

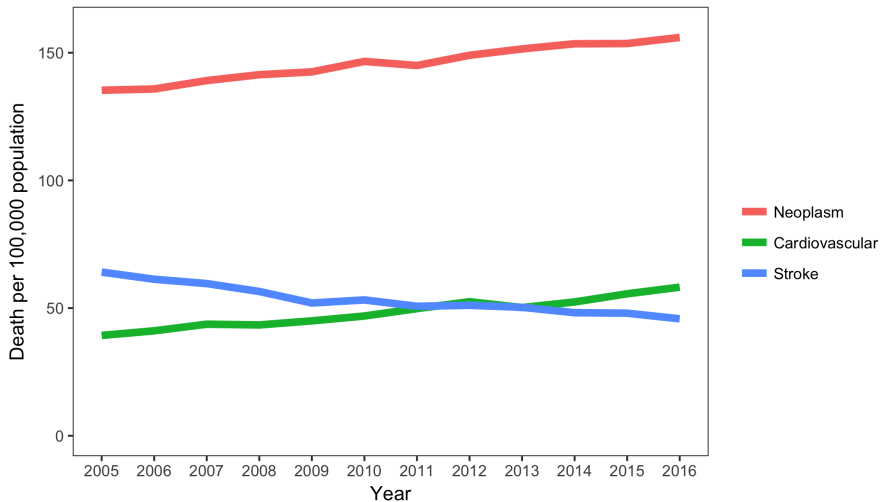
뉴로 Symposium
Differential Benefit and
Real World Clinical Practices of Edarbi



Kwang-Yeol Park

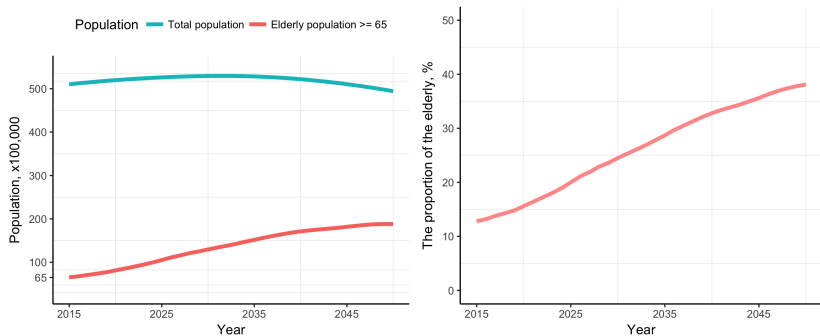
Dep. of Neurology, Chung-Ang University, Seoul South Korea

Secular trend of mortality in Korea



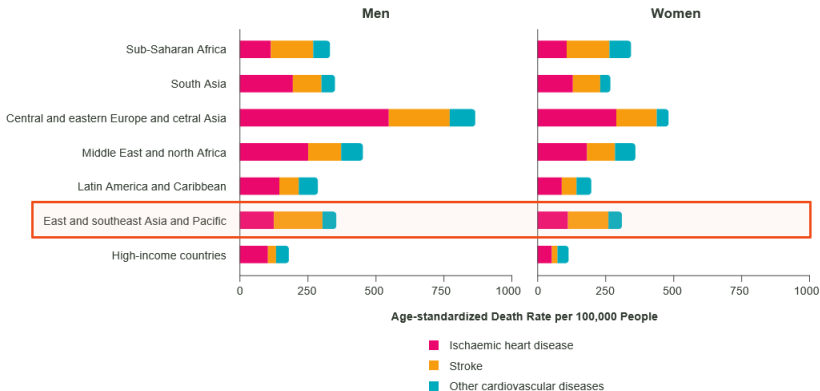
http://www.index.go.kr/potal/main/EachDtlPageDetail.do?idx_cd=1012 accessed on Aug. 26, 2018

Rapid increase of Korean elderly population



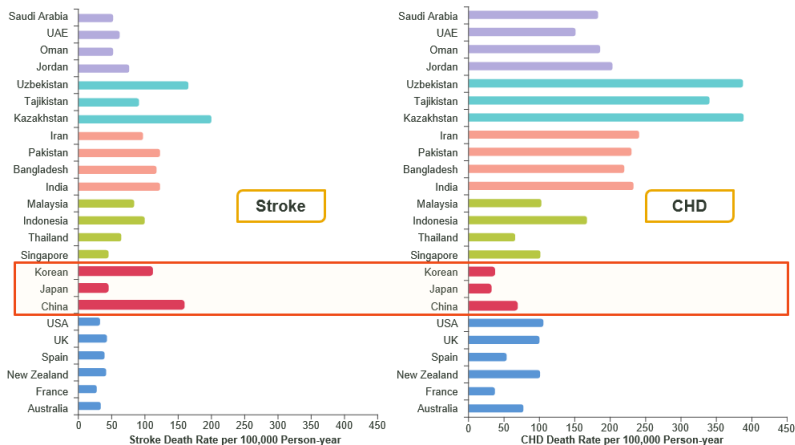
<http://kosis.kr/visual/populationKorea/>

다른 지역에 비해 동아시아에서 높은 발병률을 보이는 Stroke (1)



1. Tzoulaki I, et al. Worldwide Exposures to Cardiovascular Risk Factors and Associated Health Effects: Current Knowledge and Data Gaps. *Circulation*. 2016;133:2314-2333.

