

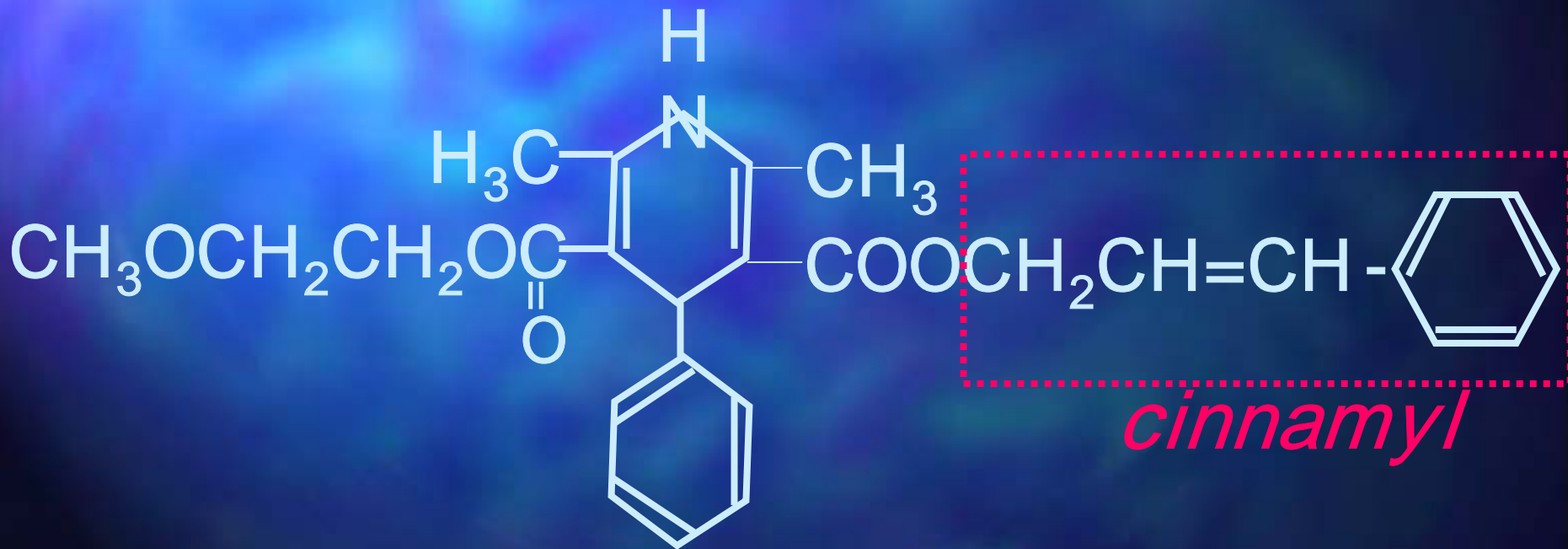
실리디핀의 교감신경 활성화제 효과와 암로디핀과의 비교 임상연구

고려대학교 순환기내과
박창규

Long acting

Ca⁺⁺ channel blocker

CILNIDIPINE



3 types of Ca channel are controlling the BP

심장, 심근세포에 존재
심박담당(pacemaking)
심 자동능억제(심박감소)

transient T

평활근, 골격근, 심근에 존재
흥분수축담당

혈관확장, 심근수축억제

long-lasting L

Neuron의 신경세포에 존재
신경전달물질 유리담당

교감신경에서 NE유리억제 !

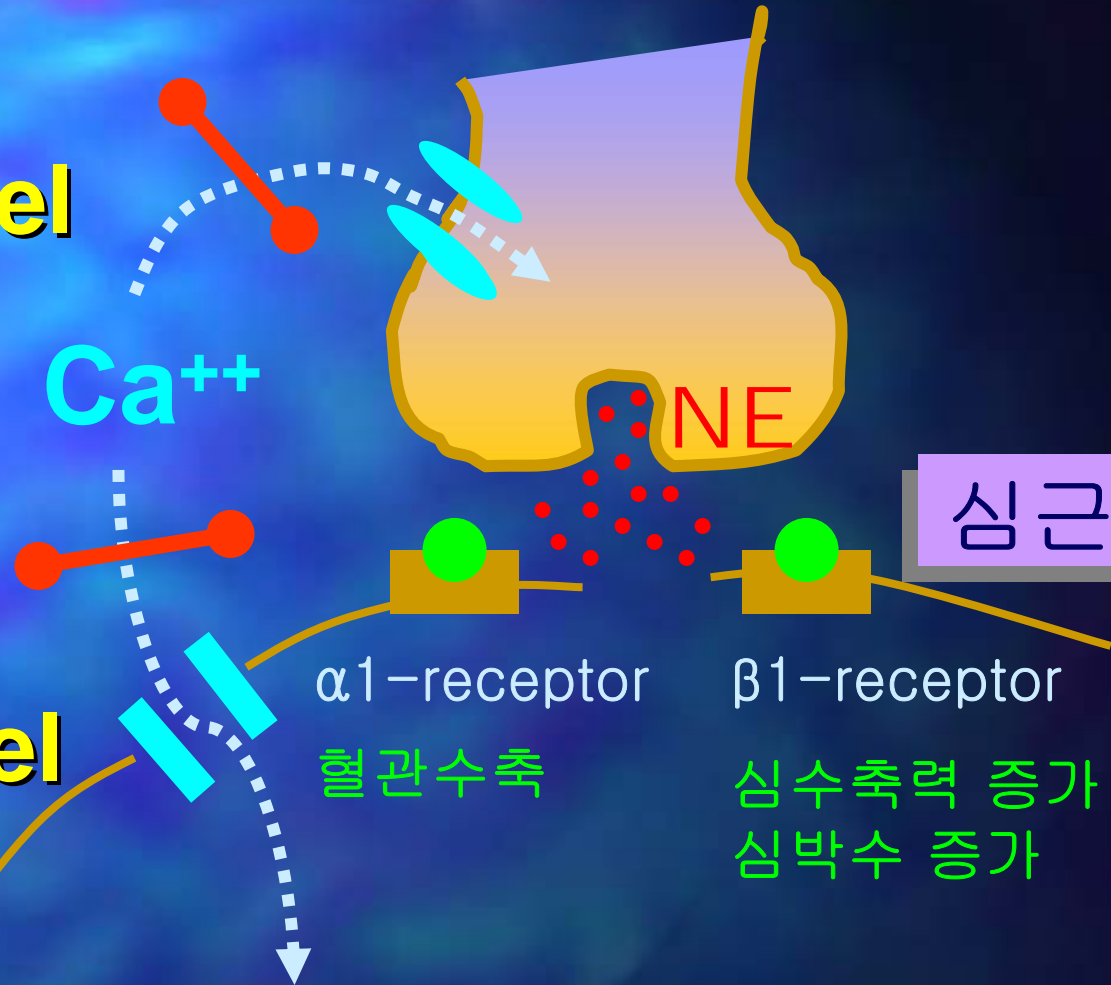
neuronal N

cilnidipine

Mechanism of Dual action

N type Ca channel

교감신경말단

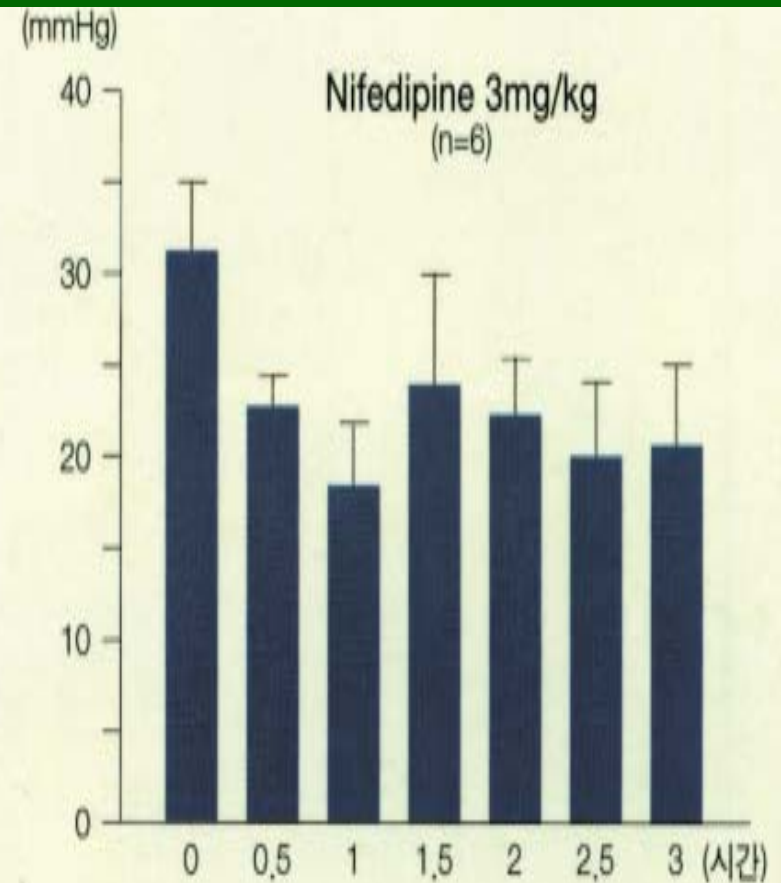
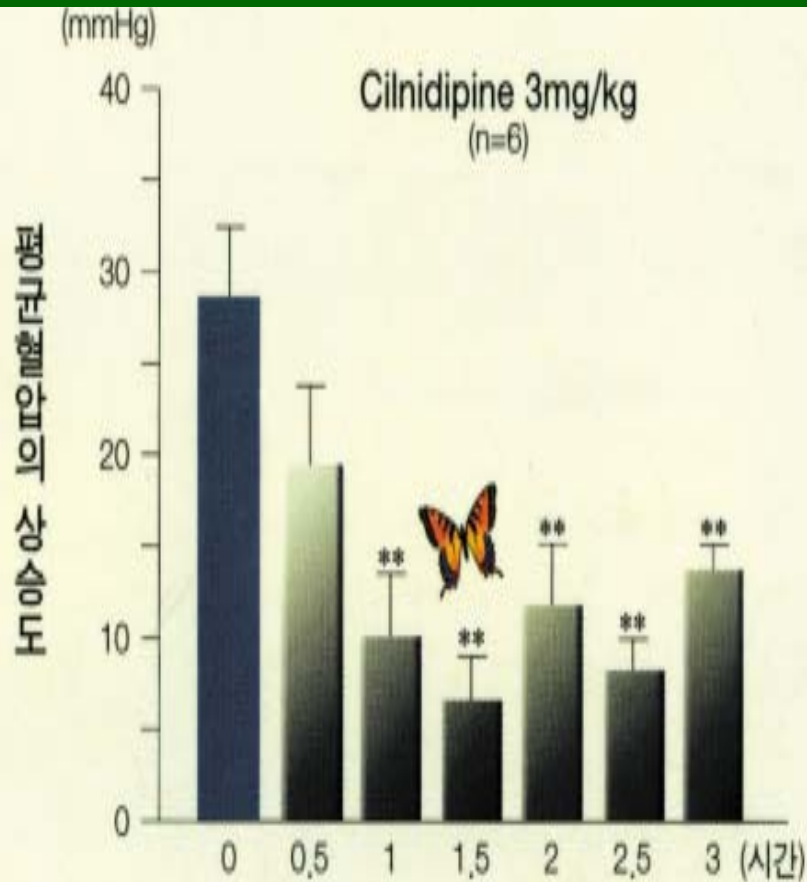


