

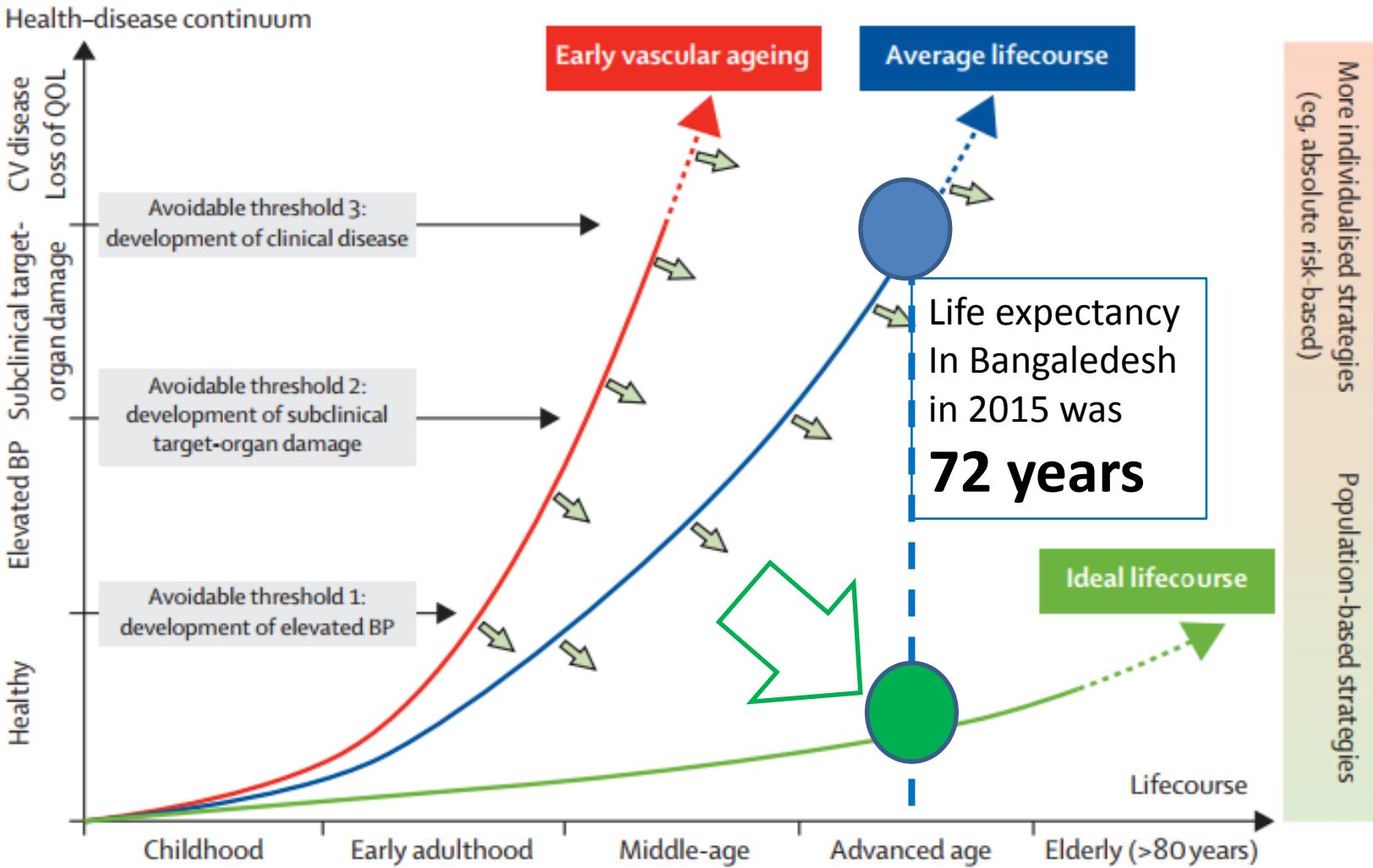
“ACE Inhibitors are the cornerstone of Hypertension Management”



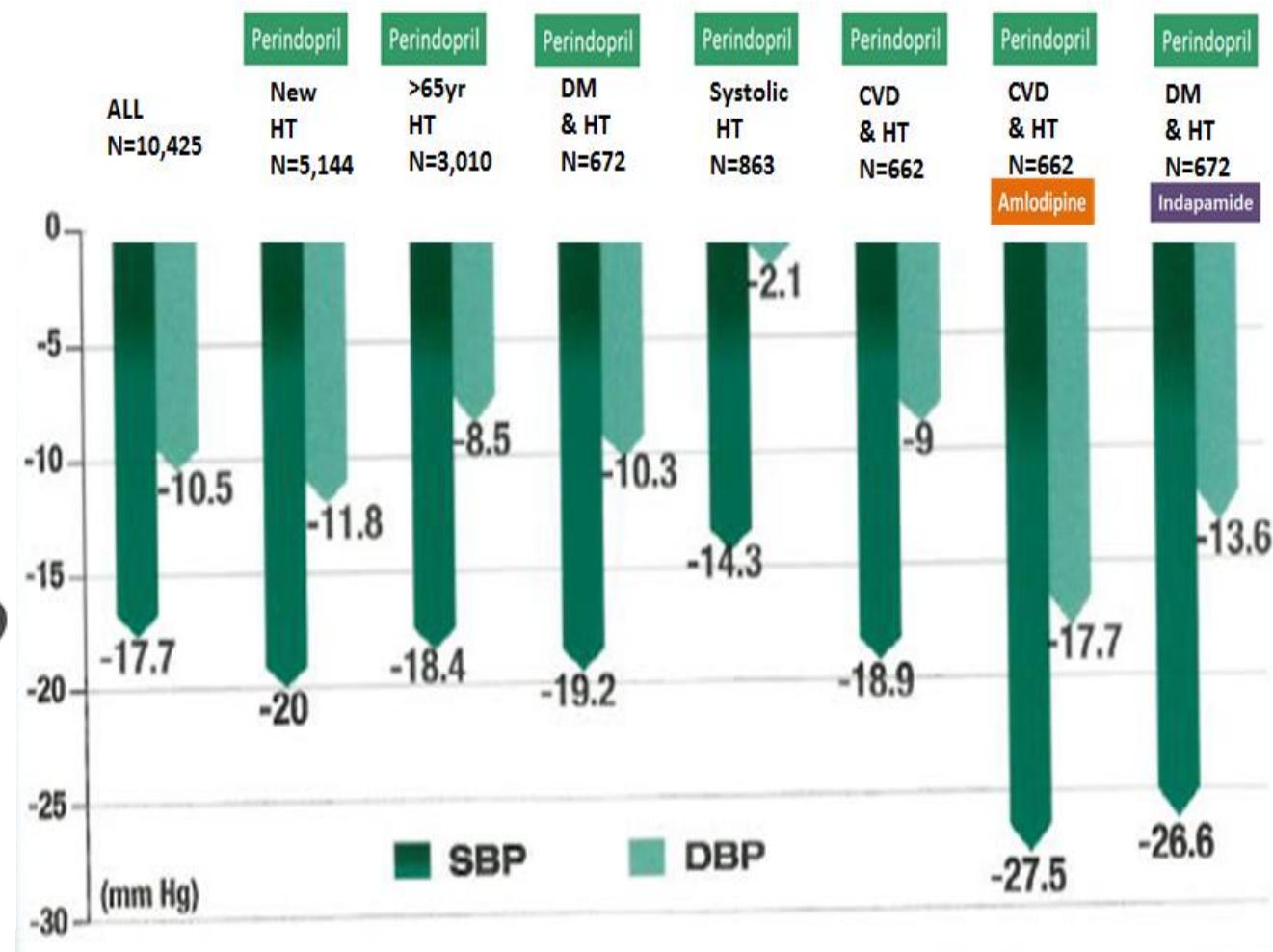
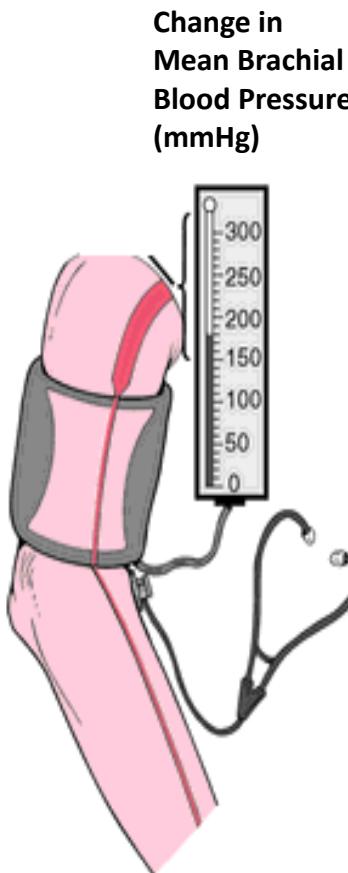
Alistair HALL Professor of Cardiovascular Epidemiology University of Leeds
UK, Clinical Director Yorkshire & Humber Local Clinical Research Network

