[Ideal Choice of Hypertension Treatment]

The Efficacy and Safety of Low-Dose Fimasartan

Young Won Yoon,

Heart Center, Gangnam Severance Hsopital
Yonsei University College of Medicine

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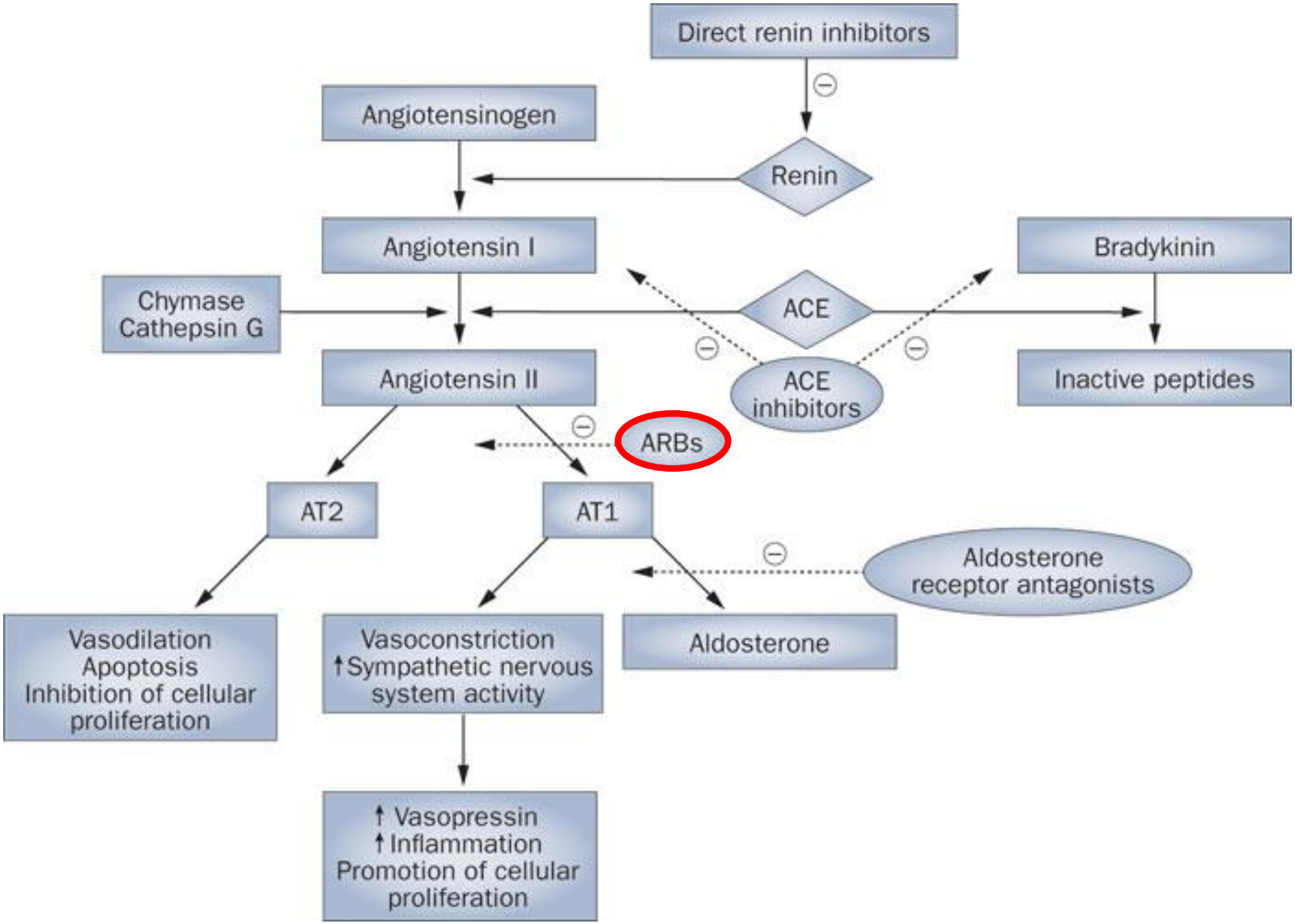
Angiotensin II and ARBs

RAS & ARBs


Direct renin inhibitors
Angiotensinogen
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Angiotensin I
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ACE inhibitors
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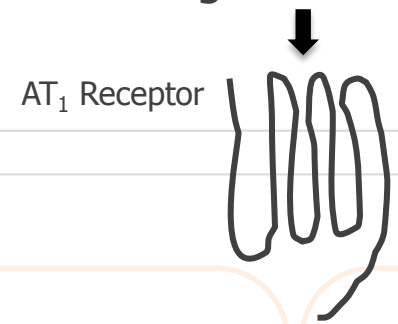
Vasodilation
Apoptosis
Inhibition of cellular proliferation
Vasoconstriction
↑Sympathetic nervous system activity
Aldosterone
↑ Vasopressin
↑ Inflammation
Promotion of cellular proliferation

ANG II's role in cardiovascular pathology

Angiotensin II



VSMCs

-Growth
-Contraction
-Migration
-Hypertrophy
-Lipid oxidation
-Fibrosis
-Cytoskeletal rearrangement

Endothelial cells

-NO imbalance
-Endothelial dysfunction
-Adhesion molecule expression
-Monocyte adhesion

Cardiac cells

-Myocyte hypertrophy
-Myofibroblast remodeling
-Conduction system disturbances

Extracellular matrix

-Synthesis
-Degradation
-Adhesion molecule expression
-MMP activation
-Cytokine induction

Inflammation, Atherosclerosis, Thrombosis, Fibrosis

MI, Stroke, Diabetic micro-and macro vascular disease, Peripheral vascular disease, CHF

Am J Physiol Cell Physiol. 2007;292:C82-C97

ACE inhibitors vs. ARBs

- Although both classes of drugs block the RAS, they differ in several important aspects [1)]

  - ACE inhibitors reduce the biosynthesis of Ang II by the action of ACE, but do not inhibit alternative non-ACE Ang II-generating pathways. ARBs block the actions of Ang II via the AT_1 receptor regardless of the biochemical pathway leading to Ang II formation.

  - Unlike ACE inhibitors, ARBs allow activation of AT_2 receptors.[2)] ARBs cause a several-fold increase in circulating levels of Ang II. Because ARBs block AT_1 receptors, this increased level of Ang II is available to activate AT_2 receptors. AT_2 receptor activation is thought to have the opposite effect of those mediated by the AT_1 receptor, which are beneficial to the cardiovascular system and help protect target organs from damage.

  - ACE inhibitors increase the levels of a number of ACE substrates, including bradykinin.

  - ACE inhibitors may increase Ang (1–7) levels more than do ARBs. ACE is involved in the clearance of Ang (1–7), so inhibition of ACE may increase Ang (1–7) levels more so than do ARBs.

1) JAPI(Journal of the association of physicians of india). 2013;61:464-70
2) Peptides. 2005;26:1401-9

Benefits of ARBs

- Recently developed
- Excellent BP lowering effect
- Prevention of target organ damages (cardiovascular, renal protection effects)

  -LVH

  -Ischemic heart disease and arrhythmia

  -Microalbuminuria and renal dysfunction
- Recommended to heart failure, renal failure and diabetes patients
- Dry cough X(vs. ACEi), edema ↓↓(vs. CCB)
- Effective on elderly hypertension and stroke prevention

Low-dose ARBs

Benefits of low-dose ARBs

Diabetic patients with nephropathy (UAE>20㎍/min) **before and after treatment with low-dose valsartan**

	Before	After	*P* value
Body mass index (kg/m^2)	23.0 ± 2.1	23.0 ± 1.6	NS
HbA_{1c} (%)	7.1 ± 0.6	6.9 ± 0.8	NS
Systolic blood pressure (mmHg)	145.0 ± 10	143.4 ± 13	NS
Diastolic blood pressure (mmHg)	76.5 ± 8	74.5 ± 7	NS
Serum creatinine (mg/dl)	1.0 ± 0.4	1.1 ± 0.7	NS
Creatinine clearance (ml/min)	77.1 ± 16	73.9 ± 16	NS
UAE (μg/min)	219.4 ± 275	102.7 ± 141	$P<0.01$

UAE;urinary albumin excretion

In type 2 diabetic patients with diabetic nephropathy, UAE is reduced with **low-dose valsartan(40mg)** treatment for 6 months, with no concomitant reduction in blood pressure.