다른 지역에 비해 동아시아에서 높은 발병률을 보이는 Stroke (2)



UAE=United Arab Emirates; USA=United States of America; UK=United Kingdom; CHD=coronary heart disease.

1. Ueshima H, et al. Cardiovascular Disease and Risk Factors in Asia: A Selected Review. *Circulation*. 2008;118:2702-2709.

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- 1 Hypertension and Stroke
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- 3 New ARB, Azilsartan
- 4 Summary

Risk factors for Stroke

Non-modifiable factors

- ① Age
- ② Sex
- ③ Race
- ④ Family history

Modifiable factors

- ① **Hypertension**
- ② Diabetes
- ③ Dyslipidemia
- ④ Smoking
- ⑤ Carotid disease
- ⑥ Cardiac disease such as atrial fibrillation
- ⑦ Obesity
- ⑧ Inactivity

IHD vs Stroke and SBP

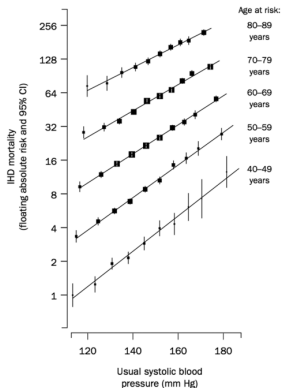


Figure 1. Ischemic heart disease (IHD) mortality

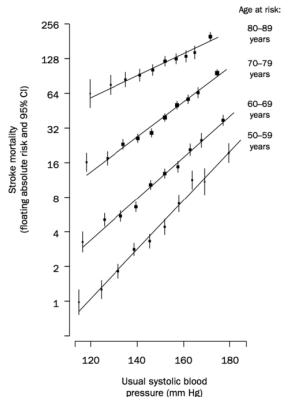
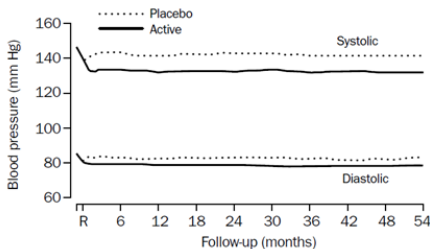


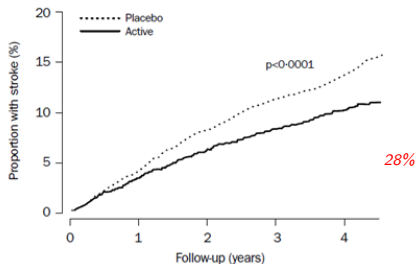
Figure 2. Stroke mortality

PROGRESS

Randomized trial enrolling 6,105 patients with a history of TIA or stroke (ischemic or hemorrhagic) to perindopril+ indapamide or placebo



BP difference: 9/4 mm Hg



Cumulative incidence of Stroke

PROGRESS Collaborative Group et al. Lancet 2001;358:1033-41

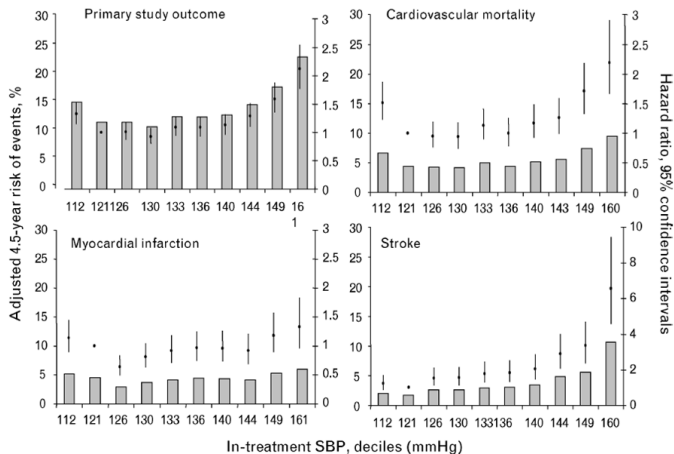
미국 및 유럽 이노제 단일제 사용현황

	USD (actual exchange rate/MNF)		
	FY 2017		
	Volume - Absolute	Share	%Growth
USA	229,241,833		-6.7%
C03A3 : THIAZIDES AND ANALOGUES PLAIN	229,241,833	100.0%	-6.7%
CHLORTALIDONE	128,377,880	56.0%	-4.2%
METOLAZONE	39,914,726	17.4%	-9.4%
HYDROCHLOROTHIAZIDE	33,875,024	14.8%	-13.1%
CHLOROTHIAZIDE	19,581,824	8.5%	0%
INDAPAMIDE	6,940,927	3.0%	-18.0%
METHYLCLOTHIAZIDE	551,452	0.2%	-20.8%
BENDROFLUMETHIAZIDE	0	0.0%	
POLYTHIAZIDE	0	0.0%	