Alistair Hall

Lancet Commission for Hypertension

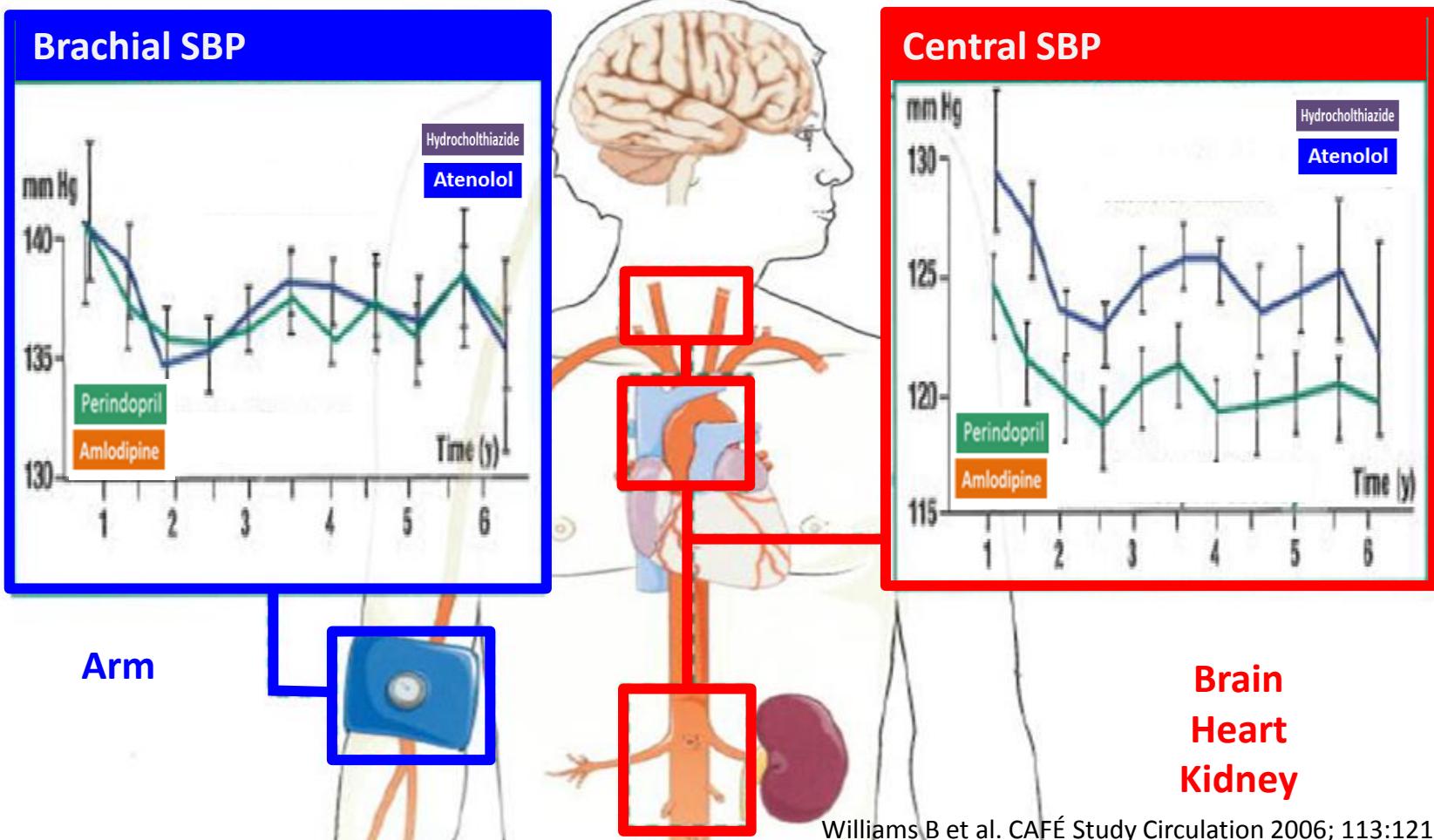


Effective Treatment of Hypertension



Ahsan Haq

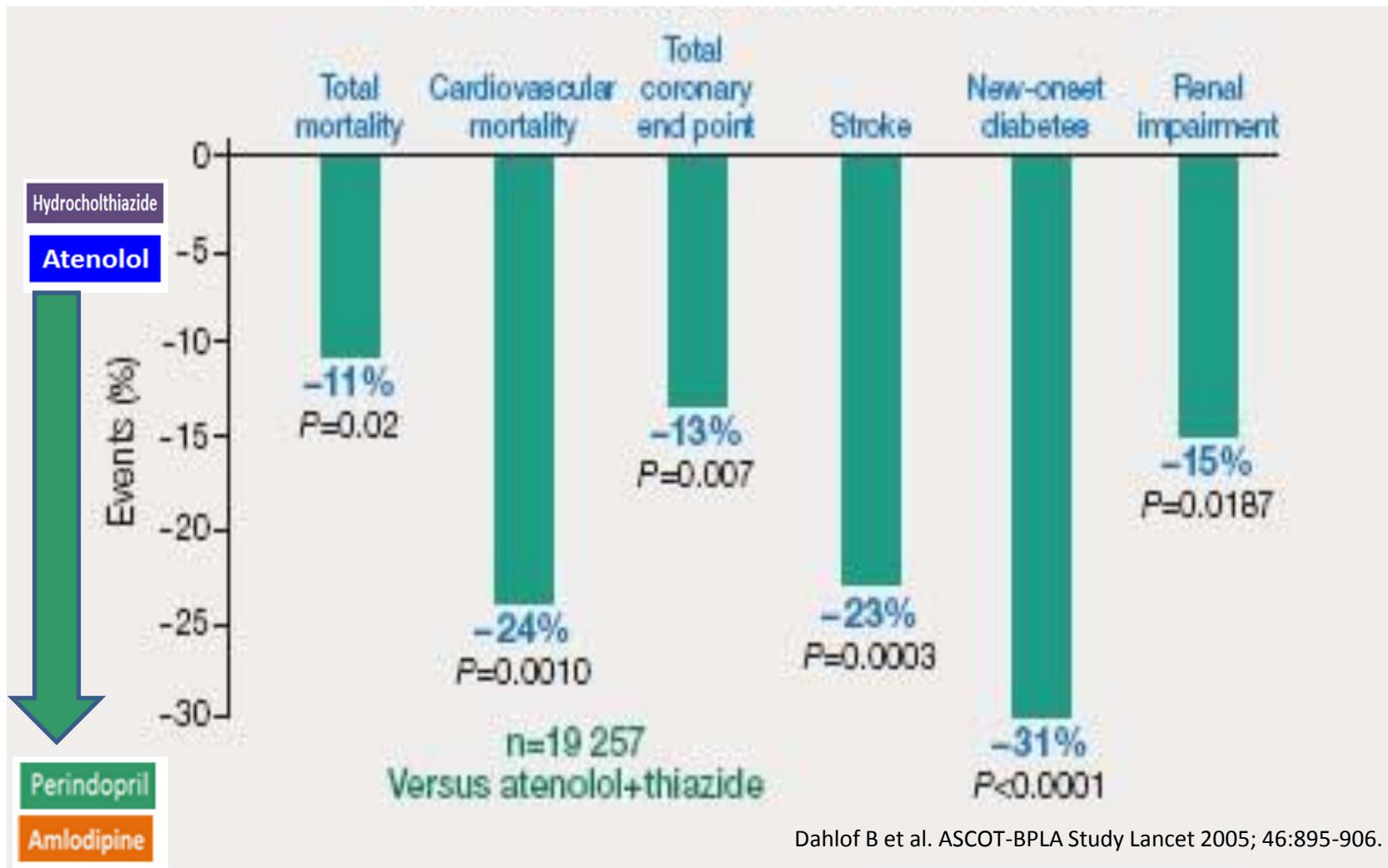
Effective Treatment of Hypertension



Williams B et al. CAFÉ Study Circulation 2006; 113:1213-25.