Diabetes Res Clin Pract. 2002;57(3):179-83

Benefits of low-dose ARBs

Changes in parameters before to after low-dose valsartan treatment

	Baseline	3 months	6 months
Body weight (kg)	66.7 ± 12.1	67.5 ± 12.3	69.1 ± 11.1
Systolic blood pressure (mmHg)	149 ± 19	145 ± 22	148 ± 20
Diastolic blood pressure (mmHg)	85 ± 13	86 ± 13	85 ± 11
HbA1c (%)	6.8 ± 0.7	7.0 ± 1.1	7.1 ± 1.1
Lipid peroxide (μmol/L)	3.0 ± 0.8	2.7 ± 0.6	3.0 ± 0.8
Paraoxonase activity (unit/L)	245 ± 74	238 ± 92	232 ± 76
PAF-AH (μmol/L/min)	19.3 ± 5.1	19.5 ± 4.7	18.1 ± 6.1
AGEs (unit/L)	2.5 ± 0.6	2.4 ± 0.5	2.2 ± 0.4*
Urine 8-isoprostane (pg/mL)	383 ± 249	269 ± 196	204 ± 136*
Creatinine (Cr) (mg/dL)	0.9 ± 0.1	–	0.9 ± 0.2
Calculated Ccr (mL/min)	84.4 ± 28.4	–	86.3 ± 30.0
Urine microalbumin (mg/gCr)	177 ± 274	–	127 ± 232*

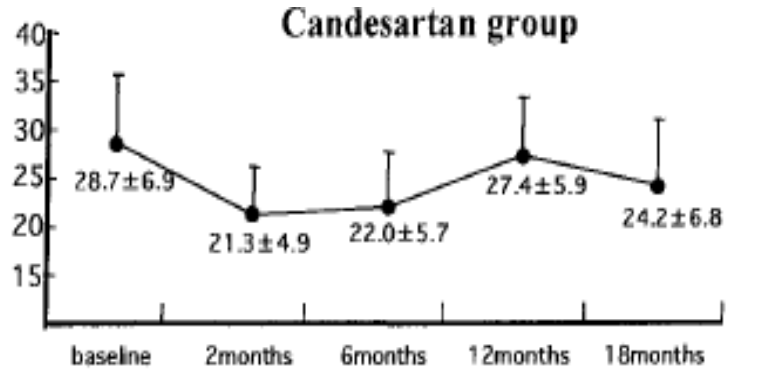
Low-dose valsartan(40mg) treatment decreased serum AGEs level in type 2 diabetic subjects, whereas blood pressure level was unchanged.

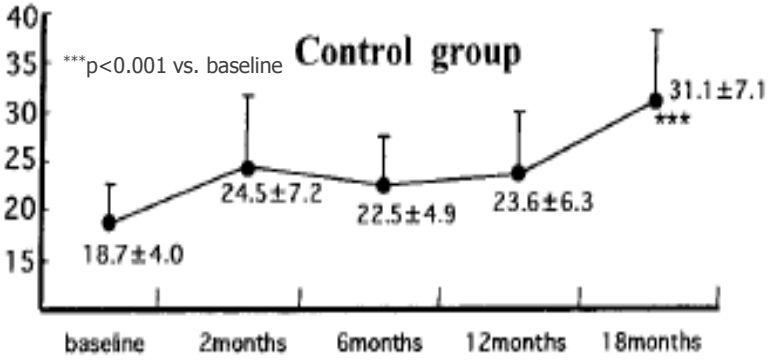
AGES; advanced glycation endproducts

Diabetes Res Clin Pract. 2006;74(2):201-3

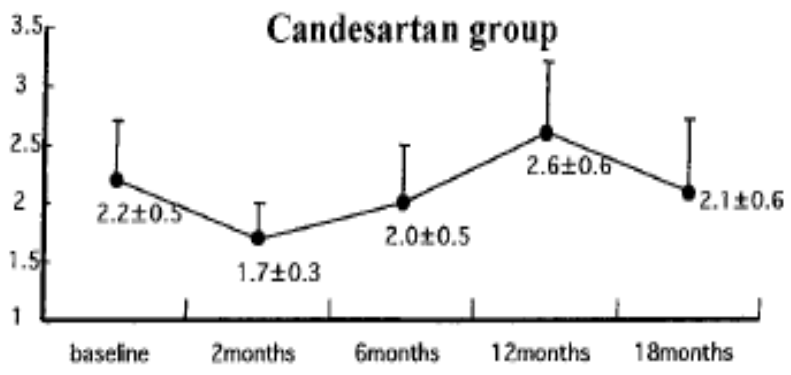
Benefits of low-dose ARBs

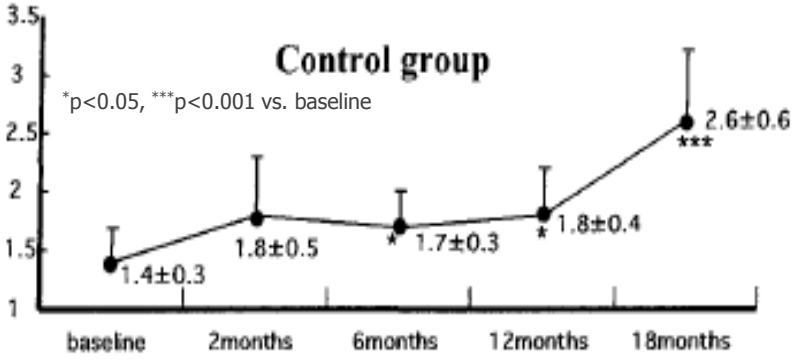
Urinary albumin excretion (mg/g. Cr)





Urinary transferrin excretion (mg/g. Cr)



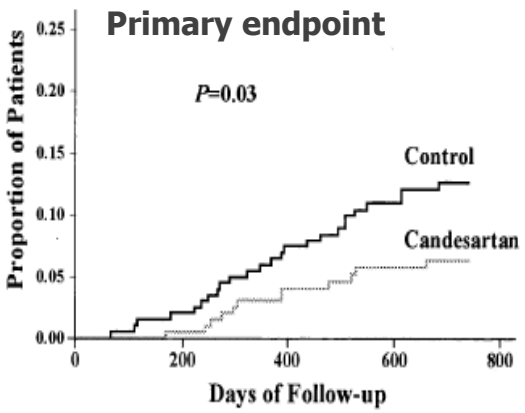


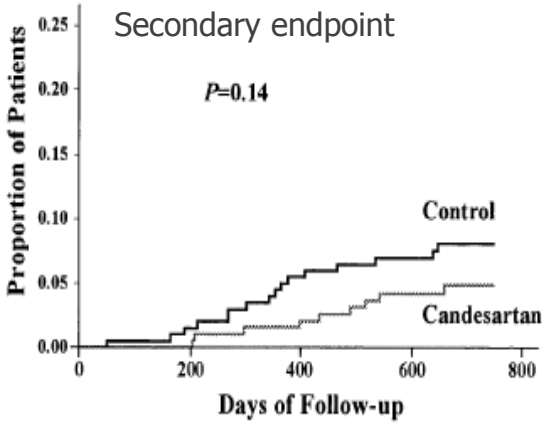
Low-dose candesartan(4mg) may be beneficial for diabetics with a mildly raised BP in order to prevent the early-stage diabetic nephropathy without causing profound hypotension.

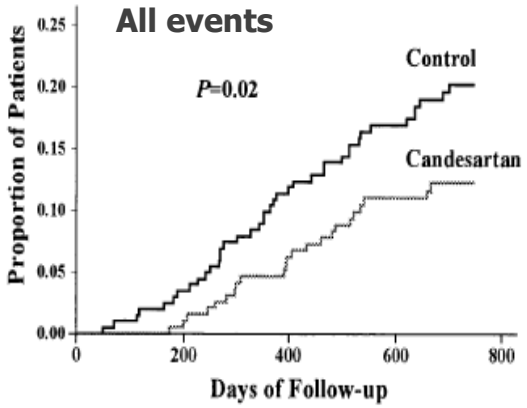
Hypertens Res 2003; 26: 453–458

Benefits of low-dose ARBs

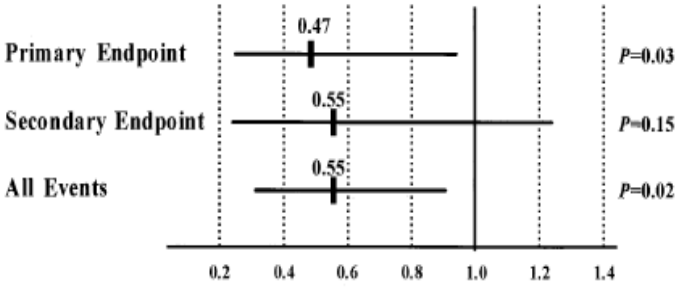
Kaplan-Meier estimates of
cardiovascular events and all events in the candesartan / the control group







Relative risk (95% CI)



Additional ARB therapy with relatively **low-dose candesartan(4mg)** inhibits cardiovascular events in high-risk patients with CAD(coronary artery disease).