L type Ca channel

혈관평활근

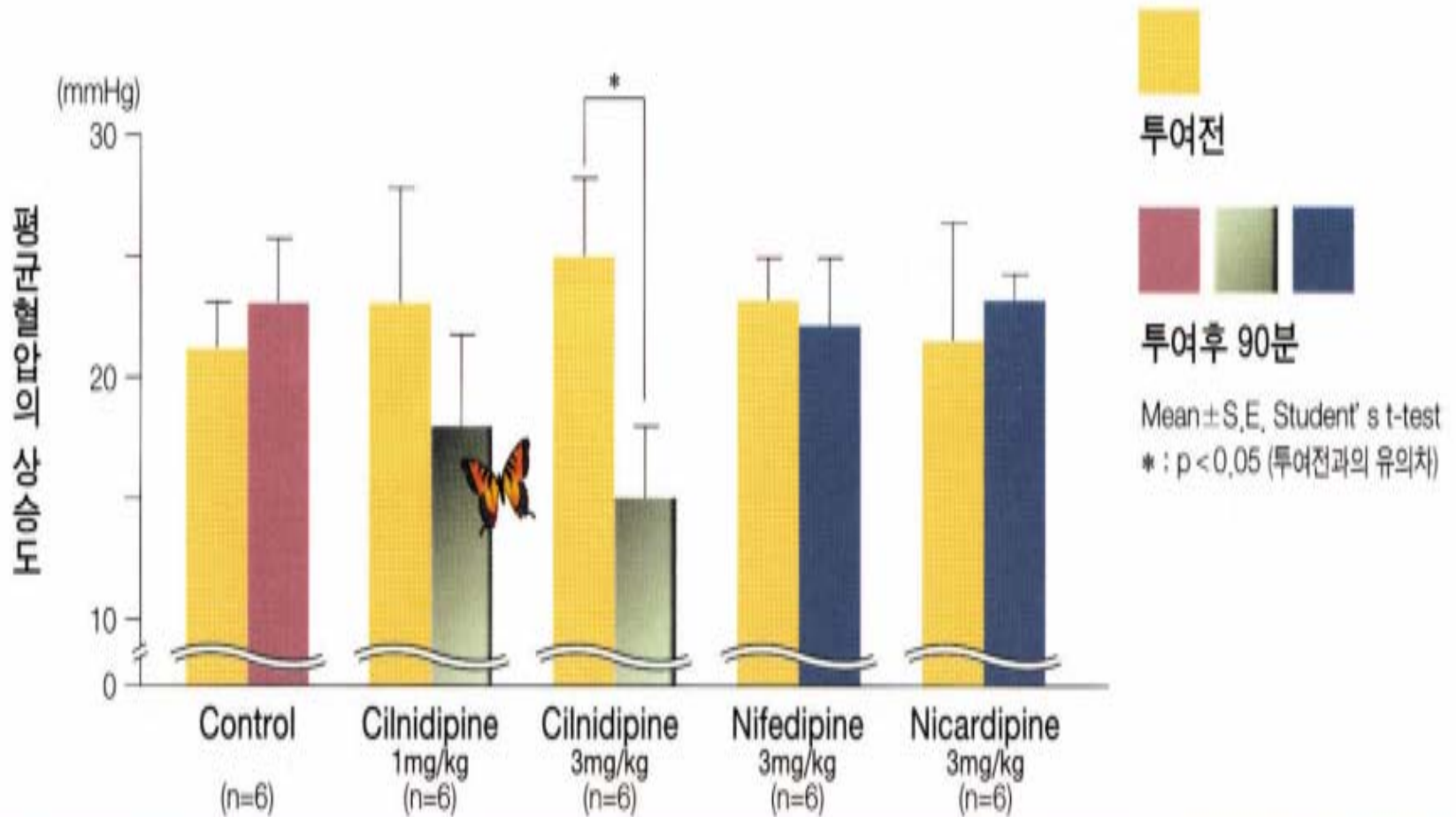
Soft on the heart!

Effect of Cilnidipine on Cold Stress



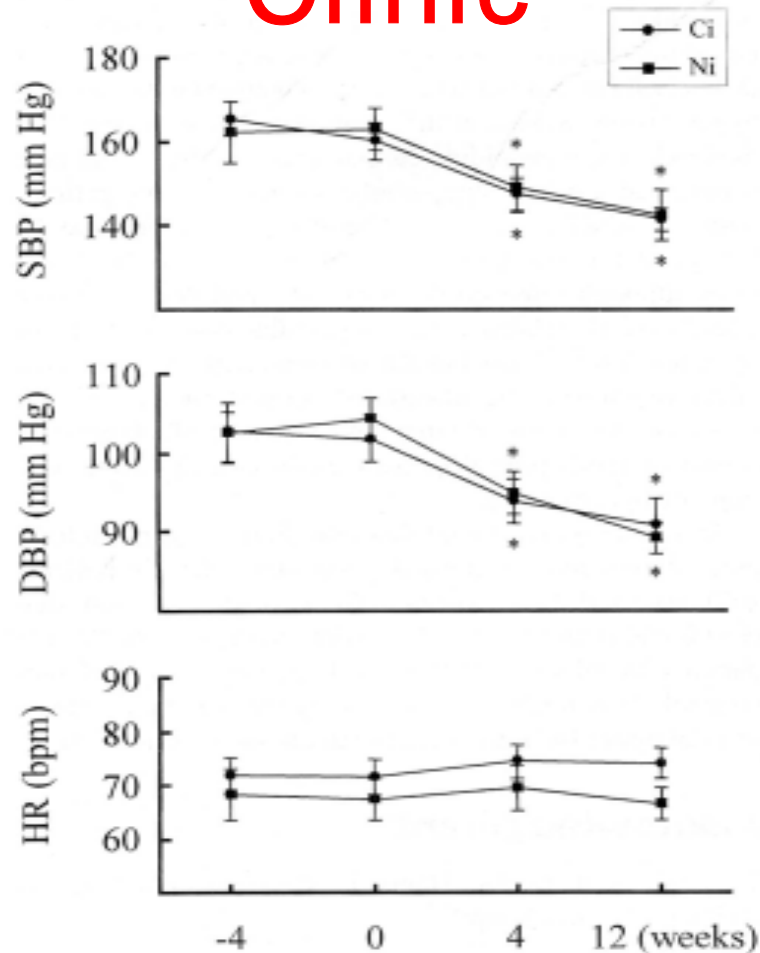
Mean \pm S.E. Dunnett 다중비교 ** : $p < 0.01$ (0시에 대한 유의차)