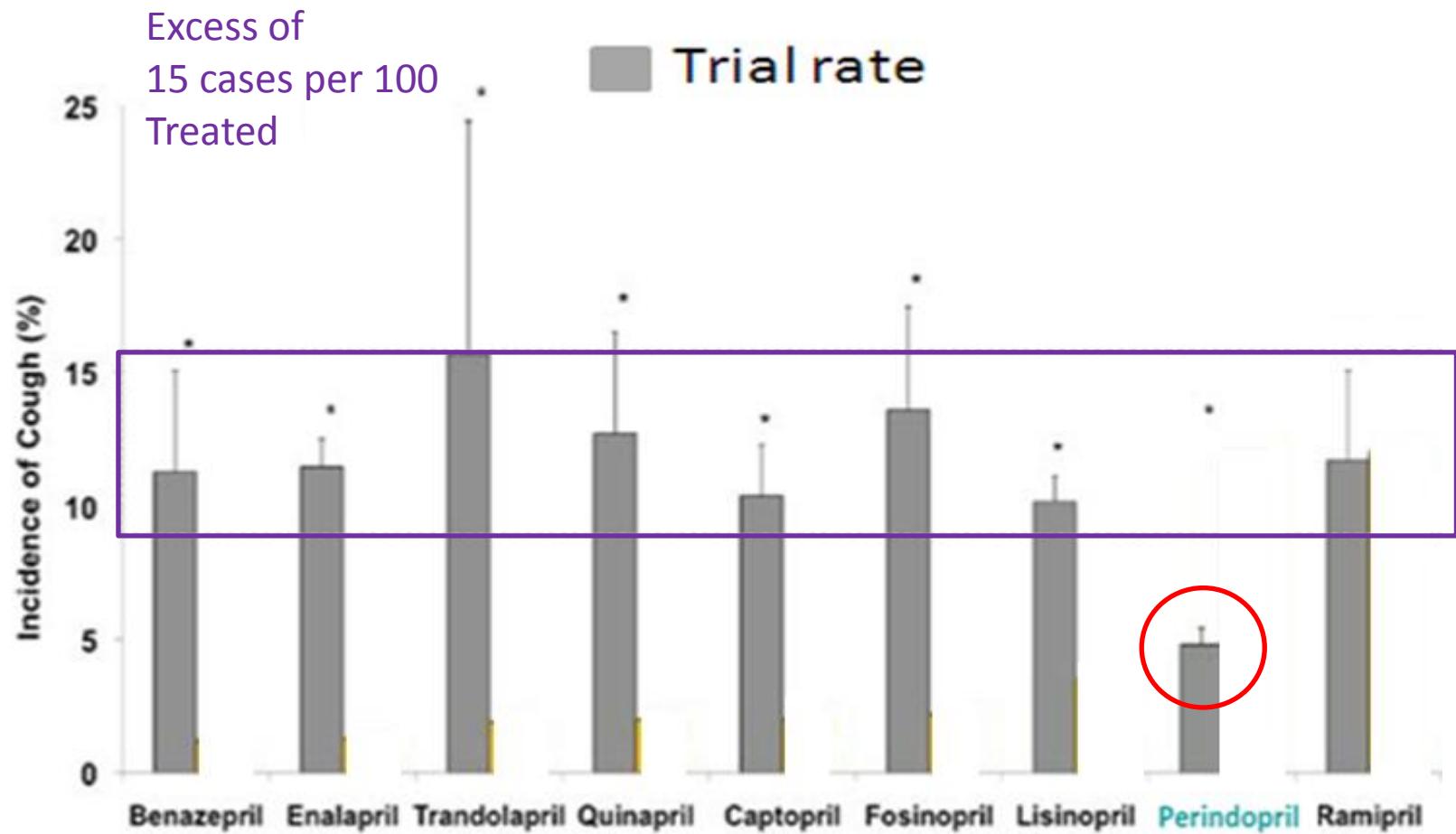
Ashish Hall

Effective Treatment of Hypertension



Ashish Hall

ACEi Cough Meta-analysis



Ashish Hall

ACEi Cough

(perindopril in combination with amlodipine)

| Adverse event ¹ | % |
|----------------------------|------|
| Ankle edema | 0.5% |
| Cough | 1.1% |
| Headache | 0.3% |
| Nausea | 0.2% |

*n = 1,250 hypertensive patients
Duration: 2 months*

**STRONG
TRIAL**

58%

Less ankle edema
compared to Amlodipine monotherapy²

61%

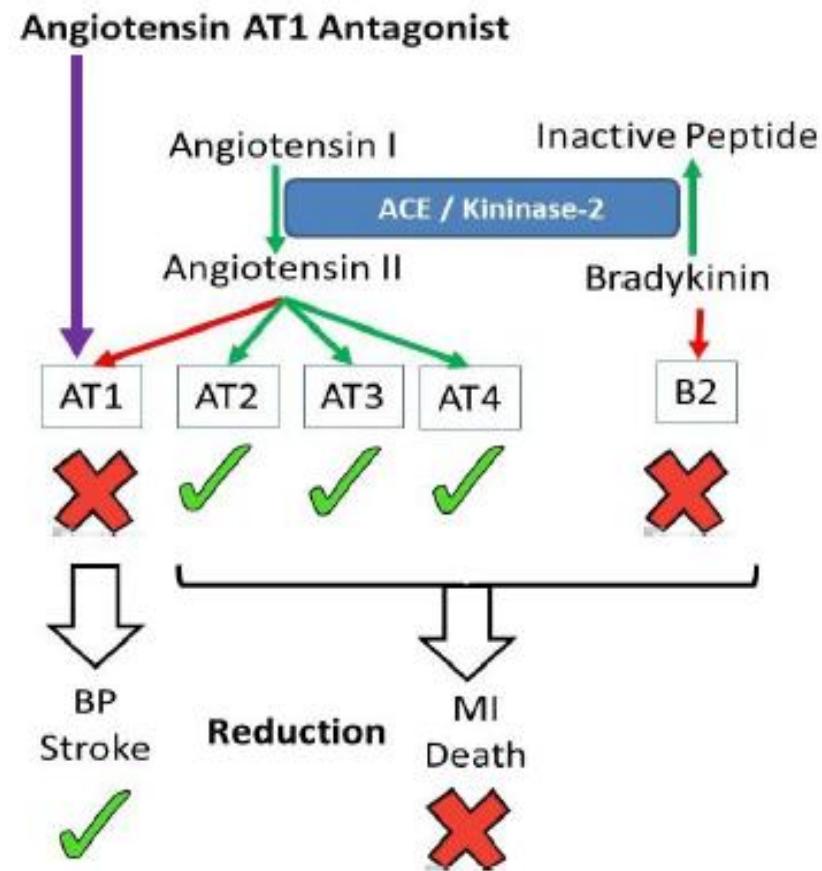
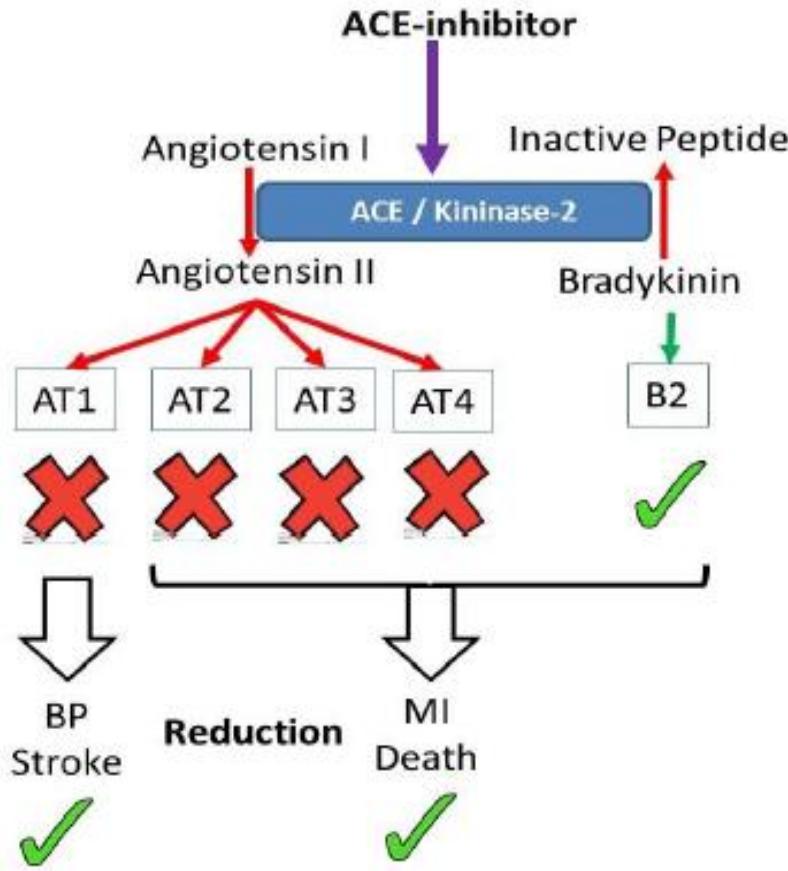
Less cough
compared to ACEi monotherapy³