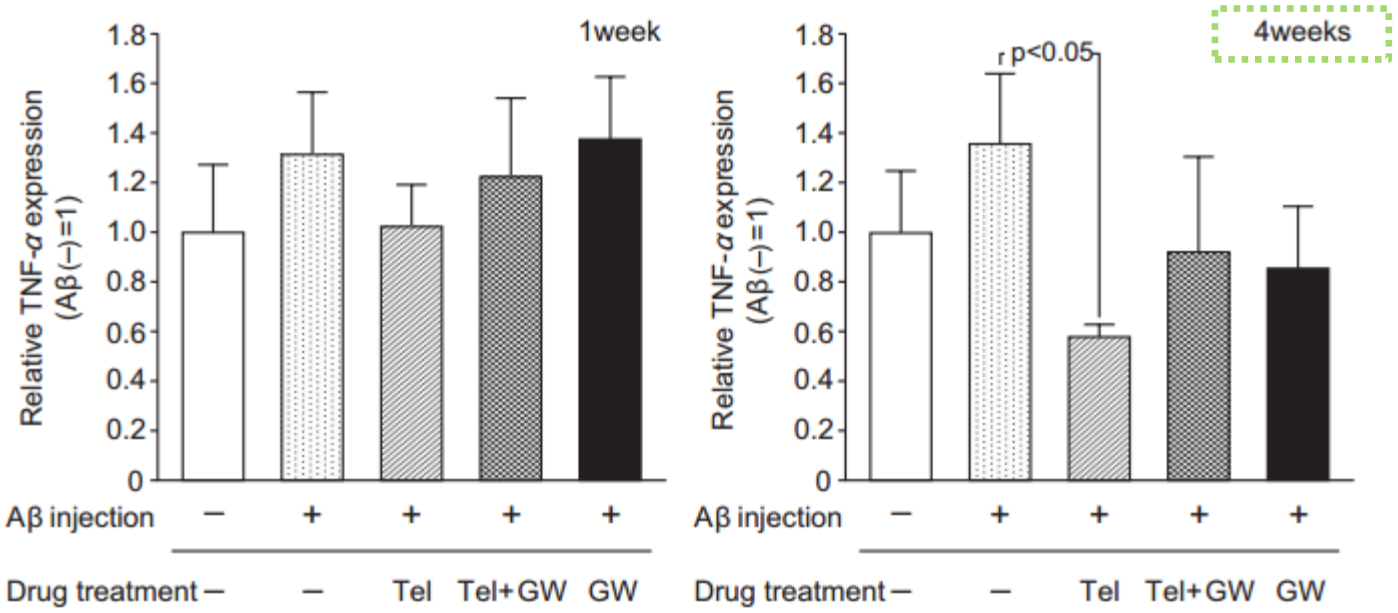
-Primary endpoint: a composite of revascularization, nonfatal myocardial infarction, or cardiovascular death
-Secondary endpoint: hospitalization for cardiovascular causes (worsening angina or heart failure)
-All events: primary end point, secondary end point, noncardiovascular death

Am Heart J. 2003;146(6):E20

Benefits of low-dose ARBs

[Preclinical trials(animal studies)]

mRNA expression of TNF-α



Treatment with telmisartan decreased TNF-α expression in the brain.
(In mice 4 weeks after Aβ injection, treatment with telmisartan significantly suppressed TNF-α expression in the brain compared with that in the Aβ-injected group.)

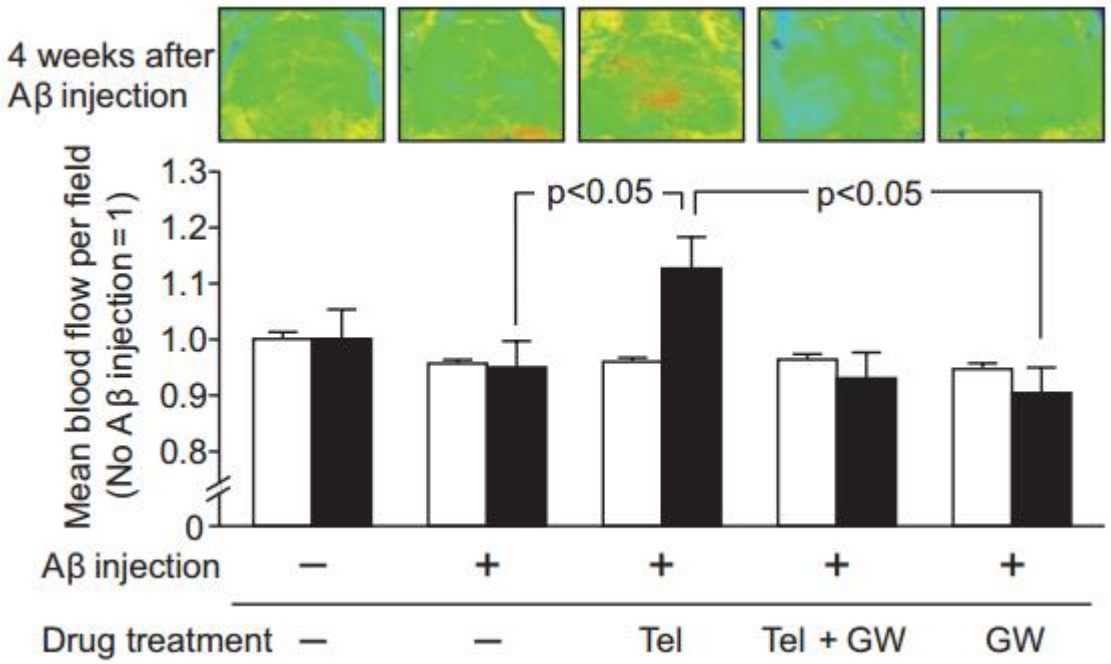
Tel indicates telmisartan at 0.35 mg/kg per day in drinking water;
GW, GW9662(a PPAR-γ antagonist) at 0.35mg/kg per day in drinking water for 2 weeks before treatment.
n=5 in each group.

Hypertension. 2009;54(4):782-7

Benefits of low-dose ARBs

[Preclinical trials(animal studies)]

CBF 1 and 4 weeks after ICV Aβ injection measured by laser speckle flowmetry



Top, Representative 2D images of CBF 4 weeks after ICV Aβ injection.
Bottom, Mean CBF in whole brain 1 week (□) and 4 weeks (■) after ICV Aβ injection.
Tel indicates telmisartan at 0.35mg/kg per day in drinking water; GW, GW9662 at 0.35 mg/kg per day in drinking water for 2 weeks before treatment.
N=6 to 7 for 1 week and 9 to 11 for 4 weeks after ICV Aβ injection in each group.

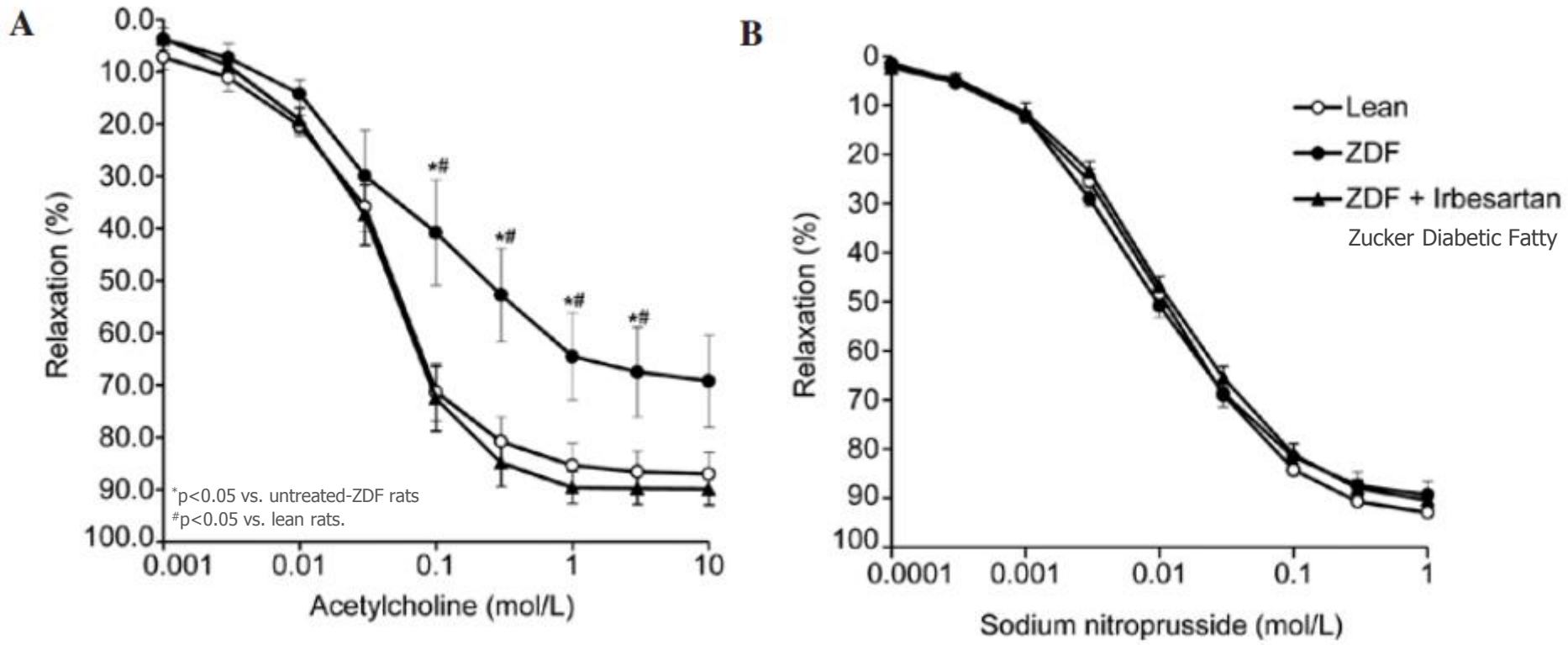
A **low dose of telmisartan** ameliorates cognitive impairment induced by Aβ injection through partial agonistic activation of PPAR-γ. These results support the notion that treatment with an even lower dose of telmisartan would prevent the onset of Alzheimer disease by reducing Aβ deposition.

