# How to select initial drugs for the hypertension management

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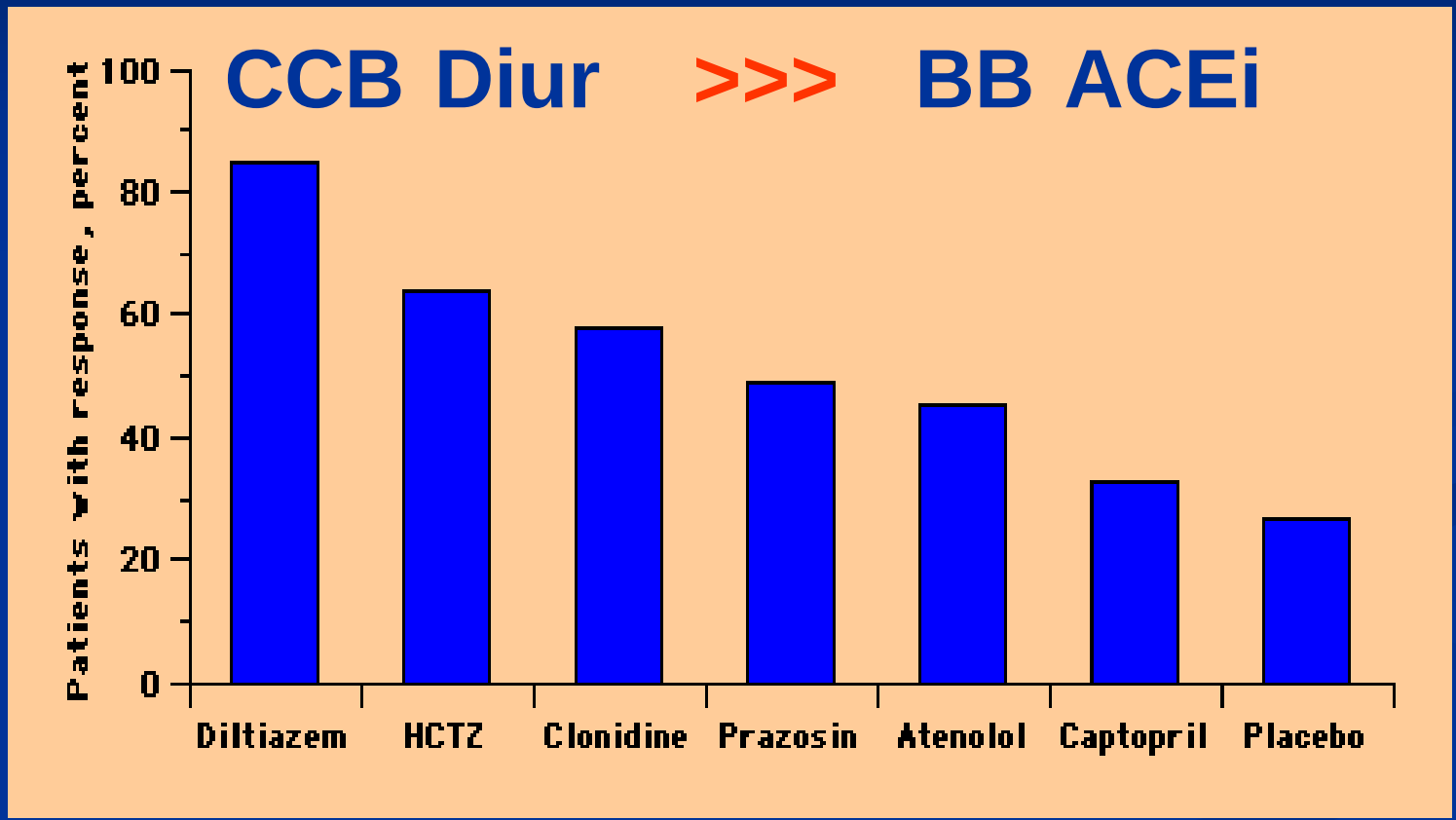
# Introduction

- Although recommendations for initiating medical therapy in essential hypertension have been proposed, there is no uniform agreement on which antihypertensive agent should be given for initial therapy.
- A variety of different drugs can be used
  - Thiazide diuretics (D),
  - Beta blockers (BB),
  - ACE inhibitors(ACEi),
  - Angiotensin II receptor blockers (ARB),
  - Calcium channel blockers (CaB).

# Efficacy

- Each of the antihypertensive agents is roughly equally effective, producing a good antihypertensive response in 30 to 50 % of cases.
- Thus, the choice among the different antihypertensive drugs is not generally made on the basis of efficacy.
- There is, however, wide interpatient variability as many patients will respond well to one drug but not to another. There are also some predictable differences, such as black patients generally responding better to monotherapy with a thiazide diuretic or calcium channel blocker and relatively poorly to an ACE inhibitor or beta blocker.