1. American Journal of Cardiovascular Drugs. 2009;9:135-142.

2. Clinical Drug Investigations 2012; 32 (9): 603-612

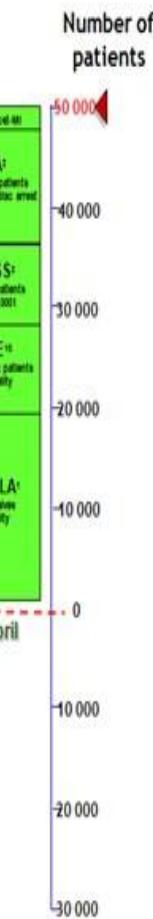
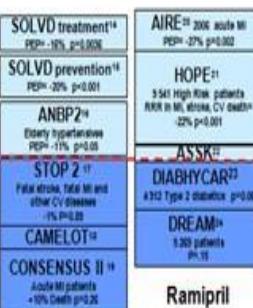
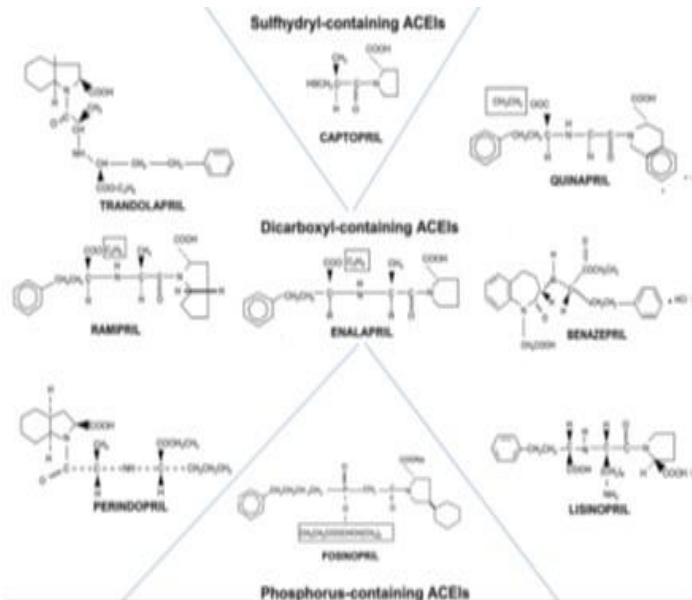
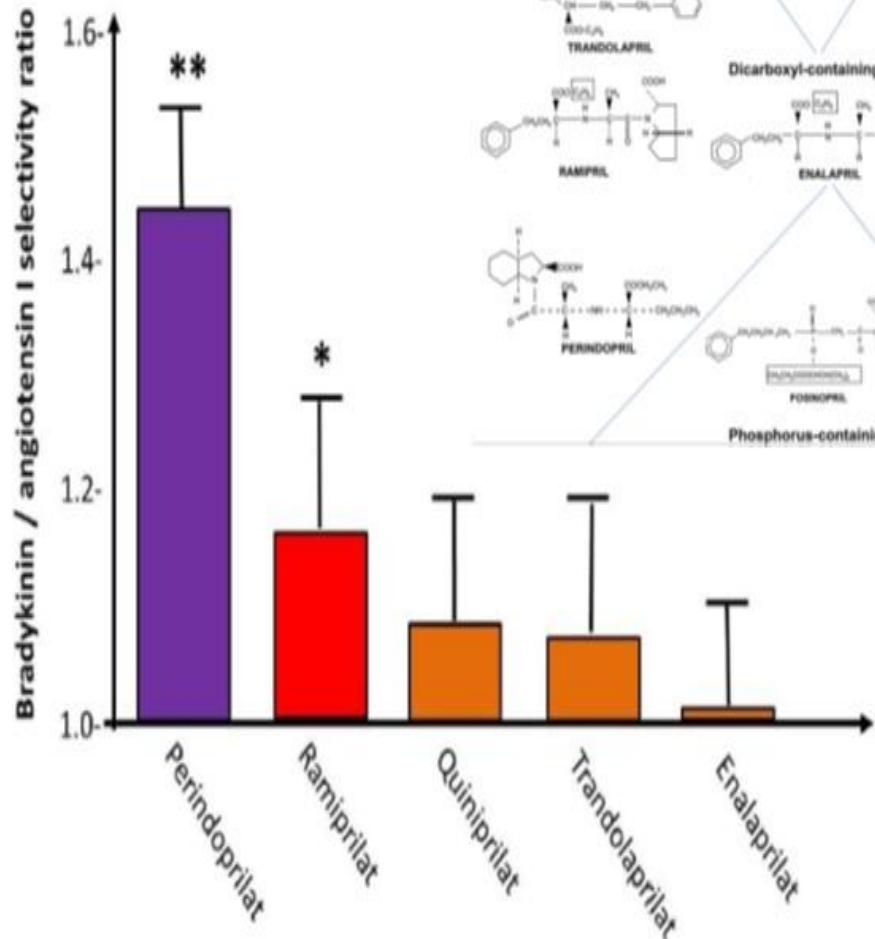
3. Current Therapeutic Research, 1999, VOL. 60, NO. 3: 120-28

Ashish Hall



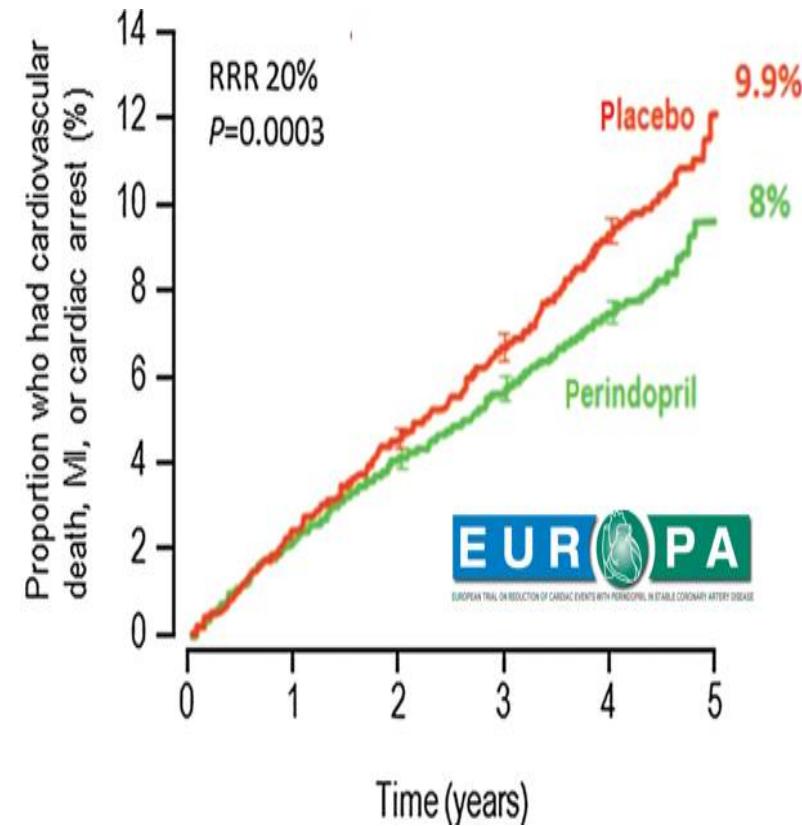
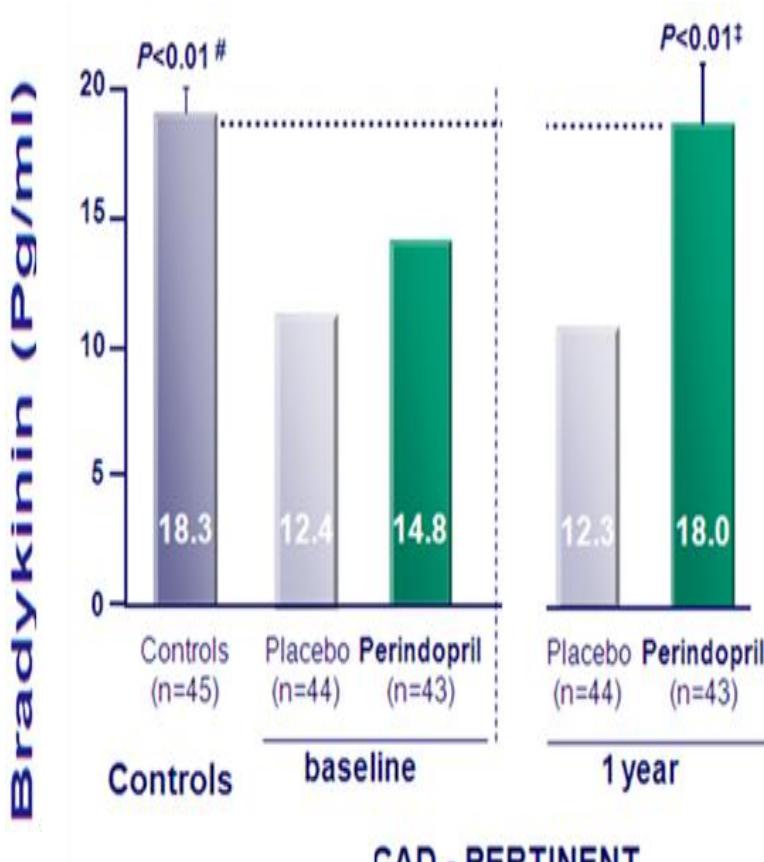
Ashish Hall

"ACE Inhibitors are the cornerstone of Hypertension Management"



Pertinent Sub-study

Perindopril Increases Bradykinin Concentration (YOUNG > OLD)

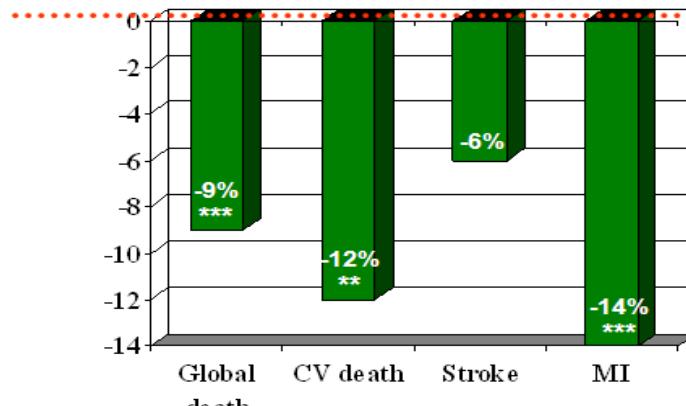


Ahshair Hall

Different Effects of ACEi and ARB

| ACE inhibitor | ARB | Effects | |
|---|-----|---------|---|
| BRADYKININ Arg ¹ Pro ² Pro ³ Gly ⁴ Phe ⁵ Ser ⁶ Pro ⁷ Phe ⁸ Arg ⁹  "Friend or Foe ?" | ↑↑↑ | ↔ | vasodilation augments renal plasma flow, increases nitric oxide and prostacyclin, ischemic preconditioning, stabilizes vascular permeability, cough, angioedema |

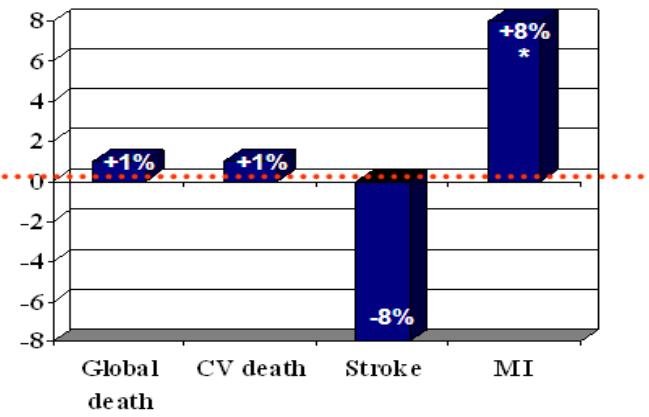
ACE inhibitors vs comparators
(39 trials, n=150 943)



** p=0.0005; *** p < 0.00001

Adapted from: Strauss MH, Hall AS. Circulation. 2006;114:838-854.