Hypertension. 2009;54(4):782-7

Benefits of low-dose ARBs

[Preclinical trials(animal studies)]

Irbesartan improves endothelial dysfunction



Treatment with irbesartan significantly improved the impaired endothelium-dependent relaxation response of isolated mesenteric artery rings, while the relaxation response to acetylcholine was significantly impaired in the ZDF rats.

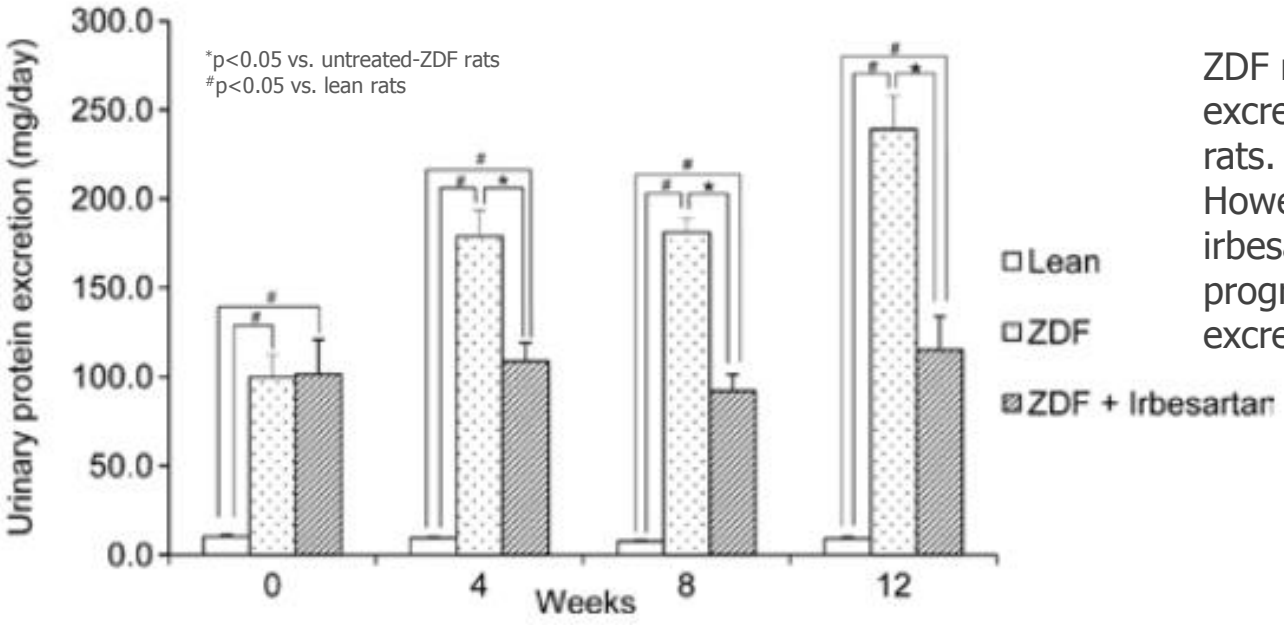
In contrast, the response to sodium nitroprusside was the same in all groups.

Exp Ther Med. 2011;2(5):957-61

Benefits of low-dose ARBs

[Preclinical trials(animal studies)]

Effects of irbesartan on urinary protein excretion



ZDF rats showed higher excretion than that of the lean rats.
However, ZDF rats treated with irbesartan showed no progression of urinary protein excretion.

A low-dose of irbesartan improves diabetic complications quickly after starting treatment, and may support the use of irbesartan for preventing progression of diabetic complications

Exp Ther Med. 2011;2(5):957-61

Fimasartan 30mg Phase III study

To evaluate **efficacy** and **safety** of

Fimasartan 30mg compared to **placebo** and

Valsartan 80mg **with mild-to-moderate hypertension**:

randomized, double-blind, multi-center, phase III

Data in BORYUNG

Overall study design

- **Number of patients**

  n= 275 (consider 15% of drop-out)

  분석 목표 피험자수: 230명

- **Period**

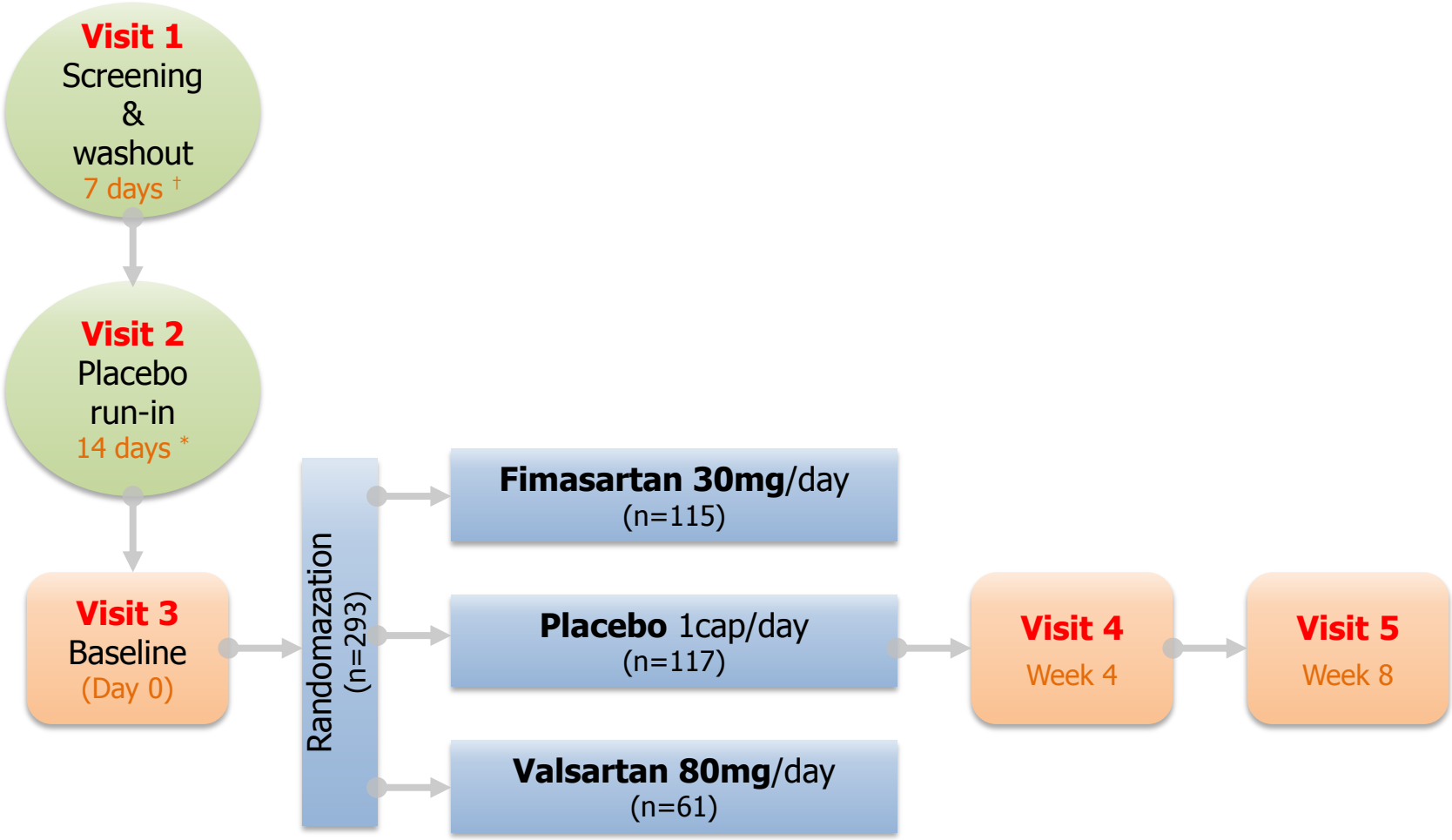
  2012. 3. 16(FPFV)[1] ~ 2013. 3. 15(LPLV)[2]

- **Centers**

  신촌세브란스병원 외 16개 기관(총 17개 기관)

1) FPFV: First Patent First Visit 2) LPLV: Last Patient Last Visit

Overall study design



† 스크리닝 당시 투약 중인 고혈압 치료제가 있는 경우 7일 휴약기를 거친다.
그렇지 않은 피험자의 경우, Visit 1과 Visit 2를 동시에 실시할 수 있었다.
* 위약 도입기는 14일이지만 피험자의 방문 일정에 따라 21일까지 연장할 수 있었다.