	USD (actual exchange rate/MNF)		
	FY 2017		
	Volume - Absolute	Share	%Growth
Europe & Canada	217,641,370		1.1%
C03A3 : THIAZIDES AND ANALOGUES PLAIN	217,641,370	100.0%	1.1%
INDAPAMIDE	119,963,659	55.1%	1.6%
HYDROCHLOROTHIAZIDE	52,278,247	24.0%	6.1%
BENDROFLUMETHIAZIDE	14,671,102	6.7%	-17.8%
CHLORTALIDONE	11,021,874	5.1%	10.0%
BENDROFLUMETHIAZIDE + POTASSIUM	10,671,011	4.9%	-3.3%
XIPAMIDE	5,121,483	2.4%	-0.7%
METOLAZONE	2,407,018	1.1%	8.0%
CLOPAMIDE	559,391	0.3%	-1.8%
CHLOROTHIAZIDE	449,720	0.2%	-3.7%
AMILORIDE + HYDROCHLOROTHIAZIDE	353,185	0.2%	-7.6%
METIPAMIDE	144,576	0.1%	-5.3%
CYCLOPENTHIAZIDE	103	0.0%	-68.5%

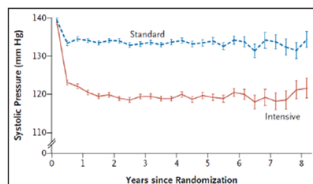
Data Source : IMS MIDAS, 2017, FY2017; 2017.4~2018.3.

Ontarget study



The lower BP looks beneficial in stroke: ACCORD

- 4733 patients with type 2 DM
- SBP
< 140 mm Hg vs. < 120 mm Hg



Outcome	Intensive Therapy (N = 2363)		Standard Therapy (N = 2371)		Hazard Ratio (95% CI)	P Value
	no. of events	%/yr	no. of events	%/yr		
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20
Prespecified secondary outcomes						
Nonfatal myocardial infarction	126	1.13	146	1.28	0.87 (0.68–1.10)	0.25
Stroke						
Any	36	0.32	62	0.53	0.59 (0.39–0.89)	0.01
Nonfatal	34	0.30	55	0.47	0.63 (0.41–0.96)	0.03

N Engl J Med. 2010 362(17):1575-85

	ACCORD
Population	4733 DM
Intervention	<120 vs. <140
Primary endpoint	MI, Stroke, CV death
SBP at 1yr	119 vs. 134
Outcome/yr	1.87% vs. 2.09%
All cause mortality/yr	1.28% vs. 1.19%
Stroke	0.32% vs. 0.53% *

Post-hoc analysis of PROFESS trial: U-shaped Relationship between Mean BP and Subsequent Vascular Events

Adjusted risk of clinical outcomes by mean SBP Level in 20,330 patients with a recent ischemic stroke

	Mean SBP Level, mmHg				
	High-Normal (130-<140; n=6,004)	Very Low-Normal (<120; n=1,919)	Low-Normal (120-<130; n=3,982)	High (140-<150; n=4,520)	Very High (≥150; n=3,905)
AHR (95% CI)					
Stroke*	1.00	1.29 (1.07-1.56)	1.10 (0.95-1.28)	1.23 (1.07-1.41)	2.08 (1.83-2.37)
Stroke, MI, or vascular death†	1.00	1.31 (1.13-1.52)	1.16 (1.03-1.31)	1.24 (1.11-1.39)	1.94 (1.74-2.16)
Fatal Stroke‡	1.00	0.63 (0.26-1.49)	1.01 (0.64-1.89)	1.50 (0.94-2.40)	2.51 (1.62-3.09)

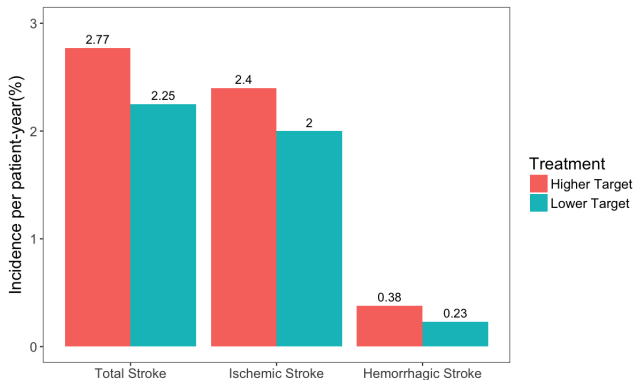
*Adjusted for age, sex, previous stroke, congestive heart failure, diabetes, MI, hypertension, current smoking status, baseline National Institutes of Health Stroke Scale score, qualifying stroke due to small vessel disease, previous transient ischemic attack, and Asian ethnicity; †Adjusted for age, sex, previous stroke, congestive heart failure, diabetes, MI, hyperlipidemia, coronary artery disease, current smoking status, antihypertensive medication use at baseline, baseline National Institutes of Health Stroke Scale score, qualifying stroke due to small vessel disease, body mass index (calculated as weight in kilograms divided by height in meters squared), black race, white race, previous transient ischemic attack, and Asian ethnicity; ‡Adjusted for age, sex, previous stroke, congestive heart failure, diabetes, MI, treatment with angiotensin receptor blocker, antiplatelet treatment at baseline, baseline National Institutes of Health Stroke Scale score, body mass index (calculated as weight in kilograms divided by height in meters squared), and previous transient ischemic attack.