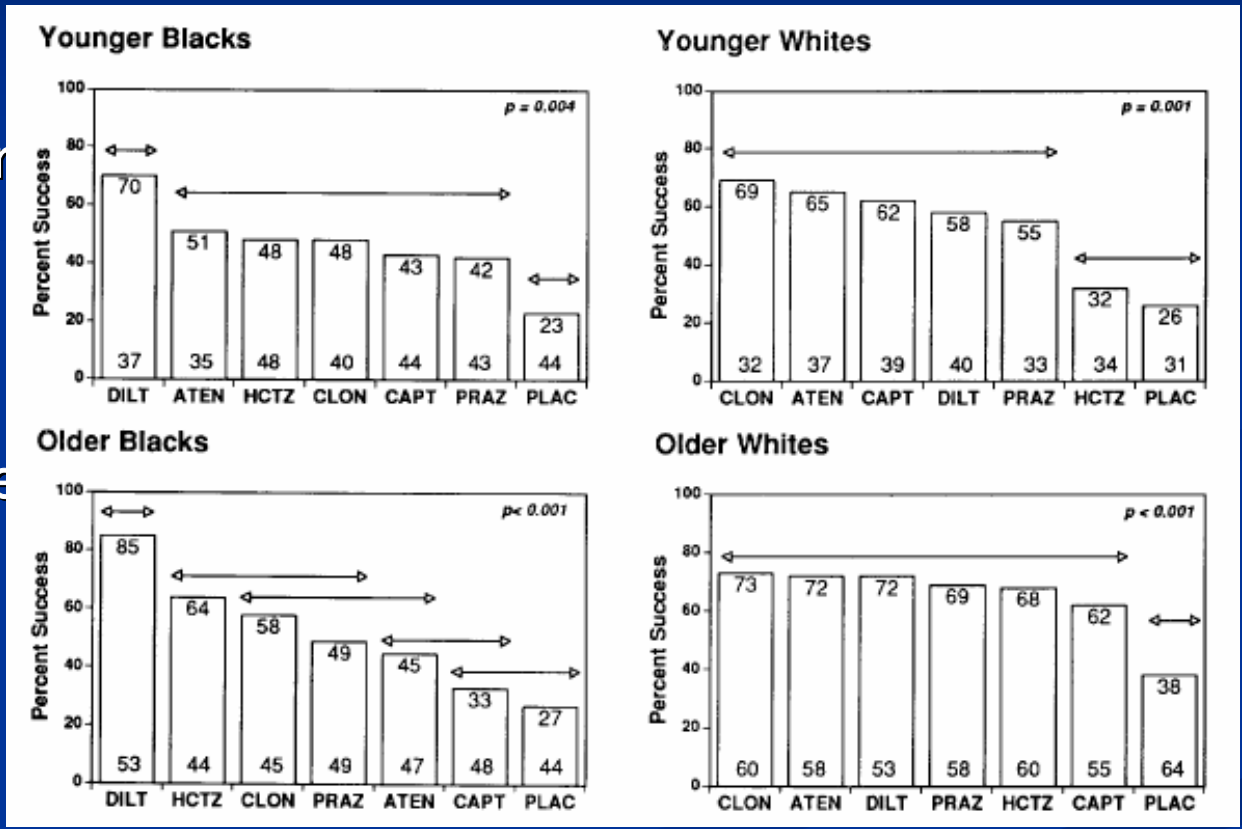
# Efficacy: HTN in Old Black




*Materson N Engl J Med 1993;328:914-21*

# Efficacy: Single-drug therapy for hypertension in men

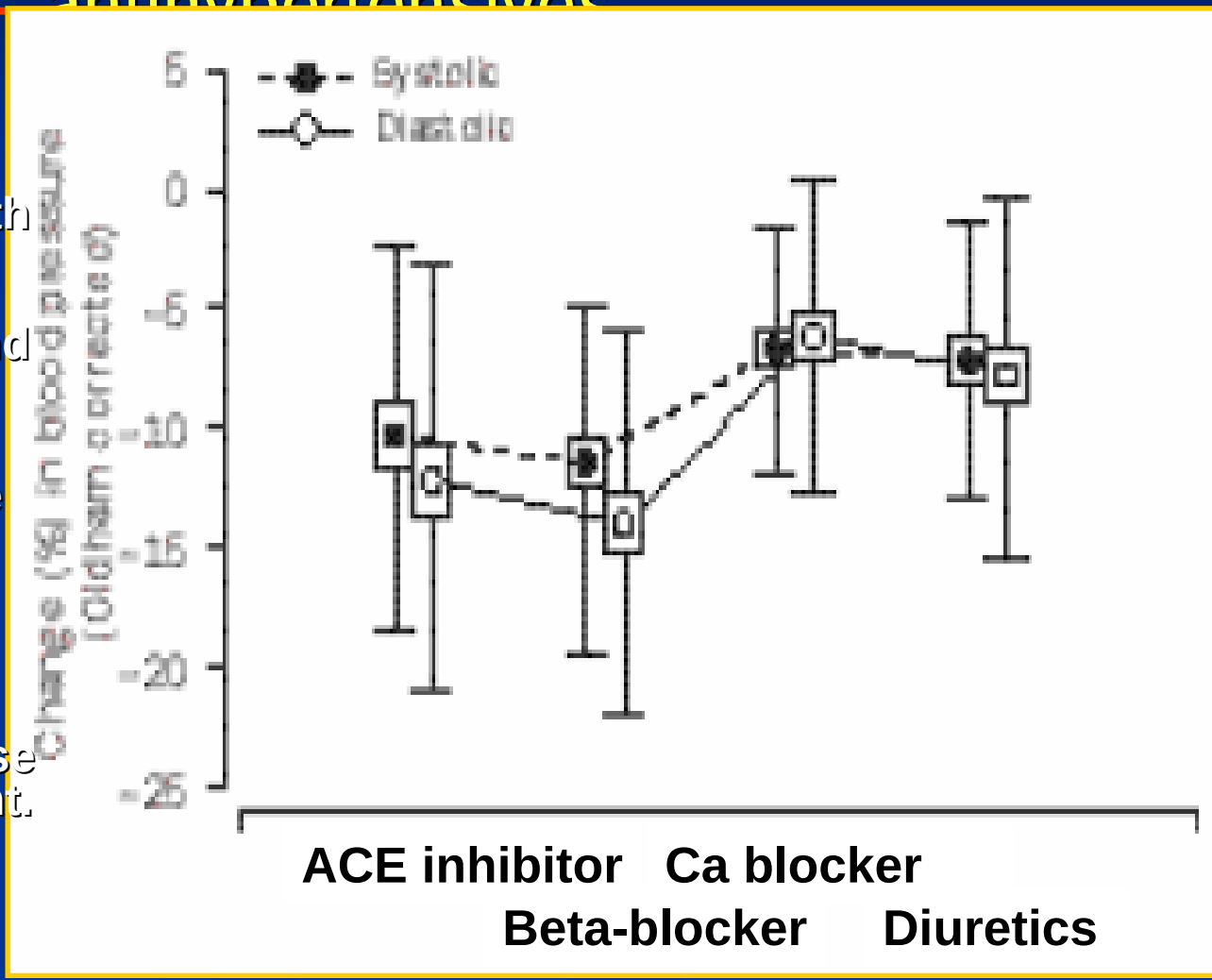
- Younger Black Patients, Younger White Patients, Older Black Patients, and Older White Patients with Responses in Each of the Study Groups.
- The arrows group the drugs whose effects do not differ from each other by more than 15 percent.




*Materson Am J Hypertens 1995;8:189-92*

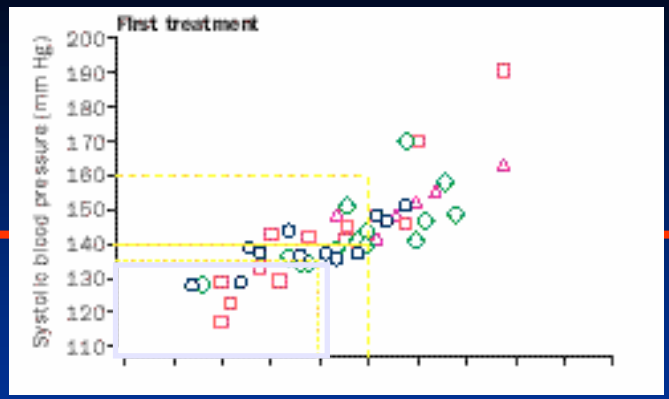
# Efficacy: Optimisation of antihypertensive treatment by crossover rotation of four major classes in young antihypertensives

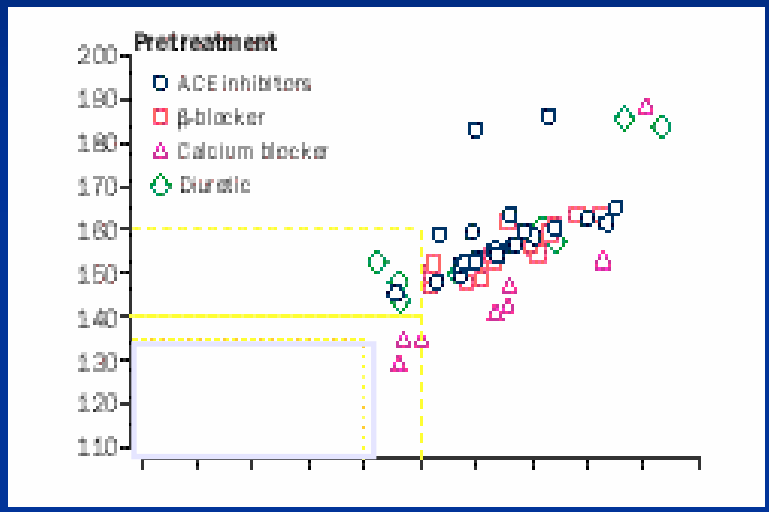
- 56 pts with 161/98 mmHg, of whom 36 received all 4 monthly cycles of treatment with lisinopril 20mg(A), bisoprolol 5mg (B), adalat LA 30mg (C), and Dyazide 25+50mg (D).
- Age and PRA might be determinants of drug efficacy. However, these factors have a relatively minor predictive value and appear to be of little use in the individual patient.

