# ARB in treatment of hypertension and Fimasartan, a new ARB

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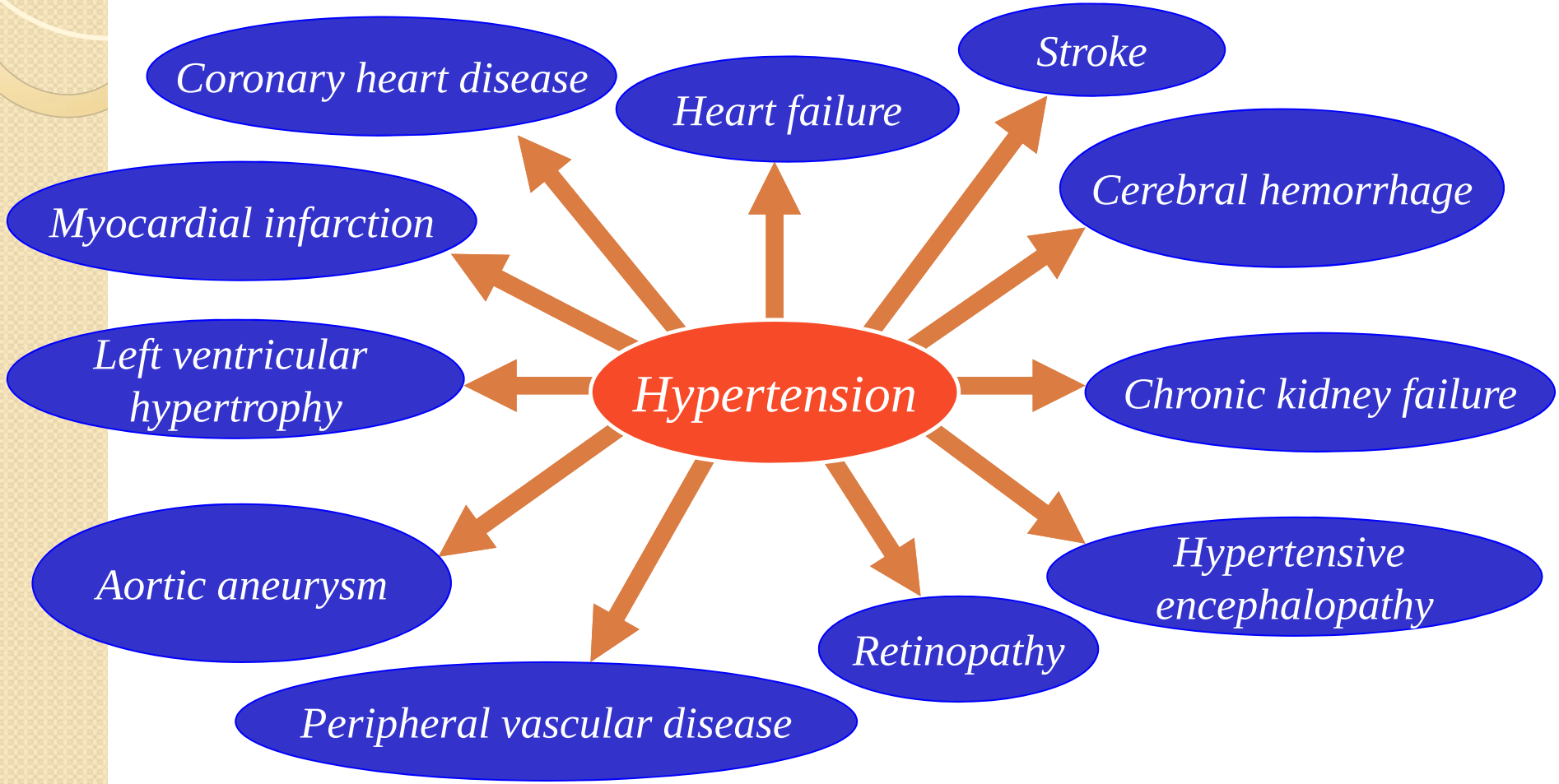
# History

- Hypertension-related morbidity and mortality over the past 45 years with antihypertensive therapy:

  70% for stroke and 55% for coronary heart disease have been decreased.

# Diseases Attributable to Hypertension

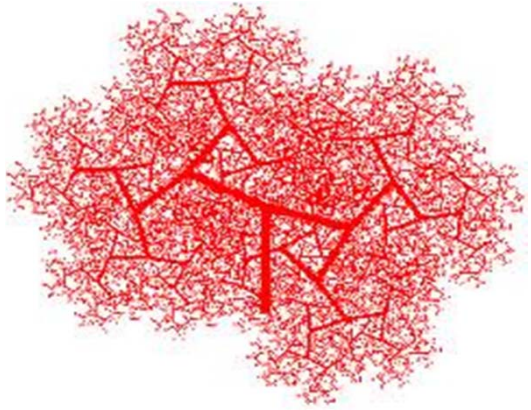


# TOD of Heart

- LV hypertrophy
- Impaired LV diastolic function
- Impaired LV systolic function
- Coronary microvascular disease
- Coronary atherosclerotic disease
- Heart Failure
- Sudden Cardiac Death
- Atrial Fibrillation
- Ventricular Arrhythmia

# TOD of Blood vessels

- Reduced arterial distensibility
- Aortic dilatation
- Aortic aneurysm
- Perpheral artery aneurysm
- Aortic aissection
- Perpheral artery disease

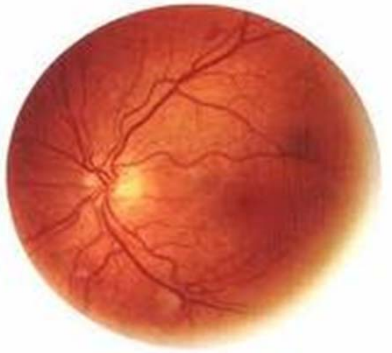


# TOD of Brain

- Hypertensive encephalopathy
- Lacune infarction
- Intracerebral hemorrhage
- Intraparenchymal hemorrhage
- Subarachinoid hemorrhage
- Transient ischemic attack
- Stroke

# TOD of Eye

- Arteriolar narrowing
- Arteriovenous nicking
- Retinal microaneurysm
- Exudate and cotton-wool spots
- Hemorrhages
- Optic neuropathy



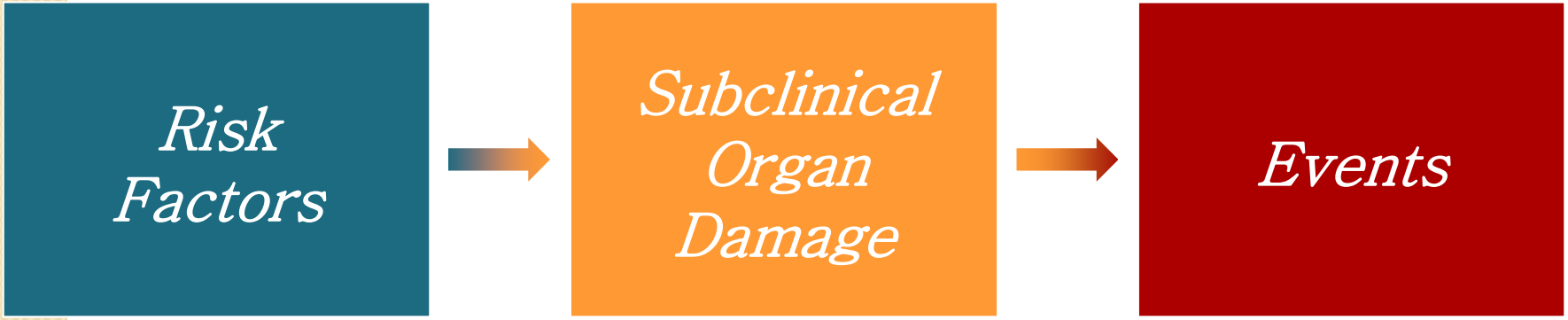
# TOD of Kidney

- Nephropathy
- Nephrosclerosis
- Microalbuminuria
- Proteinuria
- Renal failure

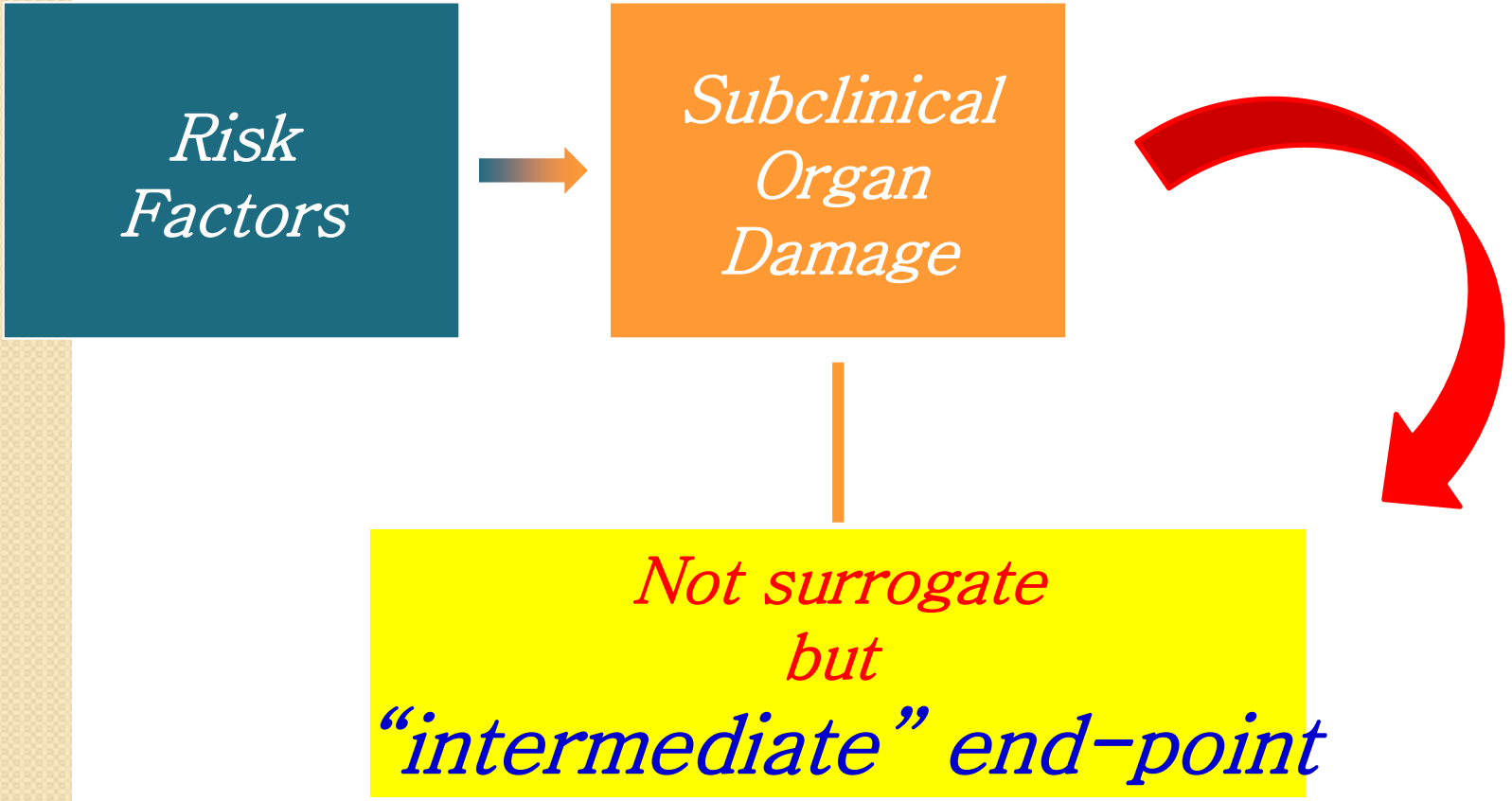
# Mechanisms of TOD

- **Hemodynamic factors**
- **Non-hemodynamic factors**
  - **Hormonal or humoral factors**
  - **Vascular or growth factors**
  - **Gender, race, age**
  - **Comorbidities: obesity, DM, hyperlipidemia**
  - **Pharmacological therapy**

# Course of TOD



# Course of SOD



# Assessment

| Target organ | Type of damage | Technique | Marker of risk |
|---|---|---|---|
| Heart | Left ventricular hypertrophy* | Electrocardiogram* | Sokoloff – Lyon index*<br>Cornell product*<br>S, PW, LVMI * |
| | Diastolic dysfunction | Echocardiography* | E/A ratio |
| Kidney | Renal function alteration* | Blood sample*<br>24-h urine collection* | Plasma creatinine*<br>Creatinine clearance* |
| | Increased renal and systemic vascular permeability | Urine sample* | Microalbuminuria* |
| Brain | Silent brain damage | Magnetic resonance imaging | Silent brain infarcts<br>Advanced deep white matter lesions<br>Microbleeds |
| Vasculature | Microvessels* | Ophthalmoscopy* | Stage III-IV (Keith – Wagener)* |
| | Diffuse atherosclerosis* | Carotid echo-Doppler* | Atheroma plaques*<br>Intima-media thickness* |
| | Increased vascular stiffness | Applanation tonometry | Pulse wave velocity<br>Augmentation index |
| | | | Stroke volume:pulse pressure ratio<br>Ankle: arm index |
| | Endothelial dysfunction | Flow-mediated vasodilation | |
| | | Blood sample | E-selectin, VCAM-1, ICAM-1… |