BP, blood pressure; PROFESS=The Prevention Regimen for Effectively Avoiding Second Strokes; AHR=adjusted hazard ratio; MI=myocardial infarction; SBP=systolic blood pressure, CI=confidence interval.

1. Ovbiagele B, et al. Level of systolic blood pressure within the normal range and risk of recurrent stroke. *JAMA*. 2011;306:2137-2144.

BP targets in recent lacunar stroke: SPS3

3020 patients assigned to a SBP target of 130–149 or < 130 mm Hg.
After 1 year, mean SBP was 138 mm Hg vs. 127 mm Hg.



The SPS3 Study Group. Lancet 2013;382:507-15

2014 AHA/ASA 2ndary Prevention of Stroke Guideline

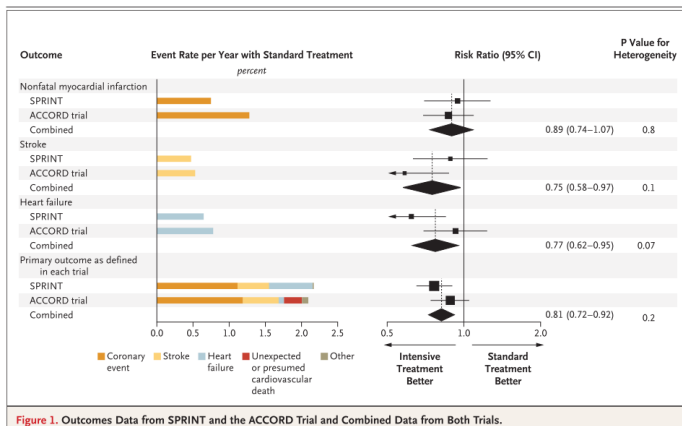
**For patients with a recent lacunar stroke, it might be reasonable to target an SBP of <130 mmHg (Class IIb; Level of Evidence B).
(Revised recommendation)**

SPRINT and ACCORD

	ACCORD	SPRINT
Population	4733 DM	9631 non-DM
Intervention	<120 vs. <140	<120 vs. <140
Primary endpoint	MI, Stroke, CV death	+ HF, other ACS
SBP at 1yr	119 vs. 134	121 vs. 136
Outcome/yr	1.87% vs. 2.09%	1.65% vs. 2.19% *
All cause mortality/yr	1.28% vs. 1.19%	1.03% vs. 1.40% *
Stroke	0.32% vs. 0.53% *	0.41% vs. 0.47%

N Engl J Med. 2010 362(17):1575-85; *N Engl J Med.* 2015 Nov 26;373(22):89mm:2103-16

SPRINT and ACCORD



2017 US - 2018 Korea and Europe

Whelton PK, et al.

2017 High Blood Pressure Clinical Practice Guideline

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASPC/NMA/PCNA
Guideline for the Prevention, Detection, Evaluation, and Management
of High Blood Pressure in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on
Clinical Practice Guidelines

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THE KOREAN SOCIETY OF HYPERTENSION

2018년 고혈압 진료지침



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ESC/ESH GUIDELINES

2018 ESC/ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the
European Society of Cardiology (ESC) and the European Society of
Hypertension (ESH)

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ESC Committee for Practice Guidelines (EPG), European Society of Hypertension (ESH) Council, ESC National Cardiac Societies having participated in the writing process. (For a complete list of the members of the Task Force, see the Appendix.)

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2017 ACC/AHA 가이드라인 진단 기준=고혈압 정의



- ✓ 14년만에 고혈압 정의를 개정함
- ✓ 낮아진 고혈압 경계치, **130-139/80-89mmHg = 고혈압 1단계**

SBP, DBP(mmHg)	JNC7	2017 ACC/AHA
<120 and <80	Normal BP	Normal BP
120–129 and <80	Prehypertension	Elevated BP
130–139 or 80–89	Prehypertension	Stage 1 hypertension
140–159 or 90–99	Stage 1 hypertension	Stage 2 hypertension
≥160 or ≥100	Stage 2 hypertension	Stage 2 hypertension

JNC=Joint National Committee; ACC=The American College of Cardiology; AHA=American Heart Association; BP=blood pressure; SBP=systolic blood pressure; DBP=diastolic blood pressure.