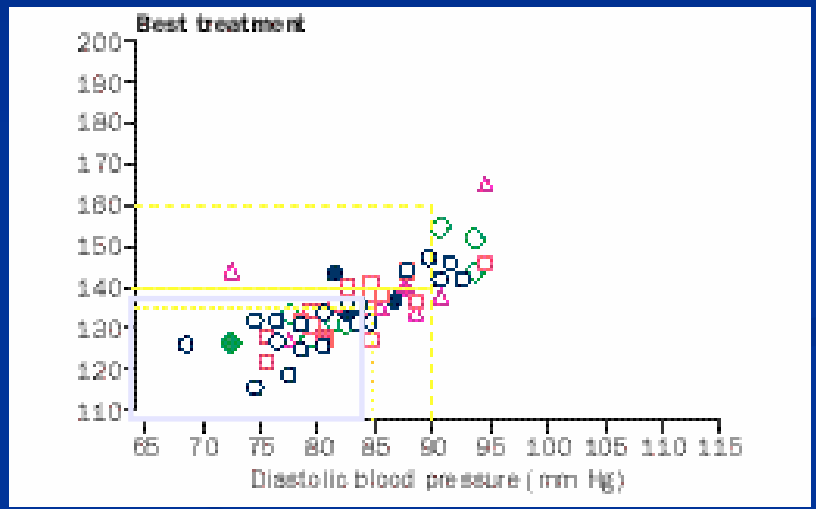



Dickerson Lancet 1999;353:2008

# Efficacy 2: Influence of rotation on blood-pressure reduction



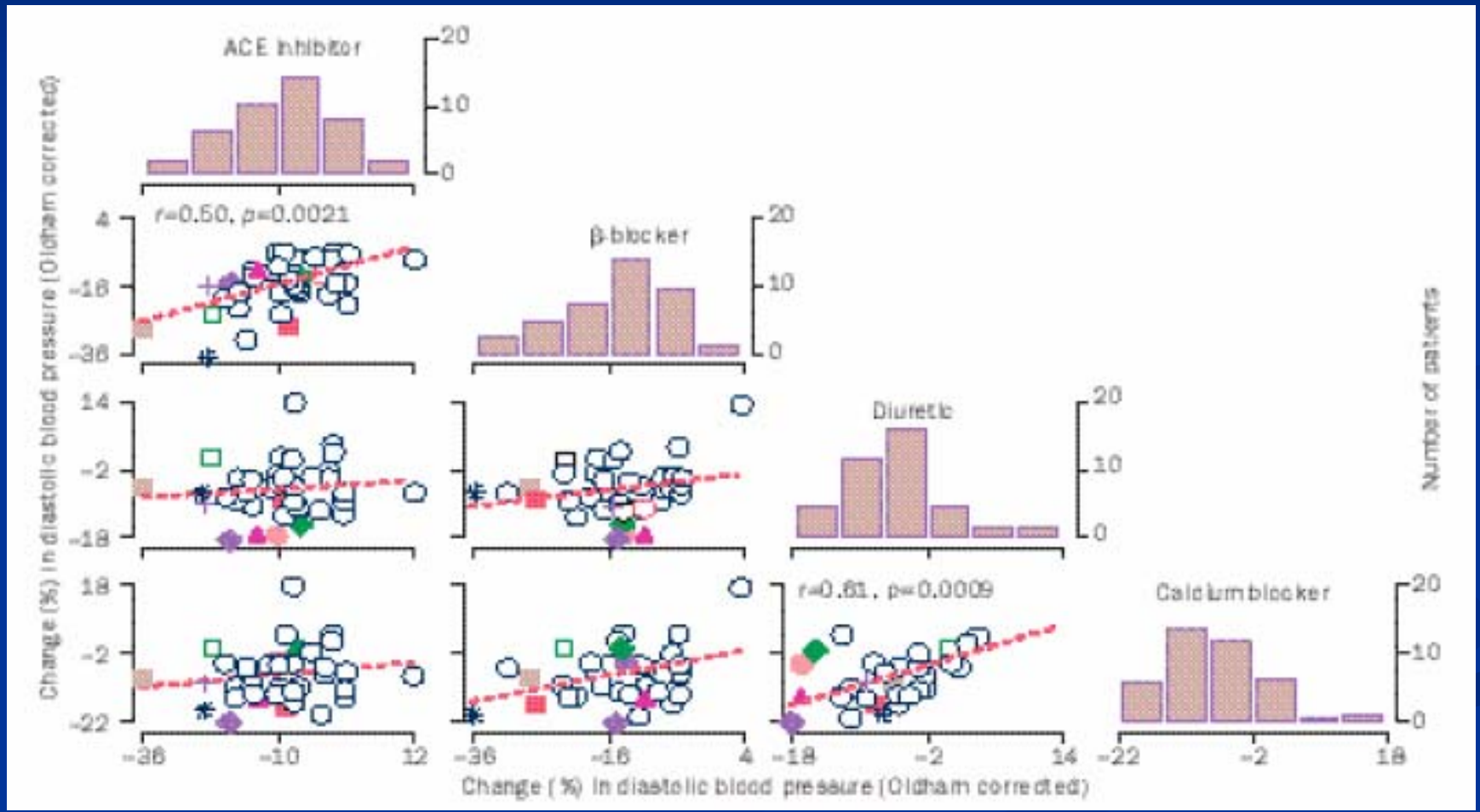




| Target (mm Hg) | on first drug | on best drug |
|---|---|---|
| <160/90 (BHS) | 36 (64%) | 49 (88%)* |
| <140/90 (JNCVI) | 22 (39%) | 41 (73%)† |
| ¶135/85 (“normal”) | 11 (20%) | 28 (50%)† |

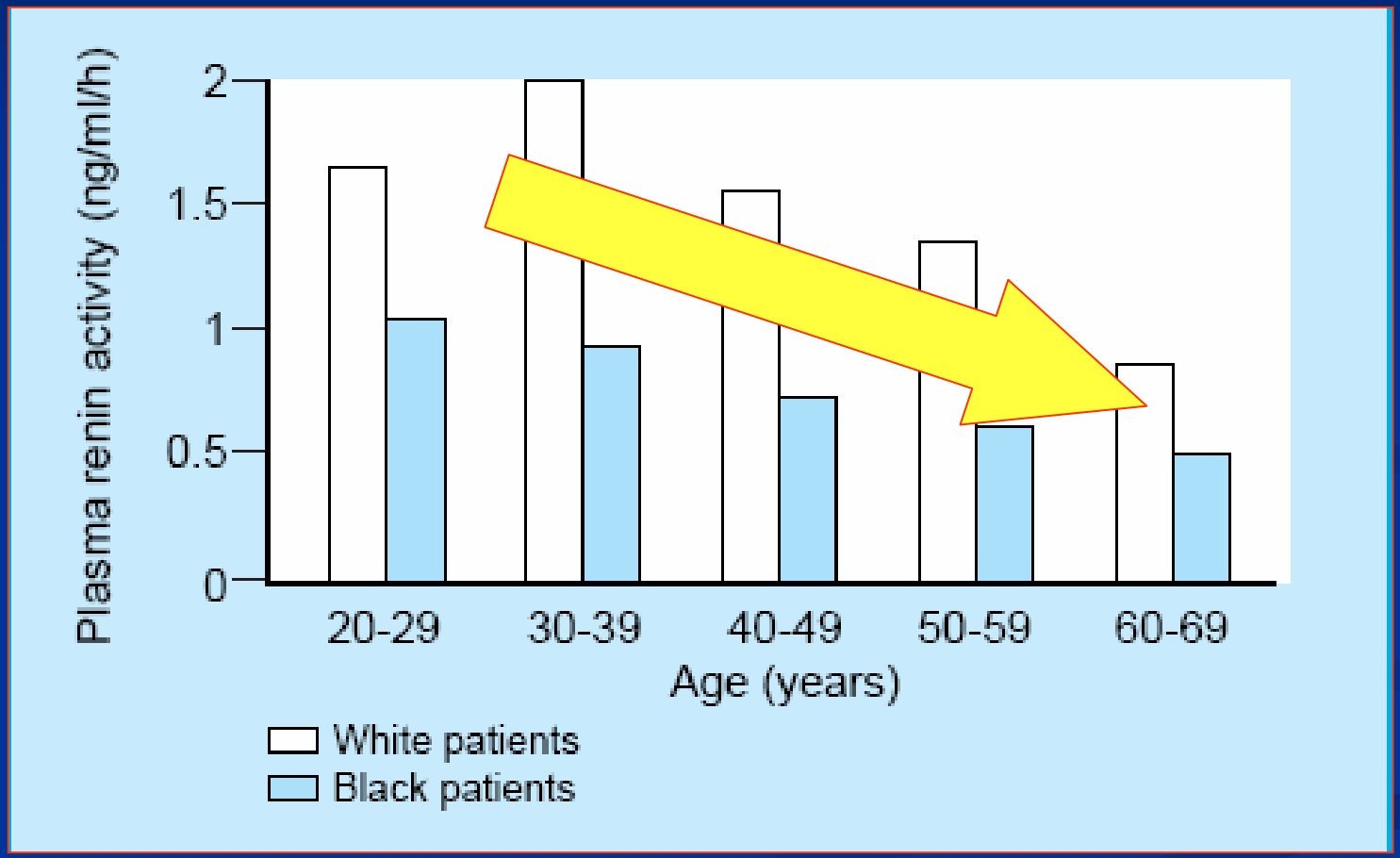
Dickerson Lancet 1999;353:2008

# Efficacy 2: Correlations betw BP falls on 4 drugs among 36 pts who completed rotation




Dickerson Lancet 1999;353:2008

# Plasma renin in black and white hypertensive patients




Freis *Am J Med* 1983;74:1029-41

# Does the choice of drug affect outcome?

- There have been limited data as to whether different antihypertensive drugs have variable effects upon patient outcomes, particularly cardiovascular morbidity and mortality.
- However, an increasing number of trials have provided evidence that, at the same level of blood pressure control, most antihypertensive drugs provide the same degree of cardiovascular protection.

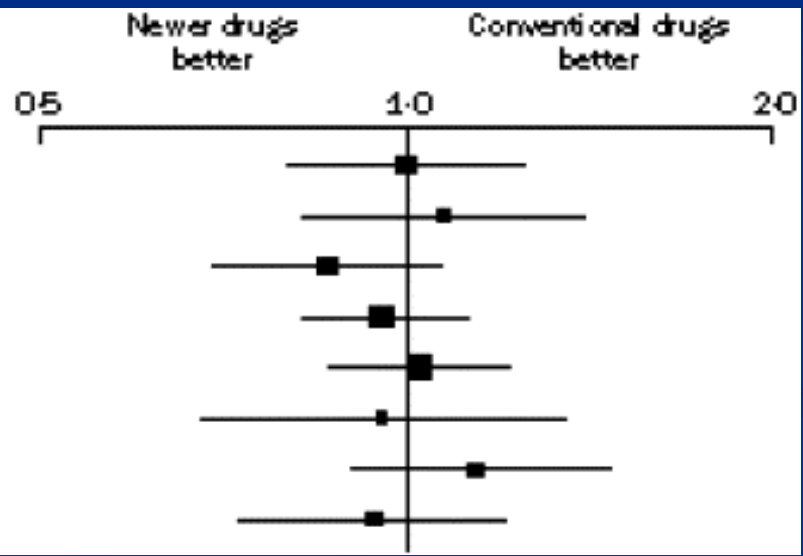
# Outcome studies

- a number of trials suggest that, at the same level of blood pressure control, most antihypertensive drugs provide the same degree of cardiovascular protection.
  - CAPPP, STOP-Hypertension-2, NORDIL, UKPDS, and INSIGHT trials found little overall difference in outcome between older (such as diuretics and beta blockers) and newer antihypertensive drugs (such as ACE inhibitors and calcium channel blockers.
  - In contrast, studies of ACE inhibitors and ARBs at high risk patients have led some experts to conclude that these agents have a unique benefit in this setting.