Effect of Cilnidipine on Air Jet Stress Model

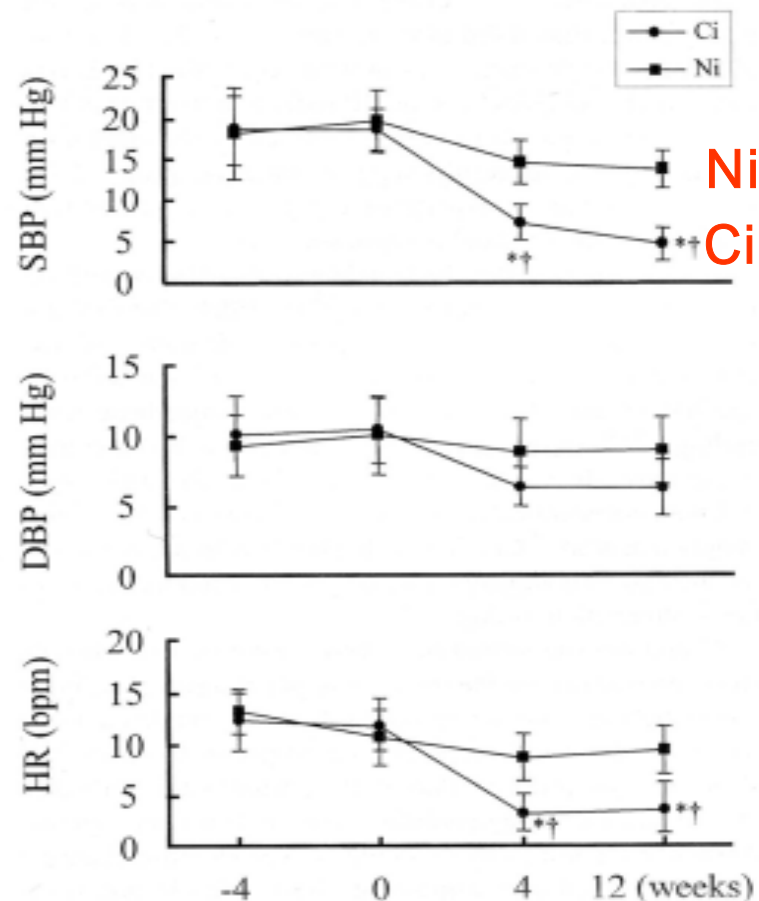


Reduction of White Coat Effect by Cilnidipine

Clinic



ABP



Nifedipine
Cilnidipine



N-type calcium channel blocker
suppress cardiac sympathetic overactivity
(without affecting plasma NE, renin activity)

Effect of Amlodipine and Cilnidipine on Cardiac Sympathetic Nervous System and Neurohormonal Status in Essential Hypertension

Hypertension

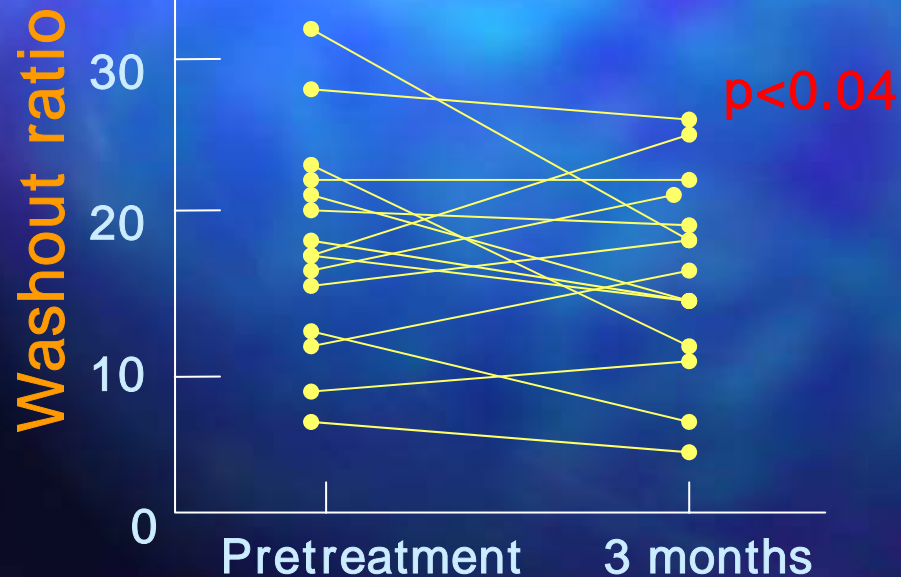
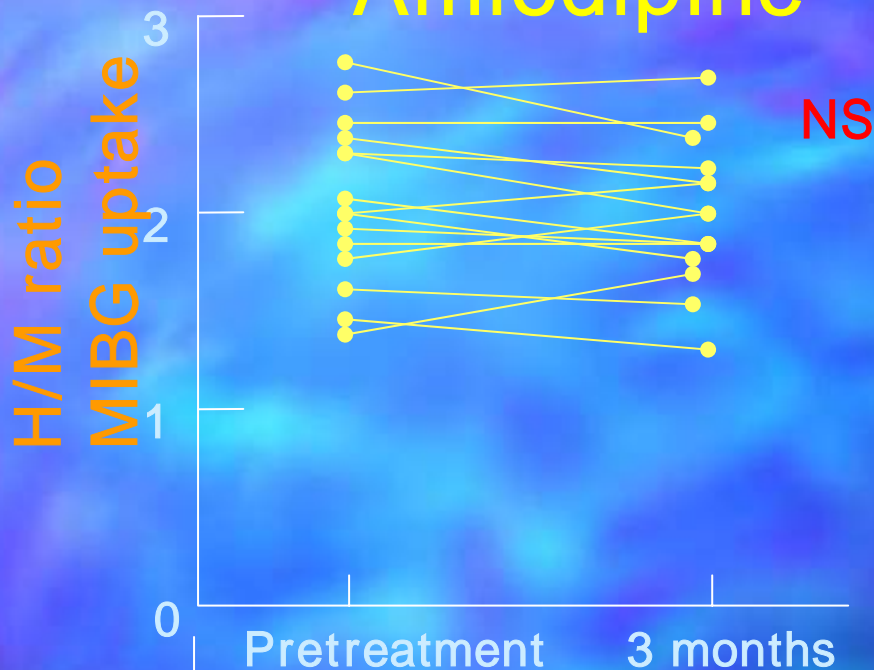
1999;33:1447-1452

Changes in Hemodynamics, Plasma Norepinephrine Concentration, and Plasma Renin Activity (n=47)

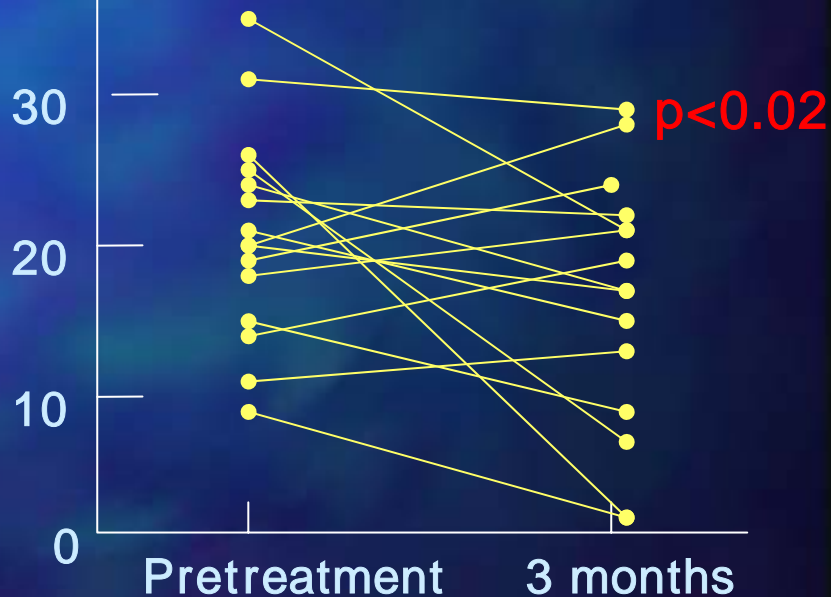
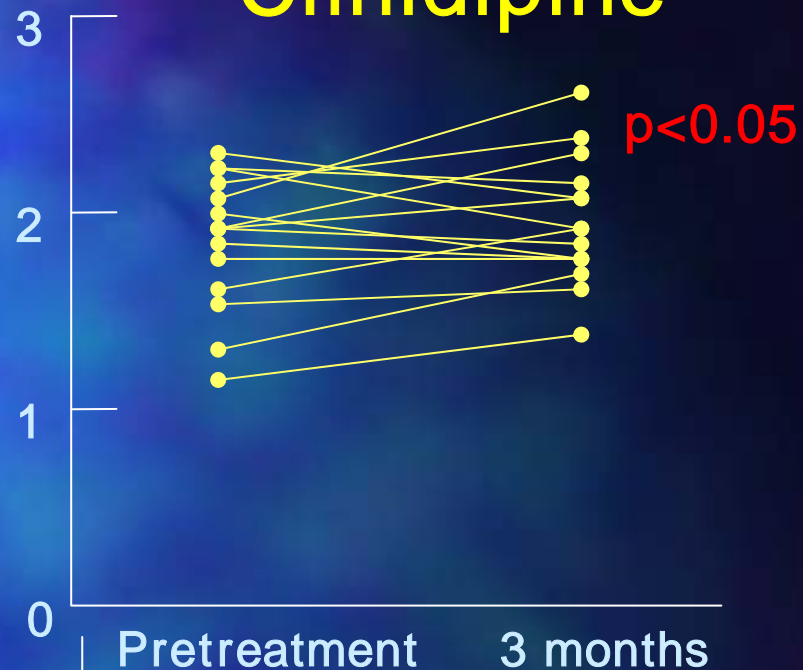
Variable	Amlodipine		Cilnidipine	
	Before	3month After	Before	3month After
Systolic BP(mmHg)	158±12	130±21 *	161±13	132±17 *
Diastolic BP(mmHg)	104±25	83±6 *	106±22	84±8 *
HR (bpm)	77±6	77±7	79±7	78±8
NE (nmol/L)	1.25±0.51	1.49±0.71	1.67±0.7	1.54±0.62
Renin (nmol/L)	0.44±0.73	0.24±0.23	0.24±0.2	0.22±0.23