1. Whelton PK, et al. *Hypertension*. 2017 Nov 13. [Epub ahead of print]

2017 ACC/AHA 가이드라인: BP Threshold and BP Goal

Clinical Condition(s)	BP Threshold (mmHg)	BP Goal (mmHg)
General		
Clinical CVD or 10-year ASCVD risk $\geq 10\%$	$\geq 130/80$	$< 130/80$
No clinical CVD and 10-year ASCVD risk $< 10\%$	$\geq 140/90$	$< 130/80$
Older persons (≥ 65 years of age; noninstitutionalized, ambulatory, community-living adults)	≥ 130 (SBP)	< 130 (SBP)
Specific comorbidities		
Diabetes mellitus	$\geq 130/80$	$< 130/80$
Chronic kidney disease	$\geq 130/80$	$< 130/80$
Chronic kidney disease after renal transplantation	$\geq 130/80$	$< 130/80$
Heart failure	$\geq 130/80$	$< 130/80$
Stable ischemic heart disease	$\geq 130/80$	$< 130/80$
Secondary stroke prevention	$\geq 140/90$	$< 130/80$
Secondary stroke prevention(lacunar)	$\geq 130/80$	$< 130/80$
Peripheral arterial disease	$\geq 130/80$	$< 130/80$

ACC=The American College of Cardiology; AHA=American Heart Association; ASCVD=atherosclerotic cardiovascular disease; BP=blood pressure; CVD=cardiovascular disease; SBP=systolic blood pressure.

1. Whelton PK, et al. *Hypertension*. 2017 Nov 13. [Epub ahead of print]

2017 ACC/AHA 가이드라인: Recommendation for Out-of-Office and Self-Monitoring

COR	LOE*	Recommendation
I	A ^{SR}	Out-of-office BP measurements are recommended to confirm the diagnosis of hypertension and for titration of BP-lowering medication, in conjunction with telehealth counseling or clinical interventions.

Clinic	HBPM	Daytime ABPM	Nighttime ABPM	24-Hour ABPM
120/80	120/80	120/80	100/65	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/85	120/70	130/80
160/100	145/90	145/90	140/85	145/90

*The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

ACC=The American College of Cardiology; AHA=American Heart Association; COR=class of recommendation; LOE=level of evidence; SR=systematic review; BP=blood pressure; HBPM=home blood pressure monitoring; ABPM= ambulatory blood pressure monitoring.

1. Whelton PK, et al. *Hypertension*. 2017 Nov 13. [Epub ahead of print]

KSH Guideline 2013 vs 2018

2013				2018			
혈압 분류	SBP (mmHg)		DBP (mmHg)	혈압분류	SBP (mmHg)		DBP (mmHg)
정상	<120	그리고	<80	정상	<120	그리고	<80
고혈압전단계 1기	120-129	또는	80-84	주의혈압	120-129	그리고	<80
고혈압전단계 2기	130-139	또는	85-89	<u>고혈압 전단계</u>	130-139	또는	80-89
고혈압1기	140-159	또는	90-99	고혈압1기	140-159	또는	90-99
고혈압2기	≥160	또는	≥100	고혈압2기	≥160	또는	≥100

SBP=systolic blood pressure; DBP=diastolic blood pressure.

1. KSH Treatment Guideline 2013. 2. KSH Treatment Guideline 2018 보도자료.

Korea Target BP Goal 2018

상황	SBP (mmHg)	DBP (mmHg)
단순고혈압	140	90
고위험군*	130	80
심혈관질환**	130	80
노인 고혈압	140	90
당뇨병		
심혈관질환 없음	140	85
심혈관질환 [†] 있음	130	80
만성콩팥병		
알부민뇨 없음	140	90
알부민뇨 동반됨	130	80
뇌졸중	140	90

*10년 심뇌혈관질환 발생률 > 15%, 노인인 노인 기준에 따름; †관상동맥질환, 말초혈관질환, 대동맥질환, 심부전 및 좌심실비대.

SBP=systolic blood pressure; DBP=diastolic blood pressure.

1. KSH Treatment Guideline 2018 보도자료.

Europe guideline

Summary - Office BP Thresholds for Treatment



Age group	Office SBP treatment threshold (mmHg)					Diastolic treatment Threshold (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke/TIA	
18–65 years	≥ 140	≥ 140	≥ 140	≥ 140 ^a	≥ 140 ^a	≥ 90
65–79 years	≥ 140	≥ 140	≥ 140	≥ 140 ^a	≥ 140 ^a	≥ 90
≥ 80 years	≥ 160	≥ 160	≥ 160	≥ 160	≥ 160	≥ 90
Diastolic treatment threshold (mmHg)	≥ 90	≥ 90	≥ 90	≥ 90	≥ 90	

^aTreatment may be considered in these very high-risk patients with high-normal SBP (i.e. SBP 130–140 mmHg)

www.escardio.org/guidelines

Williams B, Mancia G et al. Eur Heart J (2018); doi:10.1093/eurheartj/ehy339
Williams B, Mancia G et al. J Hypertens (2018); doi:10.1097/HJH.0000000000001940