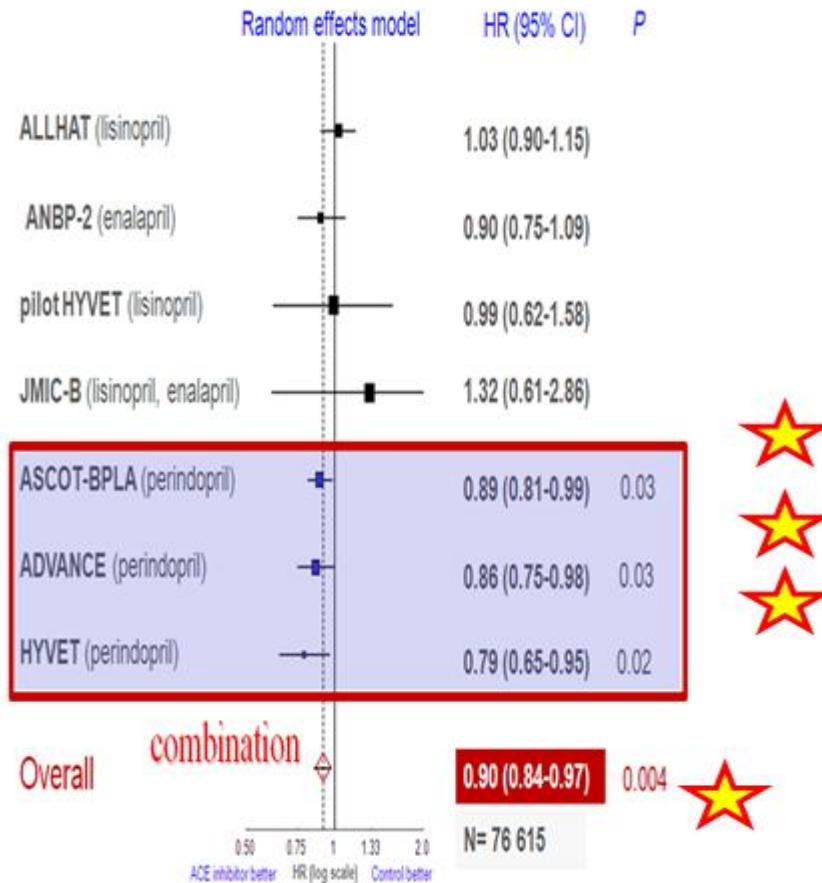
ARBs vs comparators
(11 trials, n=55 050)



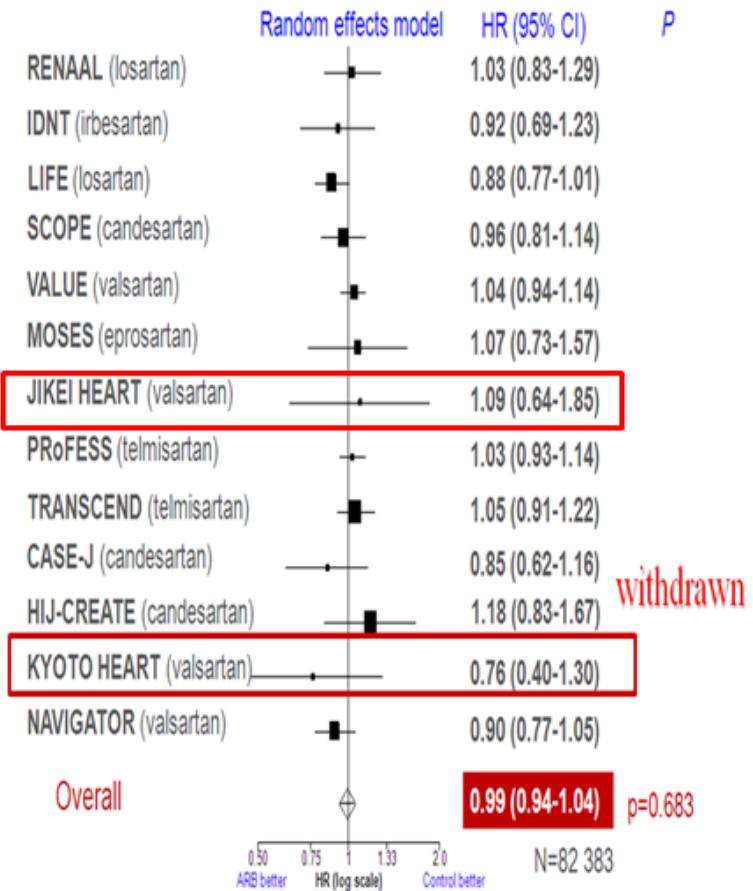
* p=0.03

Prevention of Death from All-causes

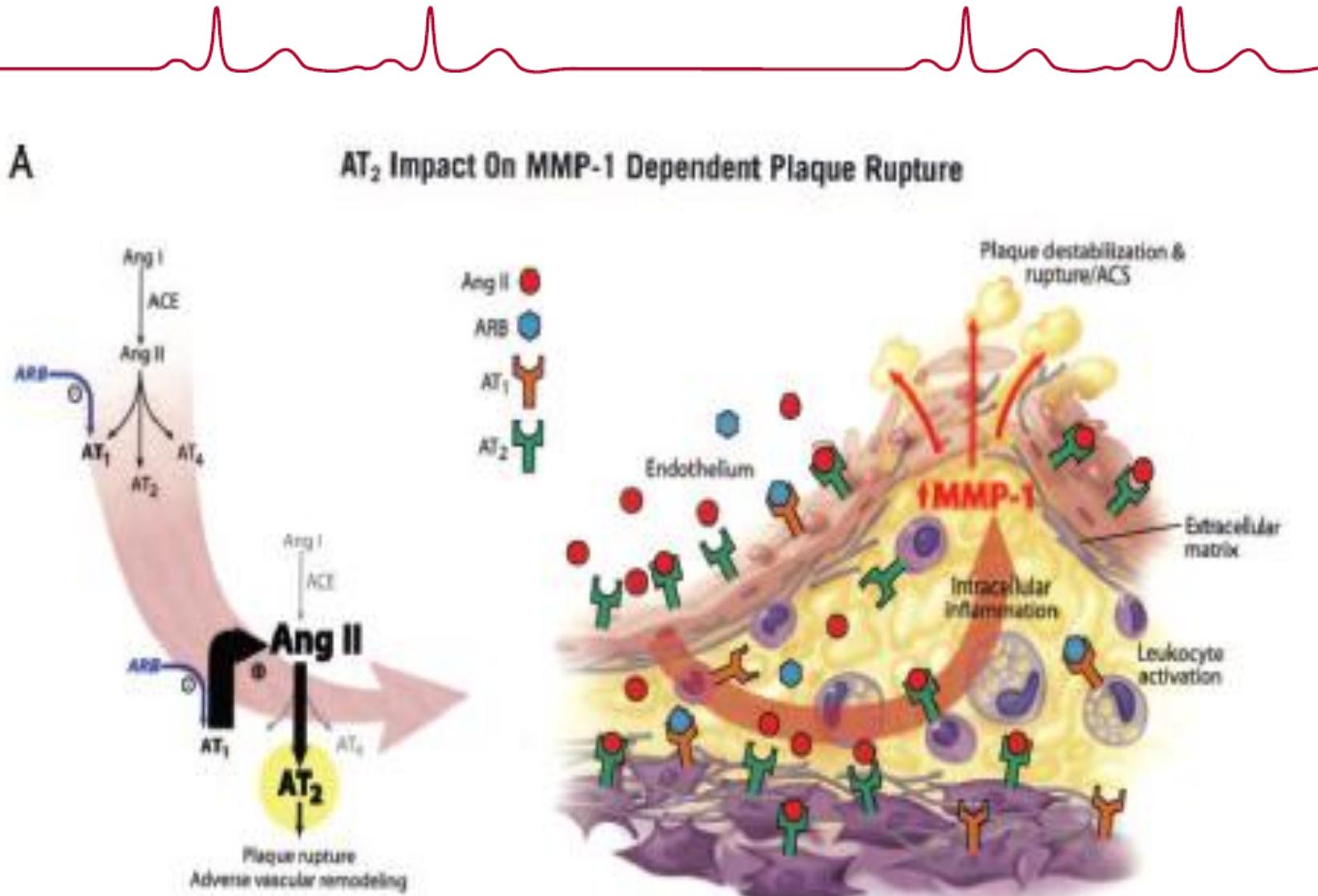
All-cause mortality: effect of ACE inhibitors



