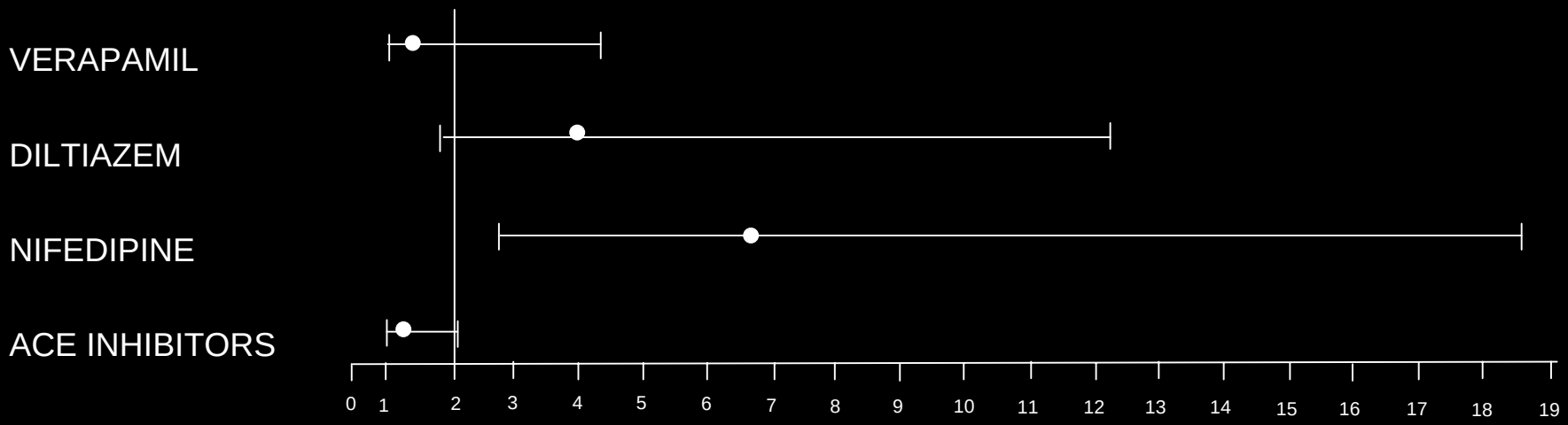
# Calcium blockers and mortality

Pahor et al, J Amer Geriatrics Soc 1995;

## Coronary Heart Disease




## Acute Myocardial Infarction

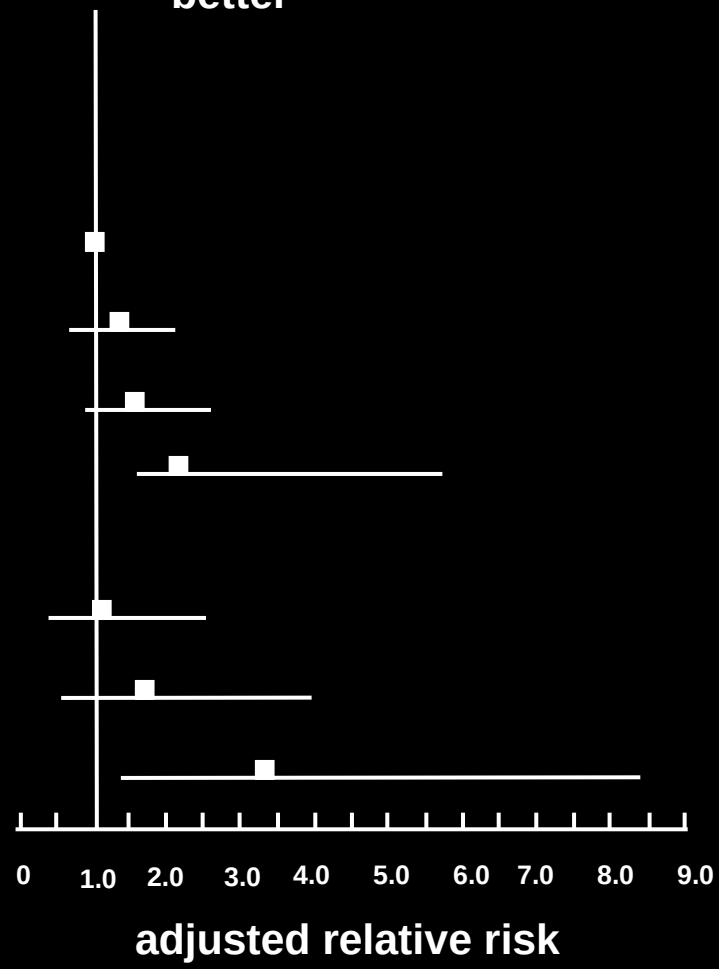



Multiple Factor Adjusted Relative Risk (95% CI)

# Are Calcium Blockers Hazardous?

**Psaty et al, JAMA 1995: 274: 620-5.**

| DRUG | | CASES | CONTROLS |
|---|---|---|---|
| **treatment worse** | | | |
| Diuretics | | 99 | 452 |
| CCB alone | Low | 17 | 70 |
| | Med | 22 | 69 |
| | High | 17 | 31 |
| CCB + Diuretic | Low | 7 | 24 |
| | Med | 8 | 22 |
| | High | 9 | 14 |

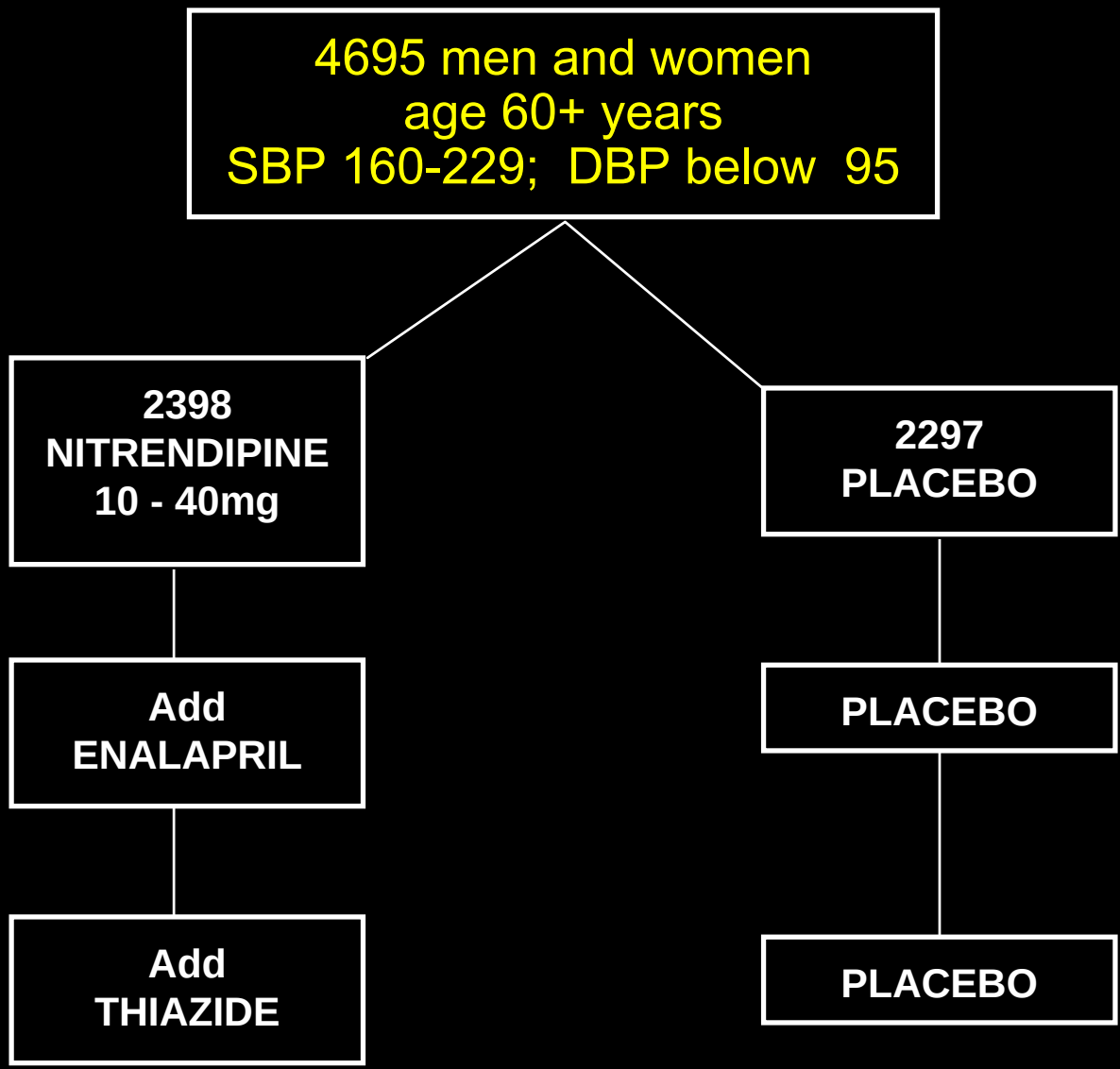


# Syst-Eur

Staessen et al. Lancet 1997;