# Recent guidelines

European Heart Journal (2007) **28**, 1462–1536
doi:10.1093/eurheartj/ehm236

ESC and ESH Guidelines

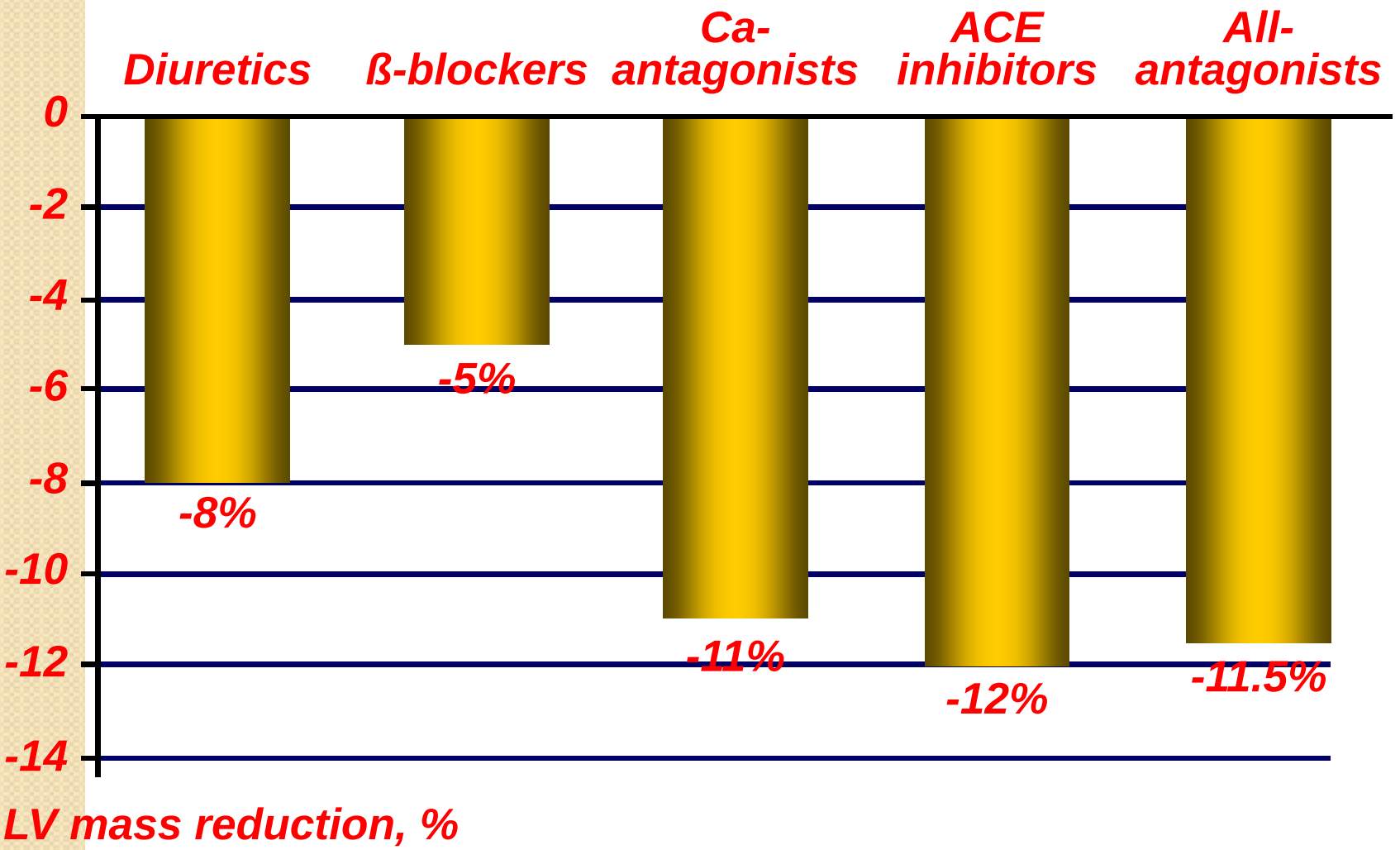
**Table 3 High/Very high risk subjects**

- BP ≥ 180 mmHg systolic and/or ≥110 mmHg diastolic
- Systolic BP > 160 mmHg with low diastolic BP (<70 mmHg)
- Diabetes mellitus
- Metabolic syndrome
- ≥3 cardiovascular risk factors
- One or more of the following subclinical organ damages:
  - Electrocardiographic (particularly with strain) or echocardiographic (particularly concentric) left ventricular hypertrophy
  - Ultrasound evidence of carotid artery wall thickening or plaque
  - Increased arterial stiffness
  - Moderate increase in serum creatinine
  - Reduced estimated glomerular filtration rate or creatinine clearance
  - Microalbuminuria or proteinuria
- Established cardiovascular or renal disease