- However, the available data are more consistent with the conclusion that the achieved blood pressure, rather than the specific drug or drug class used, is the principal determinant of benefit.

# Old vs new drugs in elderly: CV mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study (STOP-2)

| | | Relative risk (95% CI)* | p |
|---|---|---|---|
| Cardiovascular mortality | 0·99 | (0·84–1·16) | 0·89 |
| All myocardial infarction | 1·04 | (0·86–1·26) | 0·69 |
| All stroke | 0·89 | (0·76–1·04) | 0·13 |
| All major cardiovascular events | 0·96 | (0·86–1·08) | 0·49 |
| Total mortality | 1·01 | (0·89–1·14) | 0·92 |
| Frequency of diabetes mellitus | 0·95 | (0·75–1·23) | 0·77 |
| Frequency of atrial fibrillation | 1·09 | (0·92–1·31) | 0·32 |
| Frequency of congestive heart failure | 0·95 | (0·79–1·14) | 0·55 |




- Relative risk of cardiovascular mortality and morbidity for all newer drugs *vs* conventional drugs

*Adjusted for age, sex, diabetes, diastolic blood pressure, and smoking.

Hansson *Lancet 1999;354(9192):1751-6*

# CCB vs diuretics/BB on CV morbidity and mortality: the Nordic Diltiazem (NORDIL) study

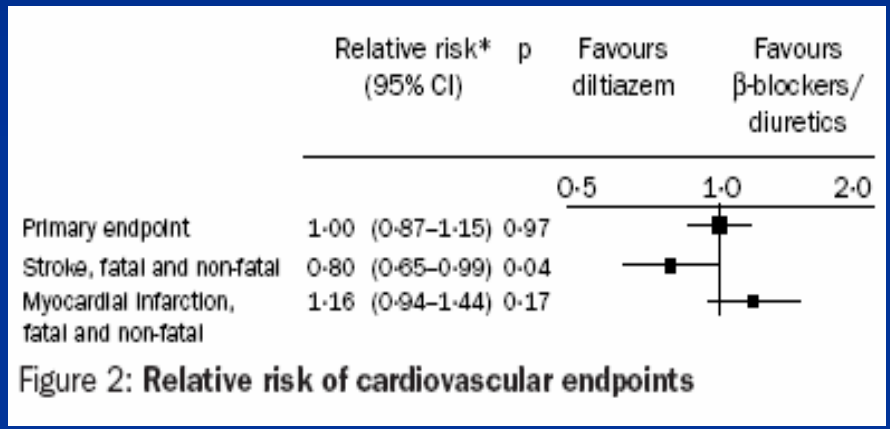
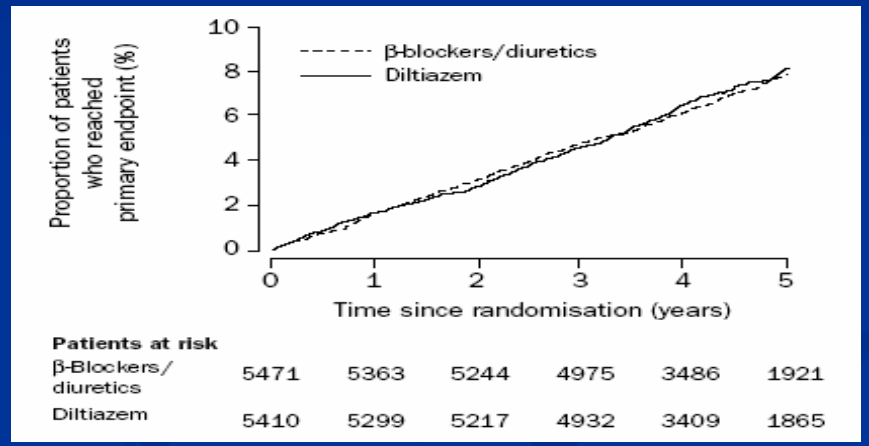


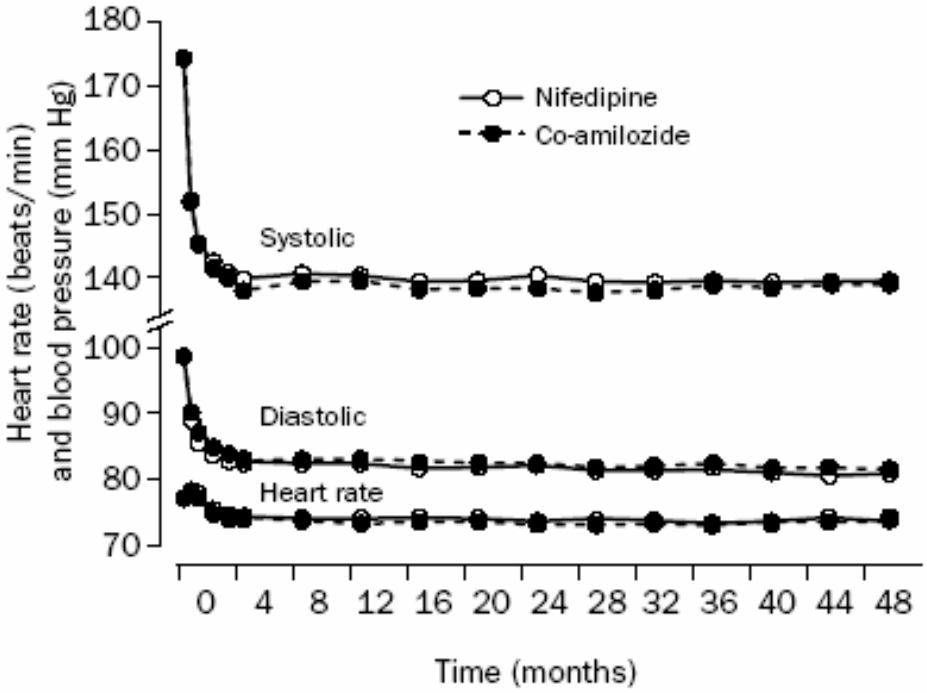

Figure 2: **Relative risk of cardiovascular endpoints**




- Relative risk of CV endpoints
- Kaplan-Meier curves of proportion of patients in each group who reached primary endpoint