All-cause mortality: effect of ARBs



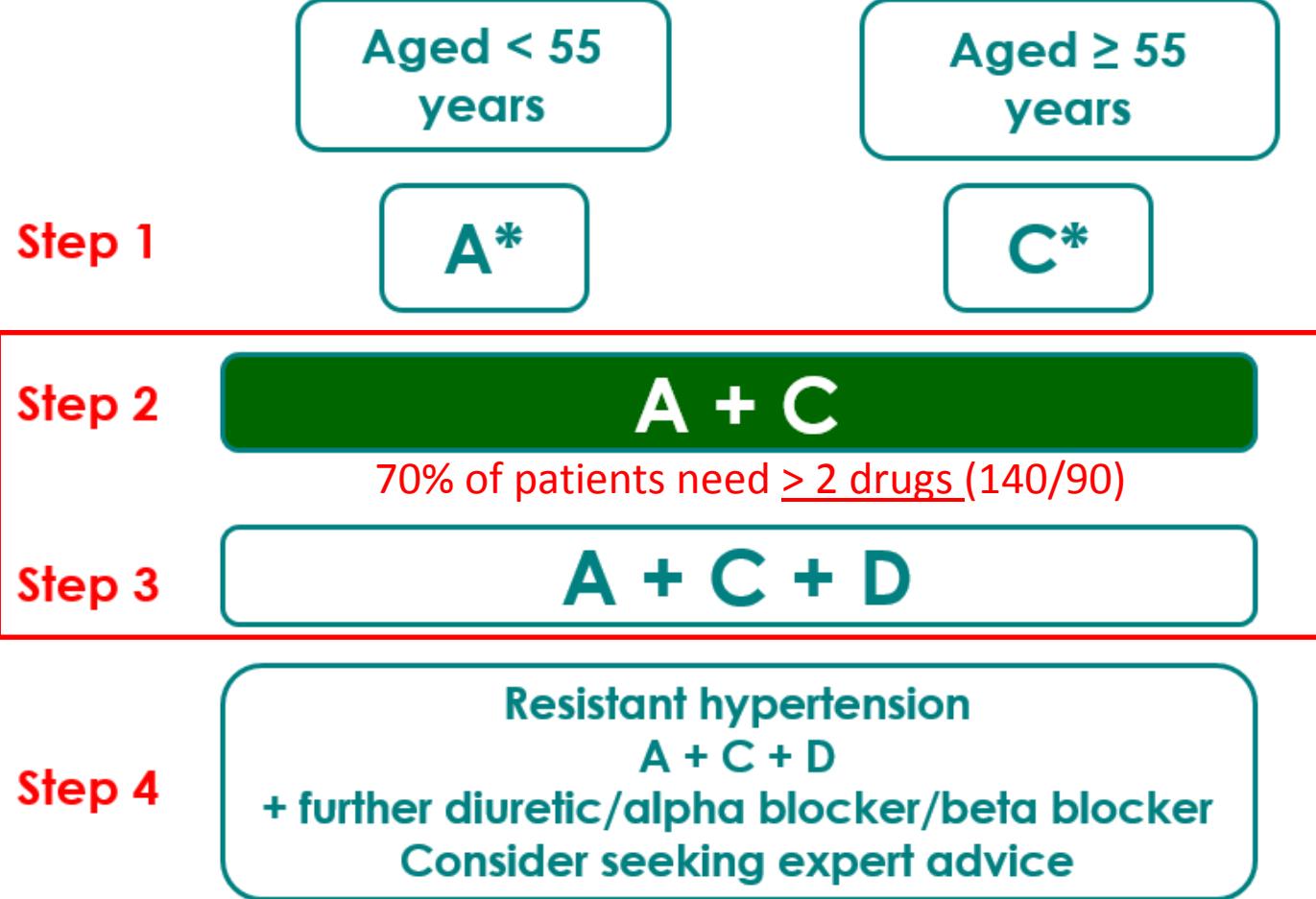
Absentee Hall



Dahlof B et al. ASCOT-BPLA Study Lancet 2005; 46:895-906.

Ashish Hall

UK NICE Guidelines



Key:

A = ACEi

C = Calcium
Channel
Blocker

D = Thiazide-
like diuretic

A* = ARB where
ACEi is not
tolerated

C* = Thiazide-
like diuretics
where CCB is
not tolerated

National Institute for
Health and Clinical
Excellence



Epidemiology -> ACEi -> ARB -> **Guidelines** -> Combinations

Ashish Hall

“Which combination ?”



European Heart Journal (2013) 34, 2159–2219
doi:10.1093/eurheartj/eht151

ESH AND ESC GUIDELINES

“if high BP consider two drug combination”

| Recommendations | Class ^a | Level ^b | Ref. ^c |
|--|--------------------|--------------------|-------------------|
| Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of OD. | IIa | C | - |
| Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline BP or at high CV risk. | IIb | C | - |

*“pick a treatment **effective in a trial** with consideration also of **other disease** present”*

Ahshair Hall

European Guidelines - Combination Therapies

ACEi & DIU

ARB & DIU

CCB & DIU

ACEi & CCB

BB & DIU

ACEi & ARB

| Trial | Comparator | Type of patients | SBP diff (mmHg) | Outcomes |
|---|--------------|---------------------------------|-----------------|--|
| <i>ACE-I and diuretic combination</i> | | | | |
| PROGRESS ¹⁰ | Placebo | Previous stroke or TIA | -9 | -28% strokes ($P < 0.001$) |
| ADVANCE ¹¹ | Placebo | Diabetes | -5.6 | -9% micro/macro vascular events ($P = 0.04$) |
| HYVET ¹² | Placebo | Hypertensives aged ≥80 years | -15 | -34% CV events ($P < 0.001$) |
| CAPP ¹³ | BB + D | Hypertensives | +3 | +5% CV events ($P = NS$) |
| <i>Angiotensin receptor blocker and diuretic combination</i> | | | | |
| SCOPE ¹⁴ | D + placebo | Hypertensives aged ≥70 years | -3.2 | -28% non fatal strokes ($P = 0.04$) |
| LIFE ¹⁵ | BB + D | Hypertensives with LVH | -1 | -26% stroke ($P < 0.001$) |
| <i>Calcium antagonist and diuretic combination</i> | | | | |
| FEVER ¹⁶ | D + placebo | Hypertensives | -4 | -27% CV events ($P < 0.001$) |
| ELSA ¹⁷ | BB + D | Hypertensives | 0 | NS difference in CV events |
| CONVINCE ¹⁸ | BB + D | Hypertensives with risk factors | 0 | NS difference in CV events |
| VALIE ¹⁹ | ARB + D | High-risk hypertensives | -2.2 | -3% CV events ($P = NS$) |
| <i>ACE-I and calcium antagonist combination</i> | | | | |
| SystEur ²⁰ | Placebo | Elderly with ISH | -10 | -31% CV events ($P < 0.001$) |
| SystChina ²¹ | Placebo | Elderly with ISH | -9 | -37% CV events ($P < 0.004$) |
| NORDIL ²² | BB + D | Hypertensives | +3 | NS difference in CV events |
| INVEST ²³ | BB + D | Hypertensives with CHD | 0 | NS difference in CV events |
| ASCOT ²⁴ | BB + D | Hypertensives with risk factors | -3 | -16% CV events ($P < 0.001$) |
| ACCOMPLISH ²⁵ | ACE-I + D | Hypertensives with risk factors | -1 | -21% CV events ($P < 0.001$) |
| <i>BB and diuretic combination</i> | | | | |
| Coope & Warrender ²⁶ | Placebo | Elderly hypertensives | -18 | -42% strokes ($P < 0.03$) |
| SHEP ²⁷ | Placebo | Elderly with ISH | -13 | -36% strokes ($P < 0.001$) |
| STOP ²⁸ | Placebo | Elderly hypertensives | -23 | -40% CV events ($P = 0.003$) |
| STOP 2 ²⁹ | ACE-I or CA | Hypertensives | 0 | NS difference in CV events |
| CAPP ¹³ | ACE-I + D | Hypertensives | -3 | -5% CV events ($P = NS$) |
| LIFE ¹⁵ | ARB + D | Hypertensives with LVH | +1 | +26% stroke ($P < 0.001$) |
| ALLHAT ³⁰ | ACE-I + BB | Hypertensives with risk factors | -2 | NS difference in CV events |
| ALLHAT ³¹ | CA + BB | Hypertensives with risk factors | -1 | NS difference in CV events |
| CONVINCE ¹⁸ | CA + D | Hypertensives with risk factors | 0 | NS difference in CV events |
| NORDIL ²² | ACE-I + CA | Hypertensives | -3 | NS difference in CV events |
| INVEST ²³ | ACE-I + CA | Hypertensives with CHD | 0 | NS difference in CV events |
| ASCOT ²⁴ | ACE-I + CA | Hypertensives with risk factors | +3 | +16% CV events ($P < 0.001$) |
| <i>Combination of two renin-angiotensin-system blockers /ACE-I + ARB or RAS blocker + renin inhibitor</i> | | | | |
| ONTARGET ³² | ACE-I or ARB | High-risk patients | -3 | More renal events |
| ALTITUDE ³³ | ACE-I or ARB | High-risk diabetics | -1.3 | More renal events |

Alistair Hall

Combination of choice: ACE inhibitors with diuretic or CCB

PERINDOPRIL / INDAPAMIDE



"If the benefits seen in ADVANCE were applied to just half the population with diabetes worldwide, more than a million deaths would be avoided over 5 years¹"

Cardiovascular mortality:
RRR -18% ($P=0.027$)¹

PERINDOPRIL / AMLODIPINE



"The amlodipine-based regimen prevented more major cardiovascular events and induced less diabetes than the atenolol-based regimen²"

Cardiovascular mortality:
RRR -24% ($P<0.001$)²

The study was stopped prematurely after median follow-up of 5.5 years²

1. Patel A; ADVANCE Collaborative Group. *Lancet*. 2007;370:829-840.
2. Dahlöf B, Sever PS, Poulter NR, et al. *Lancet*. 2005;366:895-906.