# TOD, reversible?

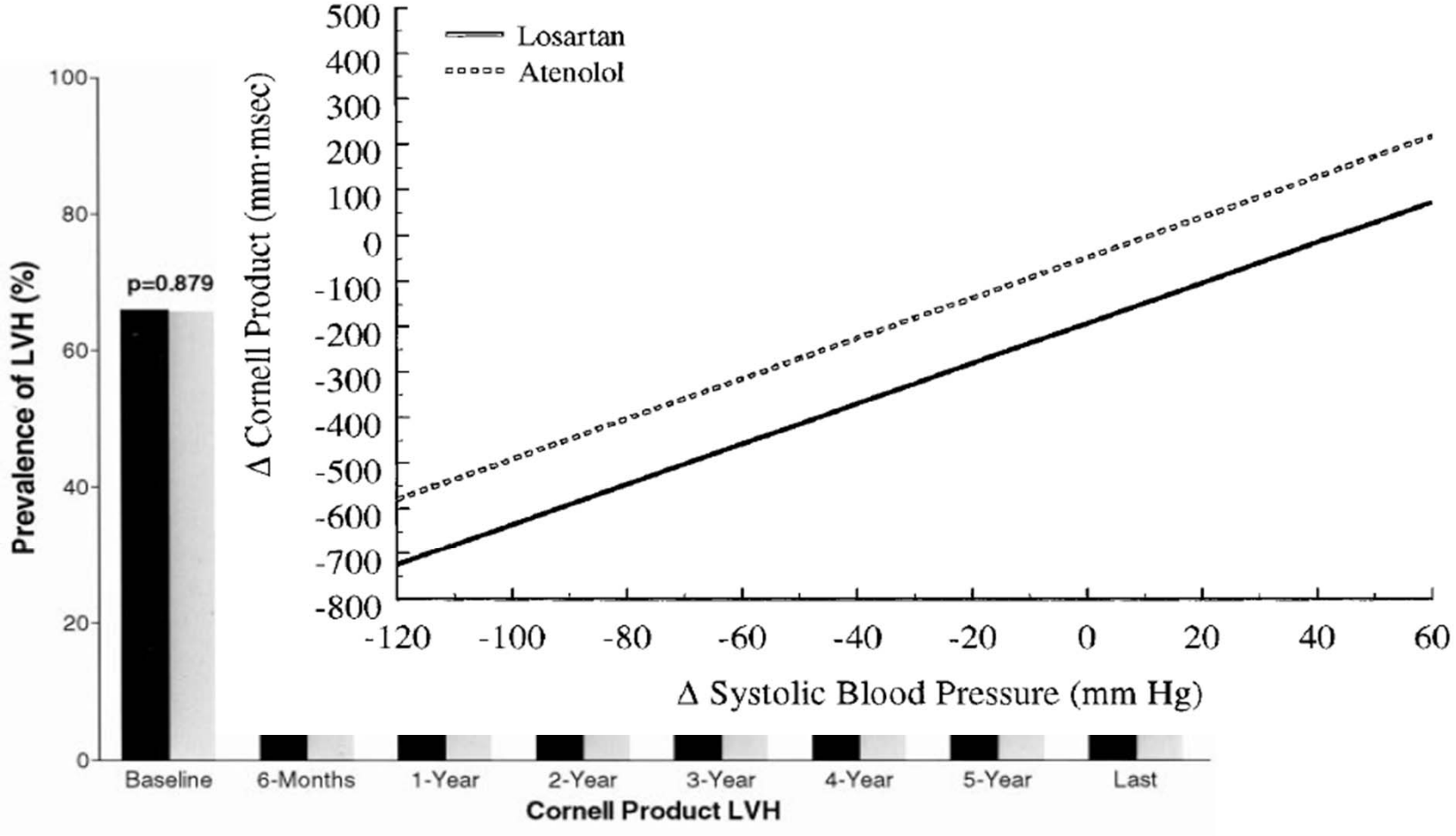
**Yes ! It is!**

## Meta-analysis of randomized, controlled trials of LV hypertrophy regression in essential hypertension




Schmieder RE et al 2001

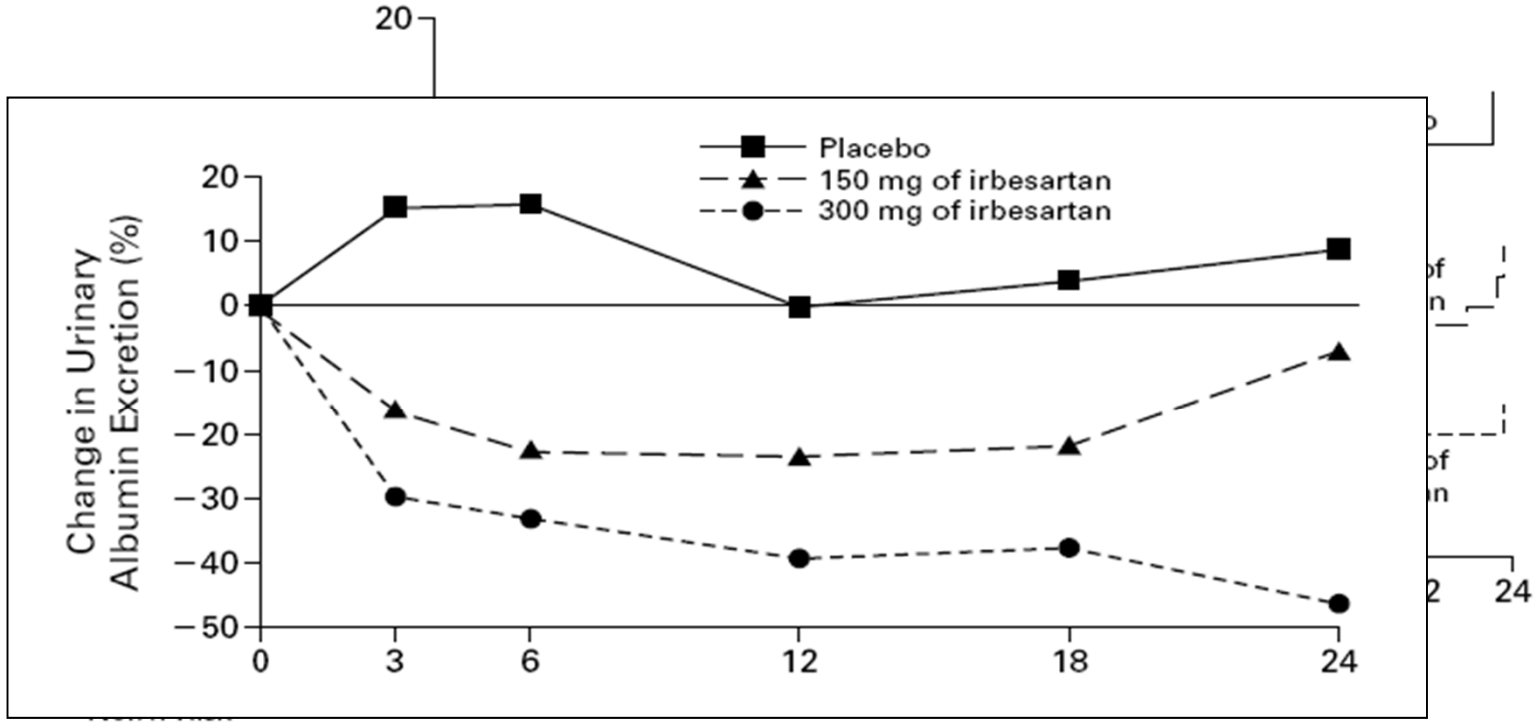
# Reversal of Cardiac TOD




*LIFE substudy*

*Nishikimi T et al. Hypertension 1996;93:1946*

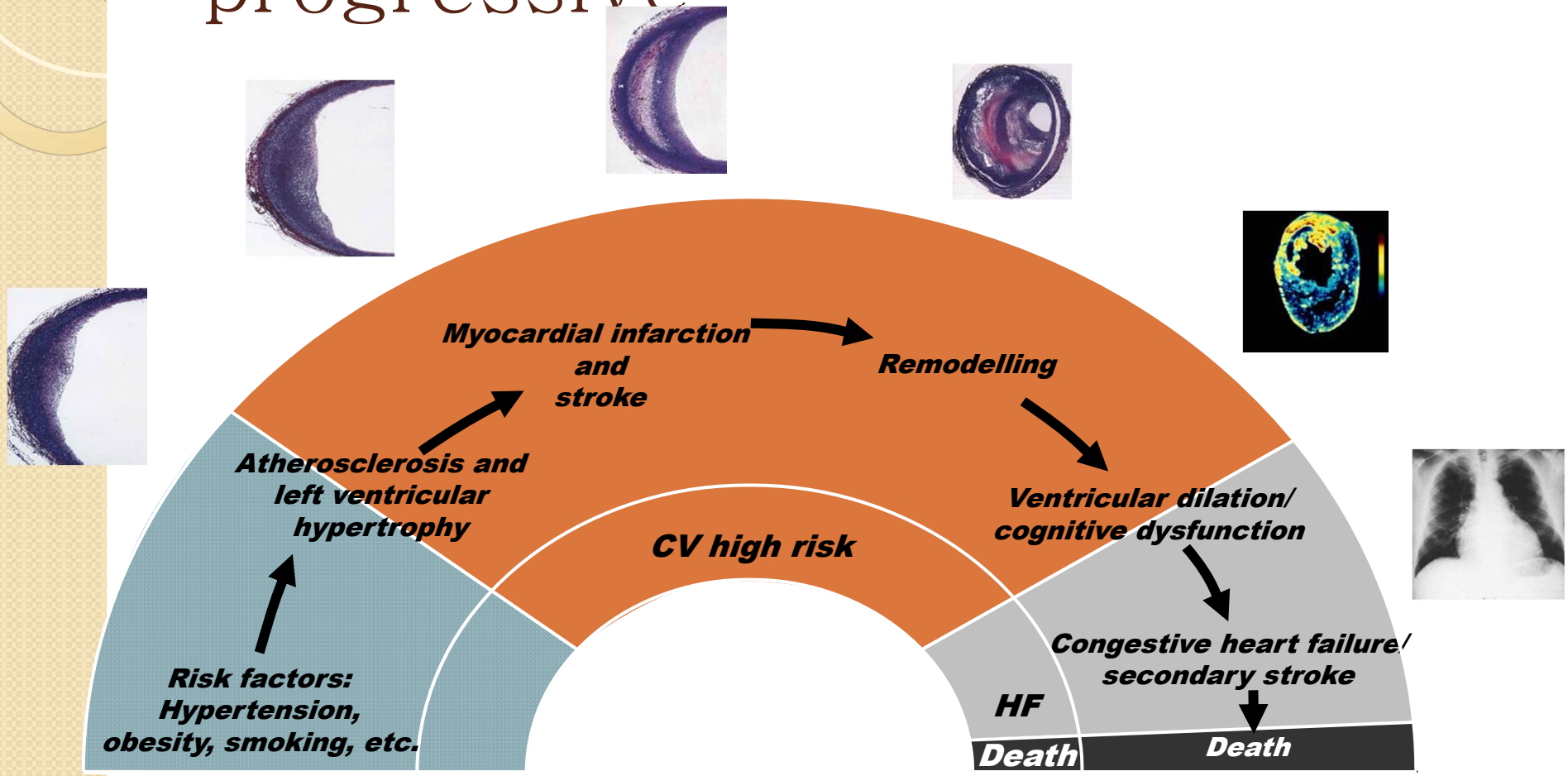
# Reversal of Renal TOD




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo | 201 | 201 | 164 | 154 | 139 | 129 | 36 |
| 150 mg of irbesartan | 195 | 195 | 167 | 161 | 148 | 142 | 45 |
| 300 mg of irbesartan | 194 | 194 | 180 | 172 | 159 | 150 | 49 |

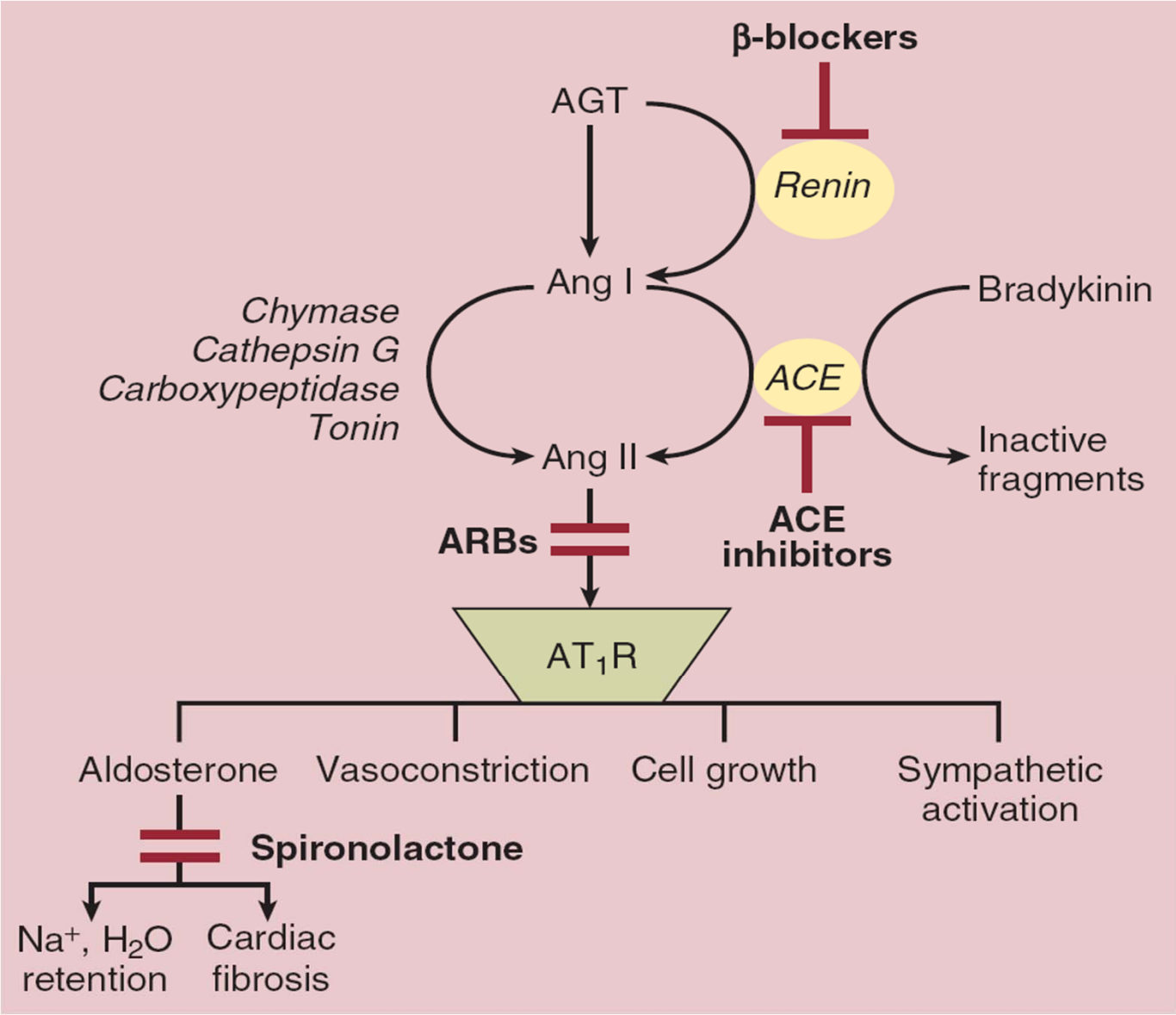
*Parving HH, Lehnert H. NEJM 2001;345:870*

# Cardiovascular disease is progressive

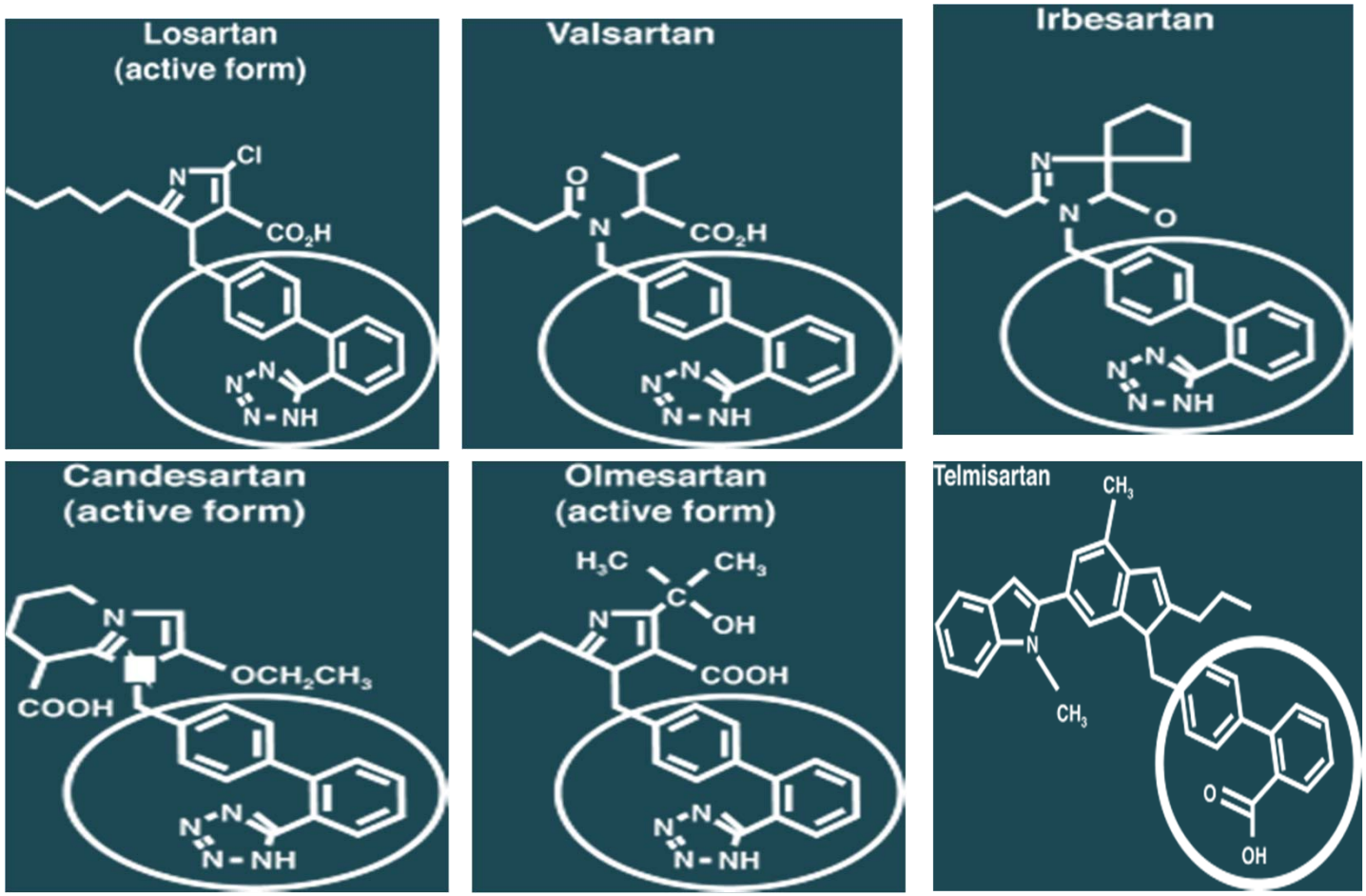



*Adapted from*
*Dzau VJ, et al. Circulation 2006;114:2850–2870; Figure adapted from Dzau V, Braunwald E. Am Heart J 1991;121:1244–1263; Yusuf S, et al. Lancet 2004;364:937–952*
*Image reproduced with kind permission of Professor Böhm*

# Antihypertensives in RAAS

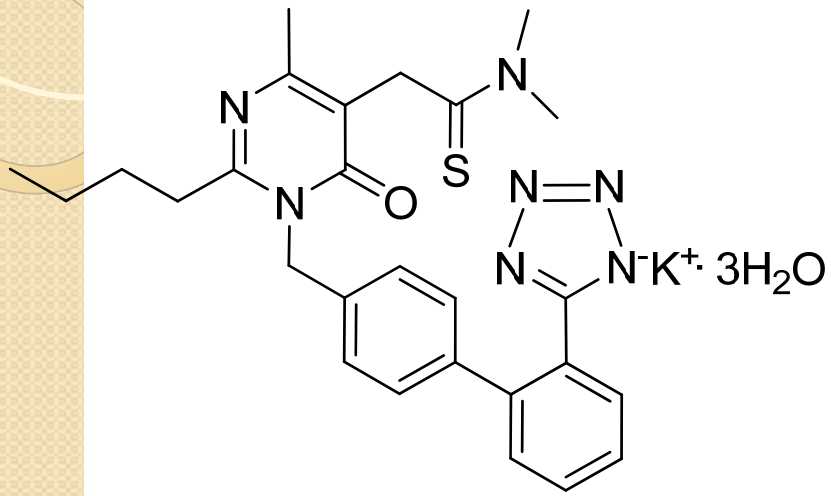


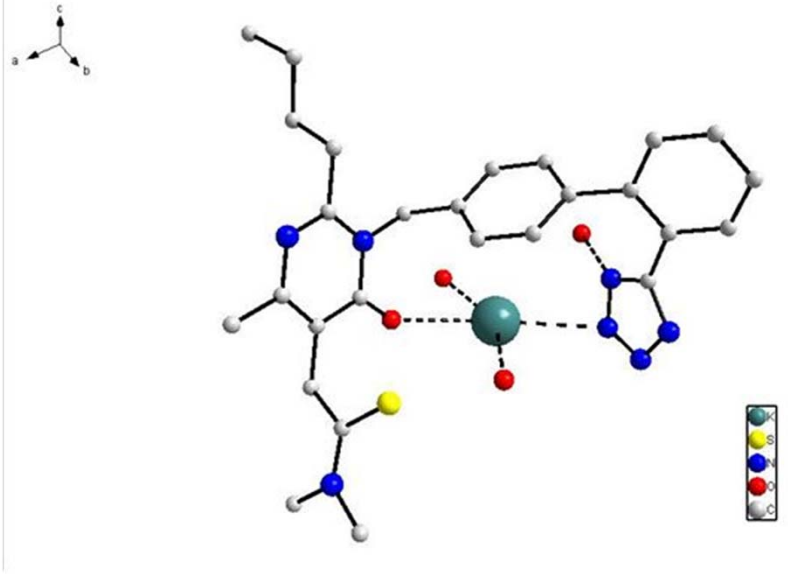
# Structures




*Ries et al. J Med Chem 1993;36:4040–4051*

# Fimasartan: Structure



- **Molecule**
  - Fimasartan potassium trihydrate: $C_{27}H_{30}N_7OS{\cdot}K{\cdot}3H_2O$: 593.79