Hansson *Lancet 2000;356(9227):359-65*

# Morbidity and mortality with a long-acting CCB or diuretic (INSIGHT)

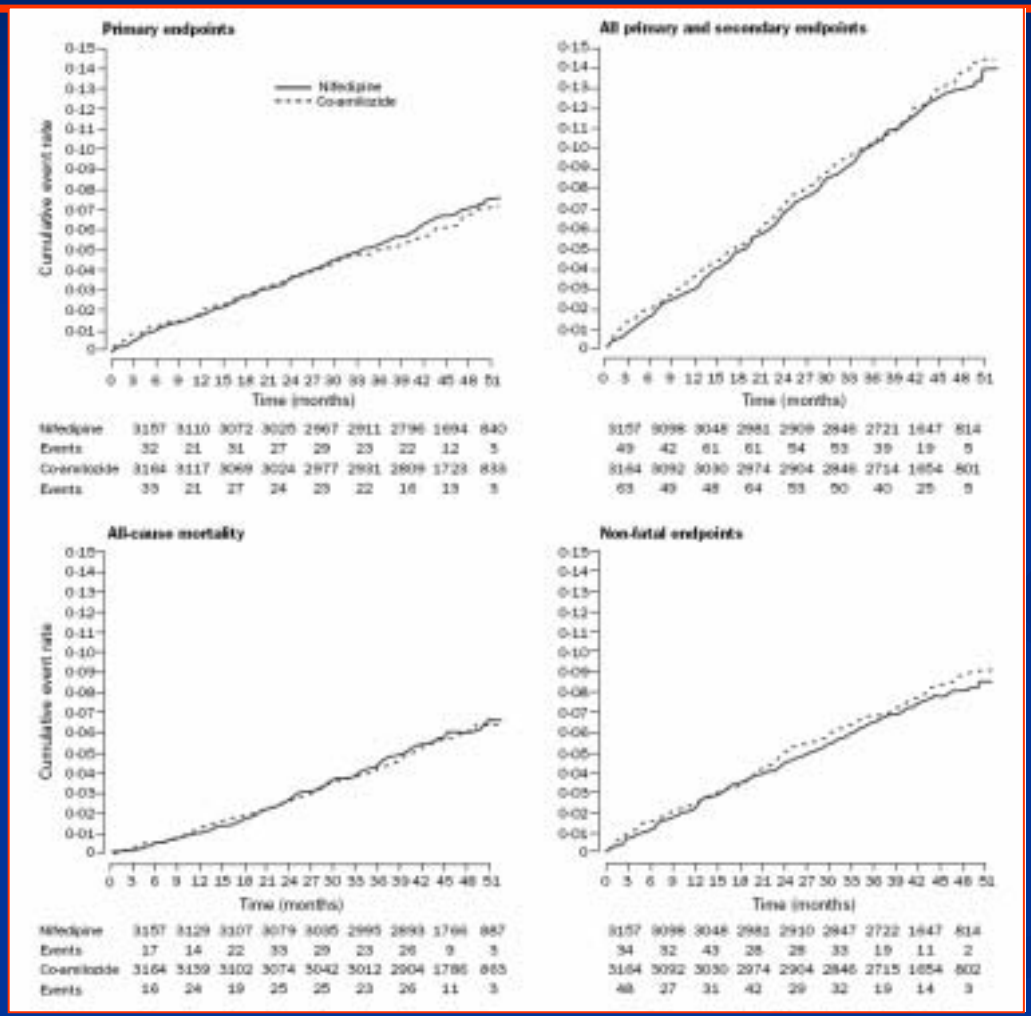



**Patients remaining on treatment**

| Month | 0 | 4 | 12 | 24 | 36 | 48 |
|---|---|---|---|---|---|---|
| Nifedipine | 3157 | 2735 | 2498 | 2234 | 2058 | 831 |
| Monotherapy (%) | | 72 | 68 | 66 | 63 | 69 |
| Blood pressure controlled (%) | | 56 | 54 | 54 | 56 | 58 |
| Co-amilozide (n) | 3164 | 2877 | 2693 | 2469 | 2288 | 944 |
| Monotherapy (%) | | 66 | 66 | 65 | 63 | 72 |
| Blood pressure controlled (%) | | 59 | 57 | 59 | 57 | 57 |

Brown Lancet 2000;356(9227):366

# Morbidity and mortality with a long-acting CCB or diuretic (INSIGHT)




- Kaplan-Meier curves and life tables for survival for primary and secondary endpoints
- Life tables show numbers of patients and number of events every 6 months

Brown Lancet 2000 Jul 29;356(9227):366-72

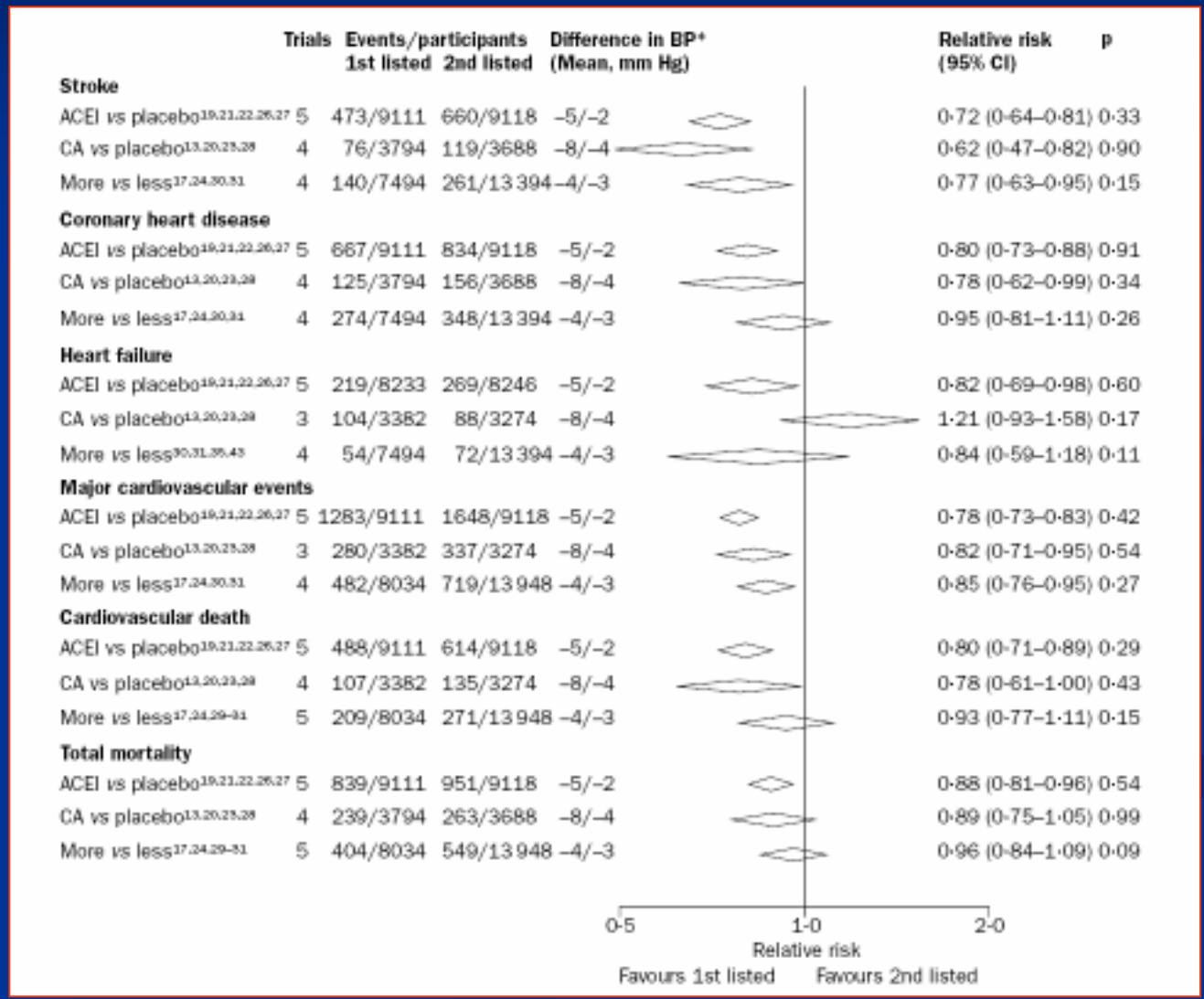
# Drug safety

- In the late 1990s when controversy first emerged about the safety of CCBs (especially short-acting CCBs); may be associated with an enhanced risk of CHD
- CCBs (amlodipine), especially short-acting ones, ALLHAT study was specifically powered to test the CHD hypothesis as its primary end point and definitively showed effective CHD prevention with a CCB), including in those with diabetes.
- VALUE trial; amlodipine was actually superior to valsartan-based therapy at protecting against fatal and nonfatal MI, as well as reducing the frequency of angina.
- *the Intervention as a Goal In Hypertension Treatment (INSIGHT) study, the Nordic Diliazem (NORDIL) study, ALLHAT, CONVINCE, the International Verapamil- Trandolapril Study (INVEST), and VALUE also*

- No one class of blood pressure-lowering drug has been shown to be any less or any more effective than any other
- Their benefits are primarily determined by how effectively they lower blood pressure

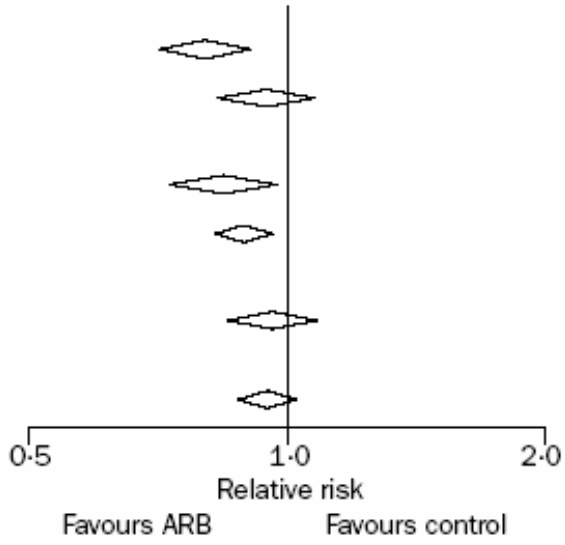
# Effects of different BP-lowering regimens on major CV events: results of prospectively-designed overviews of randomised trials (2003)

- ACEi and CCB vs placebo, and more and less intensive BP-lowering regimens
- Negative values indicate lower mean follow-up blood pressure in 1st listed groups (ACE, CA, and more) than in 2nd listed groups (placebo and less).
- Turnbull *Lancet 2003;362:1527-35*