Selection of study population

[Inclusion criteria]

› 만 20세 이상 ~ 75세 이하의 성인 남녀

› 위약도입기(placebo run – in period)를 거친 후, baseline(day0)에 측정한 **평균 sitting DBP**가 **≥90mmHg, < 110mmHg** 본태성 고혈압 환자

[Exclusion criteria]

› 중증의 고혈압 환자
(스크리닝 시점 및 무작위 배정 시점에서 측정된 평균 siDBP가 ≥110mmHg 및/또는 평균 siSBP가 ≥180mmHg)

› Screening 및 baseline 평가 시 동일한 팔에서 측정한 혈압이 siDBP 10mmHg 또는 siSBP 20mmHg 이상 차이 나는 자

› 중증의 심장질환 환자(심부전 NYHA class3, 4), 최근 6개월 이내 허혈성 심장질환(협심증, 심근경색), 경피 경혈관 관상동맥확장술 또는 관상동맥우회술 치료 등을 받은 자 또는 말초혈관질환 환자

› 기타

Efficacy variables

[Primary endpoint]

› **Baseline 대비 8주 투여 후의 Fimasartan 30mg과 placebo의 siDBP의 변화**

[Secondary endpoint]

› Baseline 대비 8주 투여 후의 Fimasartan 30mg과 Valsartan 80mg의 siDBP의 변화

› 각 군*의 baseline 대비 4주 투여 후의 siDBP의 변화

› 각 군*의 baseline 대비 4, 8주 투여 종료 후의 siSBP의 변화

› 각 군*의 8주 투여 후 responder의 비율
(siDBP<90mmHg 또는 투여 전 대비 8주 투여 후 ΔsiDBP≥10mmHg)

› 각 군*의 8주 투여 후 혈압 정상화 비율
(siDBP<90mmHg & siSBP<140mmHg에 도달한 피험자 비율)

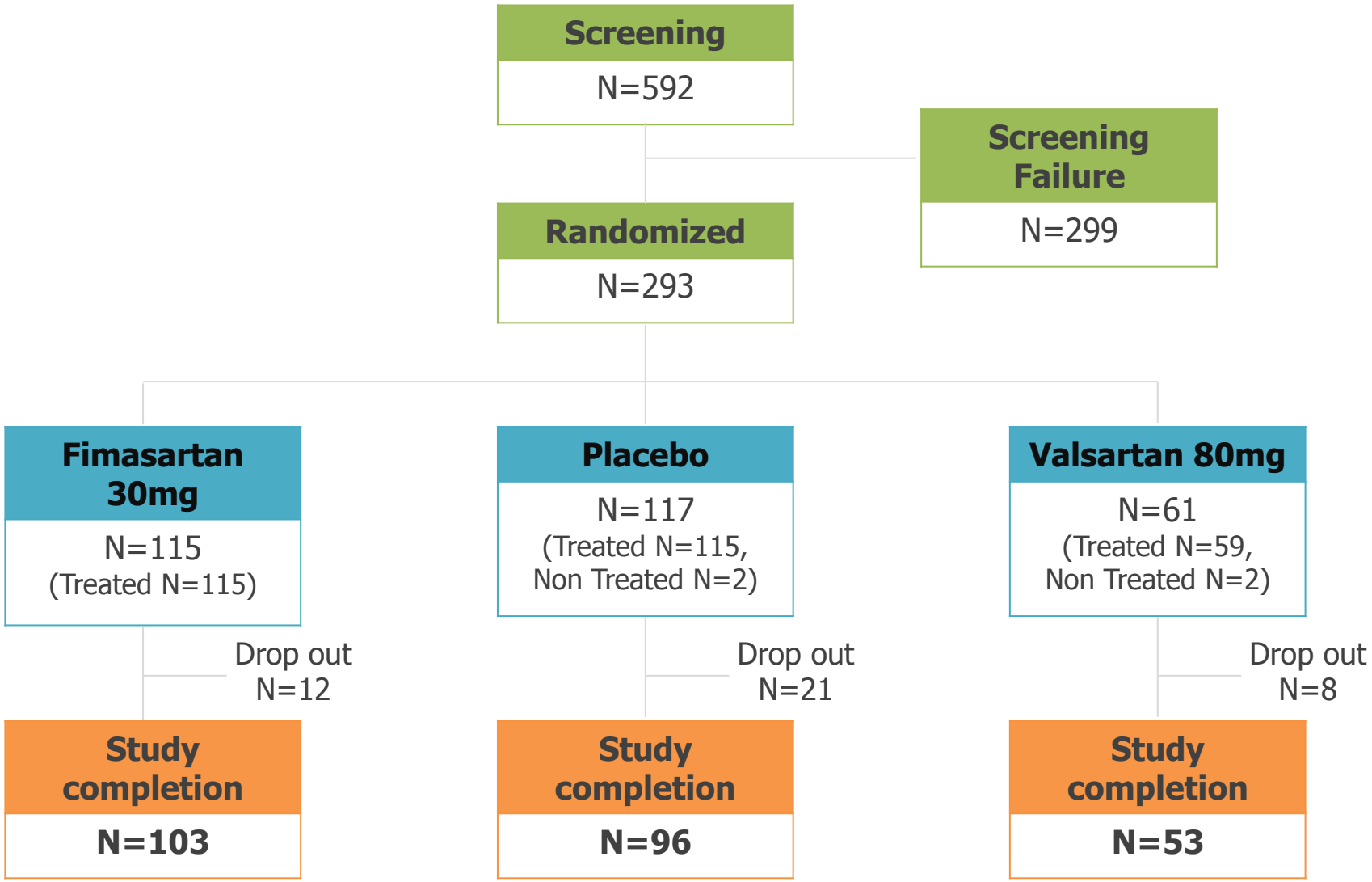
* 각 군은 fimasartan 30mg(시험군), placebo(대조군), valsartan (reference군) 투여군을 의미함

Safety variables

- 이상반응
- 실험실적 검사

  (혈액학적/혈액생화학적, 요검사, Chest X-ray, ECG 포함)
- 신체검진, 활력징후(맥박)

Subject disposition



Primary efficacy results

- Change from baseline in **siDBP** compared to placebo at **week 8** (FAS*)

Mean±SD

Visit	Fimasartan 30mg (N=112)	Placebo (N=112)	Difference in Change	95% CI[1)]	p-value[2)]
Baseline	98.64±5.20	98.06±5.44	-	-	-
Week 8	88.71±9.21	95.98±9.76	-	-	-
Change[3)]	**-9.93±8.86**	-2.08±9.47	**-7.85±9.17**	(-10.27, -5.44)	<.0001

1) 95% Confidence interval

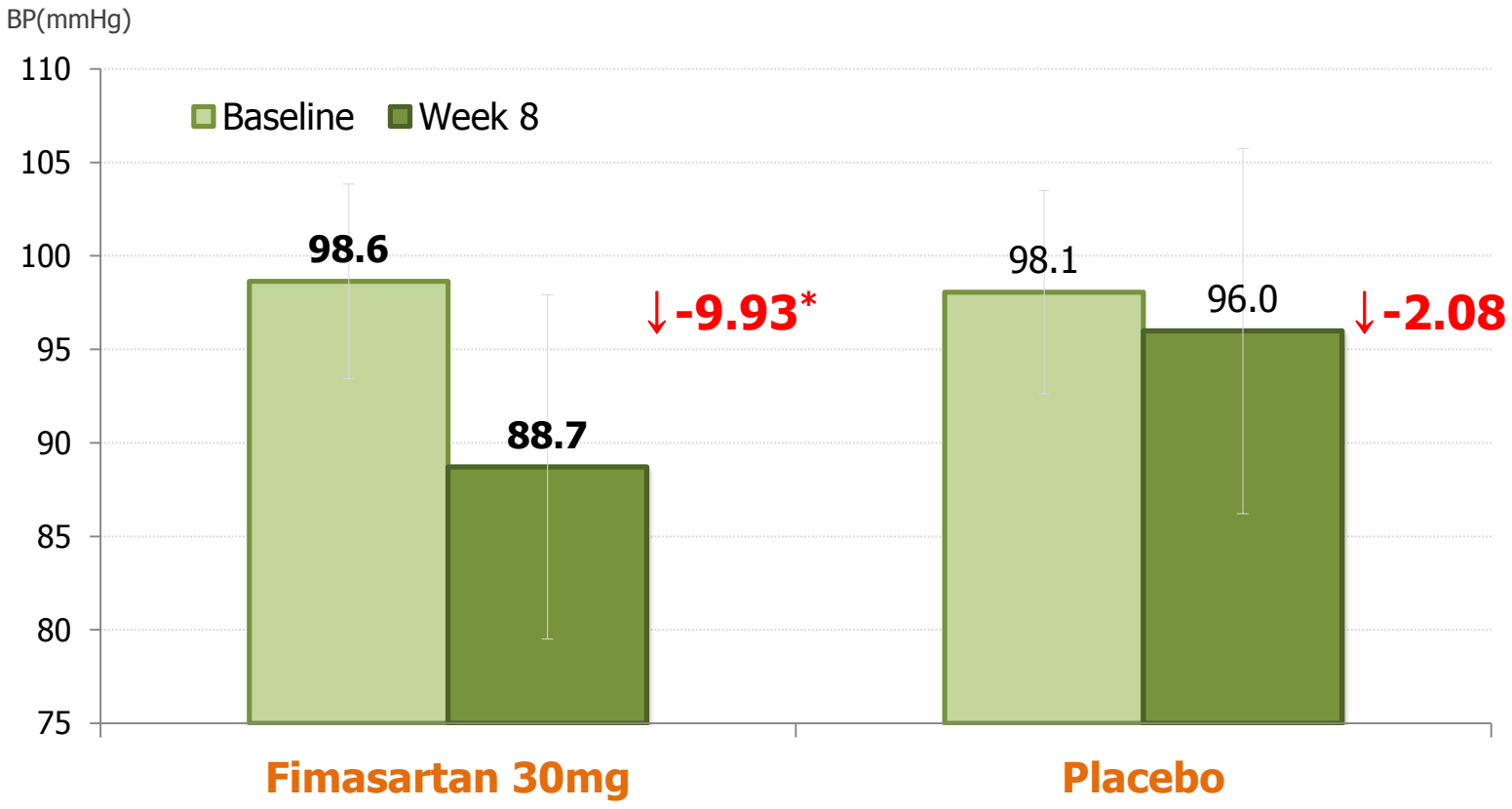
2) Fimasartan 30mg compared to Placebo(two sample t-test)

