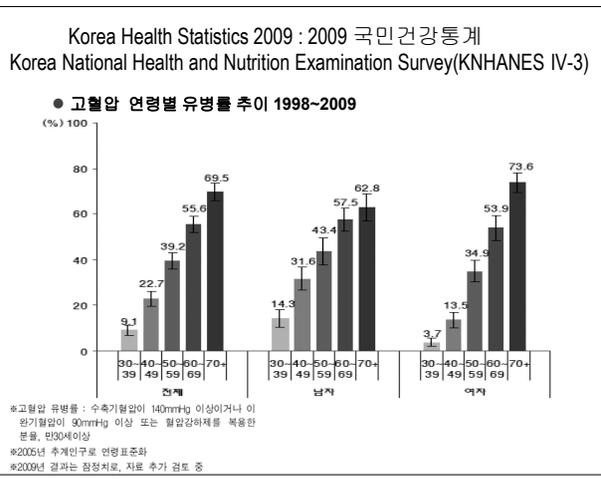
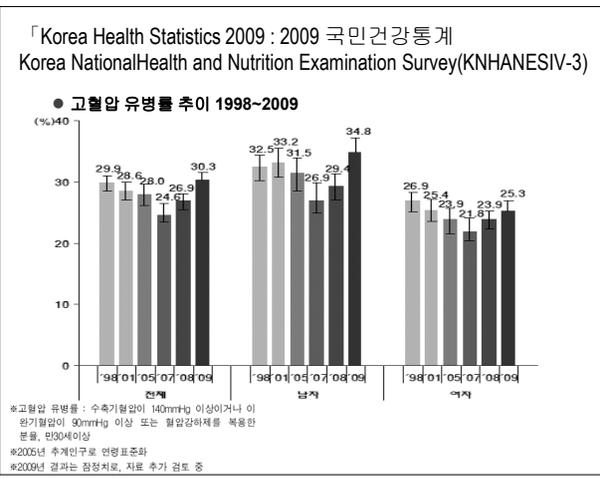


고혈압 치료의 최신 근거

선우성
울산의대 서울아산병원 가정의학과



Blood Pressure Reduction of 2 mmHg Decreases the Risk of Cardiovascular Events by 7-10%

2 mmHg decrease in mean systolic blood pressure

7% reduction in risk of ischaemic heart disease mortality or other vascular causes

10% reduction in risk of stroke mortality

- Meta-analysis of 61 prospective, observational studies
- 1 million adults
- 12.7 million person-years

Lewington et al. Lancet 2002;360:1903-13

Classification of Hypertension(JNC 7, 2003)

	Systolic (mmHg)	&	Diastolic (mmHg)
Normal	<120	&	<80
Prehypertension	120 - 139	or	80 - 89
Stage 1	140 - 159	or	90 - 99
Stage 2	≥160	or	≥100

Pharmacological Treatment (2)

- ◆ Recommended Drugs for specific conditions (Harrison's textbook)
 - Heart Failure
Loop diuretics, BB, ACEI, ARB, Aldo Ant
 - post-Myocardial Infarction
BB, ACEI, CCB
 - High Risk for Ischemic heart disease
BB, CCB
 - Diabetes Mellitus
ACEI, ARB
 - Chronic Renal Disease, proteinuria
ACEI, ARB, Loop diuretics
 - Prevention of Cerebro-vascular Disease
Thiazide, ACEI

Other Evidences for Choosing anti-hypertensive drug

- ◆ ESH/ESC hypertension guideline (intermediate outcome)
 - 1) ARB better than BB in usual therapy, esp. LVH or elderly for stroke prevention
Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359:995-1003.
 - 2) thiazide diuretics is effective in Heart Failure prevention
 - 3) ACEI & ARB is effective in reducing progression of nephropathy in diabetic and non-diabetic nephropathy Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Intern Med* 2001; 135:73-87
 - 4) ARB is more effective than BB for recovering LVH
Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359:995-1003.
 - 5) CCB is more effective than BB or diuretics for reducing progression of carotid atherosclerosis
effects of fosinopril and pravastatin on progression of asymptomatic carotid atherosclerosis in hypertension: results of the Plaque Hypertension Lipid Lowering Italian Study (PHYLLIS) [Abstract]. *J Hypertens* 2003; 21 (suppl 4):S346