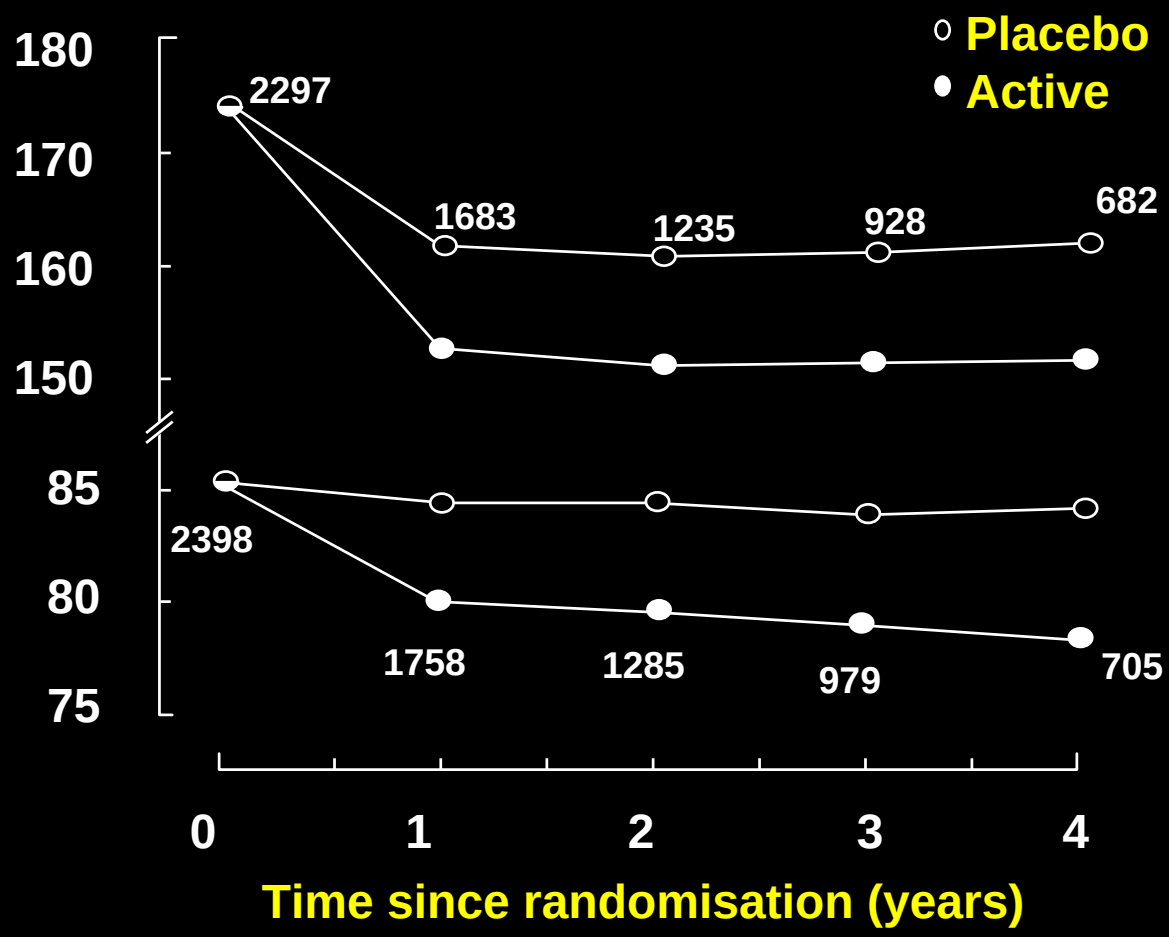
The first long-term outcome trial of a DHP-CCB in essential hypertension

# SYST-EUR


4695 men and women
age 60+ years
SBP 160-229; DBP below 95
2398
NITRENDIPINE
10 - 40mg
Add
ENALAPRIL
Add
THIAZIDE
2297
PLACEBO
PLACEBO
PLACEBO

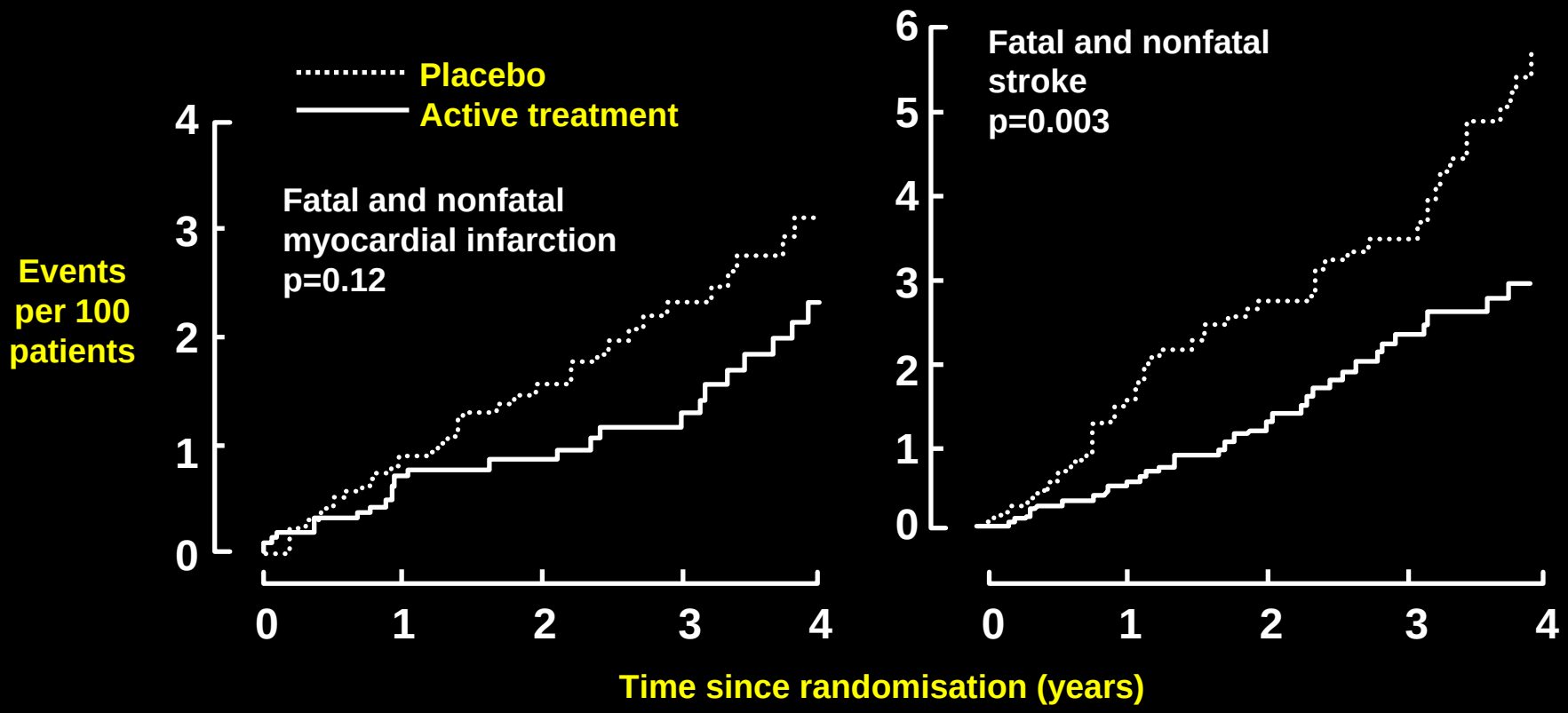
# SYST-EUR

## Nitrendipine vs Placebo



# SYST-EUR Main results

Staessen et al, Lancet 1997;



# SYST-EUR

Fatal and non-fatal cardiovascular endpoint rate per 1000 patients years

| | Placebo | Active | % Reduction | p |
|---|---|---|---|---|
| Stroke | 13.7 | 7.9 | -42 | 0.003 |
| Cardiac endpoints | 20.5 | 15.1 | -26 | 0.03 |
| Heart failure | 8.7 | 6.2 | -29 | 0.12 |
| Myocardial infarct | 8.0 | 5.5 | -30 | 0.12 |
| All endpoints | 33.9 | 23.3 | -31 | <0.001 |

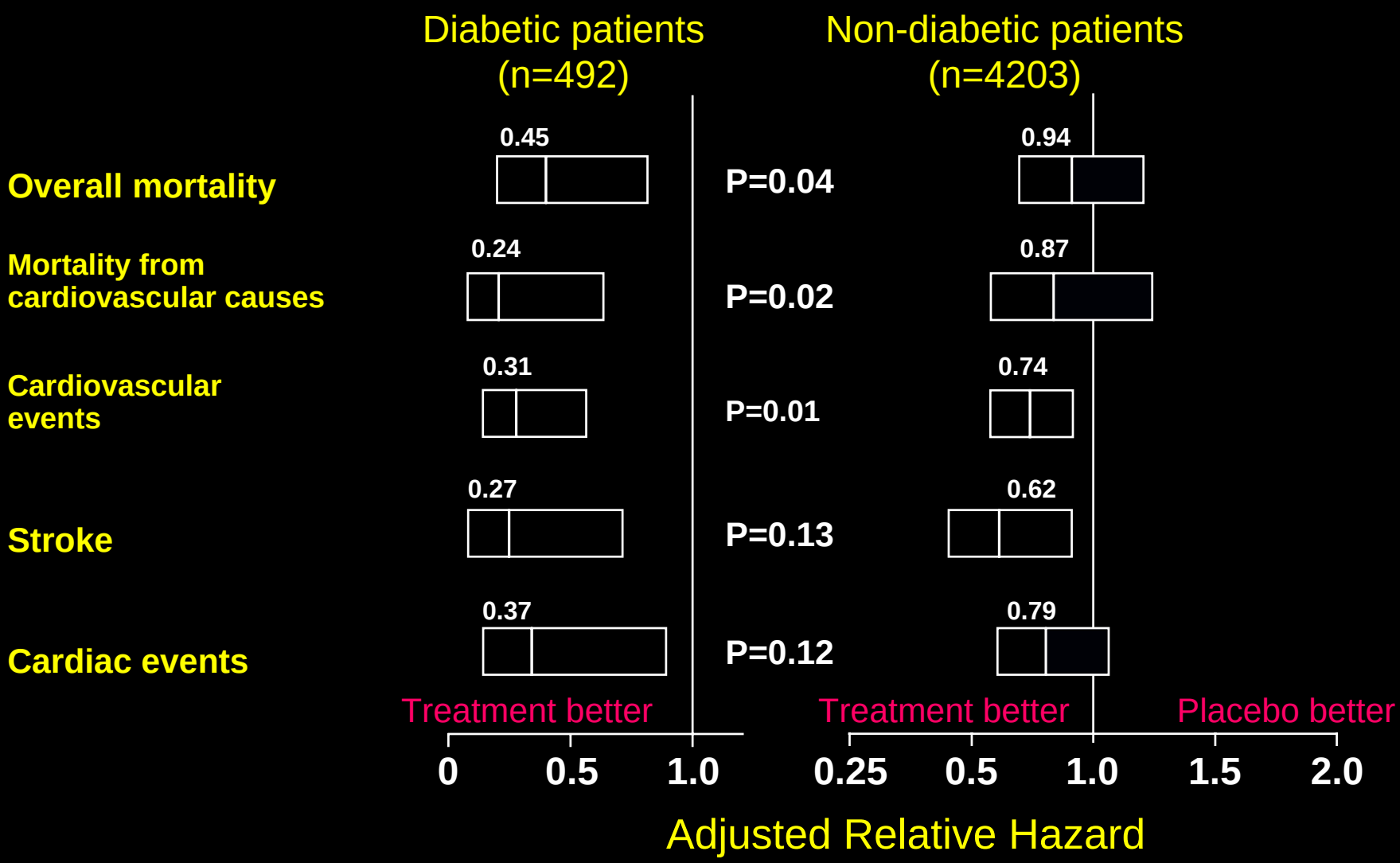
# SYST-EUR

Cancer and bleeding rates per 1000 patient years

| | Placebo | Active | % Change |
|---|---|---|---|
| Cancer | 14.7 | 12.4 | -15 |
| Benign Neoplasm | 3.0 | 4.0 | +35 |
| Intercurrent disease | 31.4 | 33.1 | +5 |
| Bleeding | 3.5 | 3.2 | -10 |

# SYST-EUR DIABETIC SUB-GROUP

Tuomilehto et al, NEJM 1999; 340: 677-84.