* p<0.001

Amlodipine

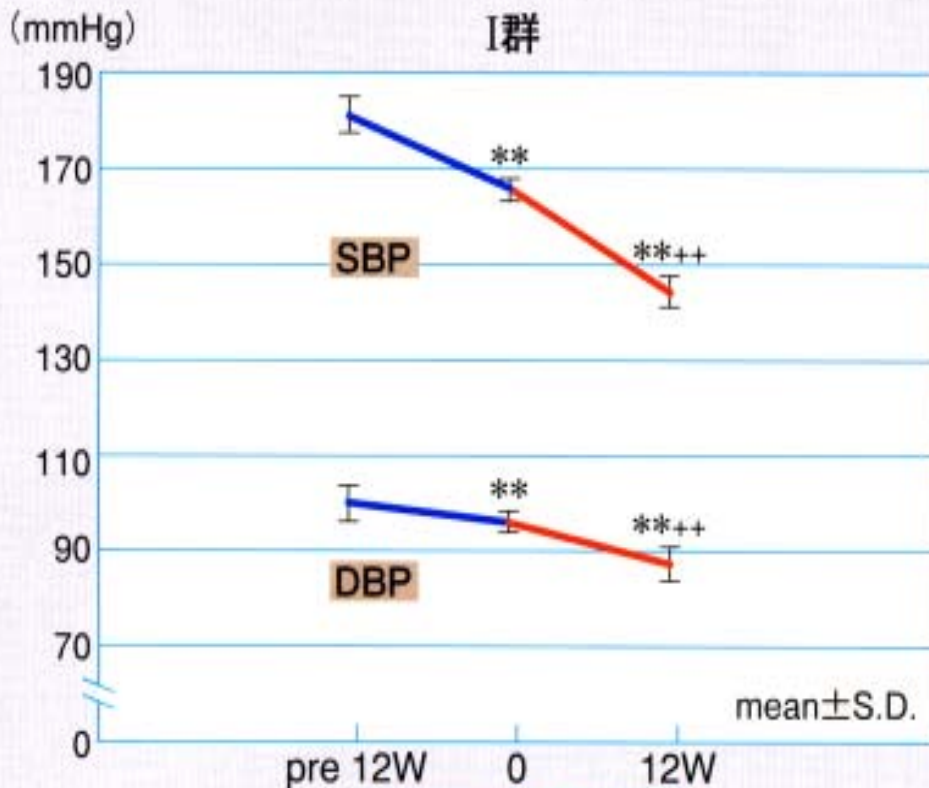


Cilnidipine

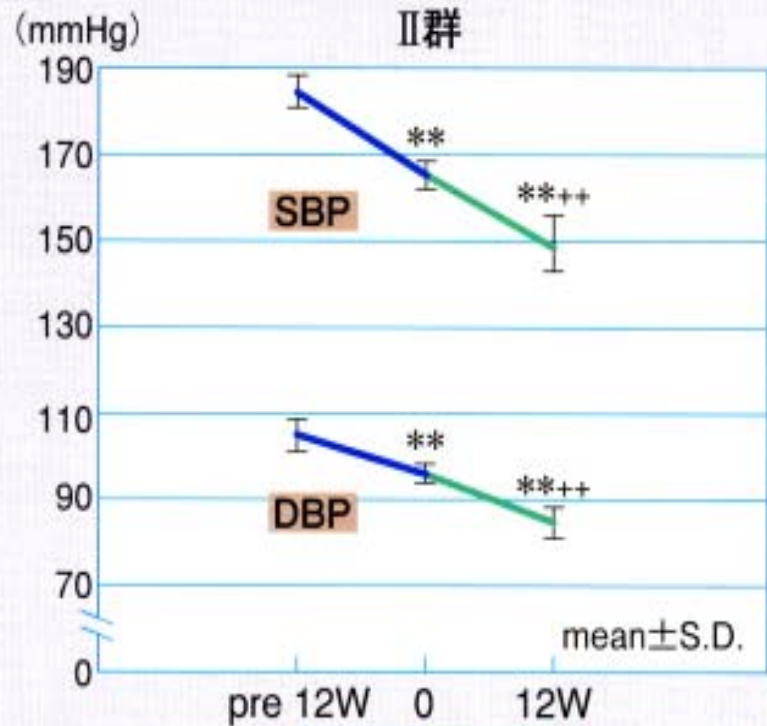


Effect of antianxiety drug,
cilnidipine on workday
blood pressure elevation and
cardiac hypertrophy

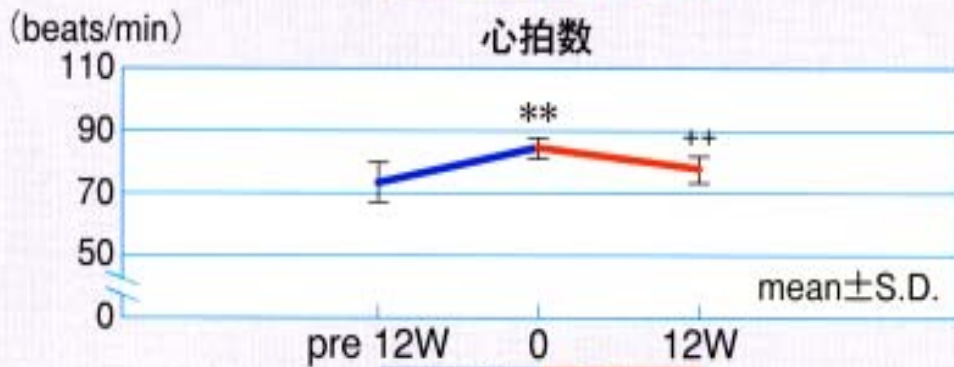
Journal of Japan Physicians Association.
2001;16:1-12.



Amlodipine Cilnidipine



Amlodipine Amlodipine + 항불안약



Amlodipine Cilnidipine

**p < 0.01 (Pre12W와의 비교)
 ++p < 0.01 (Amlodipine 단독투여 종료시와의 비교 ; Dunnett의 다중 비교)

Ambulatory Blood Pressure
Monitoring in patients with
Essential Hypertension Treated
with a New Calcium Antagonist,
Cilnidipine

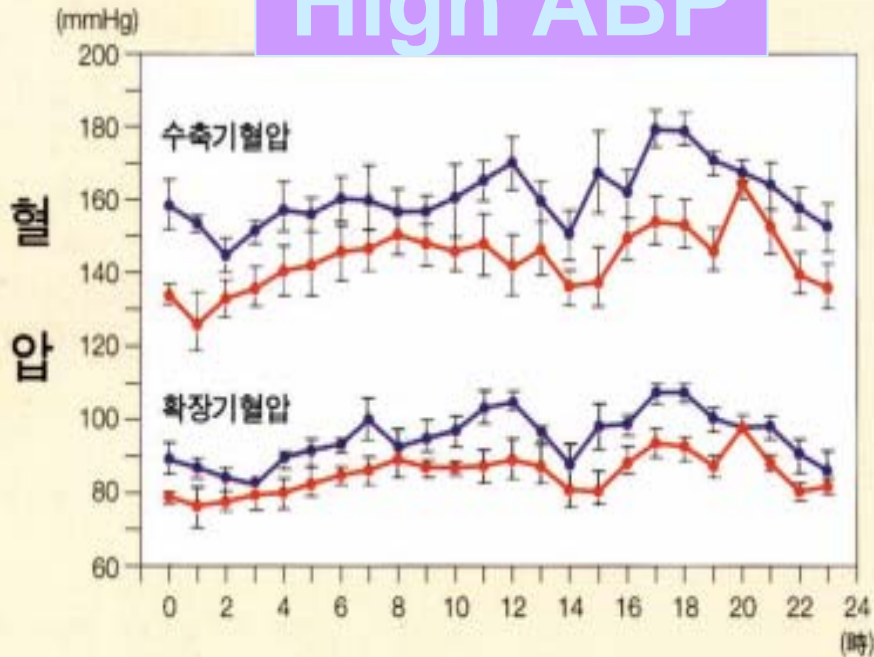
Cardiovascular Drugs and Therapy

1997;11:43-48

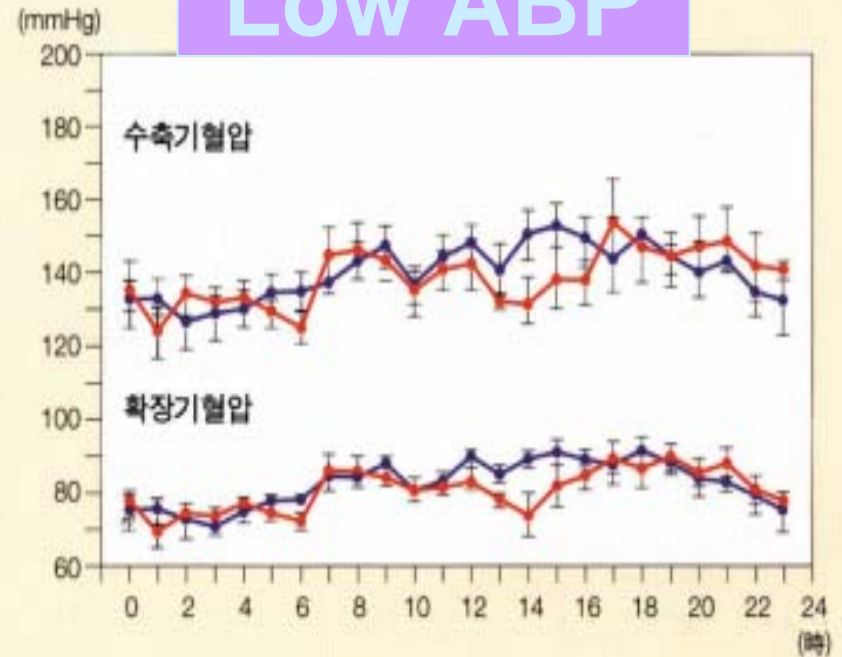
Effect of Cilnidipine on High and Low ABP