Summary - Office BP Target Ranges

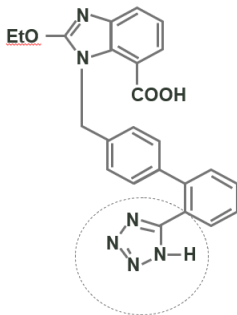


Age group	Office SBP treatment target ranges (mmHg)					DBP treatment target range (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke/ TIA	
18–65 years	Target to 130 or lower if tolerated Not <120	Target to 130 or lower if tolerated Not <120	Target to <140 to 130 if tolerated	Target to 130 or lower if tolerated Not <120	Target to 130 or lower if tolerated Not <120	<80 to 70
65–79 years	Target to <140 to 130 if tolerated	Target to <140 to 130 if tolerated	Target to <140 to 130 if tolerated	Target to <140 to 130 if tolerated	Target to <140 to 130 if tolerated	<80 to 70
≥ 80 years	Target to <140 to 130 if tolerated	Target to <140 to 130 if tolerated	Target to <140 to 130 if tolerated	Target to <140 to 130 if tolerated	Target to <140 to 130 if tolerated	<80 to 70
DBP treatment target range (mmHg)	< 80 to 70	< 80 to 70	< 80 to 70	< 80 to 70	< 80 to 70	

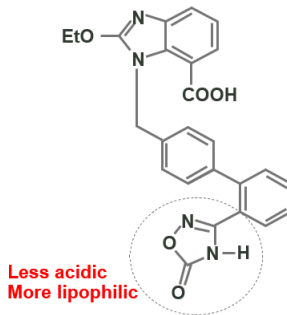
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Azilsartan 개발 History

Candesartan

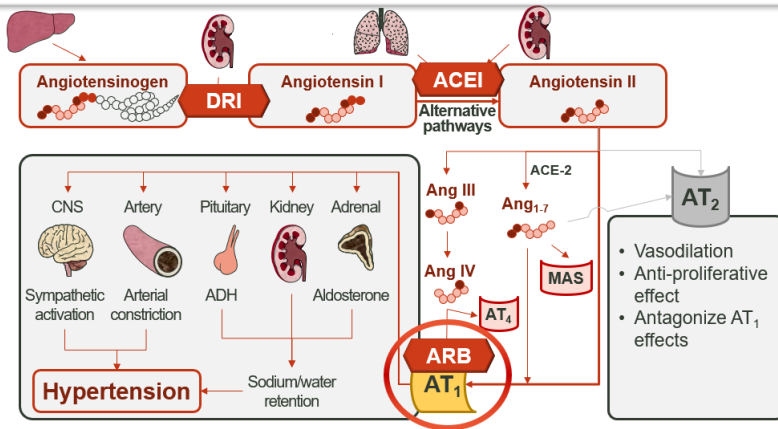


Azilsartan



1. Kurts TW, et al. Differential pharmacology and benefit/risk of azilsartan compared to other sartans. *Vasc Health Risk Manag*. 2012;8:133-143.

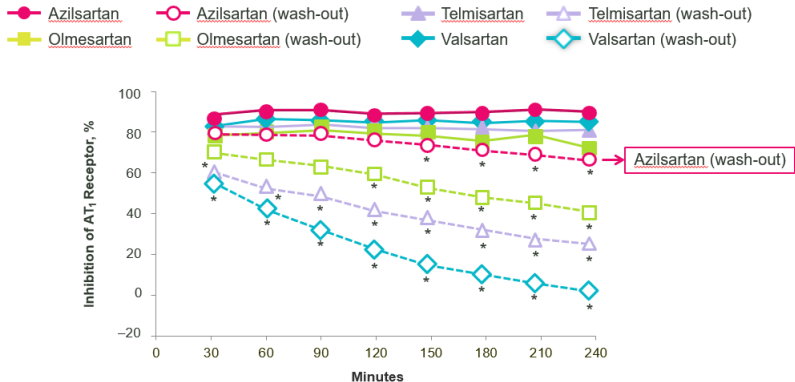
RAAS 수용체 차단제



ACE=angiotensin converting enzyme; ACEI=ACE inhibitor; ADH=antidiuretic hormone; Ang=angiotensin; ARB=angiotensin receptor blocker; AT₁₋₄=angiotensin II type 1-4 receptor; DRI=direct renin inhibitor; RAAS=renin-angiotensin-aldosterone-system.

1. Victor RG. In: Bonow RO, et al, eds. *Braunwald's Heart Disease*. 9th edition. Volume I. 2. Philadelphia, PA: Elsevier, 2012:935-954. 3. Santos PCJL, et al. *J Pharmacol Sci*. 2012;120:77-88. 4. Volpe M, et al. *Vasc Health Risk Manag*. 2012;8:371-380. 5. Becari C, et al. *Braz J Med Biol Res*. 2011;44:914-919.