- **Chemical Name**
  - 2-n-Butyl-5-dimethylaminothiocarbonylmethyl-6-methyl-3{[2′-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}pyrimidin-4(3H)-one potassium trihydrate

- **INN**
  - Fimasartan
  - Fimasartan potassium trihydrate

- **CAS** 247257-48-3

- **BR-A-657**

- **Regislation Number**:
  - Material Patency: KR10-0354654-0000 (2002. 09. 16)
  - Product Patency: KR10-0617953-0000 (2006. 08. 23)

# Physicochemical characteristics

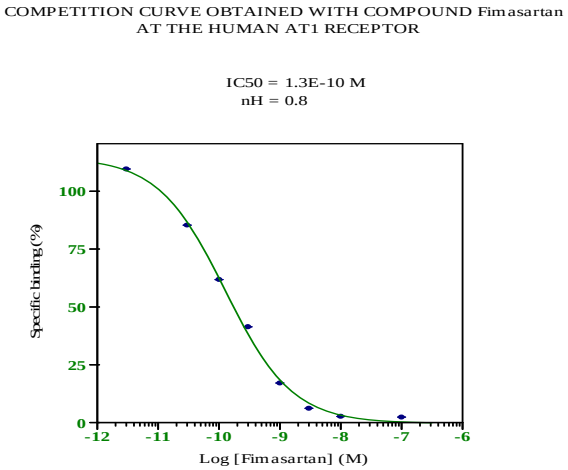
- White – yellowish crystal powder
- Melting point : 262~268°C
- Melt well in methalol, melt in ethanol, hard to melt in water, and not melt in isopropyl alcohol and ether.
- pH= 6.0~8.0 (50mg/10mL of water)
- No absorption of water
  (at 40±2°C/ 75±5% of humidity, or at room temperature wit t88±5% of humidity for 1 week-exposure)
- Pseudo-polymorphism : typeI(trihydrate), typeII (monohydrate)

# 1. Pharmacological test- *in-vitro*

## *In-vitro* Receptor Binding Assay

| Concentration(M) | % Inhibition of Control specific Binding |
|---|---|
| 3.0E-12 | 109.6 |
| 3.0E-11 | 85.3 |
| 1.0E-10 | 61.8 |
| 3.0E-10 | 41.4 |
| 1.0E-09 | 17.1 |
| 3.0E-09 | 6.2 |
| 1.0E-08 | 2.7 |
| 1.0E-07 | 2.4 |

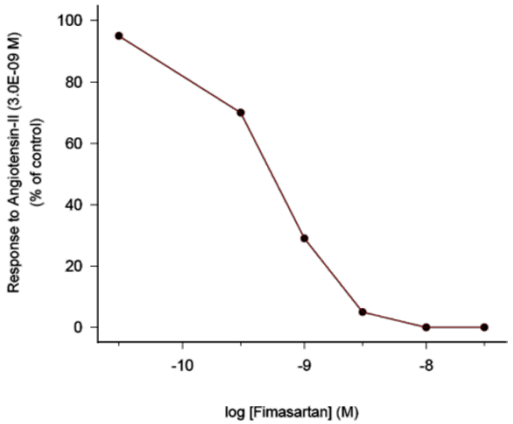
$IC_{50}$ = 1.3E-10M




## Effect on rabbit aorta of BR-A-657

| Compounds | Concentration | % Control response to Ang.-II |
|---|---|---|
| Ang. II | 3.0E-09M | 100 |
| BR-A-657 | 3.0E-11M | 95 |
| | 3.0E-10M | 70 |
| | 1.0E-09M | 29 |
| | 3.0E-09M | 5 |
| | 1.0E-08M | 0 |
| | 3.0E-08M | 0 |

$IC_{50}$ = 4.2E-10M

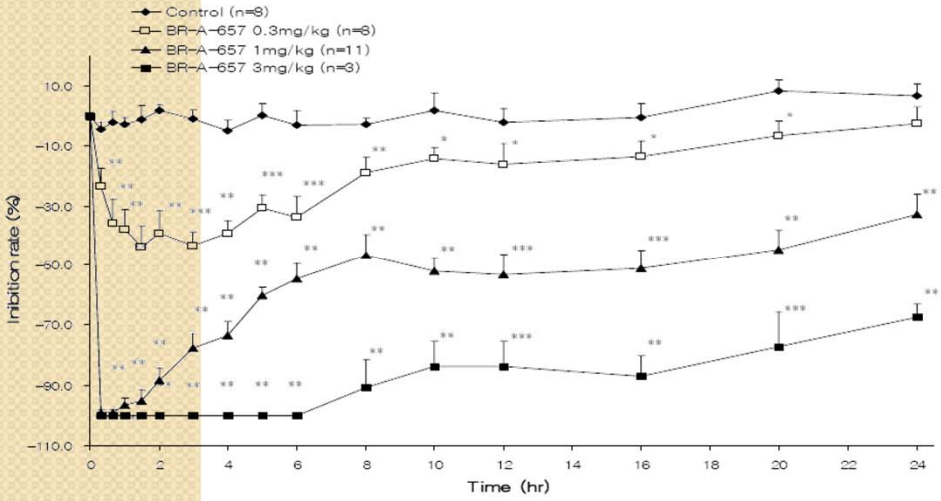


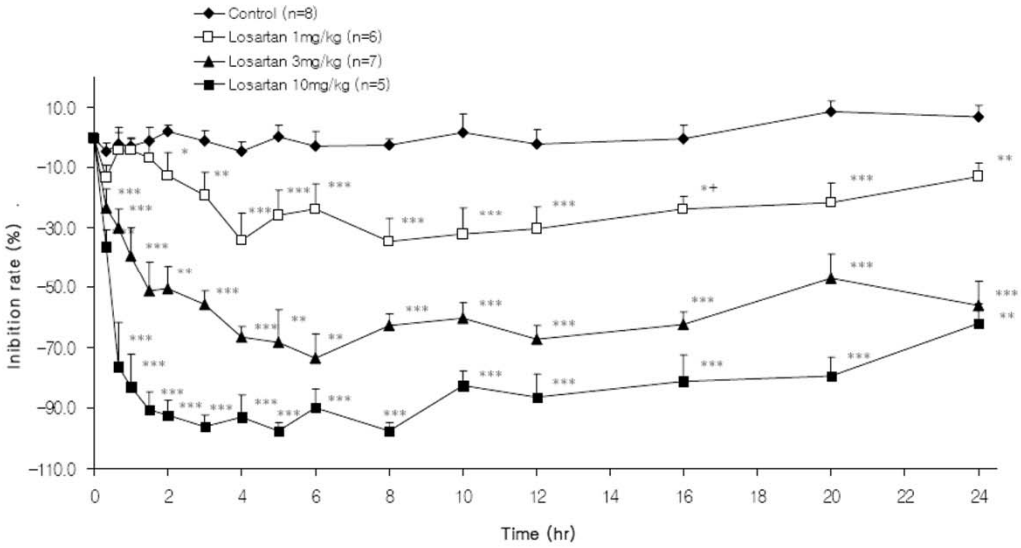
# 1. Pharmacological test- *efficacy test*

**Single dose effect on rat**

**BR-A-657(0.3, 1, 3mg/kg) and Losartan (1, 3, 10mg/kg ) on hypertensive rats after IV Ang II**

| | 투여군(mg/kg) | 0.3 | 1 | 3 |
|---|---|---|---|---|
| BR-A-657 | 최대 강하 시간(min) | 90 | 20 | 20 |
| | 혈압강하효과(%) | 43 | 98 | 100 |
| | 투여군(mg/kg) | 1 | 3 | 10 |
| Losartan | 최대 강하 시간(min) | 480 | 360 | 300 |
| | 혈압강하효과(%) | 34 | 73 | 97 |