● 투여전 ● 투여중 Mean \pm S.E.
 各群 n=7

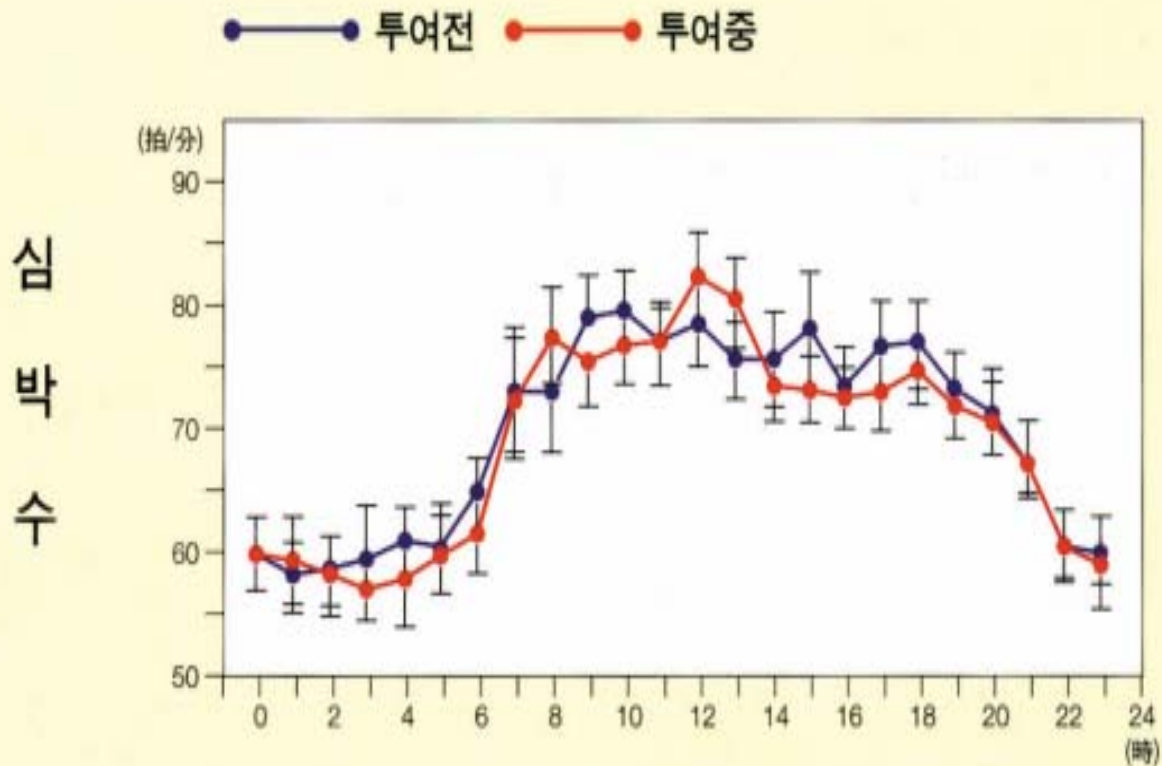
High ABP



Low ABP



Pulse rate before and after treatment with Cilnidipine

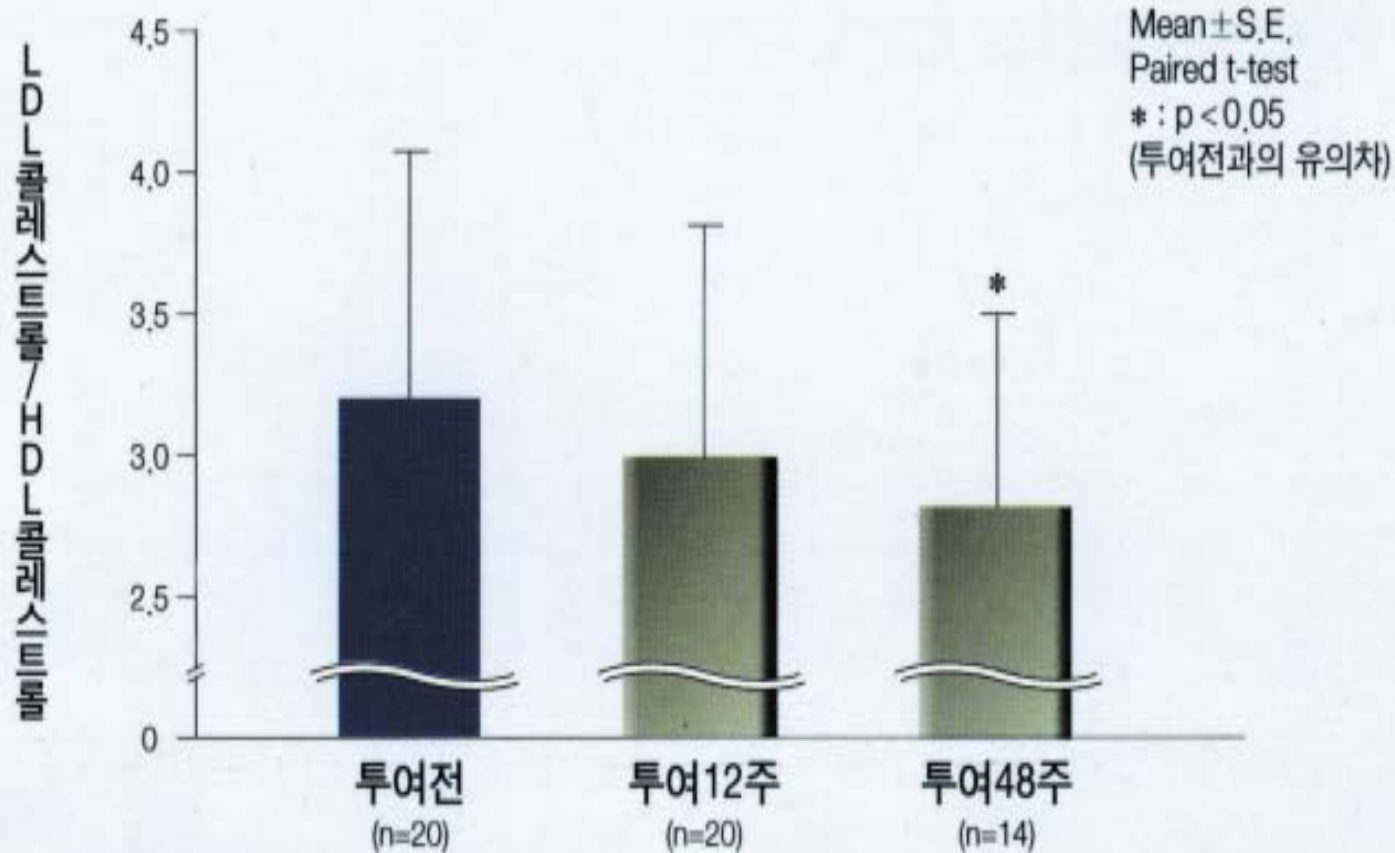


Effect of Cilnidipine on Serum Lipid Profiles, Superoxide Anion Radical, and Lipid Peroxidation in Essential Hypertension