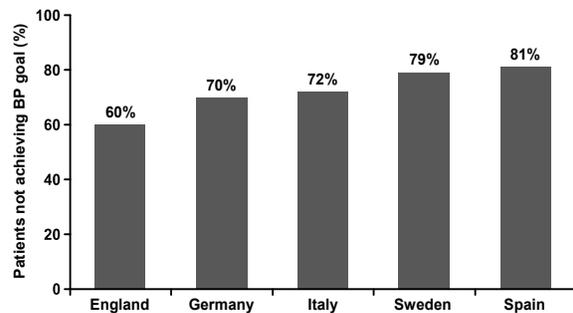
ESH-ESC and JNC 7 Guidelines Recommendations for BP Goals

	JNC 7 ¹	ESH-ESC ²
Type of hypertension	BP goal (mmHg)	BP goal (mmHg)
Uncomplicated	<140/90	130-139/80-85
Complicated		
Diabetes mellitus	<130/80	130-139/80-85
Kidney disease	<130/80	130-139/80-85
Other high risk (stroke, myocardial infarction)	<130/80	130-139/80-85

BP = blood pressure; ESH = European Society of Hypertension; ESC = European Society of Cardiology; JNC = Joint National Committee

¹Chobanian et al. *Hypertension* 2003;42:1206-52
²Mancia et al. *Blood Press* 2009;18:308-47

Approximately 70% of Patients* Who Receive Treatment Do Not Reach BP Goal (<160/95 mmHg)[#]



*Treated for hypertension; [#]BP goal <160/95 mmHg
BP = blood pressure

Wolf-Maier et al. *Hypertension* 2004;43:10-17

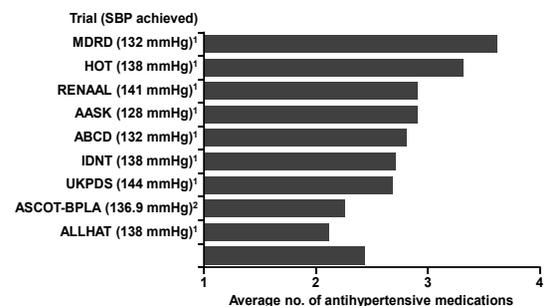
Limitations of Agents with a Single Mechanism of Action (MoA)

- Because hypertension is a multifactorial disease, in most cases at least two antihypertensive agents are needed for patients to achieve BP goal¹
- As an estimate, one-third of patients with hypertension require 2 drugs to achieve BP control* and one-third of patients will require 3 or more antihypertensive agents to achieve BP control²

*Blood pressure (BP) <140/90 mmHg

¹Milani. *Am J Manag Care* 2005;11:S220-7
²Dasing et al. *Vasc Health Risk Manag* 2010;6:321-5

Multiple Antihypertensive Agents are Needed to Reach Blood BP Goal



SBP = systolic blood pressure

¹Bakris, et al. *Am J Med* 2004;116(5A):30S-8; ²Dahlof, et al. *Lancet* 2005;366:895-906

In ASCOT BPLA Study

Up to 8 out of 10 patients need multiple medications to help reach blood pressure treatment goals¹

¹Dahlöf et al. Lancet 2005;366:895-906

Combination therapy is more effective than monotherapy

'The extra blood pressure reduction from combining drugs from 2 different classes is approximately 5 times greater than doubling the dose of 1 drug'

Conclusions from a meta-analysis comparing combination antihypertensive therapy with monotherapy in over 11,000 patients from 42 trials

Wald et al. Am J Med 2009;122:290-300

Multiple-mechanism Therapy: Potential Efficacy Benefits

Multiple-mechanism therapy results in a greater BP reduction than seen with its single-mechanism components

- Components with a different mechanism of action interact on complementary pathways of BP control
- Each component can potentially neutralize counter-regulatory mechanisms, e.g.
 - Diuretics reduce plasma volume, which in turn stimulates the renin-angiotensin-aldosterone system (RAAS) and thus increases BP; addition of a RAAS blocker attenuates this effect

BP = blood pressure

Sica. Drugs 2002;62:443-62

Multiple-mechanism Therapy: Potential Tolerability Benefits

Multiple-mechanism therapy may have an improved tolerability profile compared with its single-mechanism components

- Components of multiple-mechanism therapy can be given at lower dosages to achieve blood pressure goal than those required as monotherapy → therefore better tolerated
- Compound-specific adverse events can be attenuated, e.g.,
 - Renin-angiotensin-aldosterone system blockers may attenuate the oedema that is caused by calcium channel blockers

Sica. Drugs 2002;62:443-62

Current Guidelines Recommend Initiating Combination Therapy Early in Patients with Stage 2 Hypertension or High Cardiovascular Risk

- JNC 7 guidelines state¹:

'When BP is more than 20 mmHg above systolic goal or 10 mmHg above diastolic goal, consideration should be given to initiate therapy with 2 drugs...'