3) Change = Week 8 – Baseline

*FAS: Full Analysis Set

Primary efficacy results

- Change from baseline in **siDBP** compared to placebo at **week 8** (FAS)



*p<.0001 vs. placebo

Secondary efficacy results

- Change from baseline in **siDBP** compared to valsartan at **week 8** (FAS)

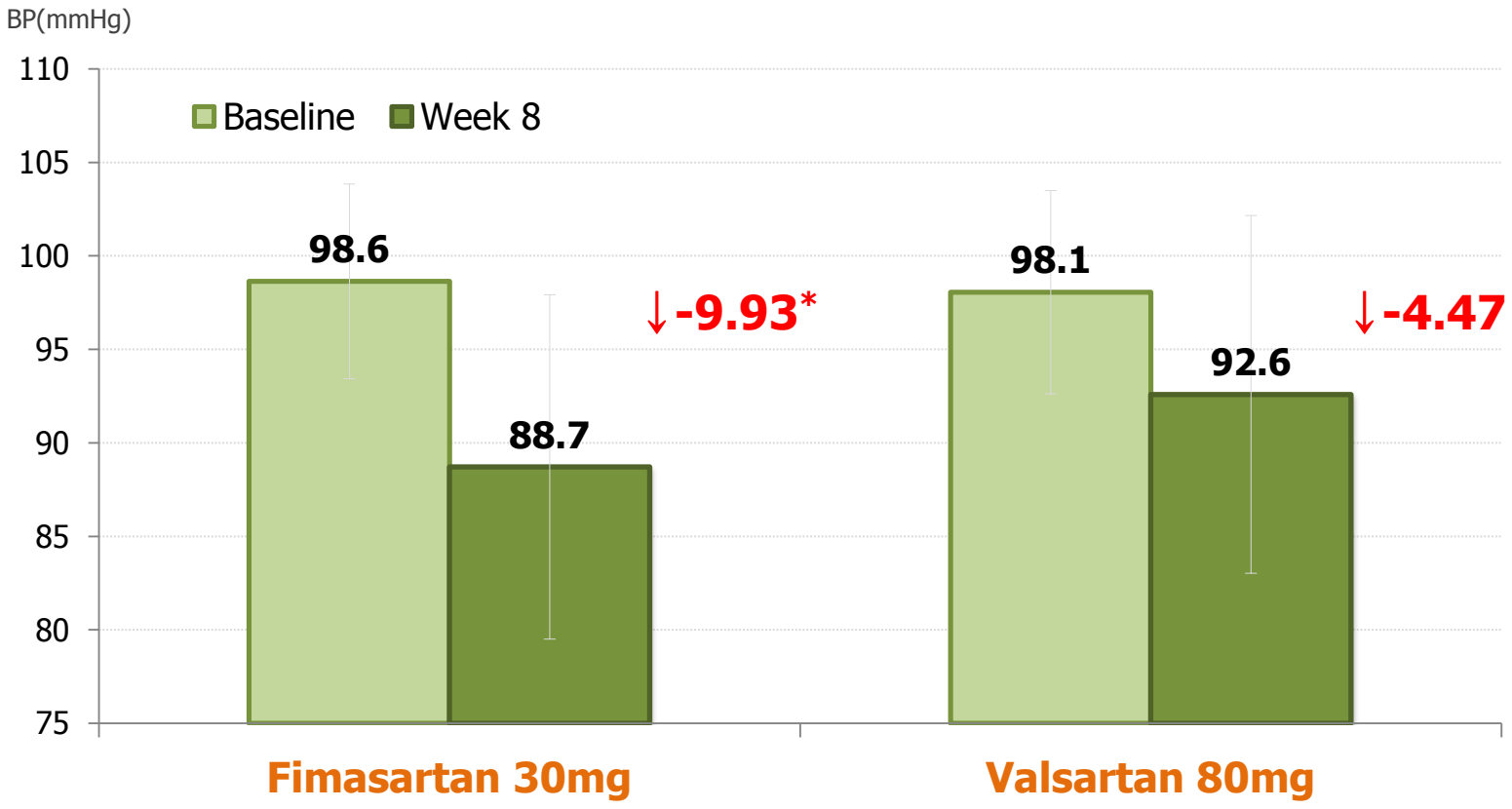
Mean±SD

Visit	Fimasartan 30mg (N=112)	Valsartan 80mg (N=59)	Difference in Change	95% CI[1)]	p-value[2)]
Baseline	98.64±5.20	98.06±5.16	-	-	-
Week 8	88.71±9.21	92.59±9.57	-	-	-
Change[3)]	**-9.93±8.86**	-5.47±8.96	**-4.47±8.89**	(-7.29,-1.64)	0.0021

1) 95% Confidence interval
2) Fimasartan 30mg compared to Valsartan 80mg(two sample t-test)
3) Change = Week 8 – Baseline

Secondary efficacy results

- Change from baseline in **siDBP** compared to valsartan at **week 8** (FAS)



*p=0.0021 vs. valsartan 80mg

Secondary efficacy results

- Change from baseline in **siDBP** compared to each treatment at **week 4** (FAS)