Rate of Dissociation of ARBs from AT₁ Receptor



Statistically significant difference. Azilsartan Medoxomil is a prodrug of Azilsartan.

* $P < 0.05$; ** $P < 0.01$ vs presence of the compound.

ARB=angiotensin receptor blocker; AT₁=angiotensin II type 1 receptor.

1. Ojima M, et al. *J Pharmacol Exp Ther*. 2011;336:801-808.

SPRINT Formulary

Class	Drug	Available Strengths	Usual Dose Range / day	Usual Daily Frequency
Diuretic	Chlorthalidone	25 mg	12.5-25 mg	1
	Furosemide	20 mg, 40 mg, 80 mg	20-80 mg	2
	Spironolactone	25 mg	25-50 mg	1
	Triamterene/HCTZ	75/50 mg	37.5/25 – 75/50 mg	1
Ace Inhibitor	Amiloride	5 mg	5-10 mg	1-2
	Lisinopril	5 mg, 10 mg, 20 mg, 40 mg	5-40 mg	1
Angiotensin Receptor Blocker	Losartan	25 mg, 50 mg, 100 mg	25-100 mg	1-2
	Azilsartan	40 mg, 80 mg	40-80 mg	1
	Azilsartan/ chlorthalidone	40/12.5 mg, 40/25 mg	40/12.5 – 40/25 mg	1
Calcium Channel Blockers	Diltiazem	120 mg, 180 mg, 240 mg, 300 mg	120-540 mg	1
	Amlodipine	2.5mg, 5mg, 10mg	2.5-10 mg	1
Beta Blockers	Metoprolol Tartate	25mg, 50mg, 100mg	50-200 mg	1-2
	Atenolol	25mg, 50mg, 100mg	25-100 mg	1
	Atenolol/ Chlorthalidone	50/25 mg	50/25 mg	1
Vasodilators	Hydralazine	25 mg, 50 mg, 100 mg	50/25 mg	2
	Minoxidil	2.5 mg, 10 mg	2.5-80 mg	1-2
Alpha 2 Agonist	Guanfacine	1 mg, 2 mg	0.5-2 mg	1
Alpha Blockers	Doxazosin	1 mg, 2 mg, 4 mg, 8 mg	1-16 mg	1
Potassium Supplements	KCL tablets	20 mEq	20-80 mEq	1-2
	KCL oral solution (10%)	20 mEq/15 ml	20-80 mEq	1-2

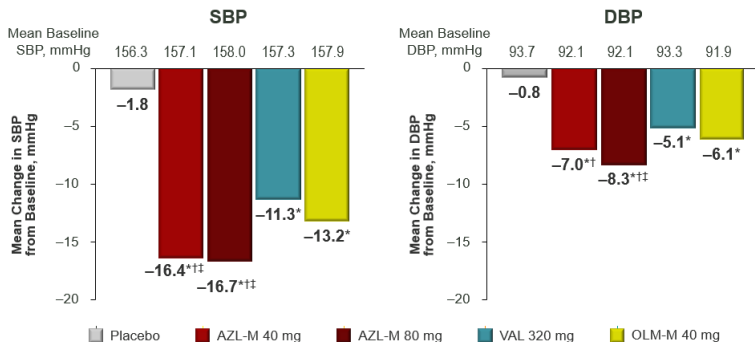
For more detailed information of SPRINT formulary, please refer to "Table S1. SPRINT Formulary" in the Supplementary Appendix.

1. SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015;373:2103-2116.

Azilsartan medoxoil vs Olmesartan and Valsartan:

Change in *Clinic* BP at Week 6

Change From Baseline to Week 6 in Clinic BP (N=1,291)

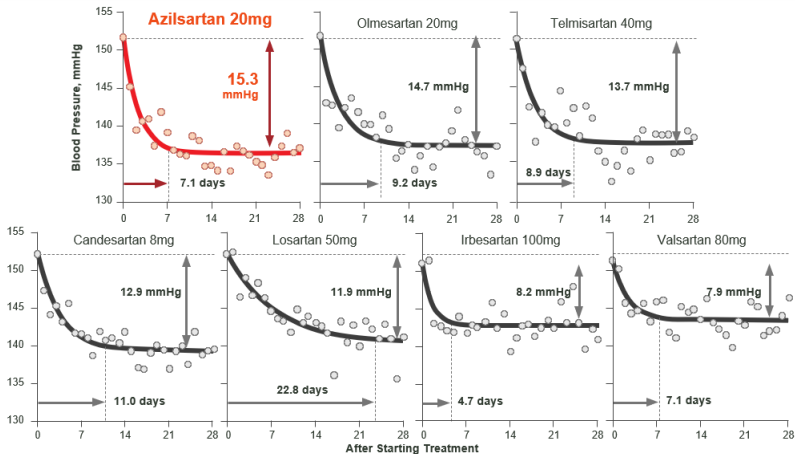


*Statistically significant difference ($P < 0.05$) vs placebo; †Statistically significant difference ($P < 0.05$) vs VAL; ‡Statistically significant difference ($P < 0.05$) vs OLM-M.