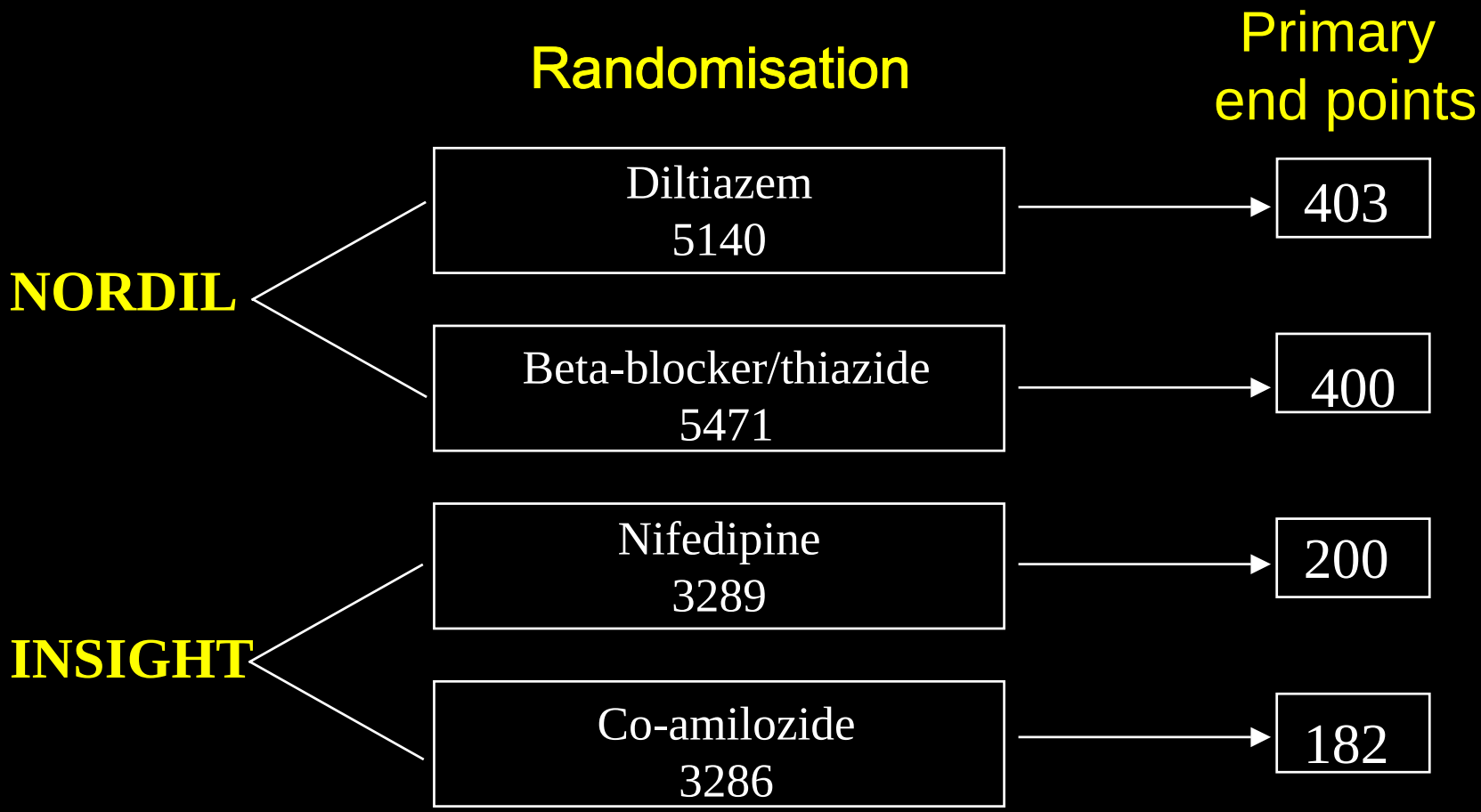
# Syst-China

Liu et al, J Hypertens 1998; 16: 1823-9.

| | Placebo (1141) | Nitrendipine (1253) | % difference | p |
|---|---|---|---|---|
| Entry BP | 170/86 | 171/86 | - | - |
| BP fall | 11/2 | 20/5 | - | - |
| Stroke (F+NF) | 59 | 45 | - | - |
| Strokes/1000 patient-years | 20.9 | 13.0 | 38% | 0.01 |
| Myocardial infarction (all) | 7 | 9 | - | - |
| AMI/1000 patient-years | 2.4 | 2.6 | -6% | 0.91 |
| Heart failure | 8 | 4 | - | - |
| CCF/1000 patient-yr | 2.8 | 1.1 | 58% | 0.13 |

# NORDIL and INSIGHT

**Lancet 2000; 356: 359 and 366.**



# VALUE

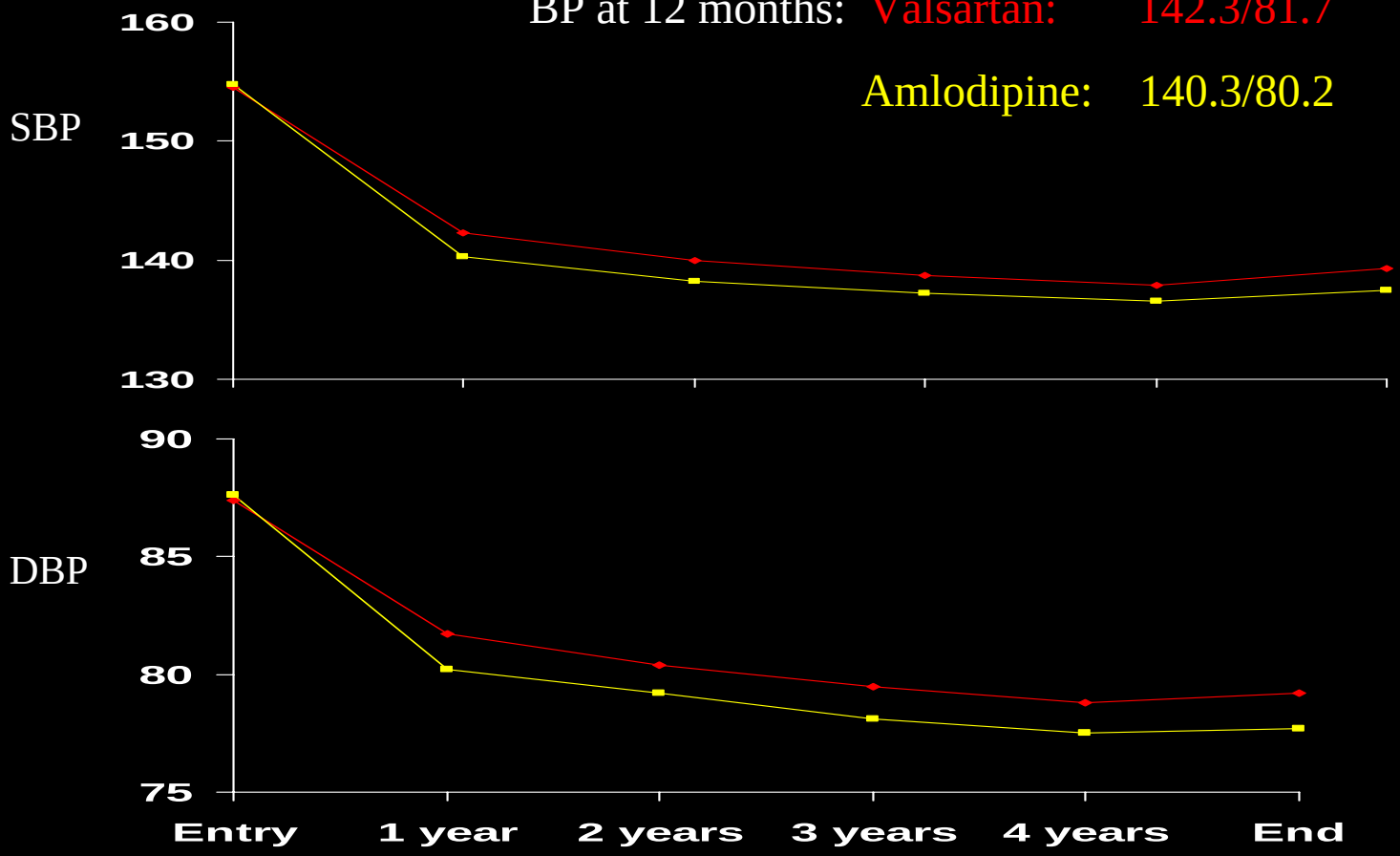
Amlodipine v valsartan

# Value: change in blood pressure

Julius et al, Lancet 2004; 363: 2022-31.