Ashish Hall

Randomized Clinical Trials - Combination Therapies

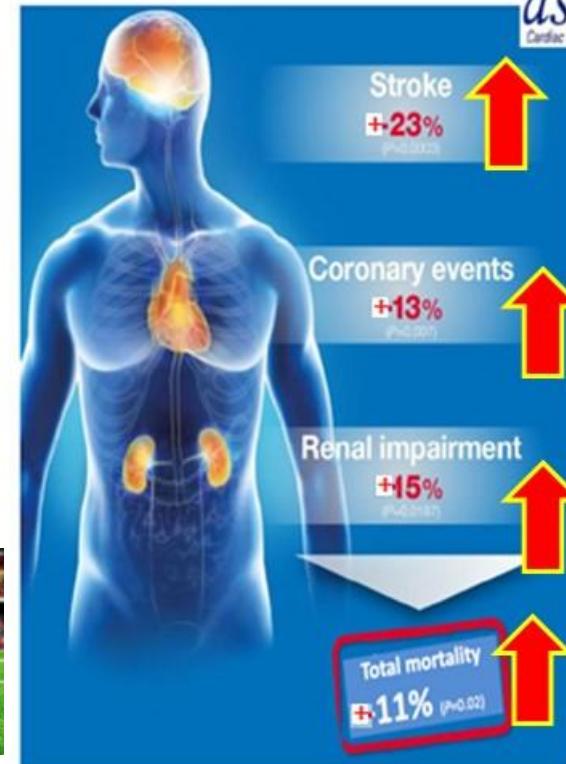
AMLODIPINE

PERINDOPRIL

Vs.

ATENOLOL

BF-TIAZIDE



| | | AMLODIPINE | PERINDOPRIL | Points | Played | Primary | DEATH | MI | STROKE | G.DIF |
|-------|-----------|------------|-------------|--------|--------|---------|-------|-----|--------|-------|
| ASCOT | LAIC 2005 | AMLODIPINE | PERINDOPRIL | 3 | 1 | YES | YES | YES | YES | 4 |
| ASCOT | LAIC 2005 | ATENOLOL | BF-TIAZIDE | 0 | 5 | NO | NO | NO | NO | .4 |

Ahsan Haq

Randomized Clinical Trials - Combination Therapies

| | | | | Points | Played | Primary | DEATH | MI | STROKE | G.DIF |
|------------|-------------|--------------|----------------|--------|--------|---------|-------|-----|--------|-------|
| ADVANCE | LANC 200 | INDAPAMIDE | PERINDOPRIL | 3 | 3 | YES | YES | YES | YES | 4 |
| ASCOT | LANC 200 | AMLODIPINE | PERINDOPRIL | 3 | 1 | YES | YES | YES | YES | 4 |
| SYST-CINN | ARCHIM 200 | NITRENDIPINE | CAPTOPRIL | 3 | 1 | YES | YES | YES | YES | 4 |
| PROGRESS | LANC 200 | PERINDOPRIL | INDAPAMIDE | 3 | 3 | YES | NO | YES | YES | 3 |
| ACCOMPLISH | NEJM 200 | AMLODIPINE | BENAZEPRIL | 3 | 1 | YES | NO | YES | NO | 2 |
| LIFE | LANC 200 | LOSARTAN | HC-THIAZIDE | 3 | 1 | YES | NO | NO | YES | 2 |
| SYST-EUR | LANC 199 | NITRENDIPINE | ENALAPRIL | 3 | 1 | YES | NO | NO | YES | 2 |
| HYVET | NEJM 200 | INDAPAMIDE | PERINDOPRIL | 1 | 3 | NO | YES | NO | NO | 1 |
| VALUE | LANC 200 | AMLODIPINE | HC-THIAZIDE | 1 | 1 | NO | NO | YES | NO | 1 |
| CAPP | LANC 199 | ATEN/METOP | HC/BF-THIAZIDE | 1 | 5 | NO | NO | NO | YES | 1 |
| SCOPE | J HYPER 200 | HC-THIAZIDE | CANDESARTAN | 1 | 1 | NO | NO | NO | YES | 1 |
| NORDIL | LANC 200 | DILTIAZEM | HC/BF-THIAZIDE | 1 | 1 | NO | NO | NO | YES | 1 |



PERINDOPRIL
AMLODIPINE
INDAPAMIDE

Ahsan Haq

European Guidelines - Combination Therapies

VALSARTAN HC-THIAZIDE

PLACEBO

PLACEBO



| | | VERAPAMIL | TRANDOLAPRIL | | | | | | | | |
|------------|--------------|-------------|----------------|----------|-------------|--|--|--|--|--|----|
| IMVEST | JAMA 2002 | | | | | | | | | | 0 |
| IMVEST | JAMA 2002 | | | ATENOLOL | HC-THIAZIDE | | | | | | 0 |
| SCOPE | J HYPER 2002 | HC-THIAZIDE | PLACEBO | | | | | | | | -1 |
| CAPP | LAJIC 1997 | CAPTOPRIL | PLACEBO | | | | | | | | -1 |
| HYVET | NEJM 2002 | PLACEBO | PLACEBO | | | | | | | | -1 |
| NORDIL | LAJIC 2000 | ATEN/METOP | HC/BF-THIAZIDE | | | | | | | | -1 |
| VALUE | LAJIC 2000 | VALSARTAN | HC-THIAZIDE | | | | | | | | -1 |
| ACCOMPLISH | NEJM 2002 | BENAZEPRIL | HC-THIAZIDE | | | | | | | | -2 |
| LIFE | LAJIC 2002 | ATENOLOL | HC-THIAZIDE | | | | | | | | -2 |
| SYST-EUR | LAJIC 1997 | PLACEBO | PLACEBO | | | | | | | | -2 |
| PROGRESS | LAJIC 2001 | PLACEBO | PLACEBO | | | | | | | | -3 |
| ASCOT | LAJIC 2005 | ATENOLOL | BF-THIAZIDE | | | | | | | | -4 |
| ADVANCE | LAJIC 2007 | PLACEBO | PLACEBO | | | | | | | | -4 |
| SYST-CHIN | ARCHIM 2007 | PLACEBO | PLACEBO | | | | | | | | -4 |

Never played e.g.