# Effects of different BP-lowering regimens on major CV events: results of prospectively-designed overviews of randomised trials (2003)

| | Trials | Events/participants ARB | Control | Difference in BP* (mean, mm Hg) | Relative risk (95% CI) | p |
|---|---|---|---|---|---|---|
| Stroke[12–15] | 4 | 396/8412 | 500/8379 | –2/–1 | 0·79 (0·69–0·90) | 0·46 |
| Coronary heart disease[12–15] | 4 | 435/8412 | 450/8379 | –2/–1 | 0·96 (0·85–1·09) | 0·43 |
| Heart failure[13–15] | 3 | 302/5935 | 359/5919 | –2/–1 | 0·84 (0·72–0·97) | 0·26 |
| Major cardiovascular events[12–15] | 4 | 1135/8412 | 1268/8379 | –2/–1 | 0·90 (0·83–0·96) | 0·78 |
| Cardiovascular death[12–15] | 4 | 491/8412 | 511/8379 | –2/–1 | 0·96 (0·85–1·08) | 0·34 |
| Total mortality[12–15] | 4 | 887/8412 | 943/8379 | –2/–1 | 0·94 (0·86–1·02) | 0·59 |

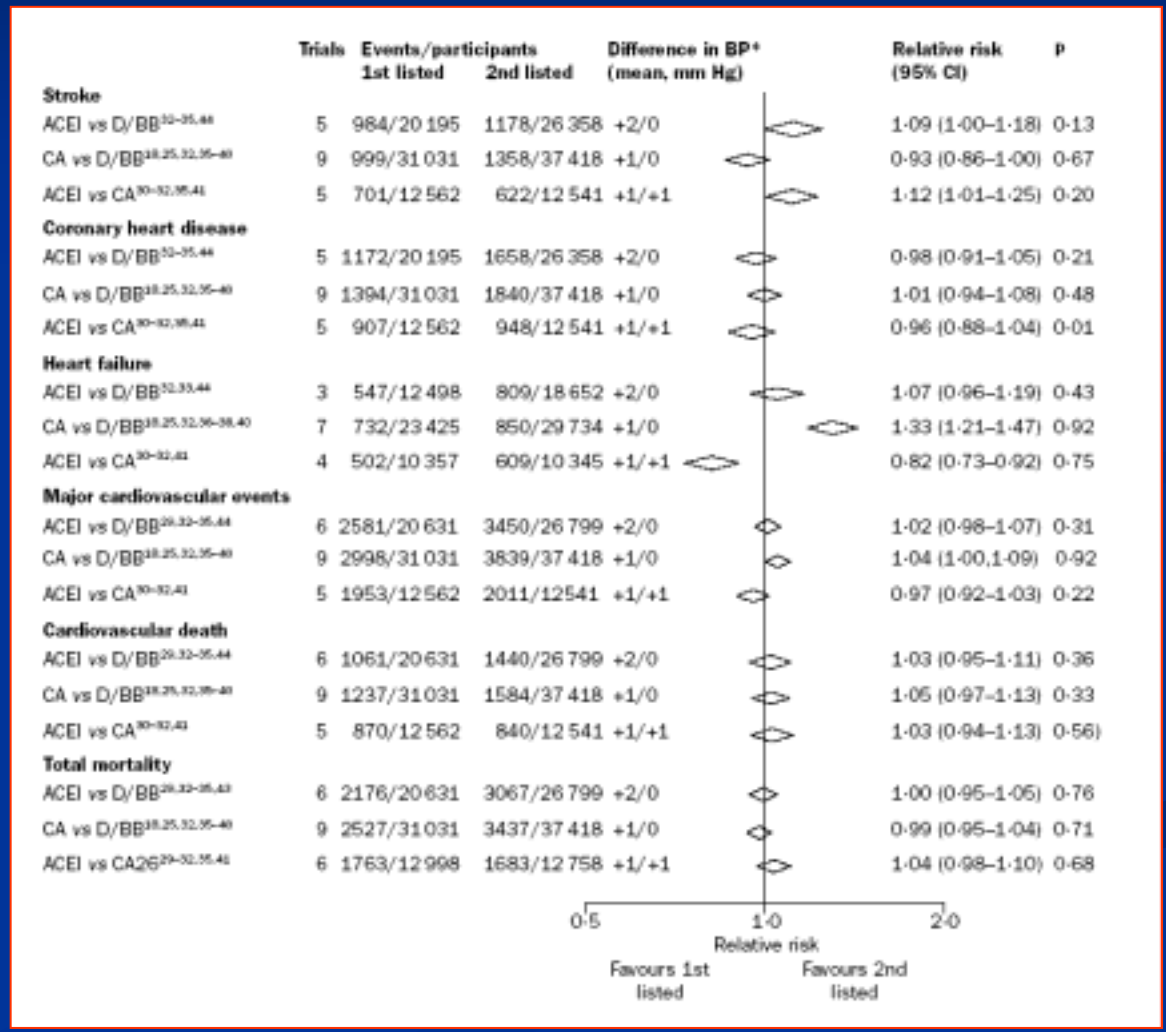



- Comparisons of ARB-based regimens with control regimens
- Turnbull *Lancet 2003;362:1527-35*

# Effects of different BP-lowering regimens on major CV events: results of prospectively-designed overviews of randomised trials (2003)

- Comparisons of blood-pressure-lowering regimens based on different drug classes
- Positive values indicate a higher mean follow-up blood pressure in the 1st listed group (ACEI and CA) than in the 2nd listed group (D/BB and CA).

Turnbull *Lancet* *2003;362:1527-35*



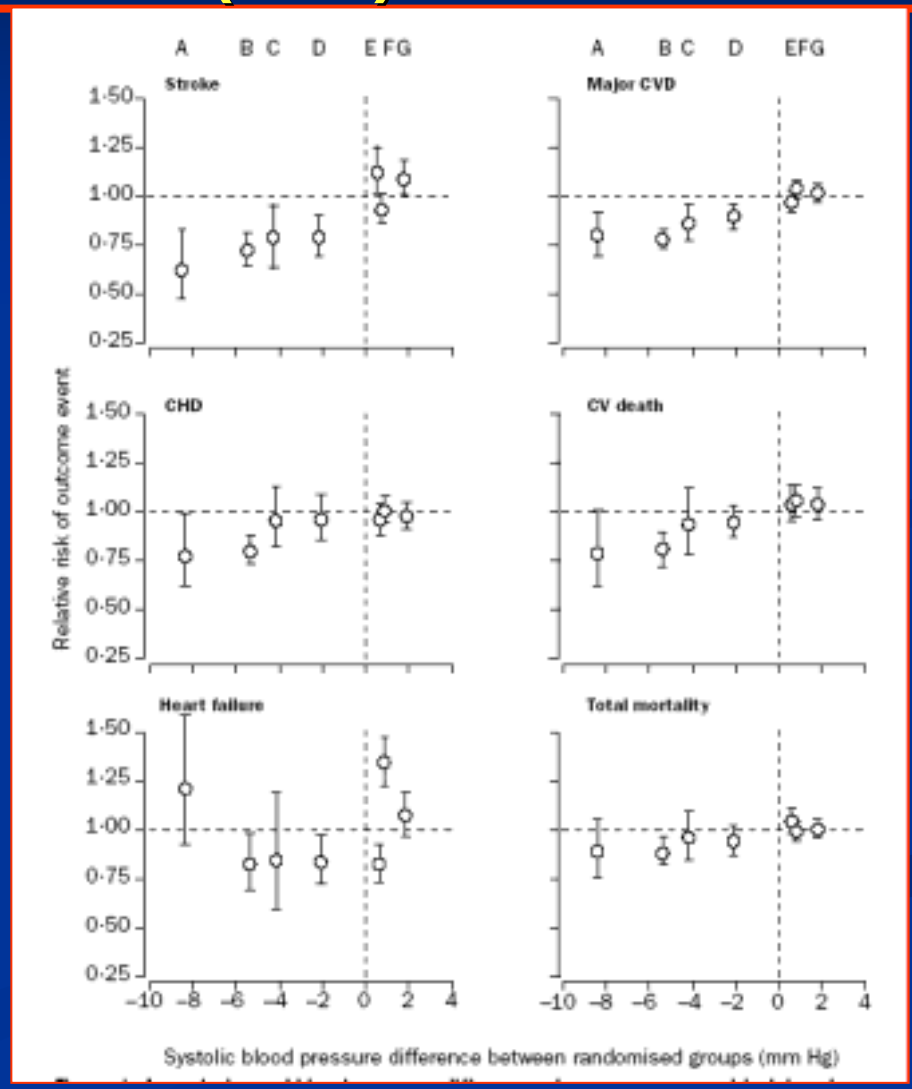
# Effects of different BP-lowering regimens on major CV events: results of prospectively-designed overviews of randomised trials (2003)

- Associations of BP differences between groups with risks of major vascular outcomes and death. The circles are plotted at the point estimate of effect for the relative risk for every event type and the mean follow-up BP in the 1st listed group compared with the 2nd listed group.