- ESH/ESC guidelines state²:

'The combination of two antihypertensive drugs may offer advantages also for treatment initiation, particularly in patients at high cardiovascular risk in which early BP control may be desirable.'

ESH = European Society of Hypertension
ESC = European Society of Cardiology
JNC = Joint National Committee

¹Chobanian et al. Hypertension 2003;42:1206-52
²Mancia et al. Blood Press 2009;18:308-47

European Guidelines now Recommend use of Single-pill Combination Therapy

- 2009 European guidelines state:

'The combination of two antihypertensive drugs may offer advantages also for treatment initiation, particularly in patients at high cardiovascular risk in which early BP control may be desirable'

'Whenever possible, use of fixed dose (or single pill) combinations should be preferred, because simplification of treatment carries advantages for compliance to treatment'

Mancia et al. Blood Press 2009;18:308-47

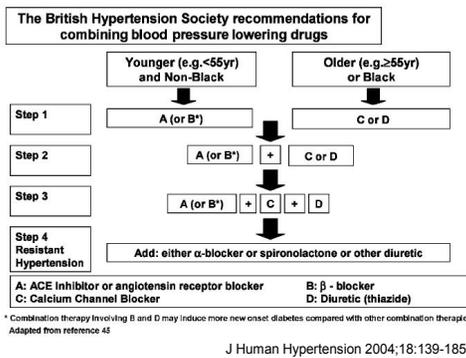
2011 NICE Guideline Updated

- Aim for a target clinic blood pressure below 140/90 mmHg in people aged under 80 years with 35 treated hypertension. [new 2011]
- Aim for a target clinic blood pressure below 150/90 mmHg in people aged 80 years and over, with 37 treated hypertension. [new 2011]
- For step 2 treatment offer a CCB in combination with either an ACE inhibitor or an ARB. [new 2011]
- When using ABPM or HBPM to monitor the response to treatment (for example, in people identified as having a 'white-coat effect' and people who choose to monitor their blood pressure at home), aim for a target average blood pressure during the person's usual waking hours of:
 - ✓ below 135/85 mmHg for people aged under 80 years 42
 - ✓ below 145/85 mmHg for people aged 80 years and over. [new 2011]

2011 NICE Guideline Updated

- 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 once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. [new 2011] [1.6.9] [KPI]

AB/CD algorithm



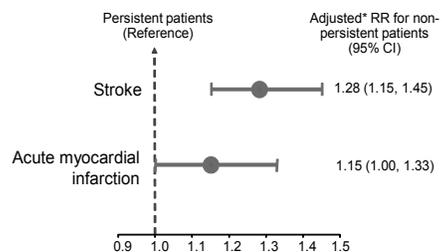
Monotherapy VS combination therapy? [Summary]

- Advantage of Combination therapy
 - Better control of BP and complications
 - Lesser probability of adverse events
 - counterbalance of regulatory mechanism : lower resistance
- Disadvantage
 - Drug abuse
 - Higher cost
 - Lower compliance

Why Single-pill Combinations?

Non-persistence with Antihypertensive Therapy is Associated with an Increased Risk of Myocardial Infarction and Stroke

Data based on 77,193 new users of antihypertensive treatment identified in the PHARMO record linkage system

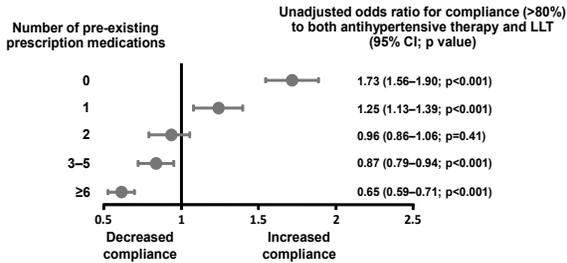


*Adjusted for gender, age, type of prescriber, use of cardiovascular co-medication, initial antihypertensive therapy, number of different antihypertensive classes during the first 2 years of therapy

Breekveldt-Postma, et al. Curr Med Res Opin 2008;24:121-7

Breekveldt-Postma et al. Curr Med Res Opin 2008;24:121-7

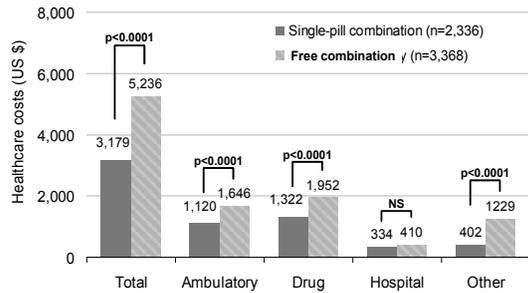
Compliance Decreases as the Number of Medications Increases