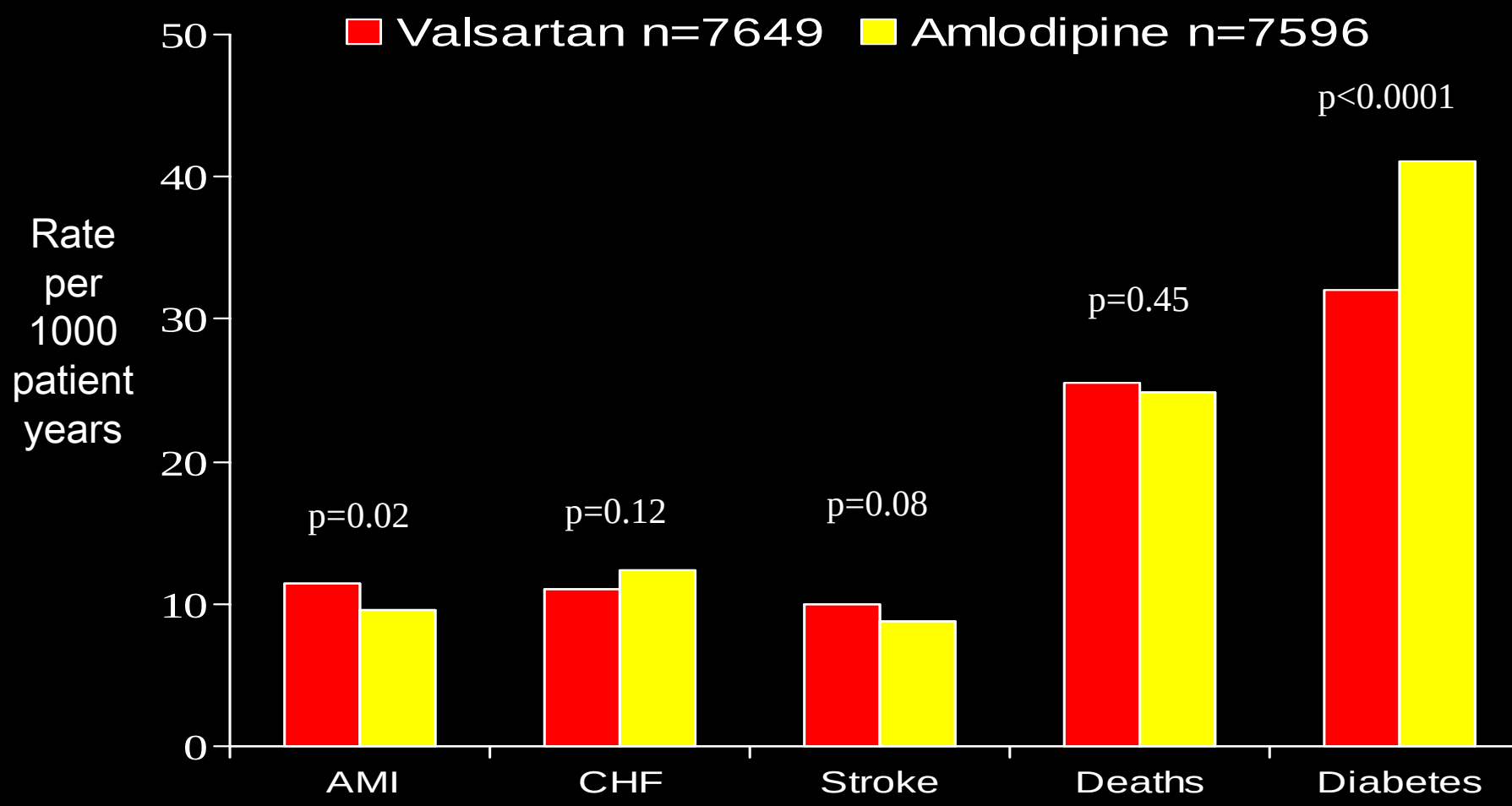
BP at 12 months: Valsartan: 142.3/81.7

Amlodipine: 140.3/80.2



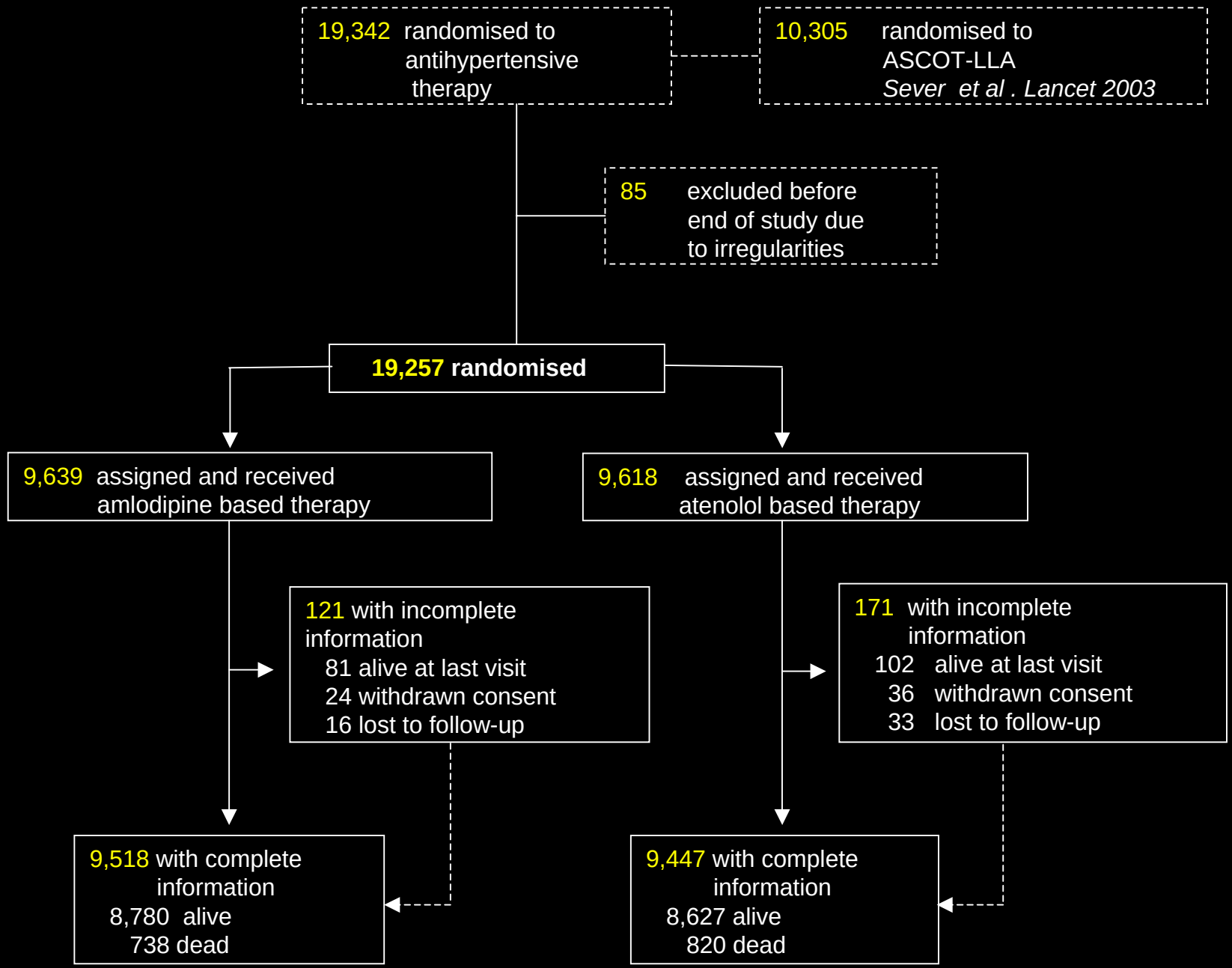
# VALUE: main results

Julius et al, Lancet 2004; 363: 2022-31 & Weber et al Lancet 2004; 363: 2049-51



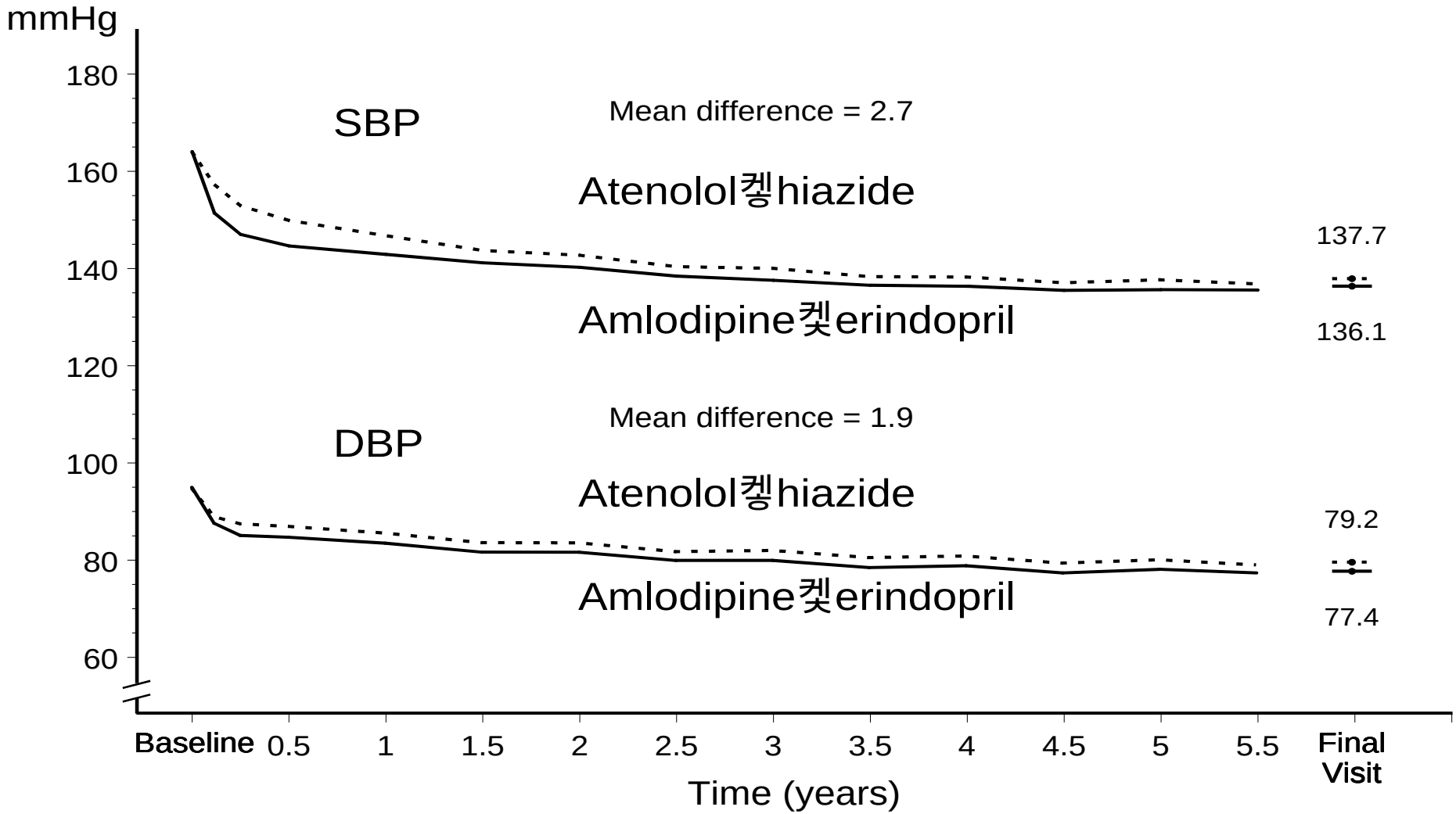
# ASCOT-BPLA

Dahlöf et al. Lancet 2005; 366: 895-906


19,342 randomised to antihypertensive therapy
10,305 randomised to ASCOT-LLA
Sever et al . Lancet 2003
85 excluded before end of study due to irregularities
19,257 randomised
9,639 assigned and received amlodipine based therapy
9,618 assigned and received atenolol based therapy
121 with incomplete information
81 alive at last visit
24 withdrawn consent
16 lost to follow-up
171 with incomplete information
102 alive at last visit
36 withdrawn consent
33 lost to follow-up
9,518 with complete information
8,780 alive
738 dead
9,447 with complete information
8,627 alive
820 dead