Therapeutic research. 1993;21(Suppl.1):S-247

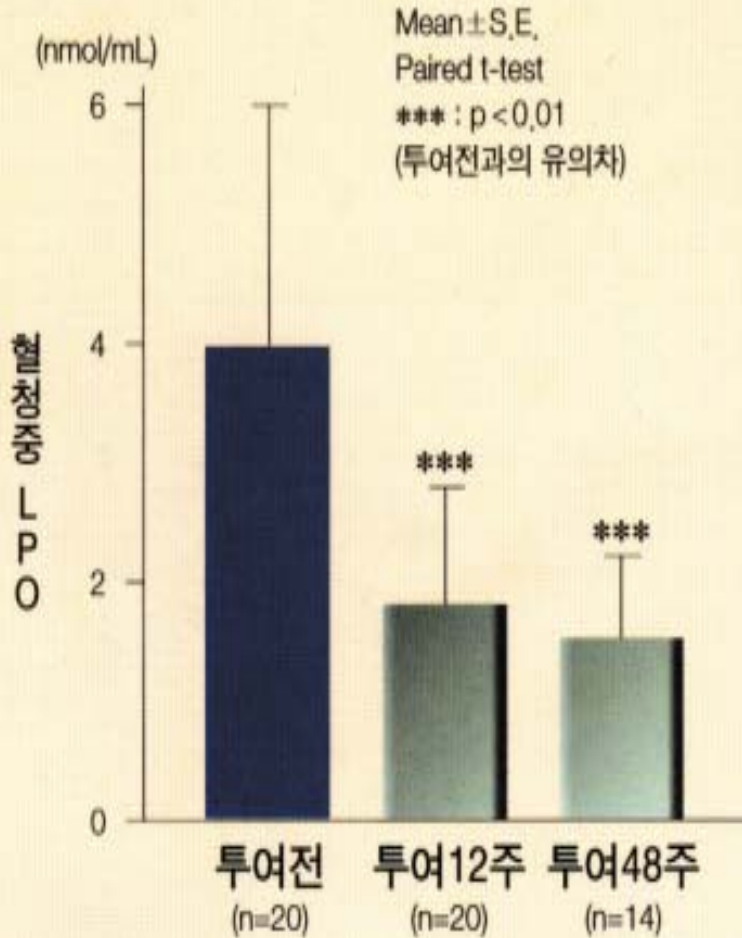
Therapeutic research. 1993;14:2785

Change of LDL/HDL cholesterol in treatment with Cilnidipine

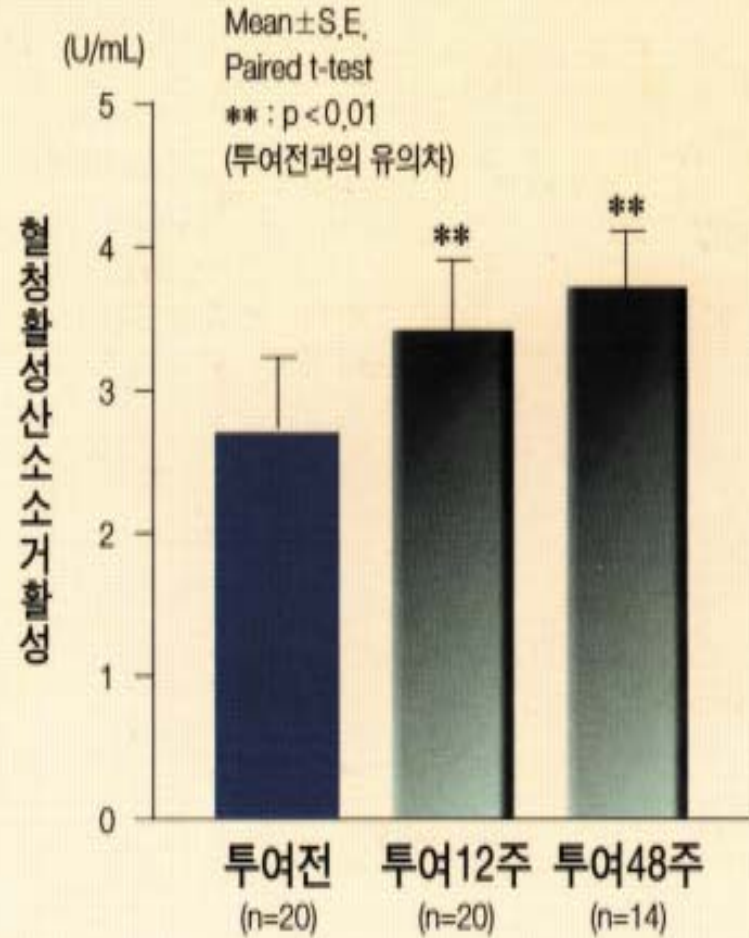


Antioxidant Effect of Cilnidipine

Lipid Peroxide



Reactive Oxygen Species



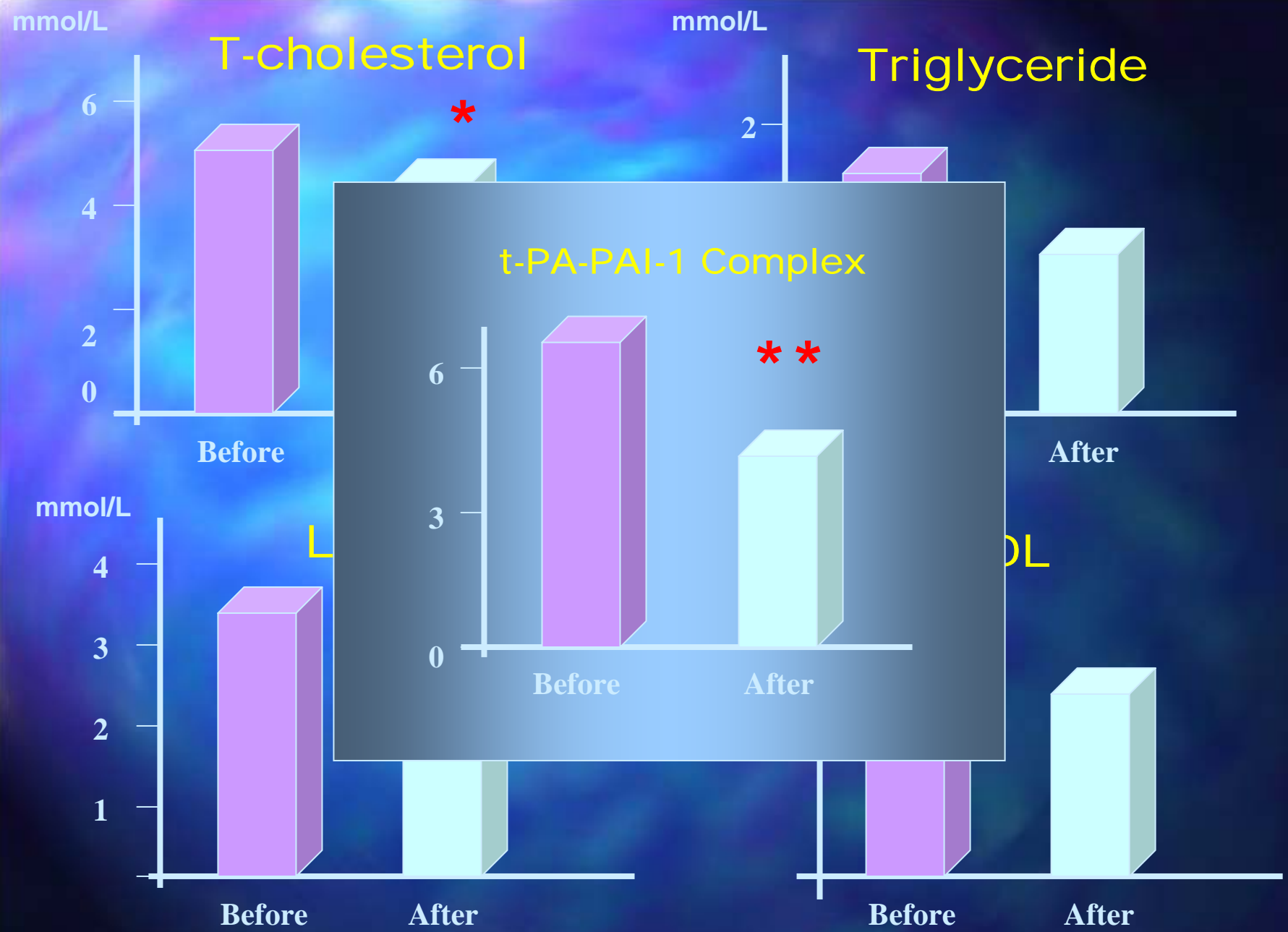
Effects of cilnidipine on lipids, lipoproteins and fibrinolytic system in hypertensive patients

Drugs Exptl. Clin Res

2000;26(4):119-123

RESULTS

N=16	Before	After	P-value
SBP (mmHg)	161.0 ± 15.1	135.5 ± 11.3	0.001
DBP (mmHg)	99.4 ± 17.9	82.5 ± 6.6	0.001
HR (beats/min)	76.2 ± 6.5	73.2 ± 7.2	0.05
NE (ng/L)	247.8 ± 117.2	247.2 ± 111.2	NS
Renin (ng/dL)	0.63 ± 0.8	0.62 ± 0.77	NS
TC (mmol/L)	5.6 ± 1.08	5.3 ± 0.85	0.05
HDLC (mmol/L)	1.35 ± 0.38	1.39 ± 0.42	NS
LDLC (mmol/L)	3.3 ± 0.89	3.2 ± 0.68	NS
TG (mmol/L)	1.69 ± 1.36	1.23 ± 0.78	NS
HDLC/TC	0.26 ± 0.09	0.27 ± 0.10	NS
t-PA (ng/mL)	7.0 ± 3.1	8.8 ± 3.4	NS
t-PA-PAI-1 (ng/mL)	6.6 ± 3.7	4.6 ± 2.3	0.01



*; p<0.05 **; p<0.01

Effects of cilnidipine on left ventricular diastolic function in hypertensive patients as assessed by pulsed doppler echocardiography and pulsed tissue doppler imaging

***Jpn Circ J* 2001;65:305-309**

RESULTS

	Baseline	1Mon	3Mon	6Mon
SBP(mmHg)	174 ± 17	148 ± 10 ^{***}	143 ± 9 ^{***}	142 ± 11
DBP(mmHg)	96 ± 10	82 ± 16 [*]	80 ± 6 [*]	78 ± 8
HR(beats/min)	59 ± 7	60 ± 11	59 ± 9	60 ± 9
NE(ng/mL)	0.5 ± 0.3	0.5 ± 0.2	0.4 ± 0.1	0.4 ± 0.2
M-mode & Pulsed Doppler Echocardiographic Variables				
LVMI(g/m ²)	131 ± 22	132 ± 17	129 ± 18	126 ± 20 [*]
E(cm/s)	55 ± 8	65 ± 10 [*]	63 ± 8 [*]	69 ± 7 [*]
A(cm/s)	73 ± 7	74 ± 11	72 ± 8	71 ± 8
E/A	0.7 ± 0.1	0.9 ± 0.2 ^{**}	0.9 ± 0.1 ^{**}	1.0 ± 0.1 ^{***}
Pulsed Tissue Doppler Imaging Variables				
Ew(cm/s)	8.6 ± 1.8	8.8 ± 1.9	11.3 ± 2.1 ^{***}	11.8 ± 2.1 ^{***}
Aw(cm/s)	9.3 ± 1.3	9.5 ± 1.5	9.7 ± 1.6	9.5 ± 1.6
Ew/Aw	0.9 ± 0.2	0.9 ± 0.4	1.2 ± 0.3 ^{**}	1.3 ± 0.4 ^{**}

*p<0.05, **p<0.01, ***p<0.0001

Cilnidipine, the N-, L-type Ca channel antagonist, reduced on 24-h urinary catecholamines and C-peptide in HT-NIDDM