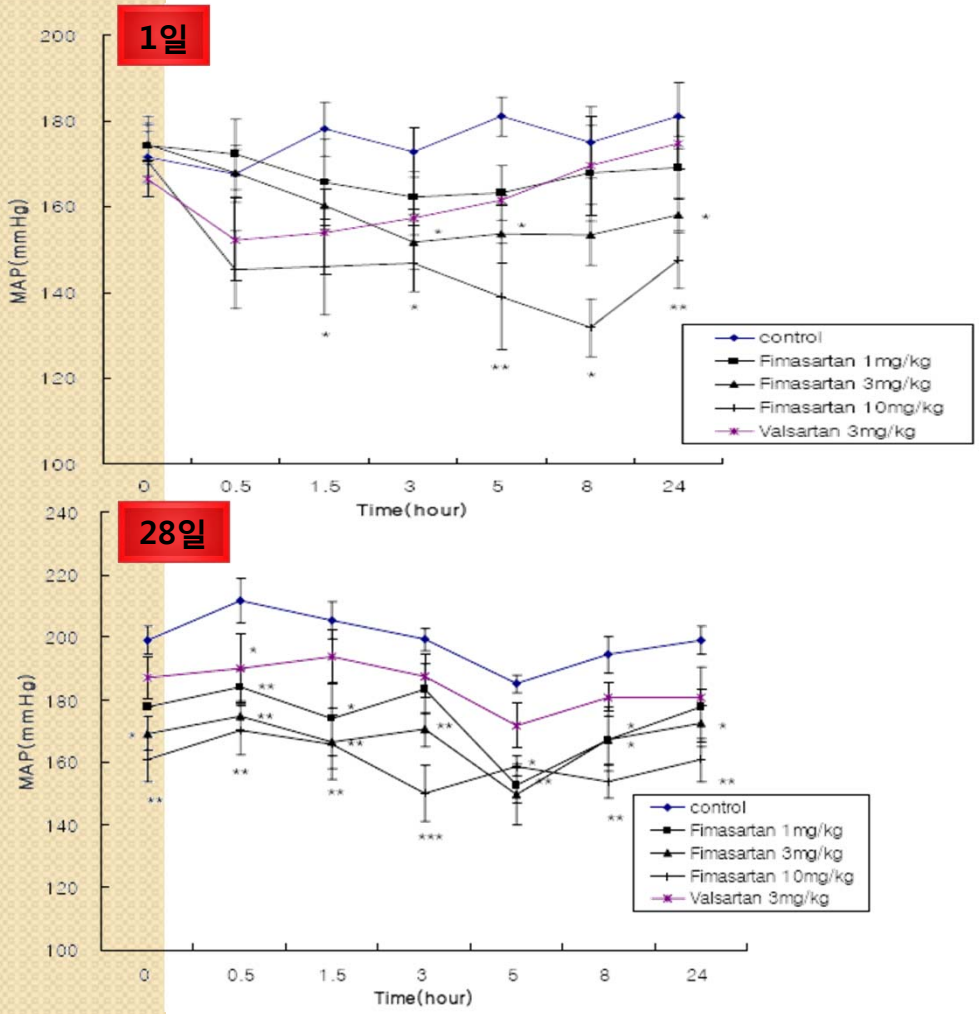


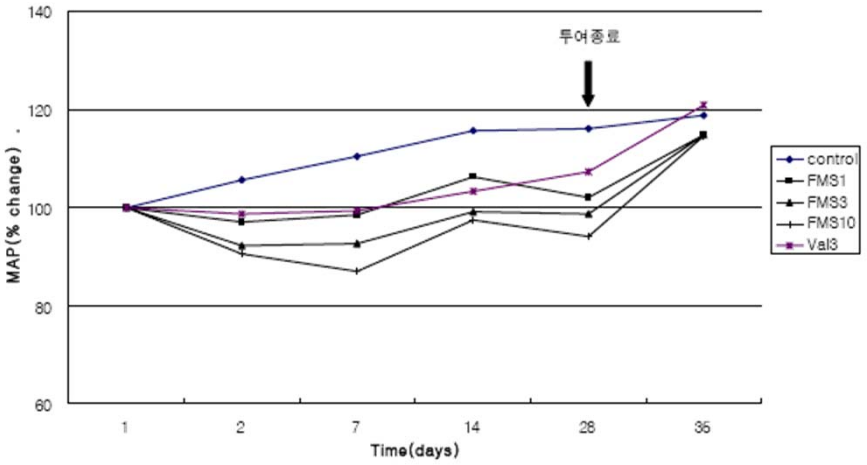
# 1. 약리시험- 1차 효력시험

**본태성고혈압랫드(SHR) 모델을 이용한 BR-A-657의 반복 경구 투여에 의한 효력 시험 (4-07)**

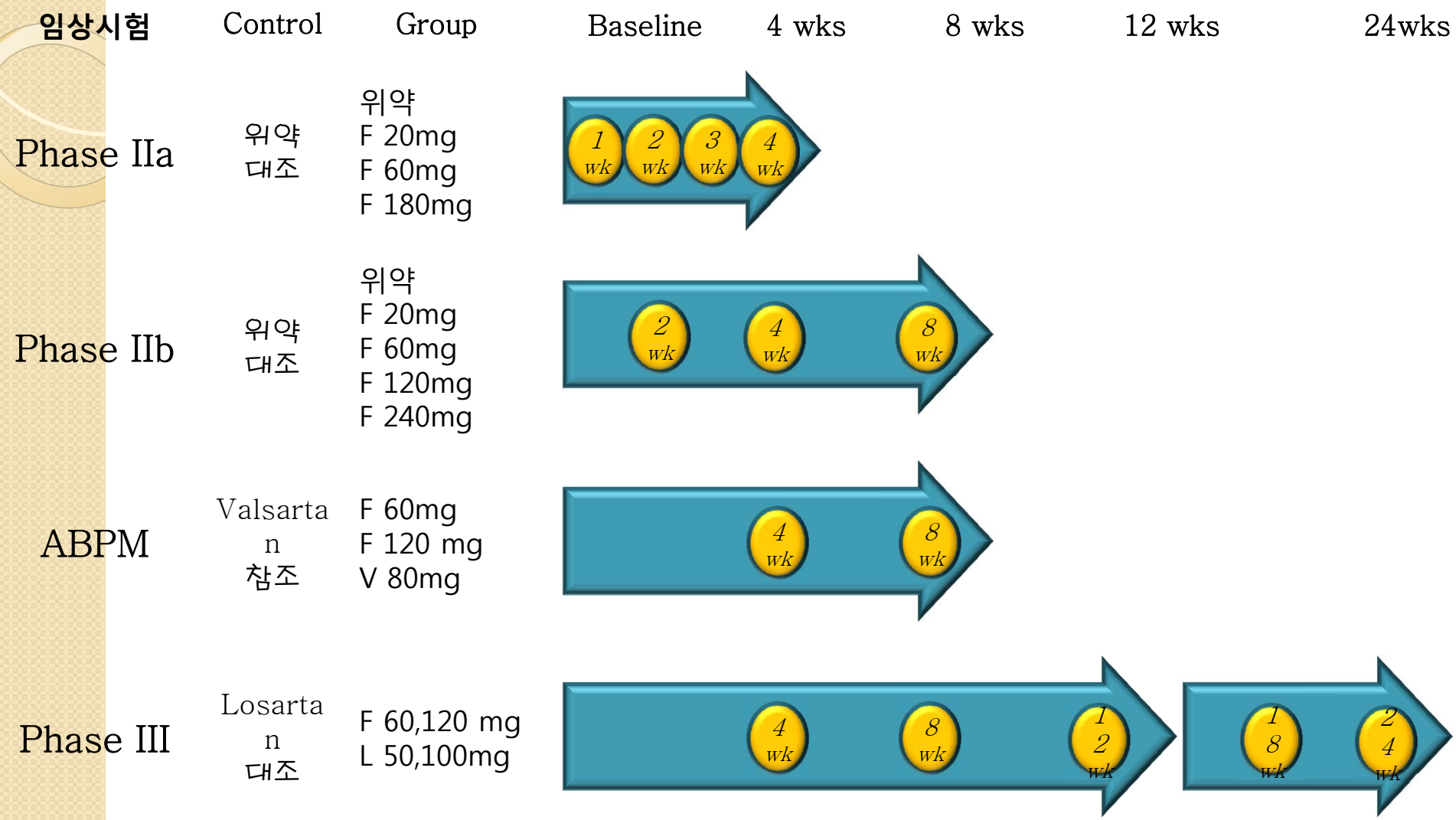
**SHR 모델에서 BR-A-657 (1, 3, 10 mg/kg, n=6~8)과 Valsartan (3 mg/kg, n=7)을 28일 반복 경구 투여 하여 24시간 평균혈압의 변화율(MAP, %) 관찰.**




| | 투여군(mg/kg) | 1 | 3 | 10 |
|---|---|---|---|---|
| BR-A-657 (1일) | 최대 강하 시간(hr) | 5 | 2.4 | 8 |
| | 혈압강하효력 (mmHg) | 18 | 23 | 43 |
| BR-A-657 (28일) | 최대 강하 시간(hr) | 5 | 1.5 | 3 |
| | 혈압강하효력 (mmHg) | 32 | 24 | 49 |
| Valsartan (1일) | 최대 강하 시간(hr) | | 1.5 | |
| | 혈압강하효력 (mmHg) | | 39 | |
| Valsartan (28일) | 최대 강하 시간(hr) | | 0.5 | |
| | 혈압강하효력 (mmHg) | | 22 | |



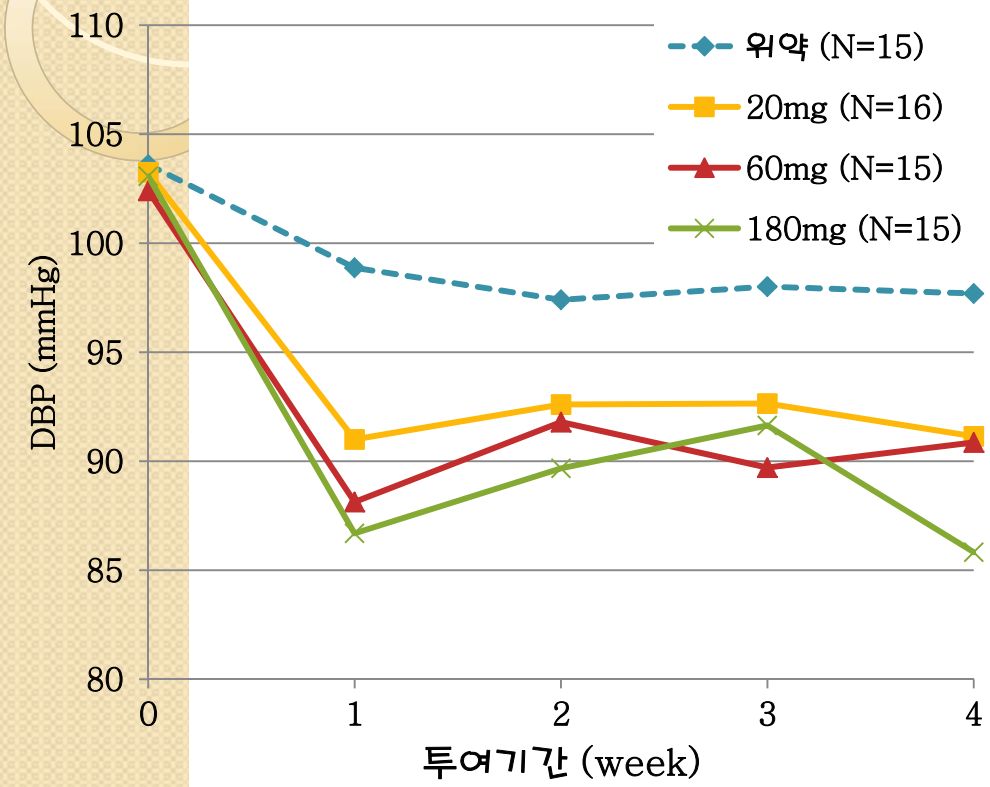
# Phase II-III studies

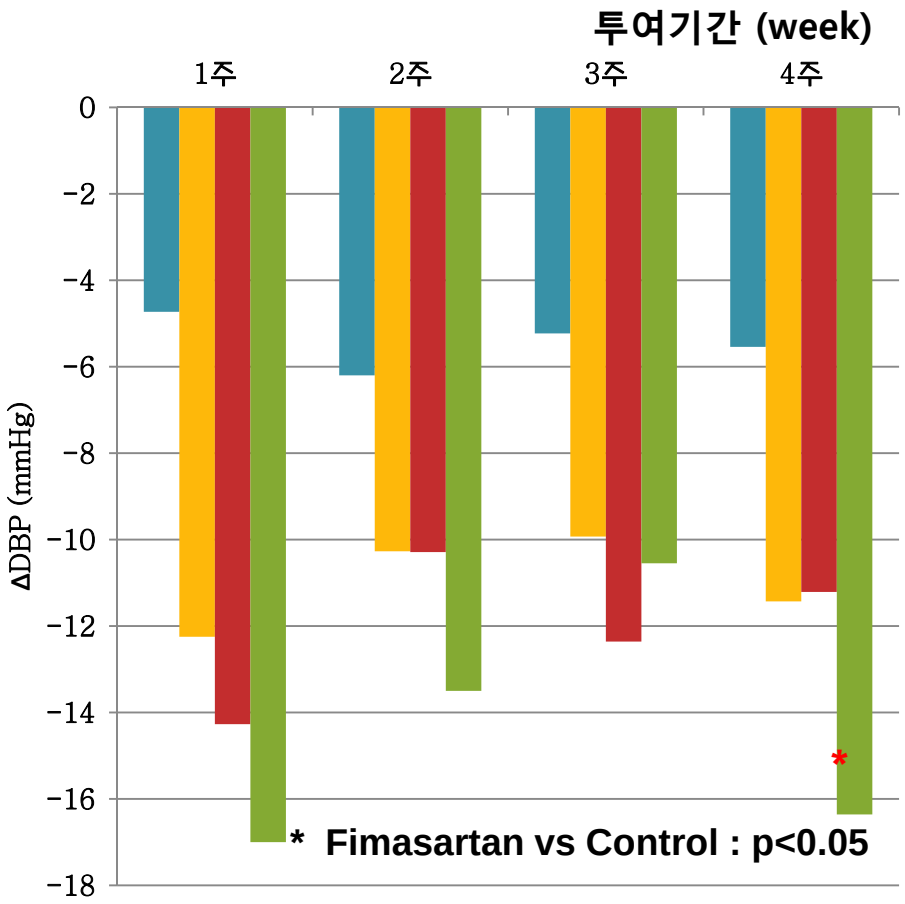



***Scheduled Visit,***

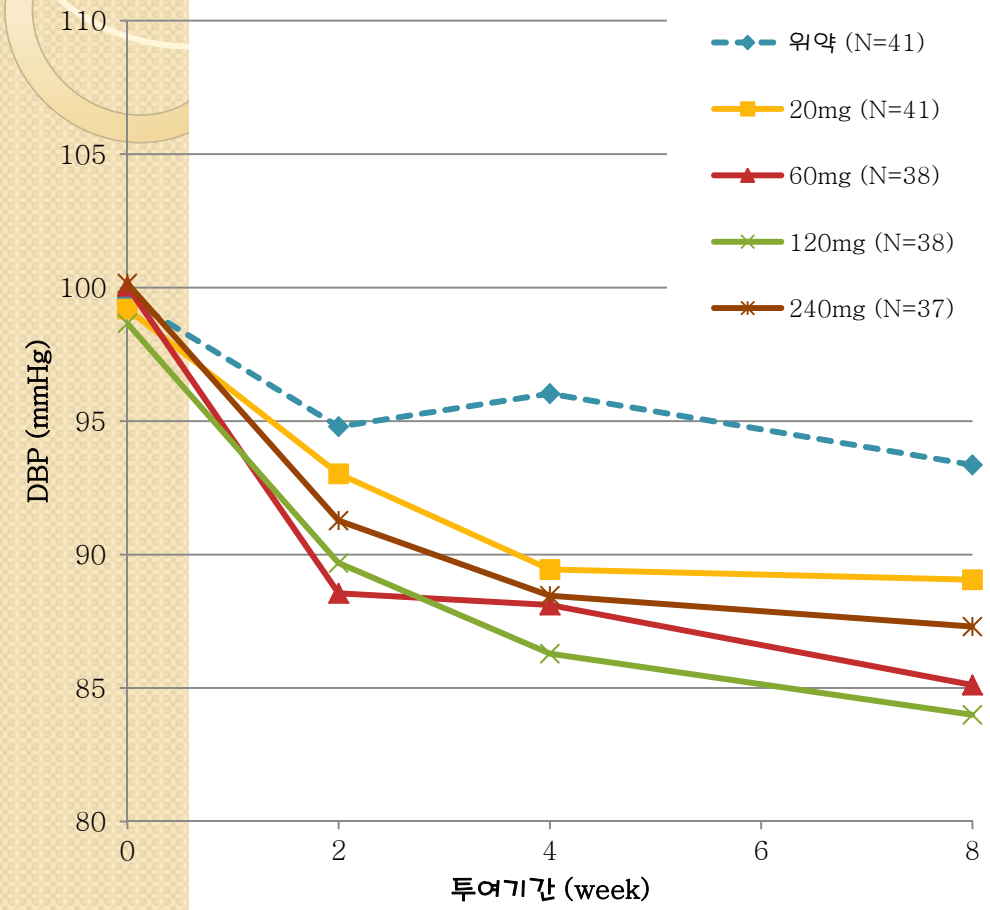
***Phase III : Optional Titration at 4, 8, 12 & 18 wk***