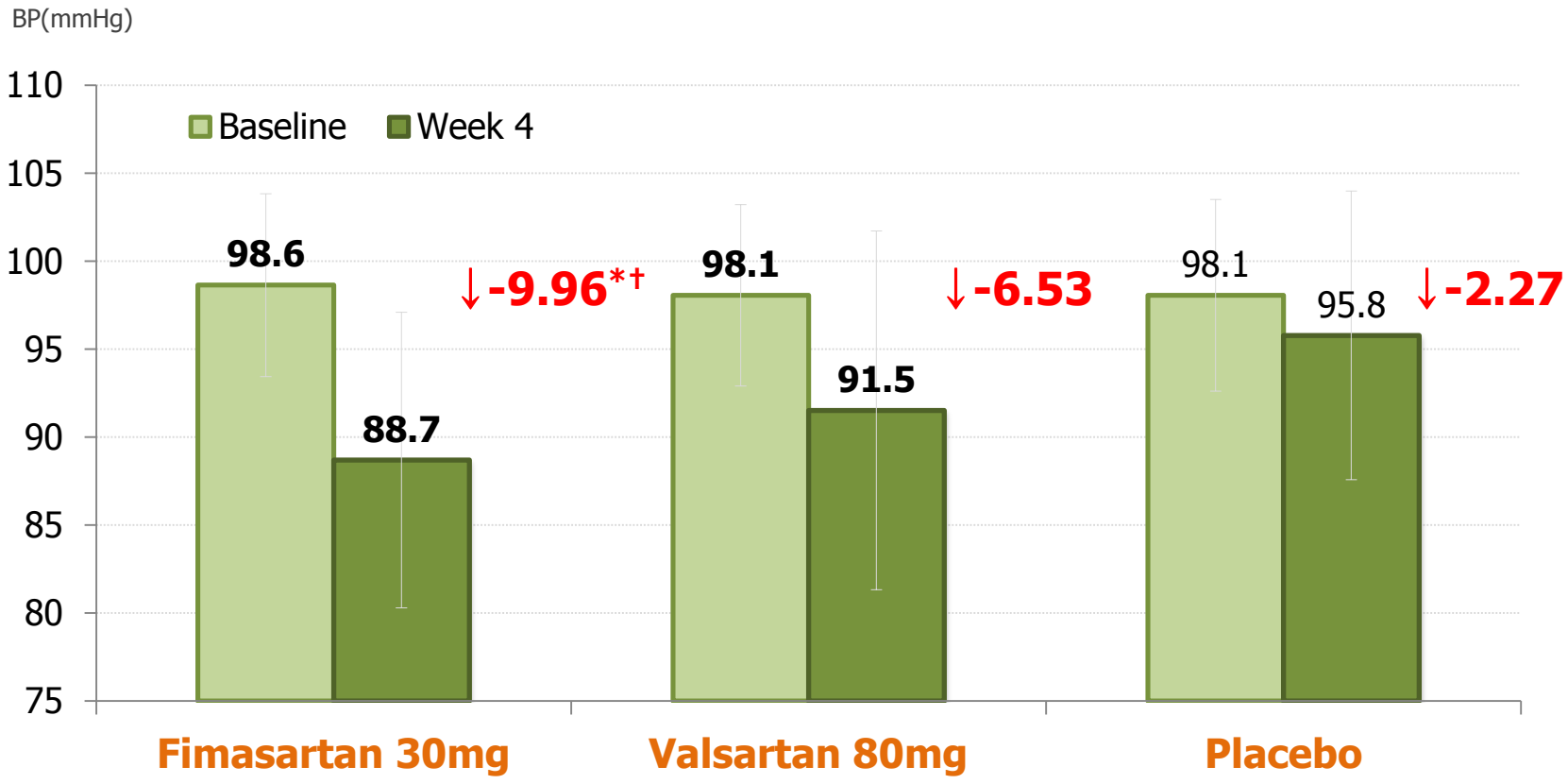
Mean±SD

Visit	Fimasartan 30mg (N=112)	Placebo (N=112)	Valsartan 80mg (N=59)	Difference in Change	95% CI[1)]	p-value[2)]
Baseline	98.64±5.20	98.06±5.44	98.06±5.16	-	-	-
Week 4	88.69±8.40	95.78±8.23	91.52±10.20	-	-	-
Change[3)]	**-9.96±7.73**	-2.27±7.85		**-7.68±7.79**	(-9.74,-5.63)	<.0001
	-9.96±7.73		-6.53±9.58	**-3.42±8.41**	(-6.10,-0.75)	0.0123

1) 95% Confidence interval
2) Two sample t-test
3) Change = Week 4 - Baseline

Secondary efficacy results

- Change from baseline in **siDBP** compared to each treatment at **week 4** (FAS)



*p=0.0123 vs. valsartan 80mg
†p<0.0001 vs. placebo

Secondary efficacy results

- Change from baseline in **siSBP** compared to each treatment at **week 4 and 8** (FAS)

Mean±SD

Visit	Fimasartan 30mg (N=112)	Placebo (N=112)	Valsartan 80mg (N=59)	Difference in Change	95% CI[1]	p-value[2]
Baseline	154.64±11.43	152.94±10.75	151.62±11.64	-	-	-
Week 4	138.46±15.56	150.98±14.52	143.97±15.88			
Week 8	139.29±18.12	150.64±16.35	144.14±15.16	-	-	-
Change[3]	**-16.18±14.44**	-1.95±13.48		**-14.22±13.97**	(-17.90,-10.54)	<.0001
	-16.18±14.44		-7.65±12.89	**-8.52±13.92**	(-12.94,-4.10)	0.0002
Change[4]	**-15.35±16.63**	-2.30±14.91		**-13.05±15.80**	(-17.21,-8.89)	<.0001
	-15.35±16.63		-7.49±13.68	**-7.87±15.68**	(-12.85,-2.89)	0.0021

1) 95% Confidence interval

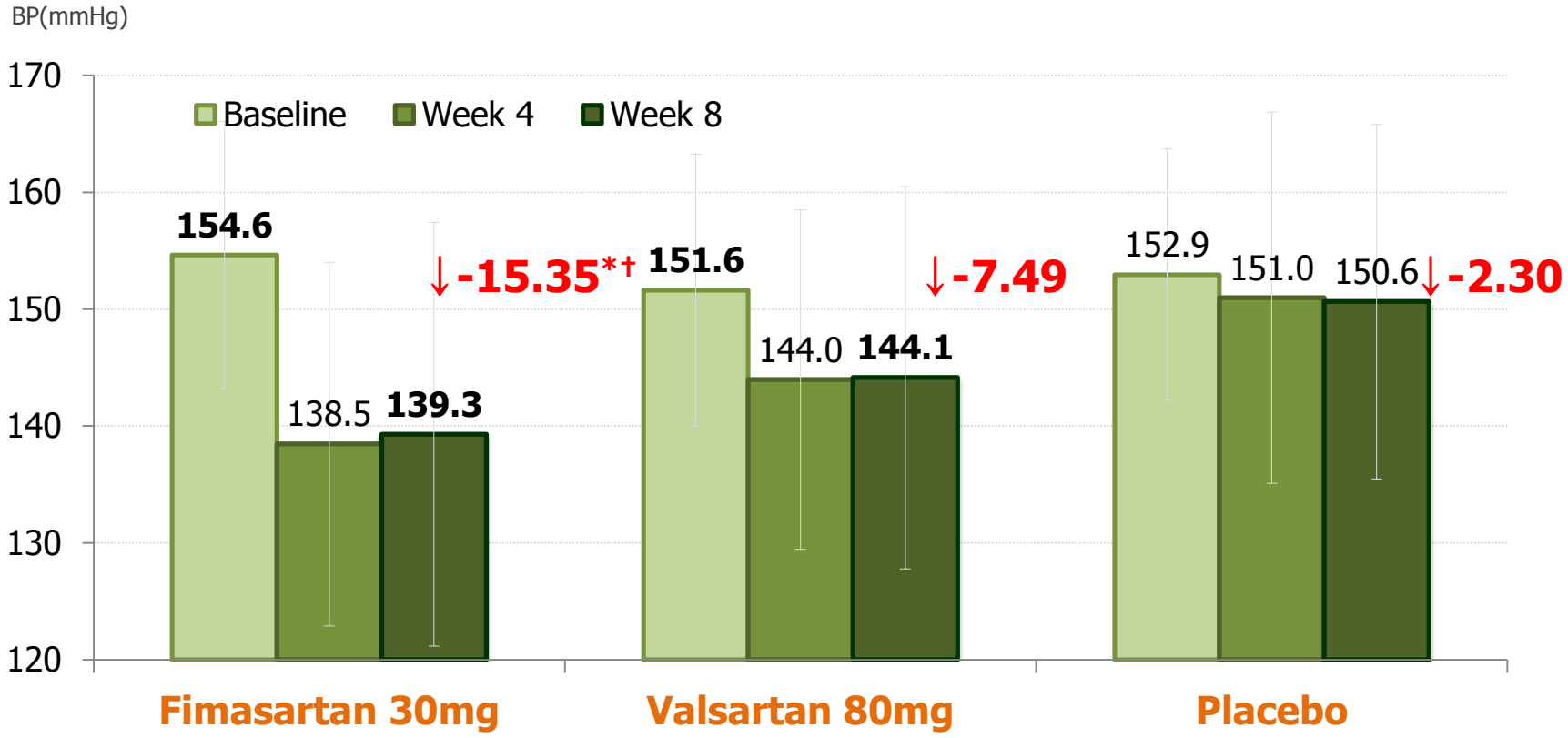
2) two sample t-test

3) Change = **Week 4 – Baseline**

4) Change = **Week 8 - Baseline**

Secondary efficacy results

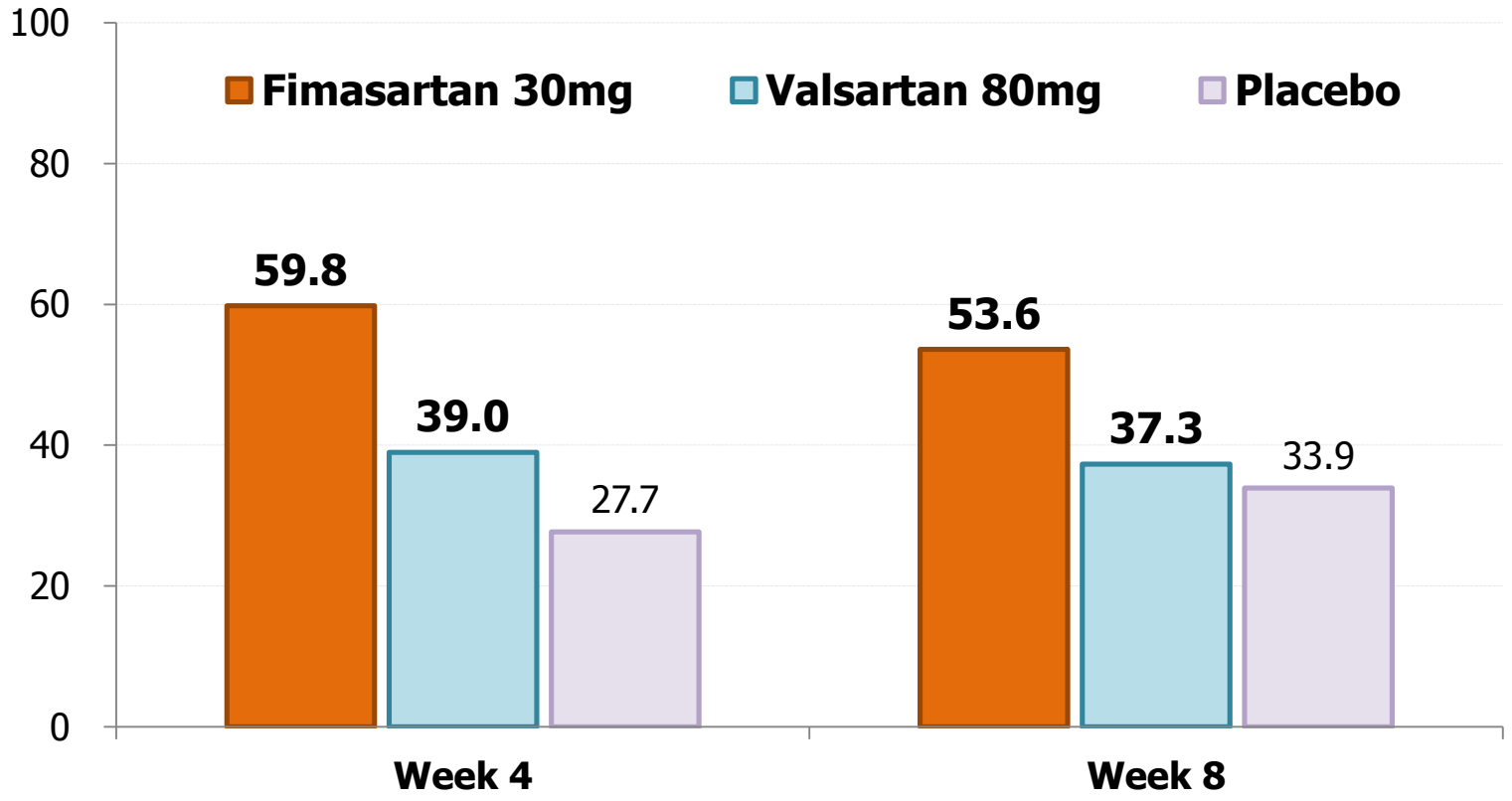
- Change from baseline in **siSBP** compared to each treatment at **week 4 and 8** (FAS)