Retrospective cohort study of MCO population. N=8,406 patients with hypertension who added antihypertensive therapy and LLT to existing prescription medications within a 90-day period. Compliance to concomitant therapy; sufficient antihypertensive and LLT prescription medications to cover ≥80% of days per 91-day period
CI=confidence interval; LLT = lipid-lowering therapy

Chapman et al. Arch Intern Med 2005;165:1147-52

Patients Treated with Single-pill Combinations Use Less Resource

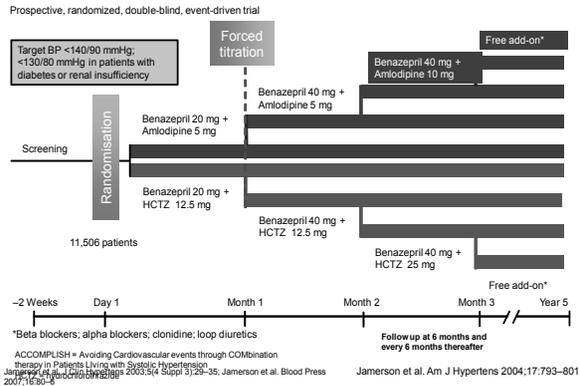


NS = not significant

Dickson, Plauschnat. Am J Cardiovasc Drugs 2008;8:45-50

Which Single-pill Combinations?

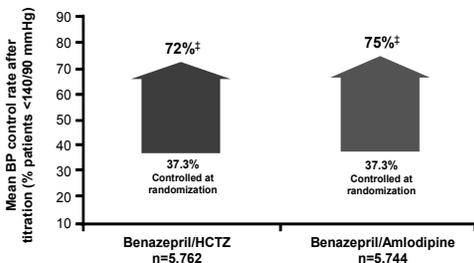
ACCOMPLISH: the First Outcomes Trial to Compare Two Single-pill Combination-based Therapies



*Beta blockers; alpha blockers; clonidine; loop diuretics
ACCOMPLISH = Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension
Jama 2002;287:2583-91
J Hypertens 2004;17:793-801

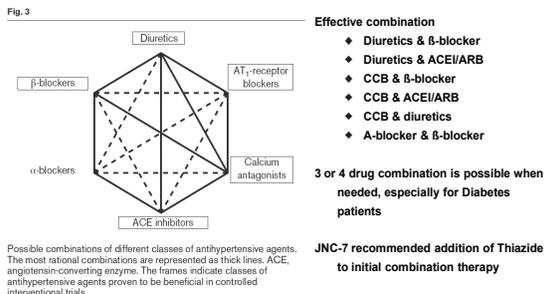
ACCOMPLISH: Impressive Blood Pressure (BP) Control* Rates Achieved with Single-pill Combination-based Therapies

Only ~37% of patients had their BP controlled at baseline despite ~74% of patients receiving ≥2 antihypertensive agents as free combination



*Control defined as BP <140/90 mmHg
[‡]Values calculated from mean BP after titration and mean BP control rate over the duration of the study
ACCOMPLISH = Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension; HCTZ = hydrochlorothiazide
Jamerson et al. N Engl J Med 2008;359:2417-28

2003 ESH,ESC guidelines for combination



Possible combinations of different classes of antihypertensive agents. The most rational combinations are represented as thick lines. ACE, angiotensin-converting enzyme. The frames indicate classes of antihypertensive agents proven to be beneficial in controlled interventional trials.

J hypertension 2003;21:1011-1053

Which Single-pill Combinations?

RAAS Blocker Plus Diuretic?

HCTZ Has Been Widely Studied in Hypertension

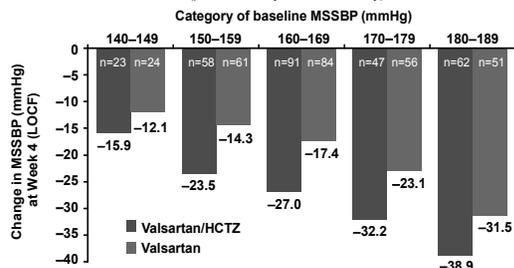
- The ALLHAT Study provided important evidence supporting the use of thiazide diuretics in patients with hypertension²
- HCTZ has been shown to enhance antihypertensive efficacy when combined with valsartan in numerous controlled clinical trials³
 - More than 4,000 patients have been included in the valsartan/HCTZ groups³
 - HCTZ resulted in additive placebo-adjusted decreases in systolic and diastolic blood pressure when combined with valsartan³

ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HCTZ = hydrochlorothiazide; JNC = Joint National Committee

²The ALLHAT investigators. JAMA 2002;288:2981-97
³DIOVAN HCT prescribing information. Novartis July 2008

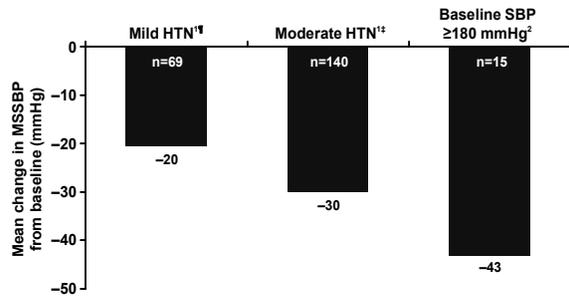
Valsartan-based Therapy* Provides Systolic BP Reductions Across Hypertension Severities

Results from a 6-week, double-blind, multicentre, forced-titration study in patients with DBP ≥ 110 mmHg and < 120 mmHg and SBP ≥ 140 mmHg and < 200 mmHg (post-hoc analysis C-DITT study)



*Valsartan 160 mg force-titrated to 320 mg at Week 2 and valsartan/HCTZ 160/12.5 mg force-titrated to 160/25 mg and 320/25 mg at Weeks 2 and 4, respectively. BP = blood pressure; DBP = diastolic BP; SBP = systolic BP; MSSBP = mean sitting SBP; LOCF = last observation carried forward; C-DITT = Co-Valsartan Initial Therapy Trial
Calhoun et al. Curr Med Opin Res 2008;24:2303-11

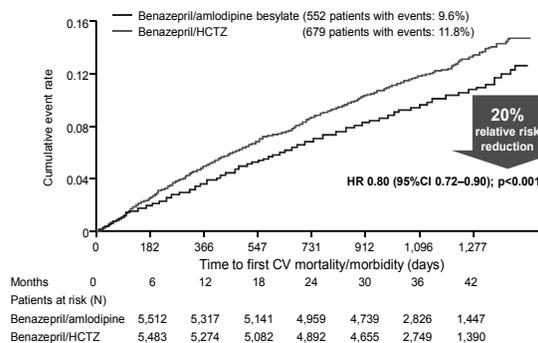
Amlodipine/Valsartan Provides Powerful BP Reductions Across Hypertension (HTN) Severities*



¹DBP 90-99 mmHg, SBP 140-159 mmHg
²DBP ≥ 100 mmHg, SBP ≥ 160 mmHg
BP = blood pressure; DBP = diastolic BP; SBP = systolic BP; MSSBP = mean sitting SBP
Poldermans et al. Clin Ther 2007;29:279-89 (Dose 5-10/160 mg)

¹Smith et al. J Clin Hypertens 2007;9:355-64 (Dose 10/160 mg)
²Poldermans et al. Clin Ther 2007;29:279-89 (Dose 5-10/160 mg)

ACCOMPLISH: Superior CV Outcomes with RAAS Blocker/Amlodipine Versus RAAS Blocker/HCTZ Single-pill Combination-based Regimens



ACCOMPLISH = Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension; CV = cardiovascular; RAAS = renin-angiotensin-aldosterone system; HCTZ = hydrochlorothiazide
Jamerson et al. N Engl J Med 2008;359:2417-28

결과 요약

- 혈압강화제의 선택은 반드시 개별화[individualize] 되어야 한다.
- 고혈압 이외의 동반 질환과 다른 적응증, 금기증 등을 고려하여 가장 적합한 혈압강화제를 선택한다.
- 목표 혈압 수치에 도달하기 위해서는 많은 환자에서 병합요법이 필요하다.
- Renin-angiotensin-aldosterone system blockers 가 병합요법의 근간이 된다.
- ARB/HCTZ와 ARB/CCB 는 매우 효과적이고 안전한 병합요법이다.
- 병합요법 시에는 단일제형요법이 순응도가 더 높고 경제적이다.

¹Dahlöf et al. Lancet 2005;366:895-906; ²Mancia et al. Blood Press 2009;18:308-47
³Yamnatopoulou et al. Eur J Cardiovasc Prev Rehabil 2005;12:243-9; ⁴Spokor et al. Med Care 2005;43:521-30
⁵Calhoun et al. Curr Med Res Opin 2008;24:2303-11; ⁶Smith et al. J Clin Hypertens 2007;9:355-64
⁷Poldermans et al. Clin Ther 2007;29:279-89; ⁸The ALLHAT Investigators. JAMA 2002;288:2981-97
⁹Julius et al. Lancet 2004;363:2022-31;