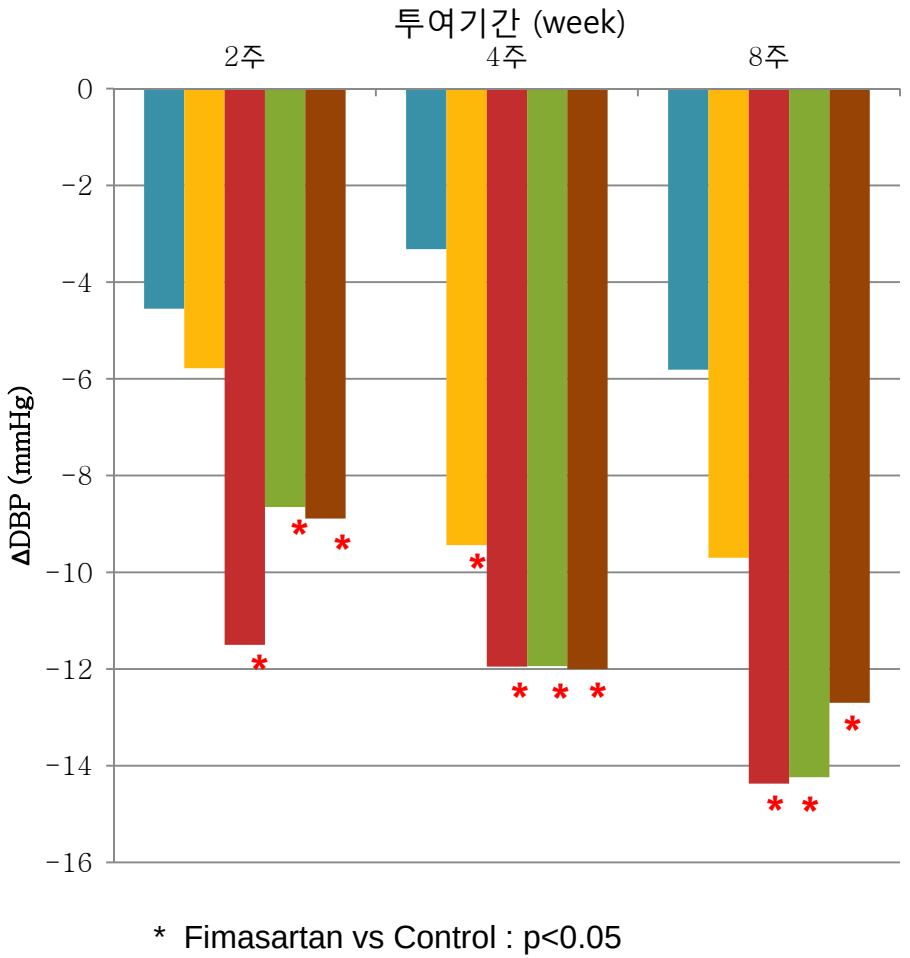
# Phase IIa


110
105
100
95
90
85
80
DBP (mmHg)
0
1
2
3
4
투여기간 (week)
위약 (N=15)
20mg (N=16)
60mg (N=15)
180mg (N=15)


투여기간 (week)
1주
2주
3주
4주
0
-2
-4
-6
-8
-10
-12
-14
-16
-18
ΔDBP (mmHg)
*
* Fimasartan vs Control : p<0.05