Diabetes Research and Clinical Practice

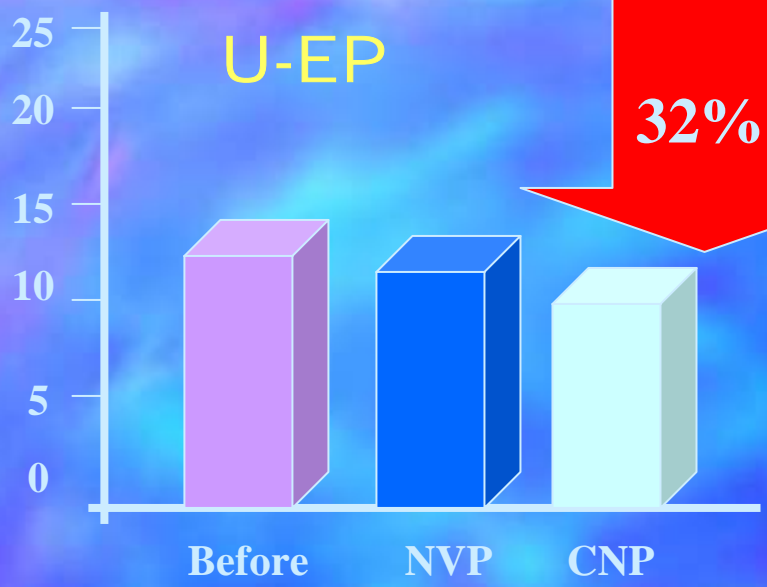
1999;44:197-205

Effects of CNP & NVP on clinical parameters (combined)

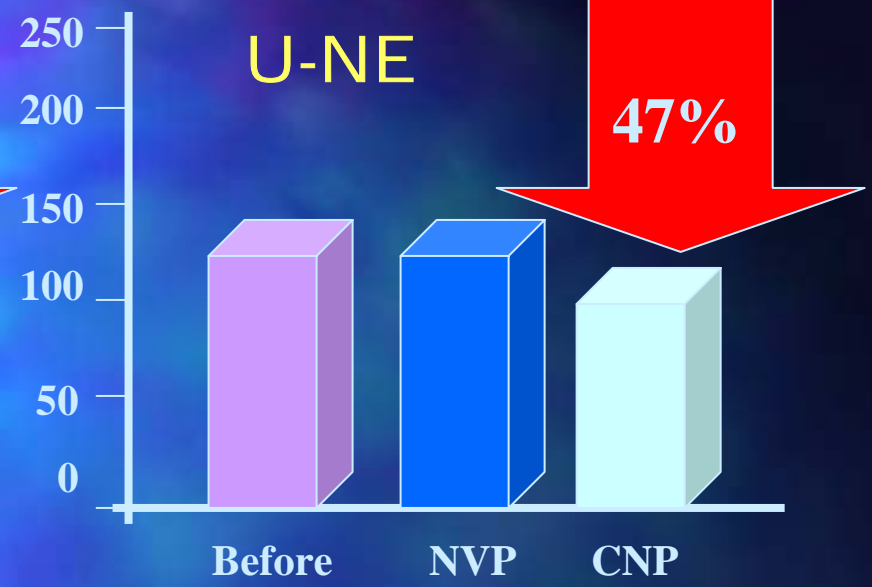
Variable	Before	Nilvadipine	Cilnidipine
SBP (mmHg)	156.4 ± 1.7	132.9 ± 1.2	129.1 ± 1.2
DBP (mmHg)	92.5 ± 1.7	76.8 ± 1.4	76.9 ± 1.3
U-EP (µg/d)	13.9 ± 1.9	12.4 ± 1.2	10.5 ± 1.2
U-NE (µg/d)	165.1 ± 12.3	154.6 ± 9.0	112.5 ± 6.0 *
U-DA (µg/d)	891.9 ± 93.1	868.9 ± 80.1	606.7 ± 31.8 *
U-CPR (µg/d)	81.7 ± 6.9	75.9 ± 5.7	52.3 ± 4.5*

* p<0.0001

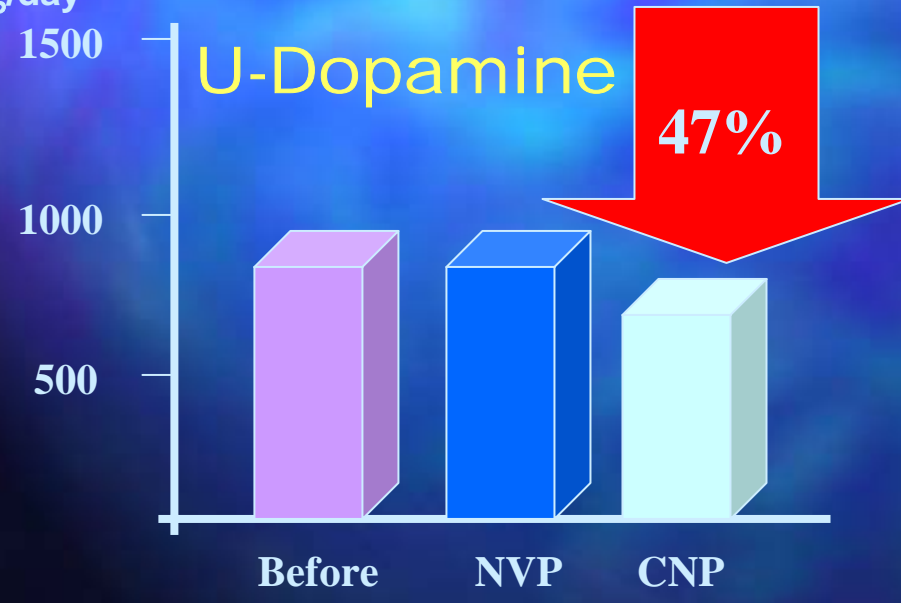
µg/day



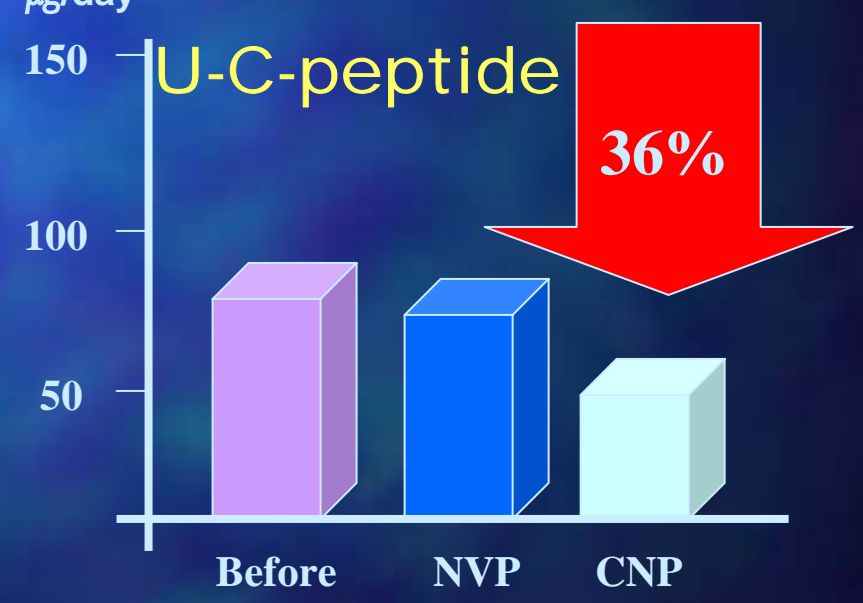
µg/day



µg/day



µg/day

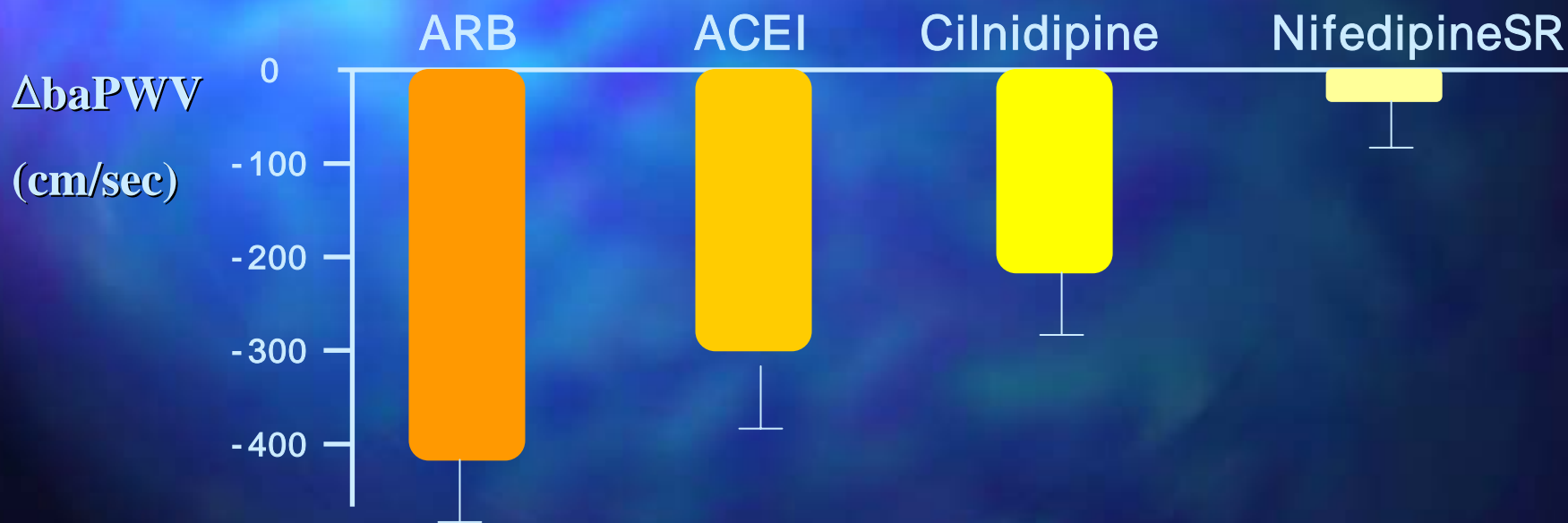


Efficacy of Various
Antihypertensive Agents as
Evaluated by Indices of
Vascular Stiffness in Elderly
Hypertensive Patients

Hypertension Research 2003;26:609-614

Vascular Stiffness; Changes in baPWV

baPWV	(Δ baPWV)		
ARB	ACEI	Cilnidipine	NifedipineSR
$409 \pm 90\text{cm/s}$	$281 \pm 99\text{cm/s}$	$209 \pm 82\text{cm/s}$	$9 \pm 146\text{cm/s}$



Summary; Effect of Cilnidipine

- L, N 칼슘채널 을 차단하는 dual channel 차단제로서 교감신경의 과활성을 억제하는 효과를 가지고 있다.
- 심박수 변화없이, 24시간동안 안정적으로 혈압을 조절하며, 스트레스성 고혈압에도 효과적이다.
- 수면 중 혈압이 높지않은 낮시간 동안에 주로 혈압상승 환자에서, 수면 중에 과도한 혈압강하 없이 안전하게 사용할 수 있다.
- 항산화작용과 지질 및 혈전 개선효과가 있다.
- LVH, LV diastolic function 및 aortic stiffness 개선효과가 있다.