Valsartan

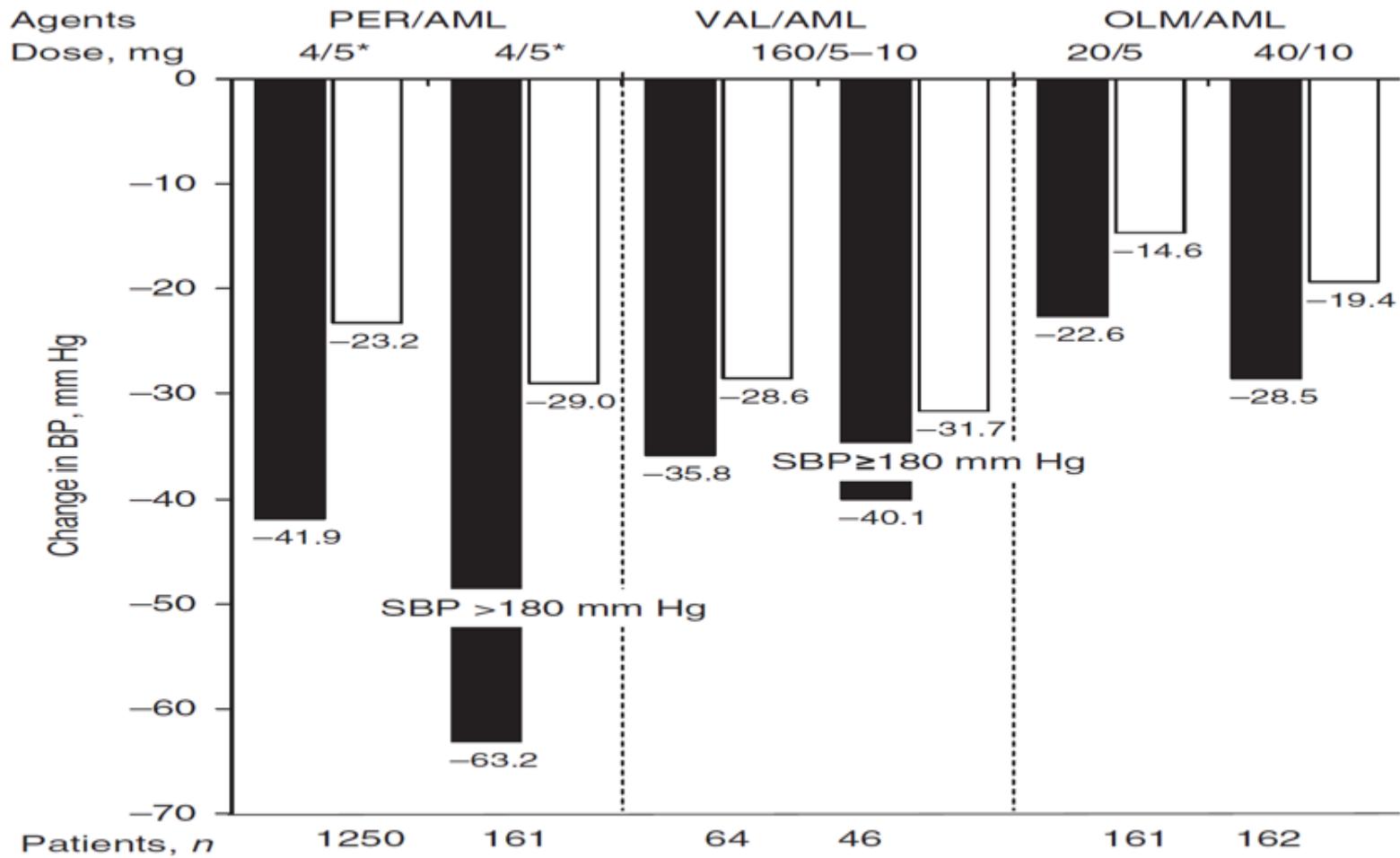
Amlodipine

Alistair Hall



Never played e.g.

Never played e.g.



Ref. Mourad JJ, et al. Current Medical Research & Opinion. 2010;26:2263-2276.

Ahsan Haq

European Guidelines - Combination Therapies

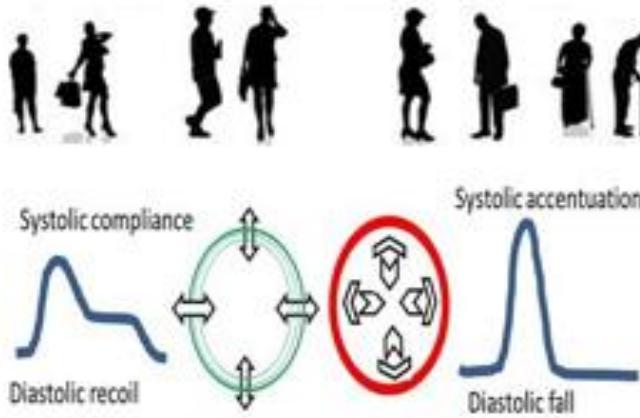
| | Points | Played | G.DIF |
|---|----------------|----------------|----------------|
| PERINDOPRIL (RAMIPRIL) | 10 (4) | 4 (2) | 12 (4) |
| CAPTOPRIL | 4 | 2 | 3 |
| ENALAPRIL | 3 | 1 | 2 |
| BENAZEPRIL | 3 | 1 | 0 |
| TRANDOLAPRIL (LISINOPRIL) | 1 (1) | 1 (1) | 0 (-1) |
| AMLODIPINE | 7 | 3 | 7 |
| NITRENDIPINE | 6 | 2 | 6 |
| DILTIAZEM | 1 | 1 | 1 |
| VERAPAMIL (NICARDIPIINE) | 1 (0) | 1 (0) | 0 (0) |
| THIAZIDE INDAPAMIDE (CHORTHALADONE) | 11 7 (1) | 12 3 (1) | -5 6 (1) |
| (OLMESARTAN) | 4 | 2 | (-1) |
| LOSARTAN | 3 | 1 | 2 |
| (EPROSARTAN) | 3 | 1 | (0) |
| (IREBESARTAN) | 3 | 1 | (0) |
| CANDESARTAN | 1 | 1 | 1 |
| (TELMESARTAN) | 1 | 3 | (0) |
| VALSARTAN | 1 | 1 | -1 |
| (PRORANOLOL) | 3 | 1 | (1) |
| METOPROLOL | 2 | 2 | 0 |
| ATENOLOL | 1 | 3 | -6 |



Ahsan Haq

Drug Combinations Able to Extend Life

COVERSYL P



YES (X3)
YES (X1)
YES (X2)

PERINDOPRIL
AMLODIPINE
INDAPAMIDE

COVERAM

PERINDOPRIL
AMLODIPINE

NATRIXAM

AMLODIPINE
INDAPAMIDE

COVERSYL PLUS

INDAPAMIDE
PERINDOPRIL

*Death
Defeated*



World Health Organization

TRIPLIXAM

PERINDOPRIL
AMLODIPINE
INDAPAMIDE

Whelton PK, et al.
2017 High Blood Pressure Clinical Practice Guideline

Table 6. Categories of BP in Adults*

| BP Category | SBP | | DBP |
|---------------------|---------------|-----|-------------|
| Normal | <120 mm Hg | and | <80 mm Hg |
| Elevated | 120–129 mm Hg | and | <80 mm Hg |
| Hypertension | | | |
| Stage 1 | 130–139 mm Hg | or | 80–89 mm Hg |
| Stage 2 | ≥140 mm Hg | or | ≥90 mm Hg |

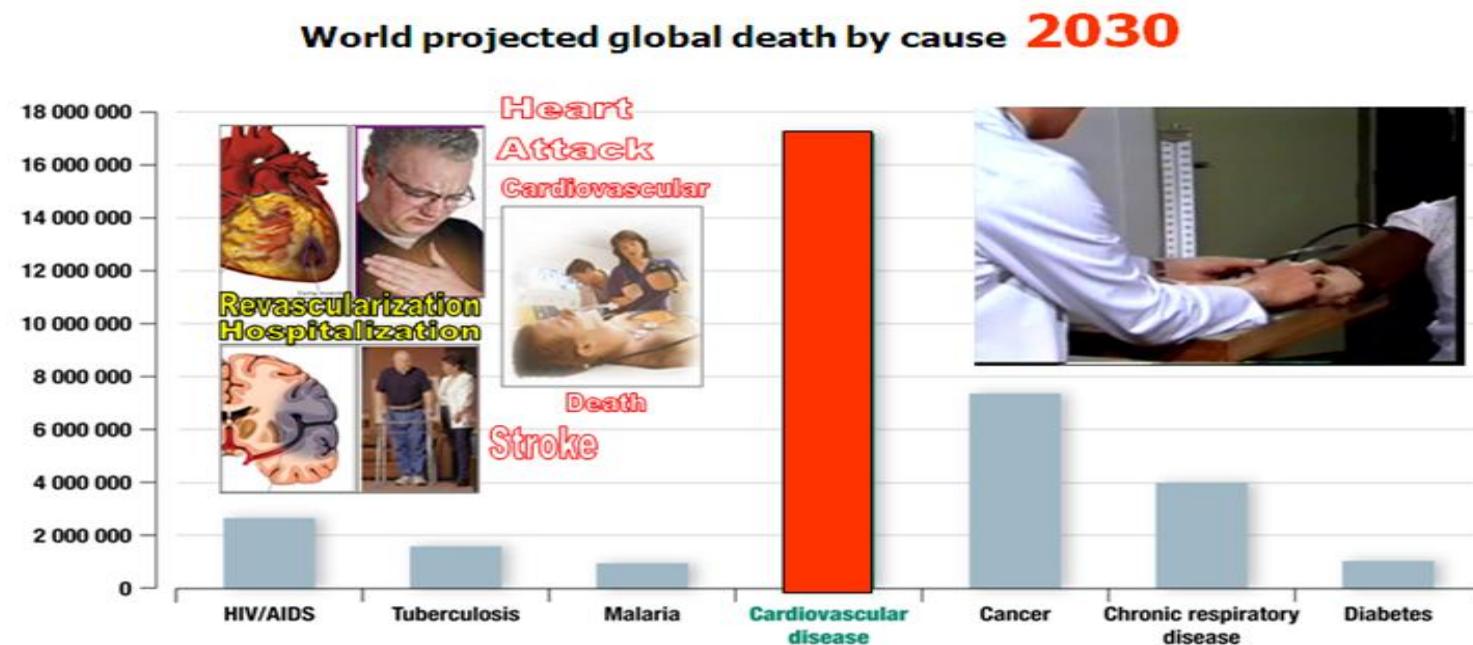
*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.

BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in Section 4); DBP, diastolic blood pressure; and SBP systolic blood pressure.

Austin Hall

Effective Treatment of Hypertension - CARDIOPROTECTION

Logic dictates that practice guidelines should recognize the unique cardiovascular benefits of ACEIs and their preferential use compared with ARBs. Were such advice to be given, the predicted impact on lives saved would be profound.



Alistair Hall