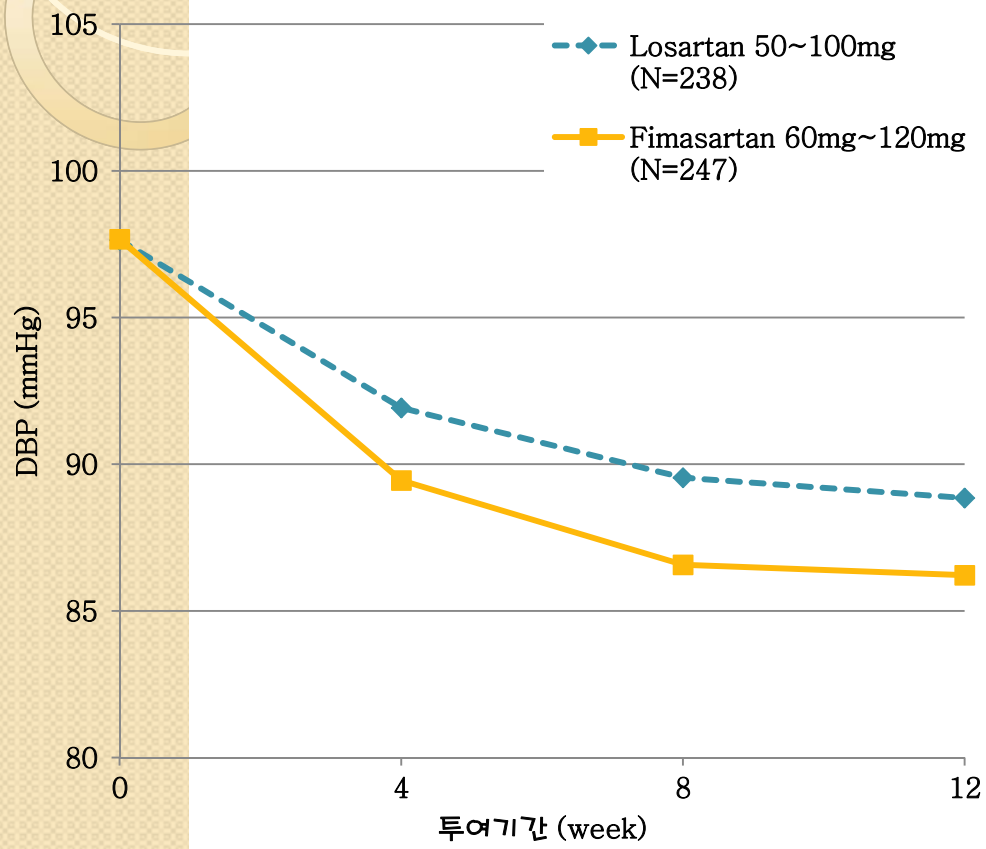
# Phase IIb

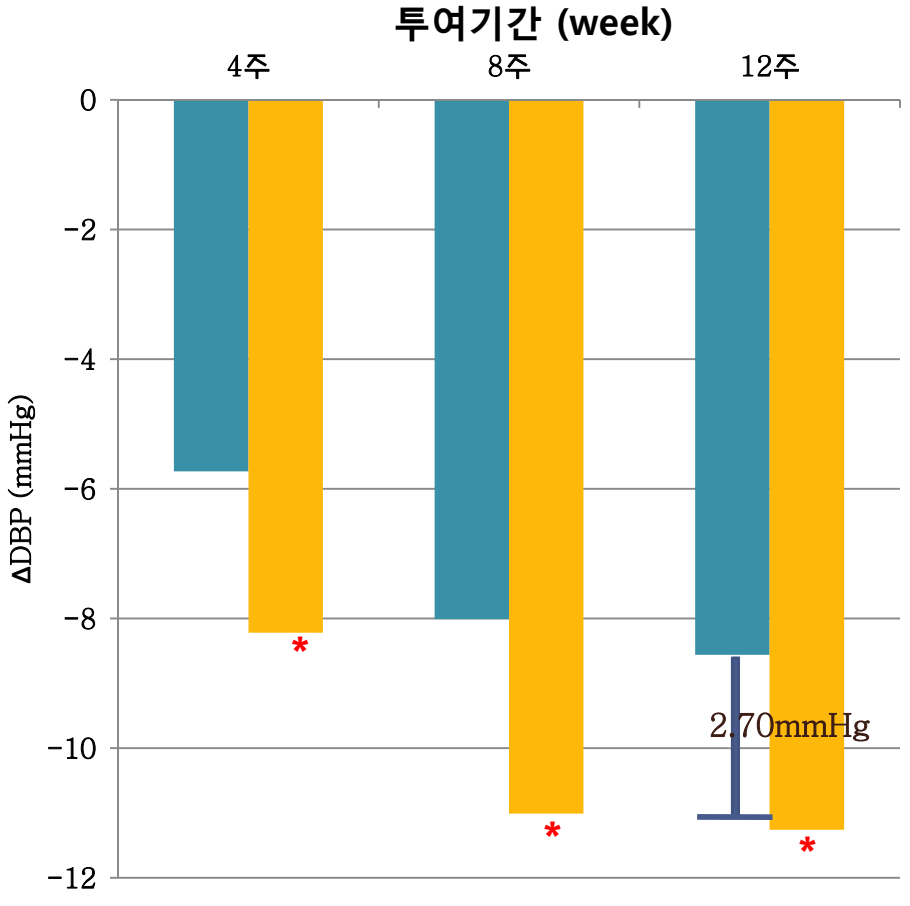



* Fimasartan vs Control : p<0.05

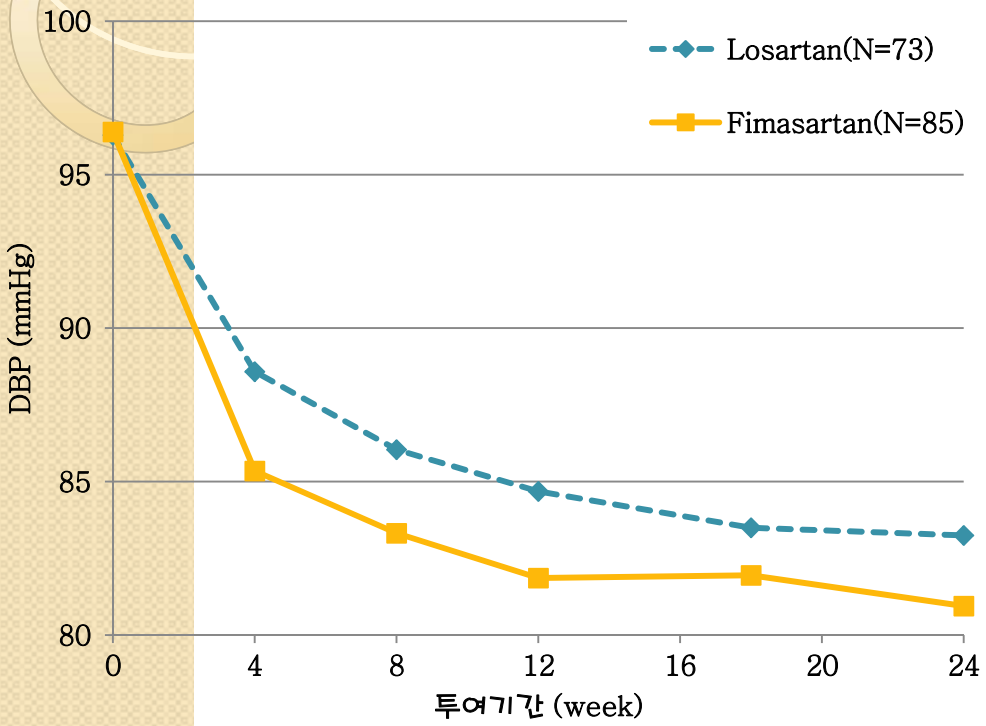
# Phase III

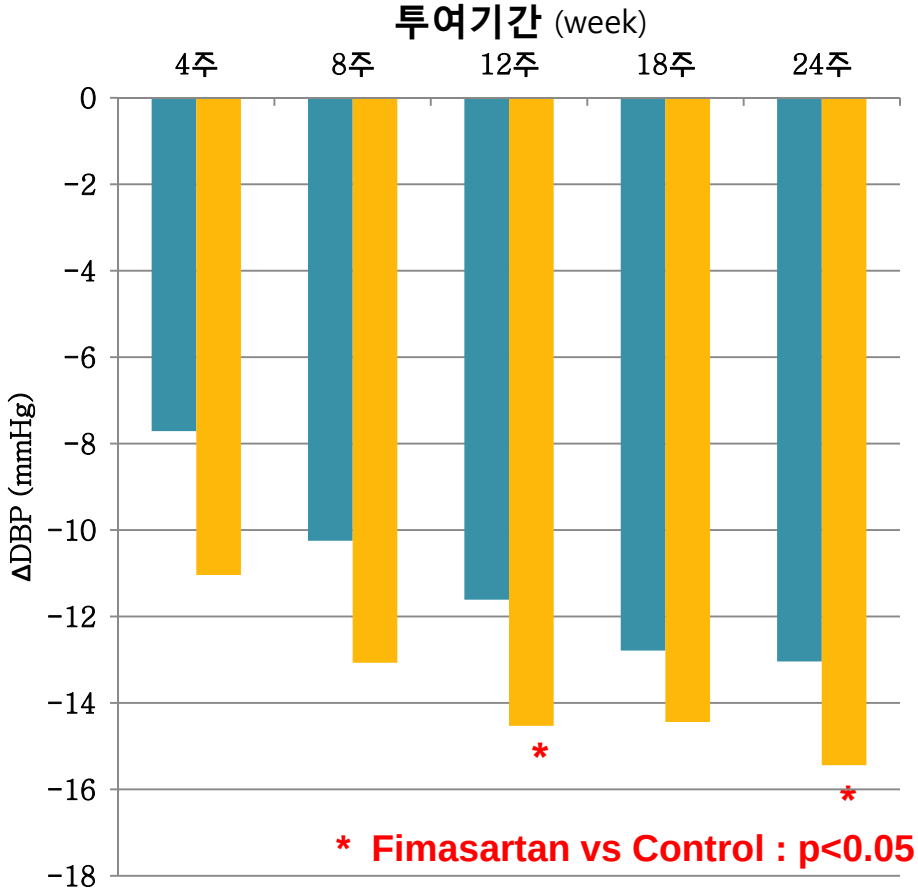


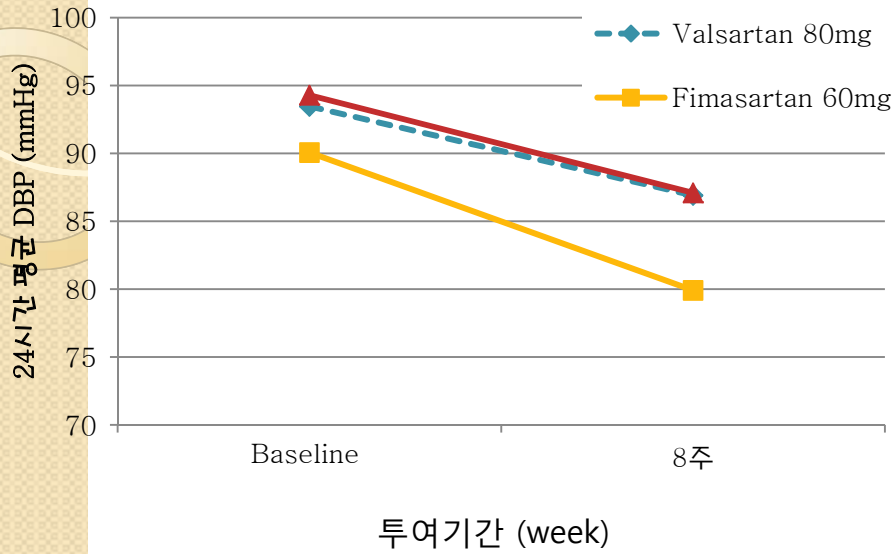

* Fimasartan vs Control : p<0.05

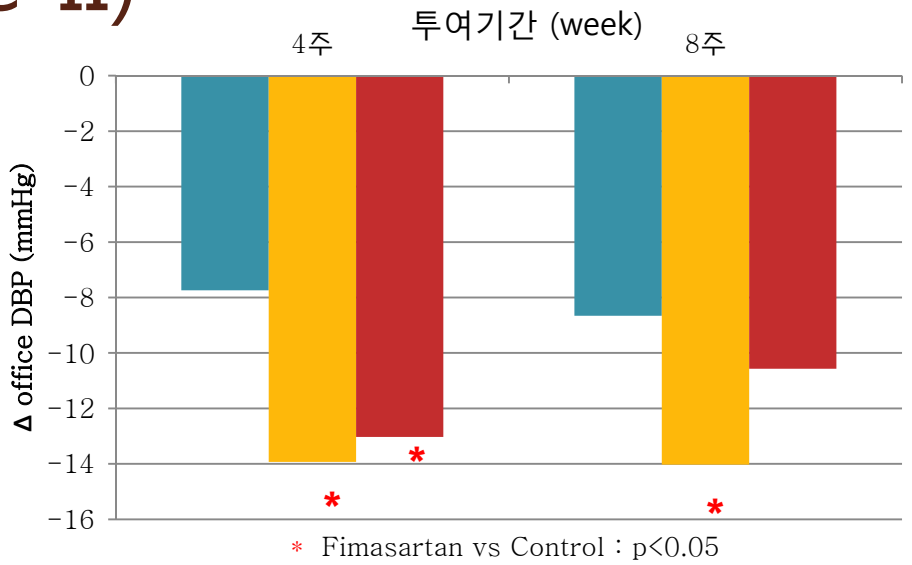
# Phase III- extended



# 24hrs ABPM (Phase II)




Trough/Peak Ratio

| Population | Statistic | F-60mg | F-120mg | V-80mg | p-value [1)] |
|---|---|---|---|---|---|
| All subjects | N | 30 | 30 | 29 | 0.0471 [1)] |
| | Mean (Median) | 0.39 (0.55) | 0.41 (0.35) | 0.28 (0.09) | (0.0831) [2)] |
| | 95% CI | 0.14~0.64 | 0.01~0.81 | 0.96~0.41 | |
| Office BP responder w/o SWCE | N | 23 | 22 | 17 | 0.3491 [2)] |
| | Mean (Median) | 0.50 (0.62) | 0.27 (0.35) | 0.29 (0.29) | |
| | 95% CI | 0.24~0.76 | 0.03~0.51 | 0.05~0.54 | |
| ABP responders[3)] w/o SWCE | N | 17 | 14 | 11 | 0.3557 [2)] |
| | Mean (Median) | 0.72 (0.73) | 0.48 (0.45) | 0.57 (0.37) | |
| | 95% CI | 0.50~0.93 | 0.28~0.68 | 0.23~0.91 | |

*w/o: without, SWCE: Subject with White Coat Effect
1)p- value from Kruskal-Wallis test for testing the difference among groups 2) p- value from ANOVA for testing the difference among groups
3) 8주에서의 24시간 평균 DBP<80mmHg 또는 baseline 대비 Δ24시간 평균DBP>10mmHg

# Response Rate on overall studies

| Study ID | 평가시점 | 치료군 | 반응자[1]의 비율 | 대조약 vs 치료군[2] | 조절자의 비율[3] | 대조약 vs 치료군[2] |
|---|---|---|---|---|---|---|
| 전기 2상 | 4주 | 위약 | 4 / 13 (30.77%) | | 4 / 15 (26.67%) | - |
| | | 20mg | 9 / 14 (64.29%) | 0.0816 (0.1283) | 5 / 16 (31.25%) | 0.7787 (1.0000) |
| | | 60mg | 9 / 14 (64.29%) | 0.0816 (0.1283) | 5 / 15 (33.33%) | 0.6903 (1.0000) |
| | | 180mg | 9 / 11 (81.82%) | 0.0124 (0.0188) | 7 / 15 (46.67%) | 0.2557 (0.4497) |
| 후기 2상 | 8주 | 위약 | 13 / 36 (36.11%) | | 12 / 41 (29.27%) | - |
| | | 20mg | 18 / 33 (54.55%) | 0.1241 (0.1506) | 16 / 41 (39.02%) | 0.3516 (0.4852) |
| | | 60mg | 29 / 35 (82.86%) | <.0001 (<.0001) | 24 / 38 (63.16%) | 0.0025 (0.0034) |
| | | 120mg | 26 / 33 (78.79%) | 0.0004 (0.0006) | 25 / 38 (65.79%) | 0.0012 (0.0016) |
| | | 240mg | 25 / 33 (75.76%) | 0.0009 (0.0015) | 20 / 37 (54.05%) | 0.0263 (0.0379) |
| ABPM | 8주 | Valsartan 80mg | 18 / 29 (62.07%) | | 16 / 32 (50.00%) | - |
| | | 60mg | 27 / 30 (90.00%) | 0.0117 (0.0153) | 26 / 30 (86.67%) | 0.0020 (0.0027) |
| | | 120mg | 22 / 30 (73.33%) | 0.3546 (0.4118) | 22 / 30 (73.33%) | 0.0594 (0.0725) |
| 3상 | 12주 | Losartan 50~100mg | 131 / 213 (61.50%) | | 123 / 238 (51.68%) | - |
| | | 60mg~120mg | 162 / 226 (71.68%) | 0.0237 (0.0260) | 155 / 247 (62.75%) | 0.0137 (0.0169) |

1) DBP<90mmHg or ΔDBP>10mmHg,
2) p-value for Chi-square test (Fisher's exact test), unadjusted pairwise comparison
3) DBP <90mmHg

# Phase IIa – Clinical Safety

| Items | TEAEs (증례수(%) [건수]) | | | | | TEAEs related to Drug(증례수(%) [건수]) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo (N=15) | F-20mg (N=16) | F-60mg (N=15) | F-180mg (N=14) | Total (N=60) | Placebo (N=15) | F-20mg (N=16) | F-60mg (N=15) | F-180mg (N=14) | Total (N=60) |
| Number of subject with TEAEs | 8 ( 53.3%) [22] | 10 ( 62.5%) [30] | 9 ( 60.0%) [21] | 11 ( 78.6%) [25] | 38 ( 63.3%) [98] | 5 ( 33.3%) [5] | 2 ( 12.5%) [2] | 3 ( 20.0%) [5] | 2 ( 14.3%) [2] | 12 ( 20.0%) [14] |
| p-value | | | 0.5474[1)] | | | | | 0.5456[2)] | | |
| Mild | 6 ( 40.0%) [13] | 9 ( 56.3%) [27] | 8 ( 53.3%) [19] | 9 ( 64.3%) [22] | 32 ( 53.3%) [81] | 2 ( 13.3%) [2] | 1 ( 6.3%) [1] | 2 ( 13.3%) [3] | 1 ( 7.1%) [1] | 6 ( 10.0%) [7] |
| Moderate | 4 ( 26.7%) [6] | 2 ( 12.5%) [2] | 2 ( 13.3%) [2] | 3 ( 21.4%) [3] | 11 ( 18.3%) [13] | 3 ( 20.0%) [3] | 1 ( 6.3%) [1] | 2 ( 13.3%) [2] | 1 ( 7.1%) [1] | 7 ( 11.7%) [7] |
| Severe | 3 ( 20.0%) [3] | 1 ( 6.3%) [1] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 4 ( 6.7%) [4] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] |
| Number of subject with SAEs | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) |

1) chi-squire test  2) Fisher's exact test

AE (>10%)

Placebo: 두통  F-20: 두통, 콧물, 기침, 습성기침, CPK 증가, 얼굴홍조

F-60: 두통  F-180: 두통, 콧물

# Phase IIb – Clinical Safety

| Items | TEAEs (증례수(%) [건수]) | | | | | | TEAEs related to Drug(증례수(%) [건수]) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo (N=41) | F-20mg (N=41) | F-60mg (N=38) | F-120mg (N=38) | F-240mg (N=37) | Total (N=195) | Placebo (N=41) | F-20mg (N=41) | F-60mg (N=38) | F-120mg (N=38) | F-240mg (N=37) | Total (N=195) |
| Number of subject with TEAEs | 15(36.6) [ 19] | 10(24.4) [11] | 12(31.6) [23] | 10(26.3) [19] | 14(37.8) [22] | 61(31.3) [94] | 8(19.5) [9] | 4 (9.8) [5] | 6(15.8) [8] | 4( 0.5) [5] | 7(18.9) [10] | 29(14.9) [37] |
| P-values[1)] | | | 0,6222 | | | | | | 0,6241 | | | |
| Mild | 14( 34.1) [16] | 9(22.0) [10] | 11( 28.9) [21] | 10(26.3) [18] | 12(32.4) [20] | 56(28.7) [85] | 8(19.5) [9] | 3(7.3) [4] | 5(13.2) [6] | 4(10.5) [5] | 5( 3.5) [8] | 25(12.8) [32] |
| Moderate | 2( 4.9) [3] | 1( 2.4%) [1] | 1( 2.6) [2] | 1(2.6) [1] | 2(5.4) [2] | 7(3.6) [9] | 0( 0.0) [0] | 1(2.4) [1] | 1( 2.6) [2] | 0(0.0) [0] | 2( 5.4) [2] | 4( 2.1) [5] |
| Severe | 0(0.0) [0] | 0(0.0) [0] | 0(0.0) [0] | 0(0.0) [0] | 0(0.0) [0] | 0(0.0) [0] | 0(0.0) [0] | 0(0.0) [0] | 0(0.0) [0] | 0(0.0) [0] | 0(0.0) [0] | 0(0.0) [0] |
| Number of subject with SAEs | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) |

1) chi-squire test

AE (>5%)