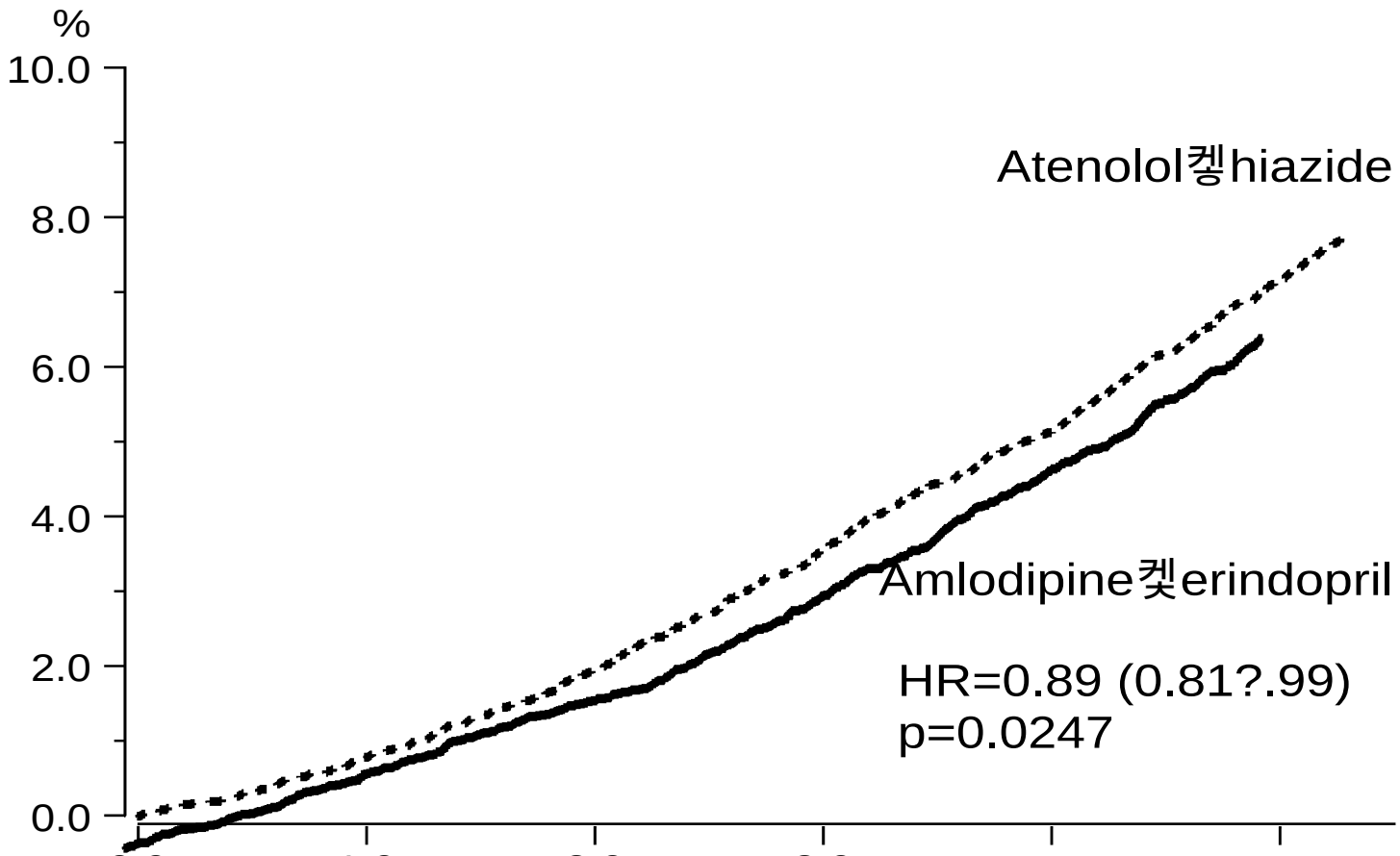
# ASCOT BPLA: Blood pressure control

Dahlöf et al. Lancet 2005;



# ASCOT BPLA: all cause mortality

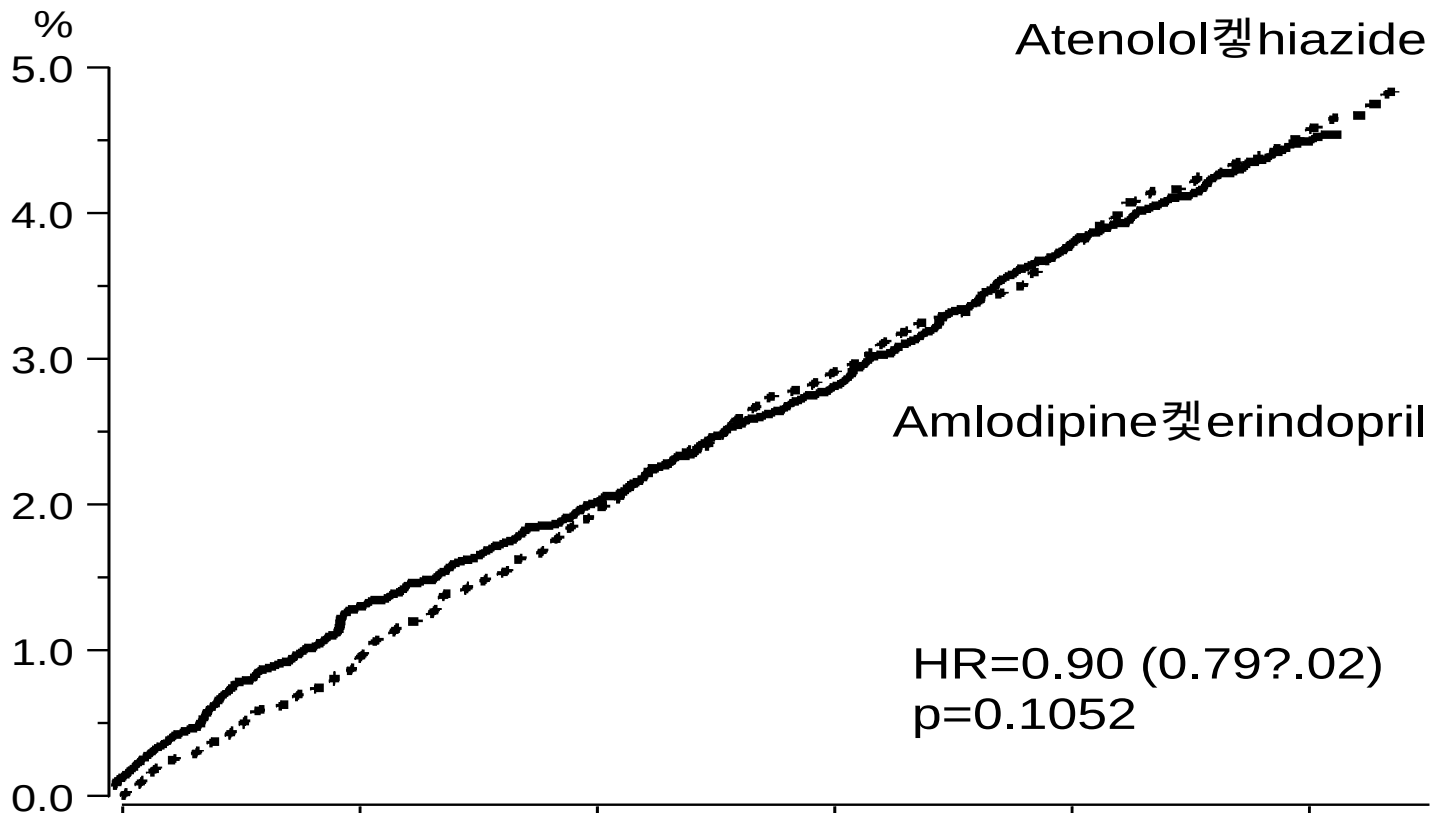
Dahlöf et al. Lancet 2005;




| Number at risk | | | | | | |
|---|---|---|---|---|---|---|
| Amlod켖erind | 9639 | 9544 | 9441 | 9322 | 9167 | 8078 |
| Ateno켕hiaz | 9618 | 9532 | 9415 | 9261 | 9085 | 7975 |