AZL-M=azilsartan medoxoil; BP=blood pressure; DBP=diastolic blood pressure; OLM-M=olmesartan medoxoil; SBP=systolic blood pressure; VAL=valsartan.

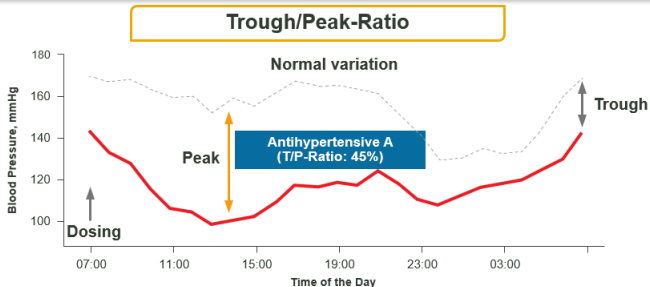
1. White WB, et al. *Hypertension*. 2011;57:413-420. 2. White WB, et al. Presented at: 25th ASH Annual Scientific Meeting, May 1-4, 2010. New York, NY. Poster PO-242.

Blood Pressure-lowering Effect and Stabilization Time



1. Satoh M, et al. The velocity of antihypertensive effects of seven angiotensin II receptor blockers determined by home blood pressure measurements. *J Hypertens.* 2016;34:1218-1223.

고혈압 치료제 효과의 일관성 평가, T/P Ratio



- ✓ 다음 약물 복용까지 얼마나 낮은 혈압으로 잘 유지되는지를 나타내는 지표
- ✓ 개별 환자에서 약제의 선택, 용량, 투약 시간 관리 등을 결정하는 데 유용
- ✓ FDA 가이드라인에 따르면, 고혈압 치료제 최소 T/P ratio는 0.5 이상

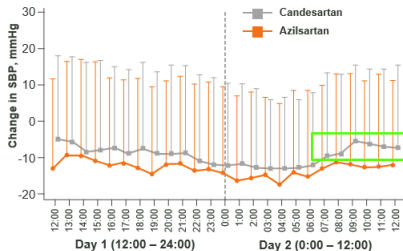
➤ 항고혈압 반응의 일관성을 나내는 유용한 지표!

T/P=through-to-peak; FDA=food and drug administration.

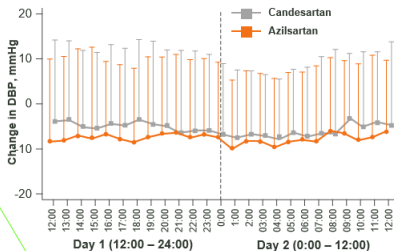
1. Morgan T, et al. Trough to peak ratio as a guide to BP control: measurement and calculation. *J Hum Hypertens*. 1998;12:49-53. 2. Elliott HL. Trough: peak ratio and twenty-four-hour blood pressure control. *J Hypertens Suppl*. 1994;12:S29-S33. 3. Meredith PA. ACE inhibition and AT(1) receptor blockers: efficacy and duration in hypertension. *Heart*. 2000;84(Suppl 1):i39-i41.

AZL vs CAND: 24-Hour Time Course BP

Change in SBP from baseline at week 14 on ABPM



Change in DBP from baseline at week 14 on ABPM



Parameter	Azilsartan (n=311)	Candesartan (n=309)
<i>Trough-to-peak ratio at week 14</i>		
DBP	0.97	0.75
SBP	0.95	0.82

Morning
surge

1. Rakugi H, et al. *Hypertens Res.* 2012;35:552-558.

SBP T/P Ratios & Half Life for Antihypertensives

Drug class	Monotherapy	SBP T/P ratio or range thereof	T _{1/2} or range thereof (h)
ARB	Azilsartan	0.95*	11
	<u>Telmisartan</u>	0.92 [†]	up to 24
	Candesartan	0.82*	9
	<u>Olmesartan</u>	0.60-0.80 [‡]	13
	Valsartan	0.65*	6
	Losartan	0.62*	2 (6-9 for metabolite)
	Irbesartan	0.57*	11-15
CCB	Amlodipine	0.85*	35-50
ACEi	Ramipril	0.50-0.63*	2



가장 안정적으로 혈압강하효과를 지속하는
Azilsartan !

*Mean values; [†]Ratio of reduction in trough BP to reduction in maximal diurnally-adjusted BP; [‡]Not mentioned.

T/P=through-to-peak; SBP=systolic blood pressure; ARB=angiotensin receptor blocker; CCB=calcium channel blocker; ACEi=angiotensin converting enzyme inhibitor; T_{1/2}=half life.

1. Parati G, et al. *Hypertens Res.* 2014;37:187-193.

Take-Home Message

- Stroke and Hypertension are big health issues in rapidly aging societies like Korea.
- Therapeutic target of BP is lowered in new guidelines.
- Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, as a single pill combination, is recommended in all guideline.