*p=0.0021 vs. valsartan 80mg
†p<0.0001 vs. placebo

Secondary efficacy results

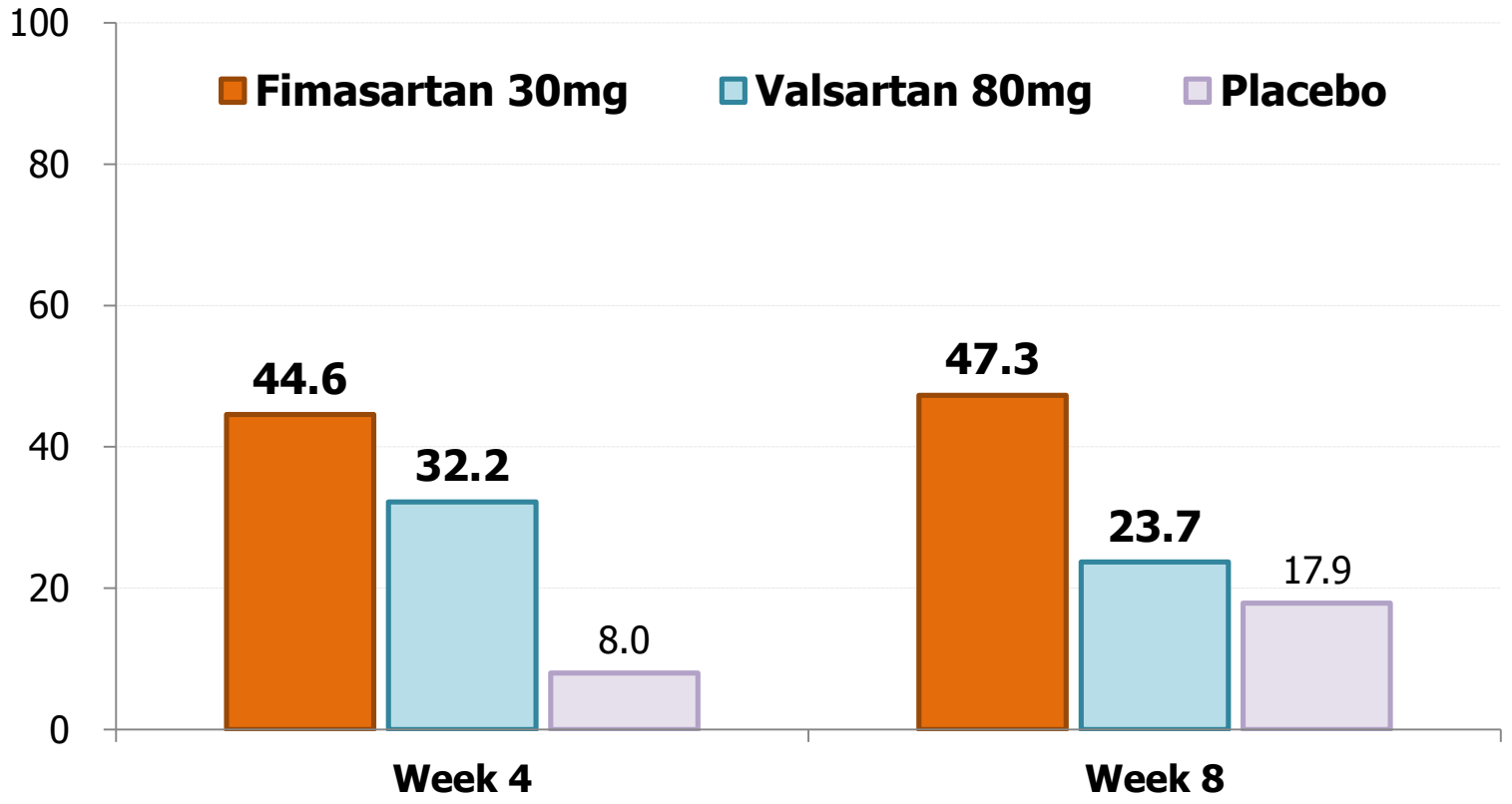
- Comparison of the **Responder rate*** at **week 4 and 8** (FAS)



p<0.0001 vs. placebo at week 4
p=0.0030 vs. placebo at week 8
p=0.0095 vs. valsartan week 4
p=0.0427 vs. valsartan week 8
*siDBP<90mmHg 또는 투여 전 대비 8주 투여 후 ΔsiDBP≥10mmHg.

Secondary efficacy results

- Comparison of the **Controlled rate*** at **week4 and 8** (FAS)



p<0.0001 vs. placebo at week 4
p<0.0001 vs. placebo at week 8

p=0.1150 vs. valsartan week 4
p=0.0027 vs. valsartan week 8

*siDBP가 90mmHg 미만이고, siSBP 140mmHg 미만인 피험자의 비율.
각 측정 시점에서 중도탈락하여 결측된 피험자들 은 모두 non-responder로 간주.

Overall Summary of TEAEs

	All TEAEs				TEAEs related to study drug			
	Fimasartan 30mg (N=115)	Placebo (N=115)	Valsartan 80mg (N=59)	Total (N=289)	Fimasartan 30mg (N=115)	Placebo (N=115)	Valsartan 80mg (N=59)	Total (N=289)
Number of Subject, n(%) [event]	22(19.1) [33]	26(22.6) [47]	8(13.6) [15]	56(19.4) [95]	1(0.9) [1]	2(1.7) [3]	0(0.0) [0]	3(1.0) [4]
95% Confidence Interval	(11.9, 26.3)	(15.0, 30.3)	(4.8, 22.3)	(14.8, 23.9)	(0.0, 4.7)	(0.2, 6.1)	(0.0, 6.1)	(0.2, 3.0)
p-value [1)]				**0.3585**				**0.804**
Severity [event]								
Mild	31	45	13	89	1	3	0	4
Moderate	2	2	2	6	0	0	0	0
Severe	0	0	0	0	0	0	0	0
Relationship to Study Drug [event]								
Certain	0	0	0	0	0	0	0	0
Probable/Likely	0	0	0	0	0	0	0	0
Possible	1	3	0	4	1	3	0	4
Unlikely	32	44	15	91	0	0	0	0
Number of Subject with Serious Aes	0	0	0	0	0	0	0	0
Exact 95% Confidence Interval	(0.0, 3.2)	(0.0, 3.2)	(0.0, 6.1)	(0.0, 1.3)	(0.0, 3.2)	(0.0, 3.2)	(0.0, 6.1)	(0.0, 1.3)
AEs Leading to Discontinuance	0	0	0	0	0	0	0	0
Exact 95% Confidence Interval	(0.0, 3.2)	(0.0, 3.2)	(0.0, 6.1)	(0.0, 1.3)	(0.0, 3.2)	(0.0, 3.2)	(0.0, 6.1)	(0.0, 1.3)

시험약을 한번이라도 투여 받은 피험자 289명 분석 (임상시험에 등록되었으나, 임상시험용의약품을 투여 받기 전에 탈락한 피험자는 안전성 분석에서 제외)
TEAEs = Treatment-Emergent Adverse Events
1) Difference between treatment groups(chi-square test)

Fimasartan 30mg

Low-dose임에도

우수한 혈압강하 효과를 확인하였고

기타 효과들을 확인하기 위한

다양한 임상이 진행 중인만큼

그 결과가 기대됨

Do you have any questions?