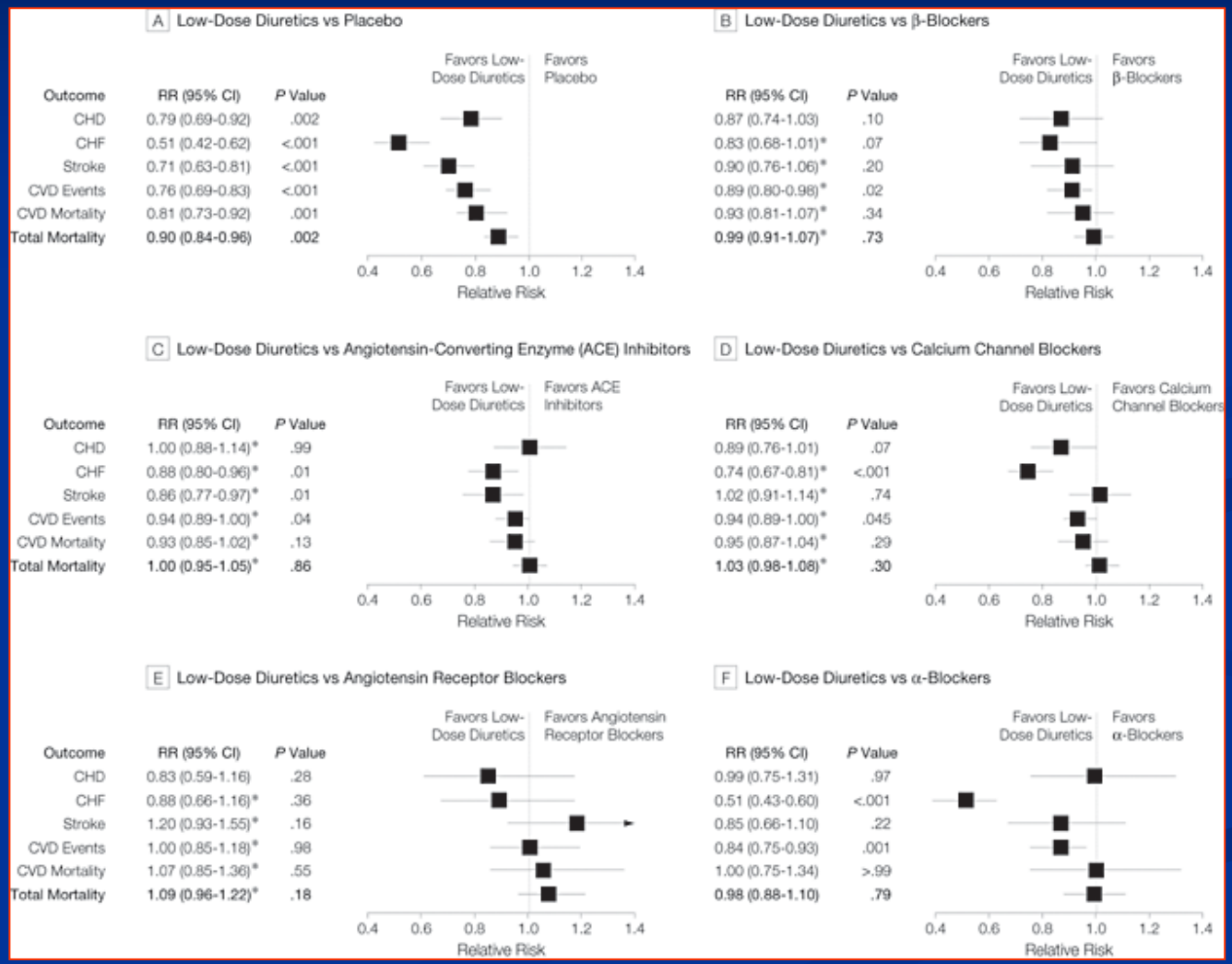
A) CCB *vs* placebo,
B) ACE inhibitor *vs* placebo
C) More intensive *vs* less intensive
D) ARB *vs* control

E) ACE inhibitor *vs* CCB,
F) CCB *vs* diuretic or BB,
G) ACE inhibitor *vs* diuretic and BB

Turnbull *Lancet 2003;362:1527-35*



# Health outcomes associated with various therapies used as first-line agents: a network meta-analysis




Psaty Jama 2003;289:2534-44

# New-onset diabetes : Impact of blood pressure-lowering drugs

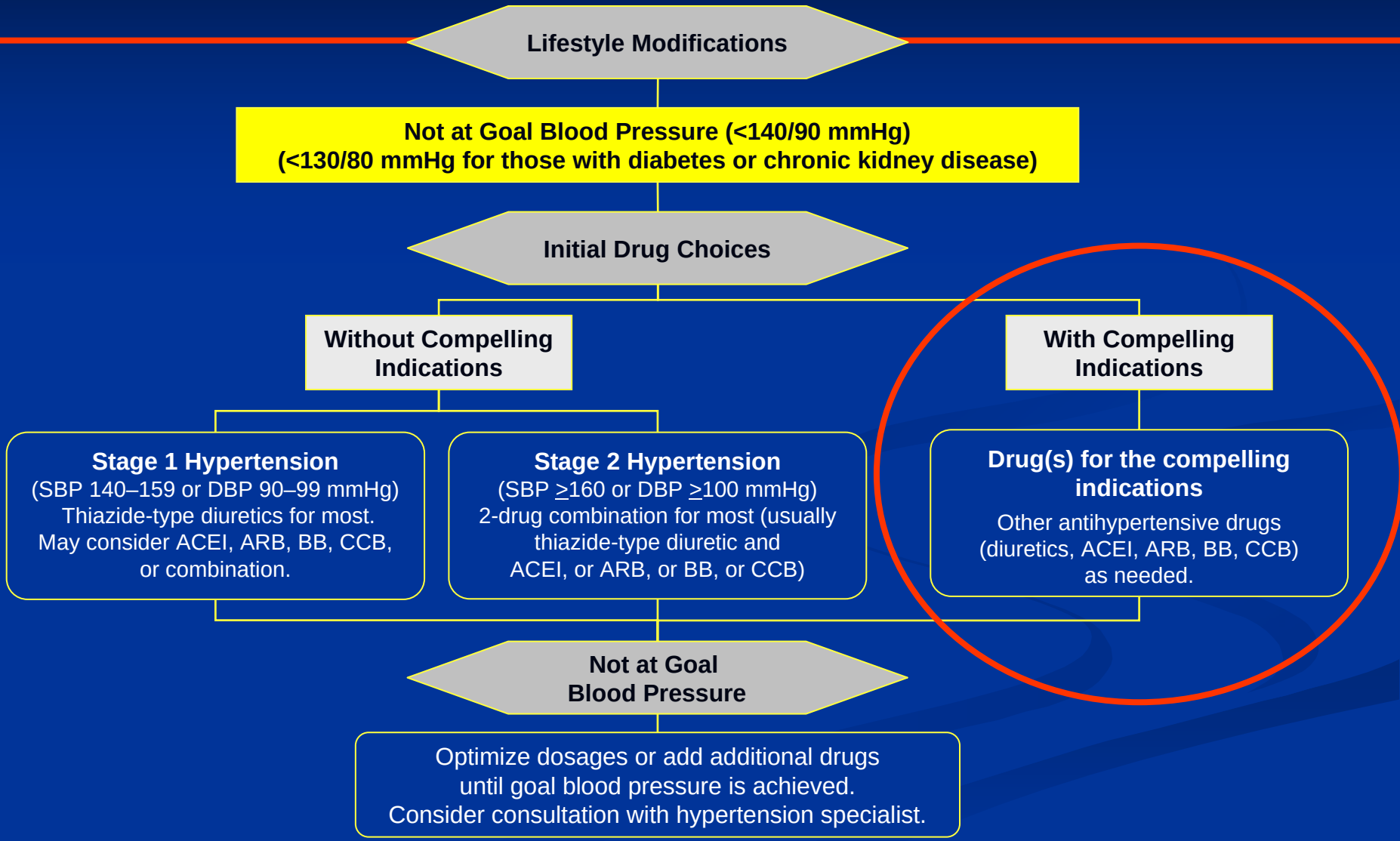
- There are clearly differences in the likelihood of developing new diabetes with the blood pressure lowering drugs
  - Conventional therapy (thiazide and/or beta-blocker), especially when combined, is associated with the highest rate of new diabetes.
  - Blockade of the renin system appears to be associated with the lowest rate of new diabetes, with CCBs sitting between the two extremes.
  - In the ALLHAT study, the rates of new diabetes were chlorthalidone>amlodipine>lisinopril.
  - In the VALUE trial, ARB-based therapy (valsartan) was associated with less new diabetes than CCB-based therapy (amlodipine).

- National treatment guidelines in the United Kingdom.
  - Recommend avoiding the combination of thiazide and beta-blockers in people at higher risk of developing new diabetes (i.e., people with a strong family history of diabetes, obesity, impaired fasting glucose levels, or those within ethnic groups that have high rates of diabetes).