# ASCOT BPLA: non-fatal MI (including silent) + fatal CHD

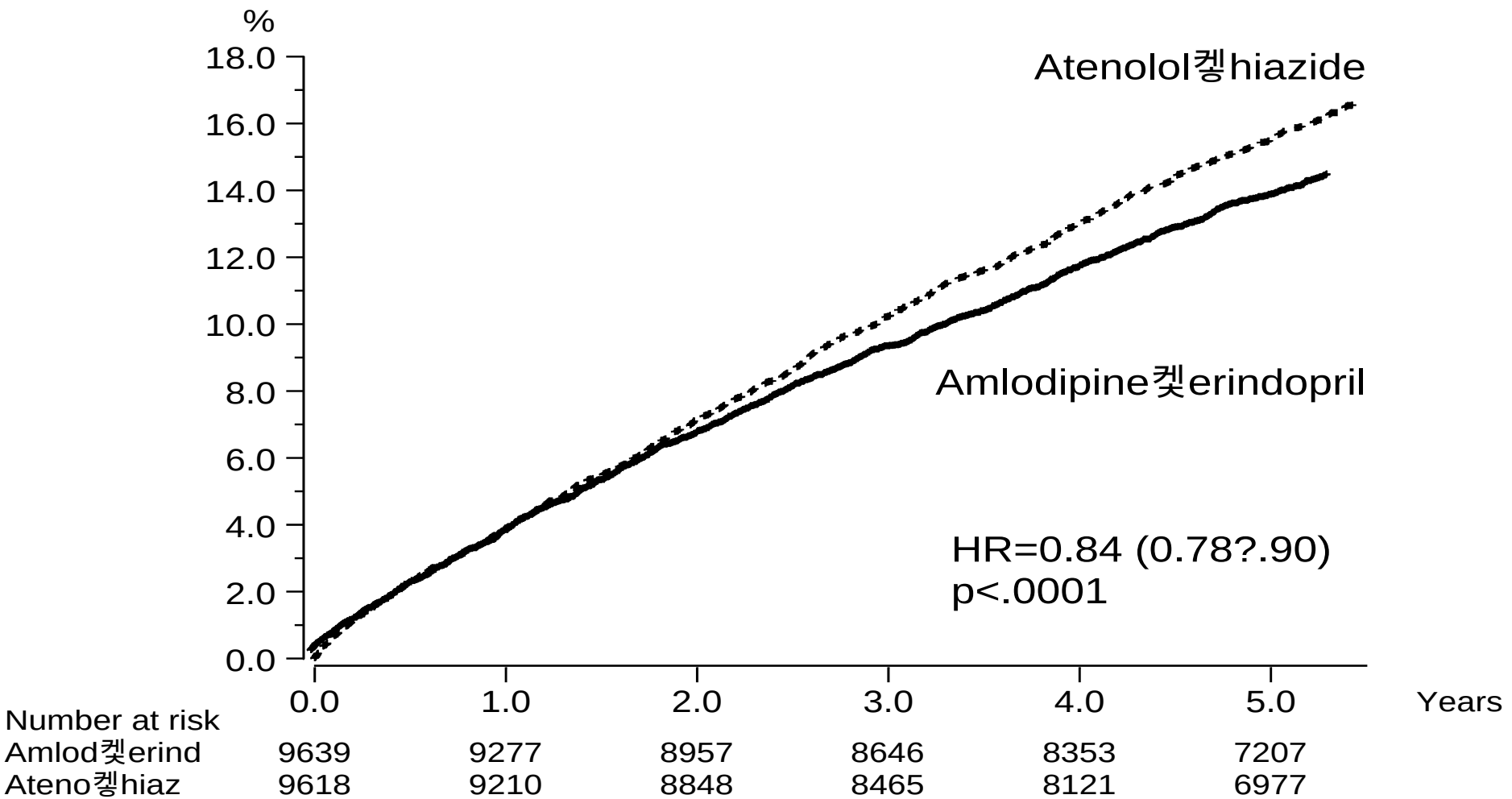
Dahlöf et al. Lancet 2005




| Number at risk | | | | | | |
|---|---|---|---|---|---|---|
| Amlod켖erind | 9639 | 9475 | 9337 | 9168 | 8966 | 7863 |
| Ateno켕hiaz | 9618 | 9470 | 9290 | 9083 | 8858 | 7743 |

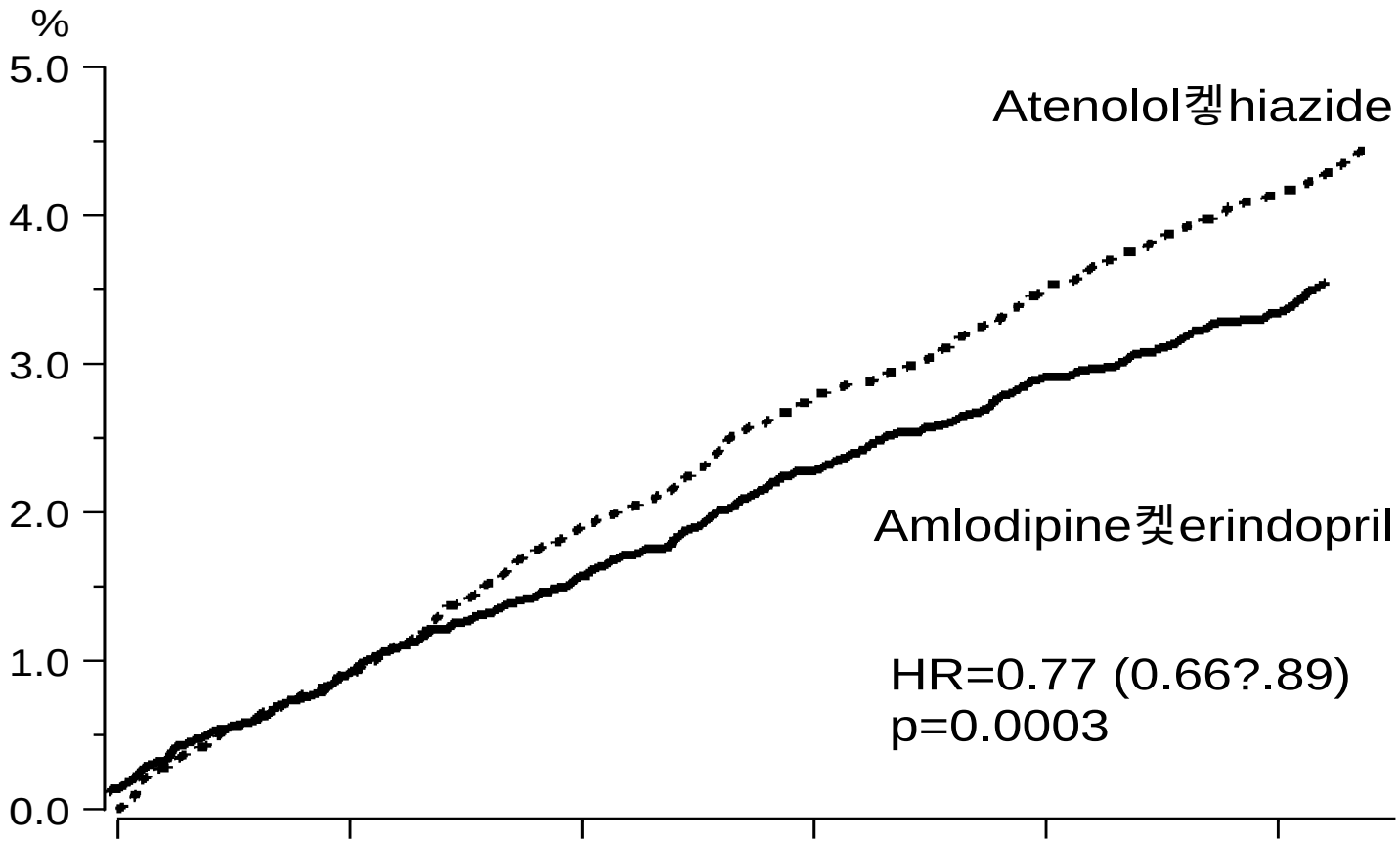
# ASCOT BPLA: CV events & procedures

Dahlöf et al Lancet 2005;



# ASCOT BPLA: fatal & non-fatal stroke

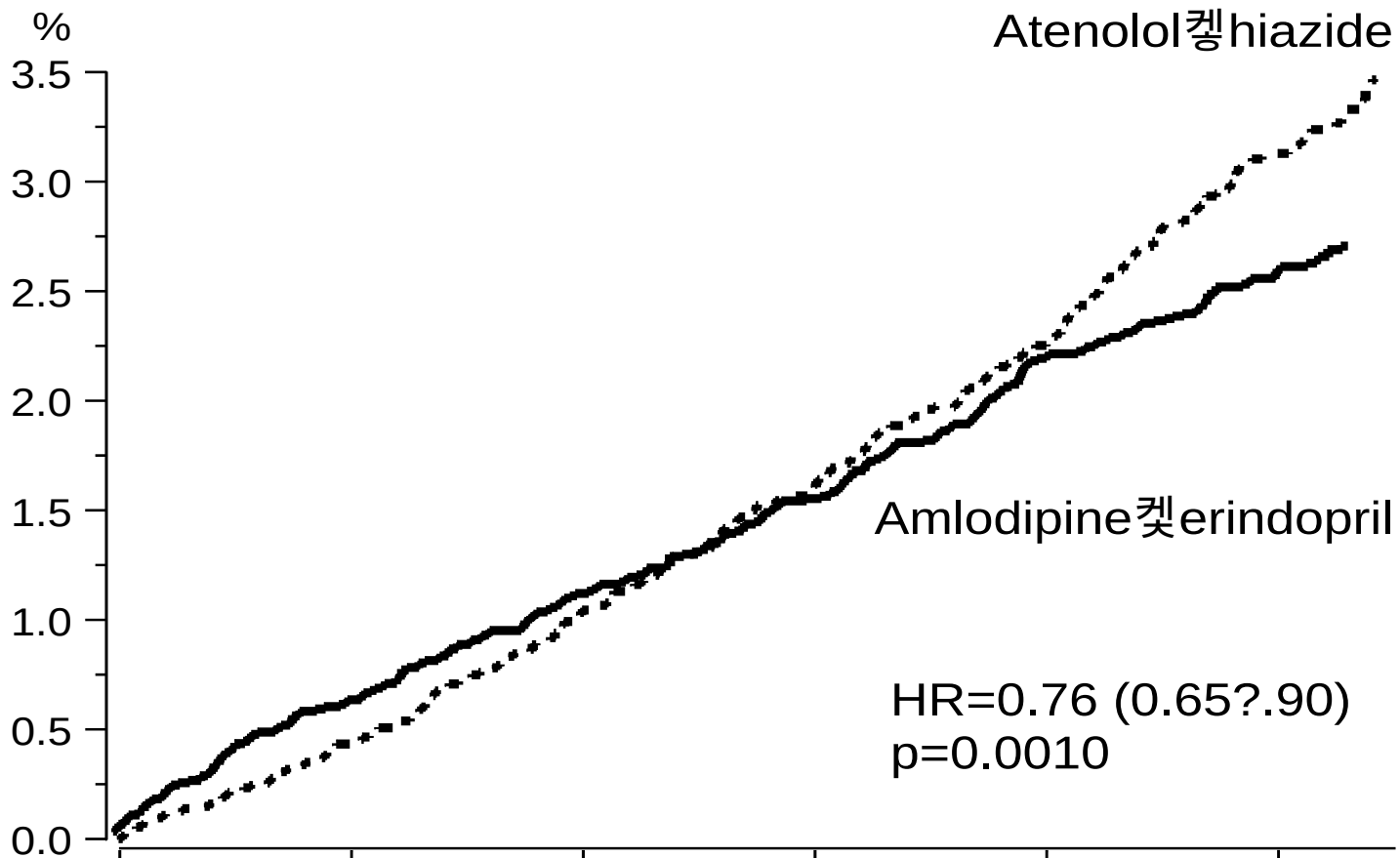
Dahlöf et al. Lancet 2005;




| Number at risk | | | | | | |
|---|---|---|---|---|---|---|
| Amlod켖erind | 9639 | 9483 | 9331 | 9156 | 8972 | 7863 |
| Ateno켛hiaz | 9618 | 9461 | 9274 | 9059 | 8843 | 7720 |