Placebo: 두통 F-20: 없음. F-60: 두통, 어지러움, 상복부통증

F-120: 어지러움, 코인두염 F-240: 상기도감염, ALT증가, AST 증가

# 24hrs ABPM (Phase II) – Clinical safety

| Items | TEAEs (증례수(%) [건수]) | | | | TEAEs related to Drug (증례수(%) [건수]) | | | |
|---|---|---|---|---|---|---|---|---|
| | F-60mg (N=30) | F-120mg (N=30) | Valsartan (N=32) | Total (N=92) | F-60mg (N=30) | F-120mg (N=30) | Valsartan (N=32) | Total (N=92) |
| Number of subject with TEAEs | 6 ( 20.0%) [8] | 8 ( 26.7%) [10] | 7 ( 21.9%) [7] | 21 ( 22.8%) [25] | 0 ( 0.0%) [0] | 2 ( 6.7%) [4] | 0 ( 0.0%) [0] | 2 ( 2.2%) [4] |
| Exact p-value | | 0.8624 | | | | 0.2078 | | |
| Mild | 5 ( 16.7%) [7] | 7 ( 23.3%) [7] | 7 ( 21.9%) [7] | 19 ( 20.7%) [21] | 0 ( 0.0%) [0] | 2 ( 6.7%) [2] | 0 ( 0.0%) [0] | 2 ( 2.2%) [2] |
| Moderate | 1 ( 3.3%) [1] | 1 ( 3.3%) [1] | 0 ( 0.0%) [0] | 2 ( 2.2%) [2] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] |
| Severe | 0 ( 0.0%) [0] | 1 ( 3.3%) [2] | 0 ( 0.0%) [0] | 1 ( 1.1%) [2] | 0 ( 0.0%) [0] | 1 ( 3.3%) [2] | 0 ( 0.0%) [0] | 1 ( 1.1%) [2] |
| Number of subject with SAEs | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] |

AE (>5%)
F-60: 두통, 어지러움　　F-120: 코인두염, ALT증가　　V-80: 없음

# Phase III – Clinical Safety(12weeks)

| Items | TEAEs (증례수(%) [건수]) | | | TEAEs related to Drug (증례수(%) [건수]) | | |
|---|---|---|---|---|---|---|
| | Fimasartan (N=255) | Losartan (N=250) | Total (N=505) | Fimasartan (N=255) | Losartan (N=250) | Total (N=505) |
| No. of subject with TEAEs | 83 ( 32.5%) [136] | 80 ( 32.0%) [119] | 163 ( 32.3%) [255] | 20 ( 7.8%) [29] | 26 ( 10.4%) [40] | 46 ( 9.1%) [69] |
| p-value | | 0.8950[1)] | | | 0.3181[2)] | |
| Mild | 65 ( 25.5%) [98] | 65 ( 26.0%) [92] | 130 ( 25.7%) [190] | 17 ( 6.7%) [21] | 23 ( 9.2%) [33] | 40 ( 7.9%) [54] |
| Moderate | 20 ( 7.8%) [35] | 16 ( 6.4%) [22] | 36 ( 7.1%) [57] | 5 ( 2.0%) [8] | 3 ( 1.2%) [5] | 8 ( 1.6%) [13] |
| Severe | 3 ( 1.2%) [3] | 4 ( 1.6%) [5] | 7 ( 1.4%) [8] | 0 ( 0.0%) [0] | 1 ( 0.4%) [2] | 1 ( 0.2%) [2] |
| No. of subject with SAEs | 3 ( 1.2%) [3] | 5 ( 2.0%) [5] | 8 ( 1.6%) [8] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] |

1) chi-squire test 2) Fisher' s exact test

AE (>1%)

Fimasartan: 두통, 어지러움, 코인두염, 상기도감염, 변비, 흉부불쾌감, ALT 증가, AST증가, 두근거림, 소양증, 기침

Losartan: 두통, 어지러움, 감각이상, 코인두염, 상기도감염, 비염, 소화불량, 오심, 위염, 등통증, 흉부불쾌감, 흉부

통증, 소양증

# Phase III – Long-tern Clinical Safety(24주)

| Items | TEAEs (증례수(%) [건수]) | | | TEAEs related to Drug (증례수(%) [건수]) | | |
|---|---|---|---|---|---|---|
| | Fimasartan (N=85) | Losartan (N=73) | Total (N=158) | Fimasartan (N=85) | Losartan (N=73) | Total (N=158) |
| No. of subject with TEAEs | 15 ( 17.6%) [24] | 13 ( 17.8%) [23] | 28 ( 17.7%) [47] | 2 ( 2.4%) [3] | 3 ( 4.1%) [4] | 5 ( 3.2%) [7] |
| p-value | | 0.8043 1) | | | 0.4159 2) | |
| Mild | 14 ( 16.5%) [19] | 13 ( 17.8%) [22] | 27 ( 17.1%) [41] | 1 ( 1.2%) [1] | 3 ( 4.1%) [3] | 4 ( 2.5%) [4] |
| Moderate | 4 ( 4.7%) [4] | 1 ( 1.4%) [1] | 5 ( 3.2%) [5] | 1 ( 1.2%) [1] | 1 ( 1.4%) [1] | 2 ( 1.3%) [2] |
| Severe | 1 ( 1.2%) [1] | 0 ( 0.0%) [0] | 1 ( 0.6%) [1] | 1 ( 1.2%) [1] | 0 ( 0.0%) [0] | 1 ( 0.6%) [1] |
| No. of subject with SAEs | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] |

1) chi-squire test 2) Fisher's exact test

**No Adverse Event over 1%*

# Demographic features of whole population involved

| Variables | Statistic | Fimasartan 60mg미만 (N=57) | Fimasartan 권장용량 (N=406) | Fimasartan 120mg초과 (N=51) | Fimasartan 전체용량 (N=514) | Placebo (N=56) | Valsartan (N=32) | Losartan (N=250) | Overall (N=852) | p-value[1)] |
|---|---|---|---|---|---|---|---|---|---|---|
| 연령 | 65세 미만 | 53 ( 93.0%) | 367 ( 90.4%) | 49 ( 96.1%) | 469 ( 91.2%) | 51 ( 91.1%) | 26 ( 81.3%) | 217 ( 86.8%) | **763 ( 89.6%)** | 0.1637 |
| | 65세 이상 | 4 ( 7.0%) | 39 ( 9.6%) | 2 ( 3.9%) | 45 ( 8.8%) | 5 ( 8.9%) | 6 ( 18.8%) | 33 ( 13.2%) | **89 ( 10.4%)** | |
| 성별 | 남자 | 35 ( 61.4%) | 280 ( 69.0%) | 33 ( 64.7%) | 348 ( 67.7%) | 35 ( 62.5%) | 19 ( 59.4%) | 173 ( 69.2%) | **575 ( 67.5%)** | 0.6273 |
| | 여자 | 22 ( 38.6%) | 126 ( 31.0%) | 18 ( 35.3%) | 166 ( 32.3%) | 21 ( 37.5%) | 13 ( 40.6%) | 77 ( 30.8%) | **277 ( 32.5%)** | |
| 체중 | 50kg이하 | 2 ( 3.5%) | 7 ( 1.7%) | 2 ( 3.9%) | 11 ( 2.1%) | 1 ( 1.8%) | 1 ( 3.1%) | 5 ( 2.0%) | **18 ( 2.1%)** | 0.6755 |
| | 50~70kg | 28 ( 49.1%) | 204 ( 50.2%) | 25 ( 49.0%) | 257 ( 50.0%) | 35 ( 62.5%) | 19 ( 59.4%) | 130 ( 52.0%) | **441 ( 51.8%)** | |
| | 70~90kg | 25 ( 43.9%) | 181 ( 44.6%) | 24 ( 47.1%) | 230 ( 44.7%) | 19 ( 33.9%) | 11 ( 34.4%) | 100 ( 40.0%) | **360 ( 42.3%)** | |
| | 90kg초과 | 2 ( 3.5%) | 14 ( 3.4%) | 0 | 16 ( 3.1%) | 1 ( 1.8%) | 1 ( 3.1%) | 15 ( 6.0%) | **33 ( 3.9%)** | |
| BMI[†] | 18.5이하 | 0 | 2 ( 0.5%) | 0 | 2 ( 0.4%) | 0 | 0 | 2 ( 0.8%) | **4 ( 0.5%)** | 0.8796 |
| | 18.5~23 | 10 ( 17.5%) | 73 ( 18.0%) | 9 ( 17.6%) | 92 ( 17.9%) | 9 ( 16.1%) | 6 ( 18.8%) | 39 ( 15.6%) | **146 ( 17.1%)** | |
| | 23~25 | 14 ( 24.6%) | 115 ( 28.3%) | 16 ( 31.4%) | 145 ( 28.2%) | 25 ( 44.6%) | 10 ( 31.3%) | 69 ( 27.6%) | **249 ( 29.2%)** | |
| | 23~30 | 29 ( 50.9%) | 191 ( 47.0%) | 25 ( 49.0%) | 245 ( 47.7%) | 18 ( 32.1%) | 15 ( 46.9%) | 123 ( 49.2%) | **401 ( 47.1%)** | |
| | 30 이상 | 4 ( 7.0%) | 25 ( 6.2%) | 1 ( 2.0%) | 30 ( 5.8%) | 4 ( 7.1%) | 1 ( 3.1%) | 17 ( 6.8%) | **52 ( 6.1%)** | |
| 고지혈증 | 유 | 3 ( 5.3%) | 61 ( 15.0%) | 2 ( 3.9%) | 66 ( 12.8%) | 4 ( 7.1%) | 7 ( 21.9%) | 49 ( 19.6%) | **126 ( 14.8%)** | 0.0039** |
| | 무 | 54 ( 94.7%) | 345 ( 85.0%) | 49 ( 96.1%) | 448 ( 87.2%) | 52 ( 92.9%) | 25 ( 78.1%) | 201 ( 80.4%) | **726 ( 85.2%)** | |
| 당뇨 | 유 | 2 ( 3.5%) | 20 ( 4.9%) | 2 ( 3.9%) | 24 ( 4.7%) | 3 ( 5.4%) | 1 ( 3.1%) | 10 ( 4.0%) | **38 ( 4.5%)** | 0.9815 |
| | 무 | 55 ( 96.5%) | 386 ( 95.1%) | 49 ( 96.1%) | 490 ( 95.3%) | 53 ( 94.6%) | 31 ( 96.9%) | 240 ( 96.0%) | **814 ( 95.5%)** | |

1) p-value from chi-square test for all treatment groups (3상에서 고지혈증 피험자가 다른 임상보다 많이 등록되었음.
* p<0.05, ** p<0.01
† 아시아 비만학회 기준 적용

# 전체 임상시험의 안전성 분석결과

| Items | TEAEs | | | | | | |
|---|---|---|---|---|---|---|---|
| | Fimasartan 60mg미만 (N=57) | Fimasartan 권장용량 (N=406) | Fimasartan 120mg초과 (N=51) | Placebo (N=56) | Valsartan (N=32) | Losartan (N=250) | Total (N=852) |
| | 증례수(%) [건수] | 증례수(%) [건수] | 증례수(%) [건수] | 증례수(%) [건수] | 증례수(%) [건수] | 증례수(%) [건수] | 증례수(%) [건수] |
| Number of subject with TEAEs | 20 ( 35.1%) [41] | 128 ( 31.5%) [217] | 25 ( 49.0%) [47] | 23 ( 41.1%) [41] | 7 ( 21.9%) [7] | 80 ( 32.0%) [119] | 283 ( 33.2%) [472] |
| EXACT (1-0.05) CI | 35.1% ( 22.9%, 48.9%) | 31.5% ( 27.0%, 36.3%) | 49.0 ( 34.8%, 63.4%) | 41.1% ( 28.1%, 55.0%) | 21.9% ( 9.3%, 40.0%) | 32.0% ( 26.3%, 38.2%) | 33.2% ( 30.1%, 36.5%) |
| p-value for TEAEs* | | | **0.0771** | | | | |
| Mild | 18 ( 31.6%) [37] | 106 ( 26.1%) [170] | 21 ( 41.2%) [42] | 20 ( 35.7%) [29] | 7 ( 21.9%) [7] | 65 ( 26.0%) [92] | 237 ( 27.8%) [377] |
| Moderate | 3 ( 5.3%) [3] | 26 ( 6.4%) [42] | 5 ( 9.8%) [5] | 6 ( 10.7%) [9] | 0 ( 0.0%) [0] | 16 ( 6.4%) [22] | 56 ( 6.6%) [81] |
| Severe | 1 ( 1.8%) [1] | 4 ( 1.0%) [5] | 0 ( 0.0%) [0] | 3 ( 5.4%) [3] | 0 ( 0.0%) [0] | 4 ( 1.6%) [5] | 12 ( 1.4%) [14] |
| Number of subject with SAEs | 0 ( 0.0%) [0] | 3 ( 0.7%) [3] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 0 ( 0.0%) [0] | 5 ( 2.0%) [5] | 8 ( 0.9%) [8] |
| EXACT (1-0.05) CI | 0.0% ( 0.0%, 6.3%) | 0.7% ( 0.2%, 2.1%) | 0.0% ( 0.0%, 7.0%) | 0.0% ( 0.0%, 6.4%) | 0.0% ( 0.0%, 10.9%) | 2.0% ( 0.7%, 4.6%) | 0.9% ( 0.4%, 1.8%) |
| p-value for SAEs* | | | **0.4088** | | | | |

*p-value from chi-square test

AE (>1%)

Fimasartan권장용량: 두통, 어지러움, 코인두염, 상기도감염, 편두통, 소화불량, 오심, 흉부불쾌감, ALT 증가, AST증가, 두근거림,소양증,기침

Losartan: 두통, 어지러움, 코인두염, 상기도감염, 비염, 소화불량, 오심, 위염, 흉부불쾌감, 소양증

건강인 대상의 임상시험에서 대조군과 시험군에서 이상반응 발현율의 차이가 있었던 임상시험은 없었음.

# Conclusions

1. Fimasartan is a new safe type1 angiotensin II receptor antagonist.
2. Fimasartan has excellent BP lowering effect.