# Recommendations

- There has been no consensus on optimal initial drug therapy of hypertension, although the ALLHAT result strongly suggests a primary role for a thiazide diuretic in most patients.
- The choice of agents is determined by the ability to achieve the ultimate goal of antihypertensive therapy: maximally reduce CV risk.
- The regimen of trying to find the one drug to which the patient is most responsive may minimize side effects and maximize patient compliance while being as effective as combination therapy. However, as noted in virtually all trials, more than one drug will be needed to control most patients with hypertension, so the initial choice becomes less important

# Algorithm for Treatment of Hypertension



# Indications for specific drugs

**TABLE 12. Clinical Trial and Guideline Basis for Compelling Indications for Individual Drug Classes**

| | Recommended Drugs | | | | | | |
|---|---|---|---|---|---|---|---|
| Compelling Indication* | Diuretic | BB | ACEI | ARB | CCB | Aldo ANT | Clinical Trial Basis† |
| Heart failure | ● | ● | ● | ● | | ● | ACC/AHA Heart Failure Guideline,[132] MERIT-HF,[133] COPERNICUS,[134] CIBIS,[135] SOLVD,[136] AIRE,[137] TRACE,[138] ValHEFT,[139] RALES,[140] CHARM[141] |
| Post–myocardial infarction | | ● | ● | | | ● | ACC/AHA Post-MI Guideline,[142] BHAT,[143] SAVE,[144] Capricom,[145] EPHESUS[146] |
| High coronary disease risk | ● | ● | ● | | ● | | ALLHAT,[109] HOPE,[110] ANBP2,[112] LIFE,[102] CONVINCE,[101] EUROPA,[114] INVEST[147] |
| Diabetes | ● | ● | ● | ● | ● | | NKF-ADA Guideline,[88,89] UKPDS,[148] ALLHAT[109] |
| Chronic kidney disease | | | ● | ● | | | NKF Guideline,[89] Captopril Trial,[149] RENAAL,[150] IDNT,[151] REIN,[152] AASK[153] |
| Recurrent stroke prevention | ● | | ● | | | | PROGRESS[111] |

Chobanian *JAMA 2003;289:2560-72*

# Compelling indications for specific antihypertensive drugs

| Compelling indications | Preferred drug | Primary endpoint |
|---|---|---|
| Elderly with ISH | Diuretic | Stroke |
| | DHPCCB | Stroke |
| Renal disease | | |
| Diabetic nephropathy type 1 | ACEI | Progression of renal failure |
| Diabetic nephropathy type 2 | ARB | Progression of renal failure |
| Non-diabetic nephropathy | ACEI | Progression of renal failure |
| Cardiac disease | | |
| Post-MI | ACEI | Mortality |
| | β-blocker | Mortality |
| Left ventricular dysfunction | ACEI | Heart failure |
| | ACEI | Mortality |
| CHF (diuretics almost always included) | β -blocker | Mortality |
| | Spironolactone | Mortality |
| Left ventricular hypertrophy | ARB | CV morbidity and mortality |
| Cerebrovascular disease | ACEI + diuretic | Recurrent stroke |
| | Diuretic | Recurrent stroke |

Journal of Hypertension 2003, 21:1983–1992

# Additional Considerations in Antihypertensive Drug Choices

**Potential favorable effects**

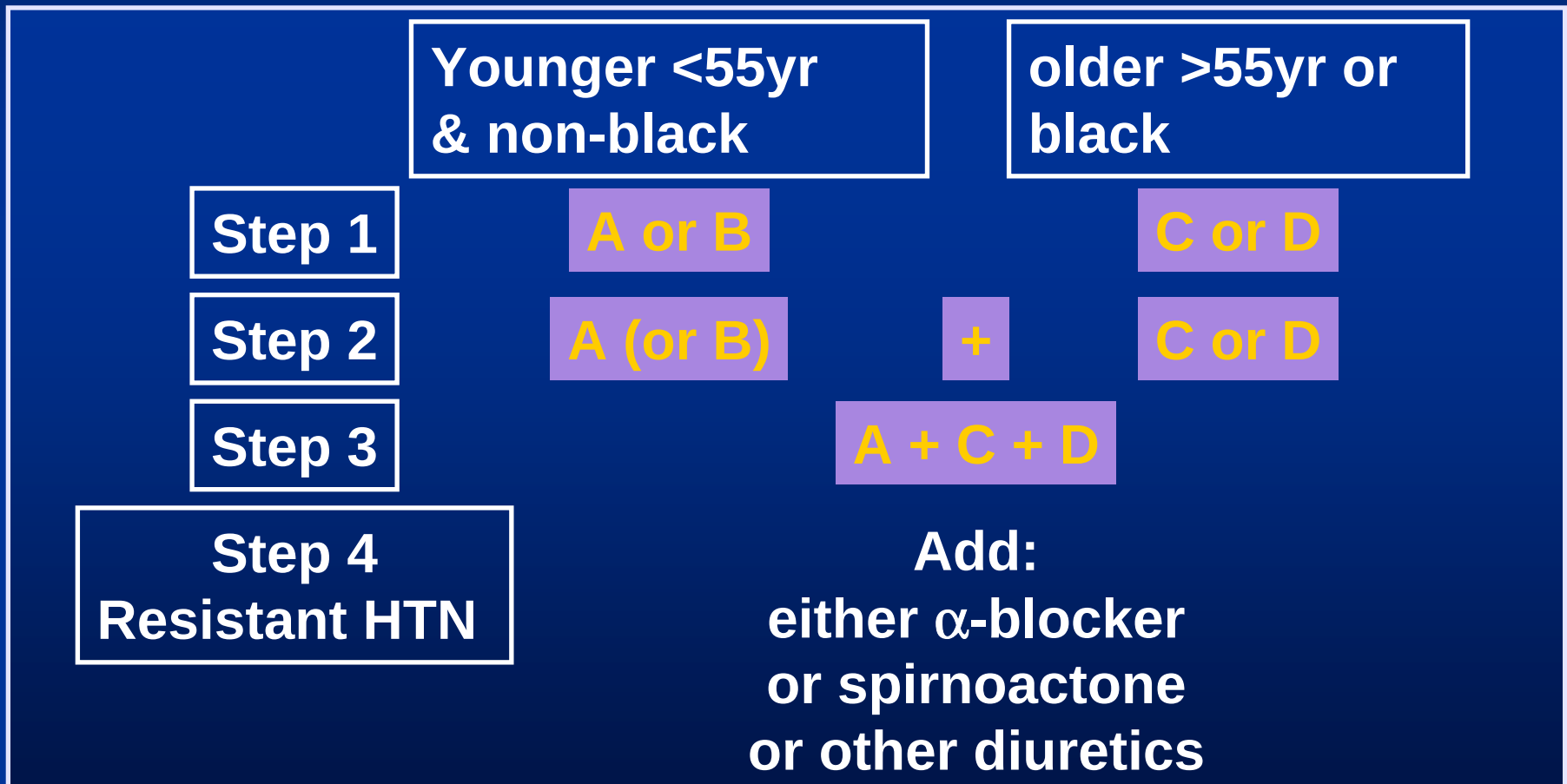
- Thiazide-type diuretics useful in slowing demineralization in osteoporosis.
- BBs useful in the treatment of atrial tachyarrhythmias, migraine, thyrotoxicosis (short-term), essential tremor, or perioperative HTN.
- CCBs useful in Raynaud's syndrome and certain arrhythmias.
- Alpha-blockers useful in prostatism.

# Additional Considerations in Antihypertensive Drug Choices

**Potential unfavorable effects**

- Thiazide diuretics; cautiously in gout or a history of significant hyponatremia.
- BBs: generally avoided in asthma, reactive airways disease, or second- or third-degree heart block.
- ACEIs and ARBs; contraindicated in pregnant women or those likely to become pregnant.
  - ACEIs should not be used in a history of angioedema.
- Aldosterone antagonists and potassium-sparing diuretics can cause hyperkalemia.

# BHS recommendations: Modified Cambridge AB/CD Rule




*A: ACE inhibitor or ATN receptor blocker, B: beta blocker, C: calcium channel blocker, D: diuretic (thiazide)*

# Implications for modern treatment : Targeting CVD risk rather than hypertension?

- **After all, the purpose of treatment is to reduce the risk of stroke and CHD, not just blood pressure!**

- This concept is important because many patients with elevated blood pressure exhibit features of the metabolic syndrome and dyslipidemia that magnify their risk of stroke and CHD, beyond that crudely attributed to blood pressure alone.

# The Polypill - Coming Soon

- "Polypill" a combination of 3 or more drugs in a single pill for the prevention of cardiovascular disease (CVD)
- Ingredients
  - Cholesterol-lowering drug,
  - Two low-dose blood pressure-lowering agents,
  - Low-dose aspirin,
  - With various other drugs added for different formulations
- Risk-reduction benefits
  - 55% to 75% risk reduction
- Side effects are likely to be rare