# ASCOT BPLA: cardiovascular mortality

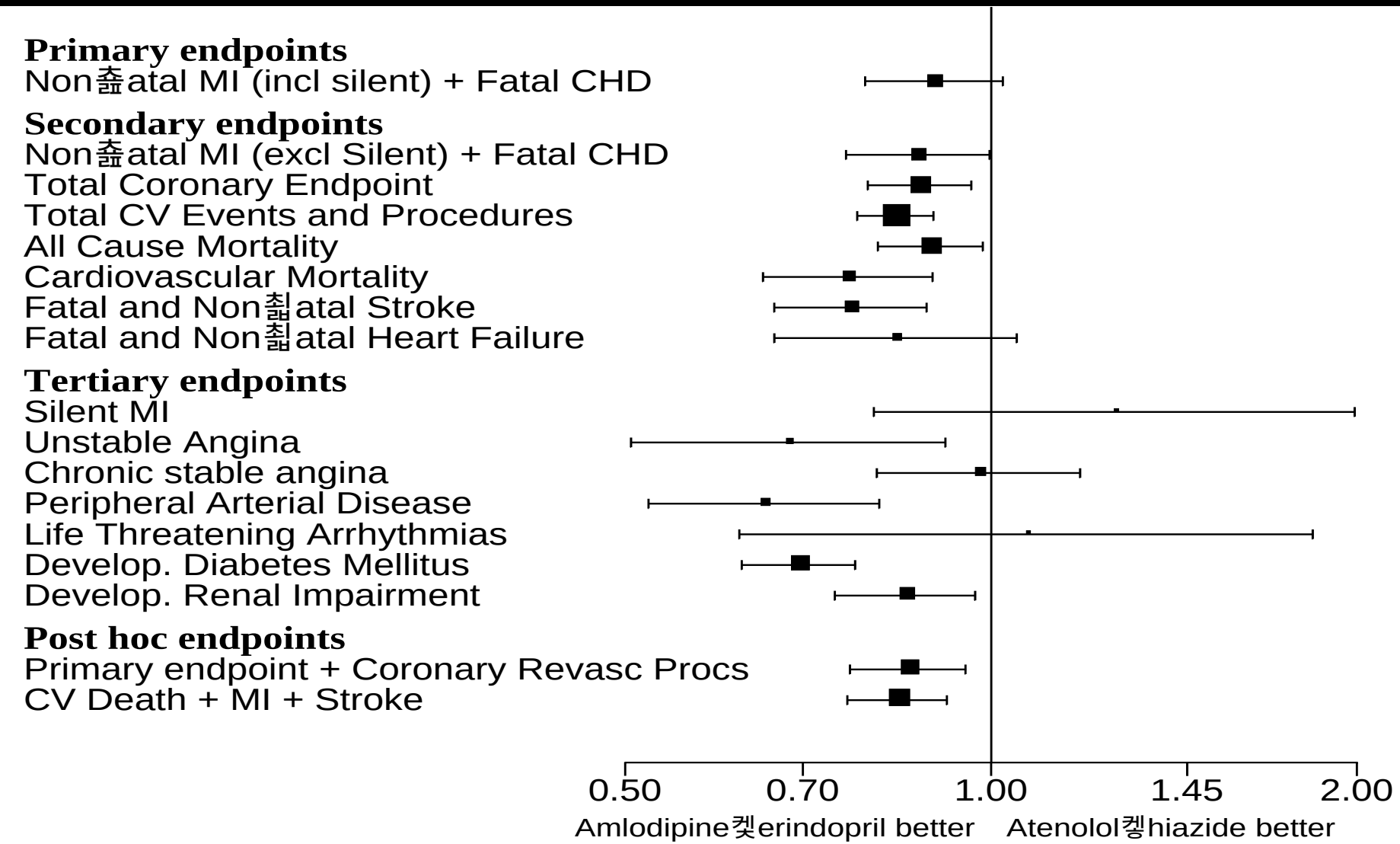
Dahlöf et al Lancet 2005;




| Number at risk | | | | | | |
|---|---|---|---|---|---|---|
| Amlod켖erind | 9639 | 9544 | 9441 | 9322 | 9167 | 8078 |
| Ateno켕hiaz | 9618 | 9532 | 9415 | 9261 | 9085 | 7975 |

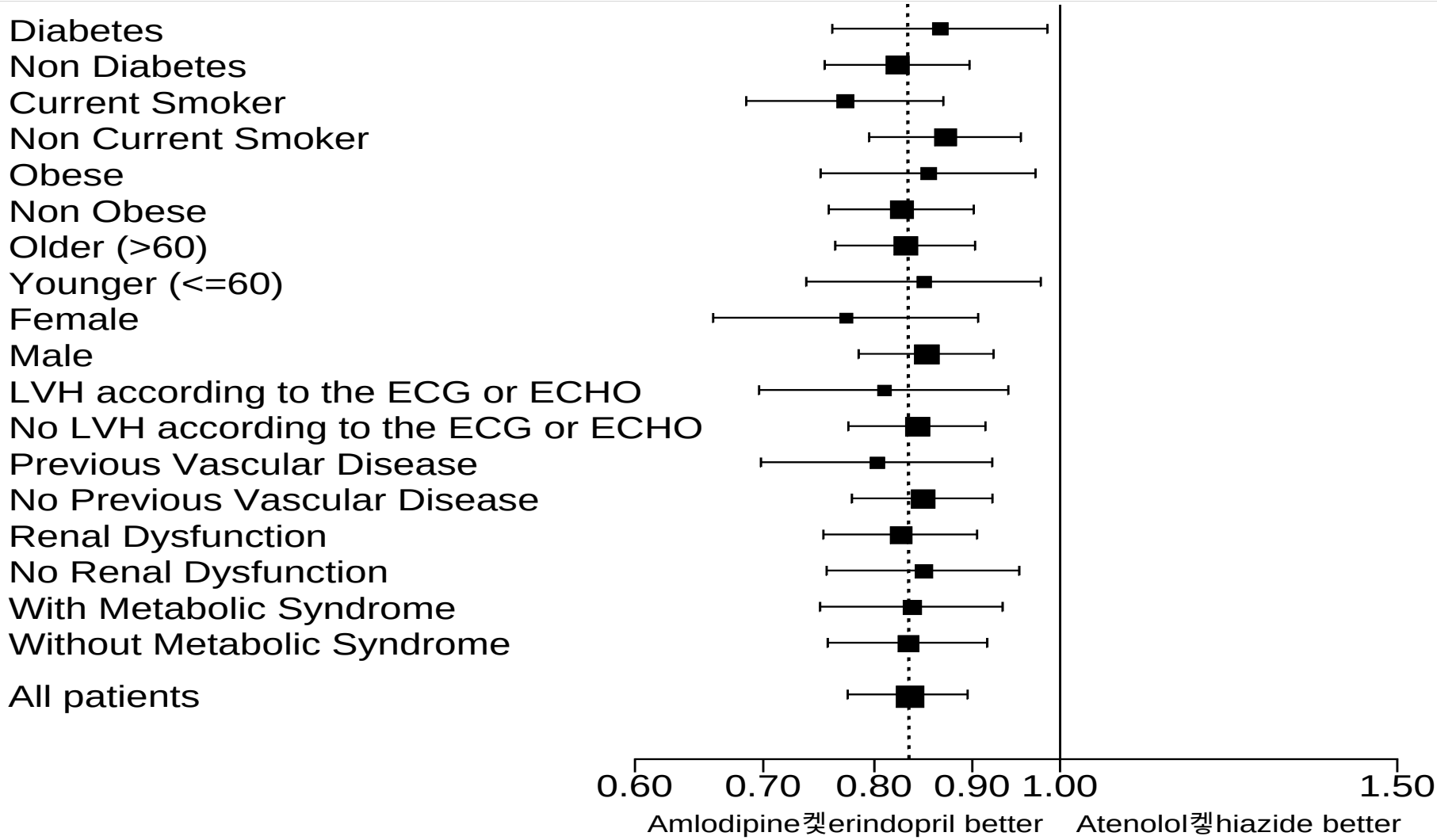
# ASCOT BPLA: endpoints

Dahlöf et al. Lancet 2005;



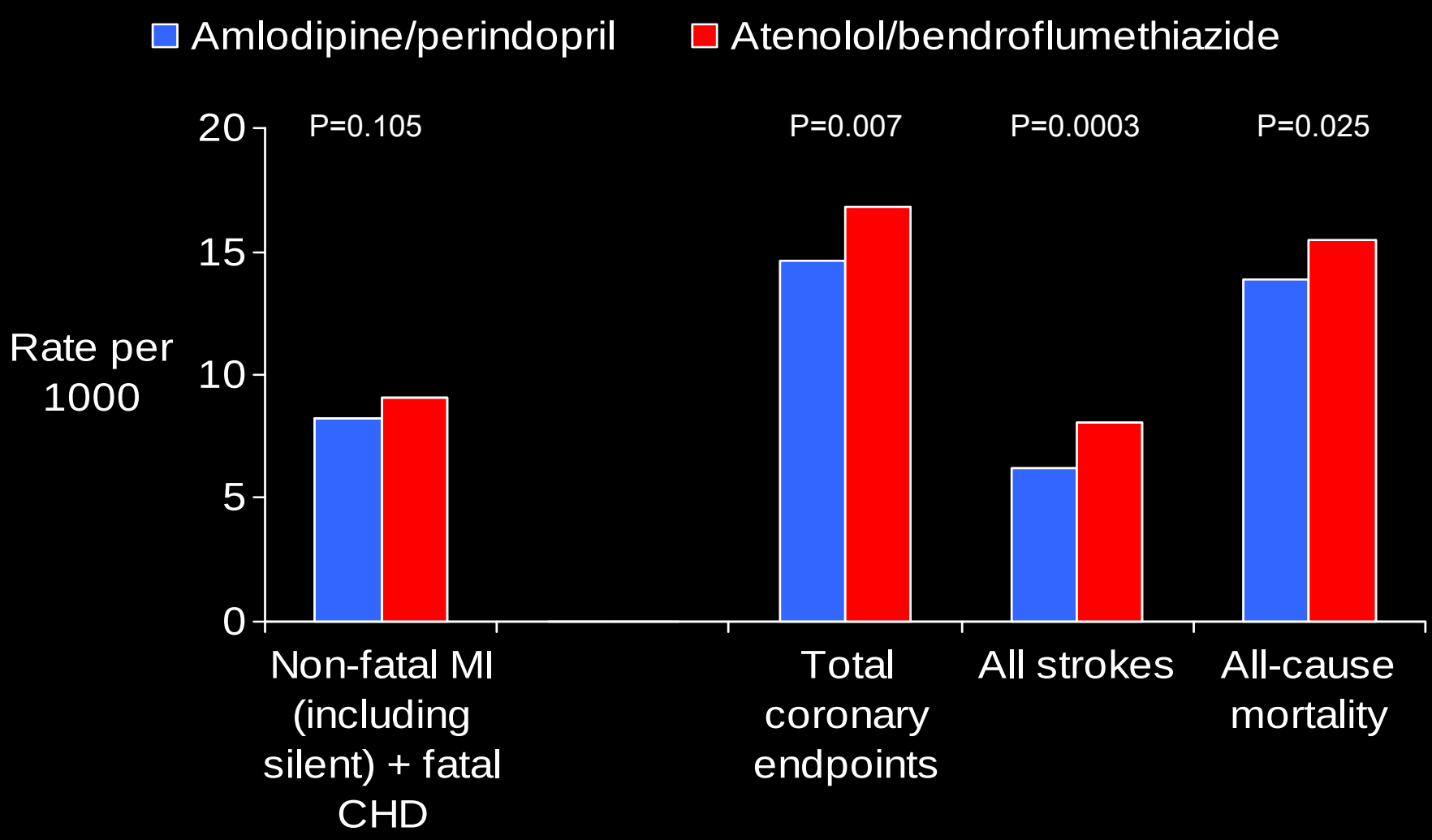
# ASCOT BPLA: total CV events & procedures

Dahlöf et al. Lancet 2005;



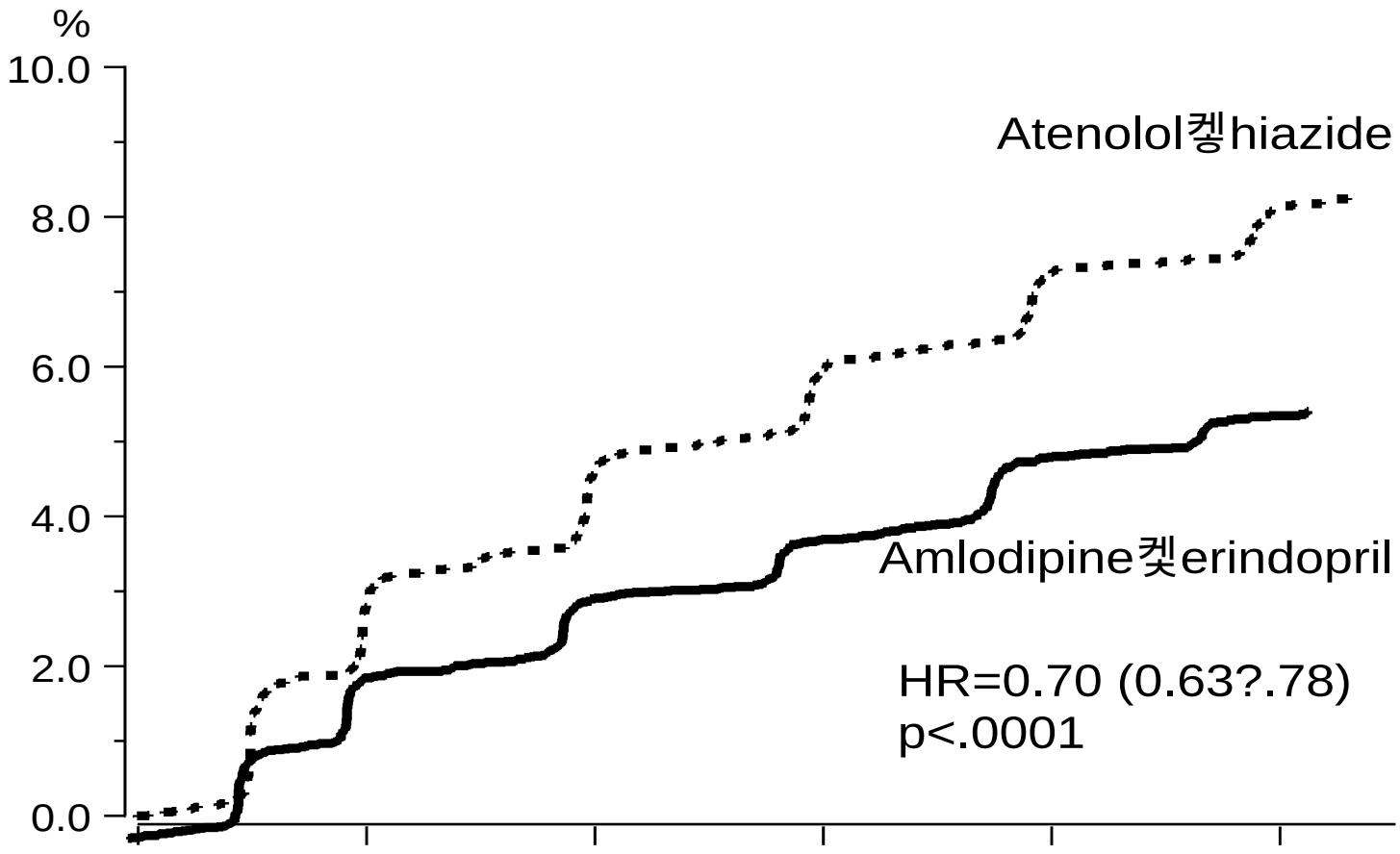
# ASCOT BPLA

Dahlöf et al. Lancet 2005; 366: 895-906.



# ASCOT BPLA: new onset diabetes

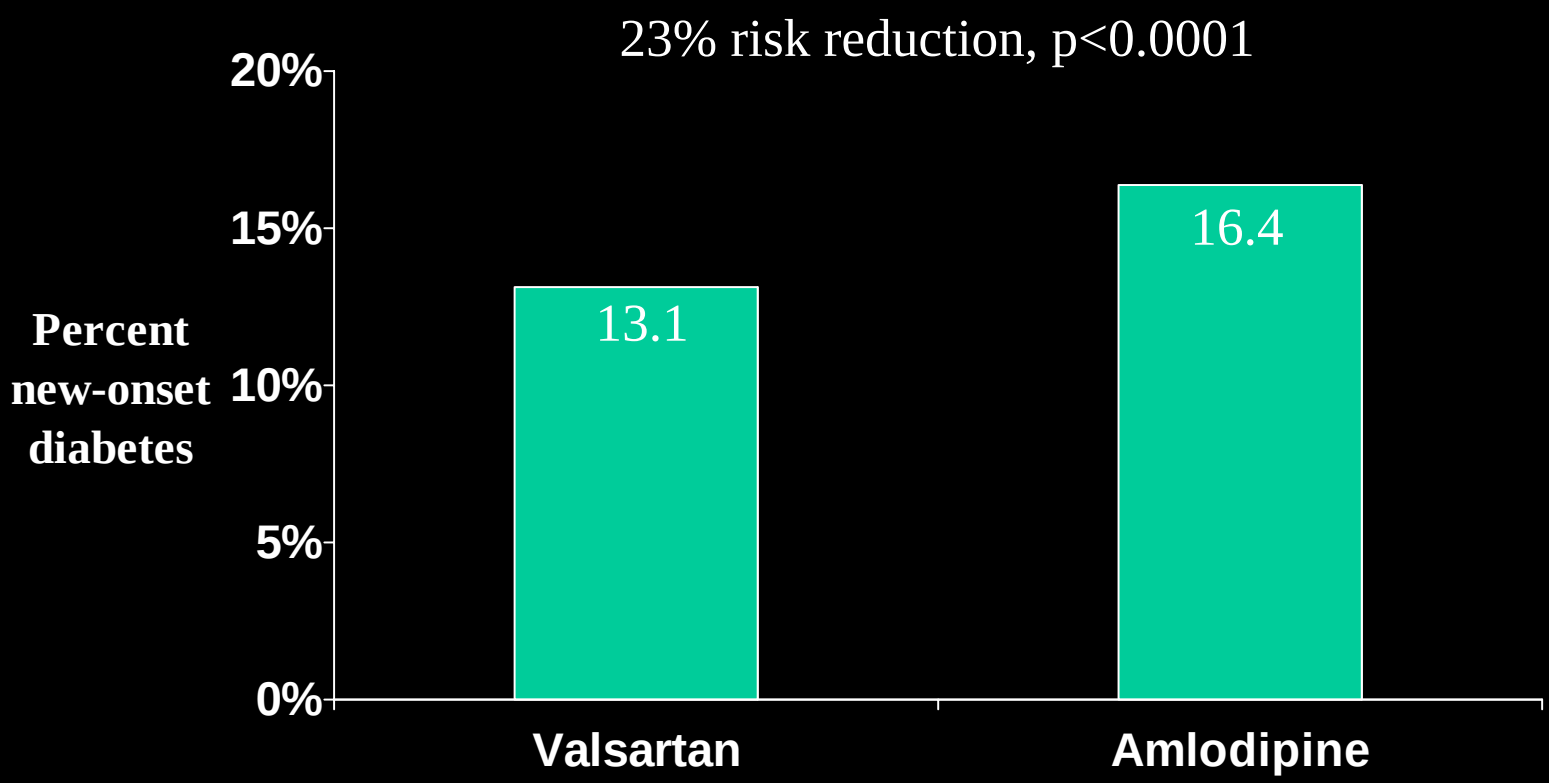
Dahlöf et al. Lancet 2005;




| Number at risk | | | | | | |
|---|---|---|---|---|---|---|
| Amlod켖erind | 9639 | 9383 | 9165 | 8966 | 8726 | 7618 |
| Ateno켕hiaz | 9618 | 9295 | 9014 | 8735 | 8455 | 7319 |

# New-onset diabetes in the VALUE trial

Julius et al, Lancet 2004; 363: 2022-31.



# Conclusions

- CCBs lower BP by about as much as other agents.
- Early anxieties about their safety have not been confirmed.
- Long-term outcome studies show they are better than placebo and about the same as other agents at preventing CVD.
- As most patients require more than one agent, mono-therapy trials not applicable to usual clinical practice.
- A CCB+ACE-I regime was superior to a BB+Thiazide regime in ASCOT-BPLA.