1~2

Cilnidipine vs. Amlodipine ABP Monitoring

24

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Agenda

- Phase IV Study Profile of Cilnidipine
- Basic characteristics
- Clinical Trial Data Analysis
- Conclusion & Clinical Plan

Purpose

- Evaluate antihypertensive efficacy of **Cilnidipine** in comparison with **Amlodipine** in essential hypertensive patients.
- Evaluate efficacy to suppress sympathetic over activity by **Cilnidipine** in comparison with **Amlodipine** in essential hypertensive patients

Phase IV study

Design : Randomized, Double-blind,
Active-controlled parallel study

Institutions : 6 Hospitals

- Yonsei University Severance Hospital
 - Korea University Guro Hospital
 - Kyungbook University Hospital ,
 - Chunnam University Hospital
 - Keimyung University Hospital
 - Wonjoo University Hospital
 - Duration : Jan 2004 ~ Feb 2005
-

Key Criteria

Inclusion Criteria

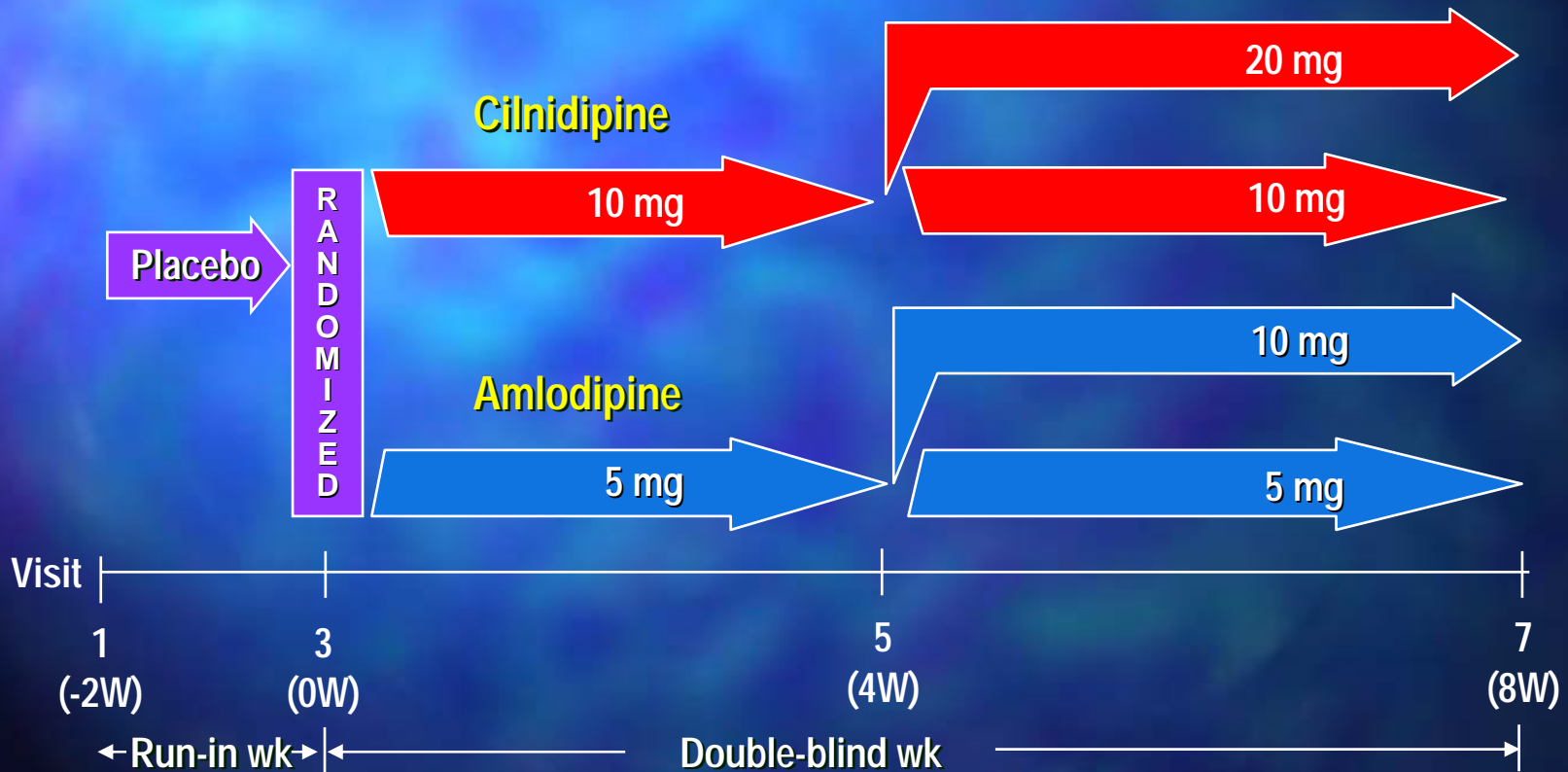
- Essential hypertension
- Age 21 to 70yr, male or female without childbearing potential or using appropriate birth control measures
- Mean DBP 95 to 114mmHg at the screening & baseline visit after 2week placebo, run in period.

Exclusion Criteria

- Severe hypertension (Mean SBP \geq 180mmHg, DBP \geq 115mmHg)
- Secondary hypertension or malignant hypertension
- Myocardial infarction, unstable angina, and severe heart failure within 6 months

Study Flow Sheet

Randomized, double-blind, multicenter, parallel-group design



Primary endpoint

- Changes of Sitting trough DBP of 8week-treatment
Cilnidipine vs. Amlodipine
- Other clinical issues; Cilnidipine vs. Amlodipine
 - Variables of 24 hour Ambulatory blood pressure
 - Variables of 24 hour Heart Rate Variability
 - Changes of plasma Norepinephrine
 - Changes of 12hour urinary Norepinephrine & Epinephrine
 - Changes of CRP of 8week-treatment

Clinical Trial Efficacy analysis criteria (PP analysis)

Enroll: 224명



Drop out: 40명

(동의철회, 연락두절, 개인사정, 검사거부 등)

Completed: 184명

Cilnidipine군: 88명
Amlodipine군: 96명



< 분석 기준 >

1) 선정기준 오류: 14명

2) Scr Visit = Base Visit 제외: 17명
(placebo or run in period 없이 Enroll된 환자)

3) ScrDBP-BaseDBP -10mmHg 제외 :10명

4) Protocol deviation: 13명

총 54례 제외

Analysis: 130명

Cilnidipine군: 59명
Amlodipine군: 71명

Baseline Characteristics

	Cilnidipine (n=59)	Amlodipine (n=71)
Age, yrs	53 ± 9	54 ± 8
Gender (F/M)	31(53%) / 28(47%)	24(34%) / 47(66%)
Heights, cm	162 ± 9	164 ± 8
SBP/DBP, mmHg	156 ± 10 / 101 ± 5	159 ± 10 / 102 ± 6
Heart rate, bpm	74 ± 10	73 ± 9

BP and Ambulatory BP before and after 3-month treatment of cilnidipine or amlodipine

	Cilnidipine			Amlodipine		
	<u>Before</u>	<u>3months</u>	<u>P*</u>	<u>Before</u>	<u>3months</u>	<u>P*</u>
BP(SBP/DBP), mmHg	156/101	135/87	P<0.001	159/102	134/86	P<0.001
Heart rate, bpm	74	72	NS	73	72	NS
24h average SBP,mmHg	156	144	P<0.001	155	141	P<0.001
24h average DBP,mmHg	102	93	P<0.001	103	93	P<0.001
24h average Heart rate	72	73	NS	71	75	P<0.05

*P: P value

24hr Ambulatory Blood Pressure before and after 3-month treatment of cilnidipine or amlodipine

	Cilnidipine(n=38)			Amlodipine(n=46)		
	<u>Before</u>	<u>3months</u>	<u>P value</u>	<u>Before</u>	<u>3months</u>	<u>P value</u>
24h average SBP,mmHg	156 ±14	144 ±11	P<0.001	155 ±16	141 ±9	P<0.001
24h average DBP,mmHg	102 ±9	93 ±7	P<0.001	103 ±9	92 ±7	P<0.001
24h average Heart rate	72 ±8	73 ±7	NS	71 ±6	75 ±8	P<0.05

Daytime Ambulatory Blood Pressure before and after 3-month treatment of cilnidipine or amlodipine

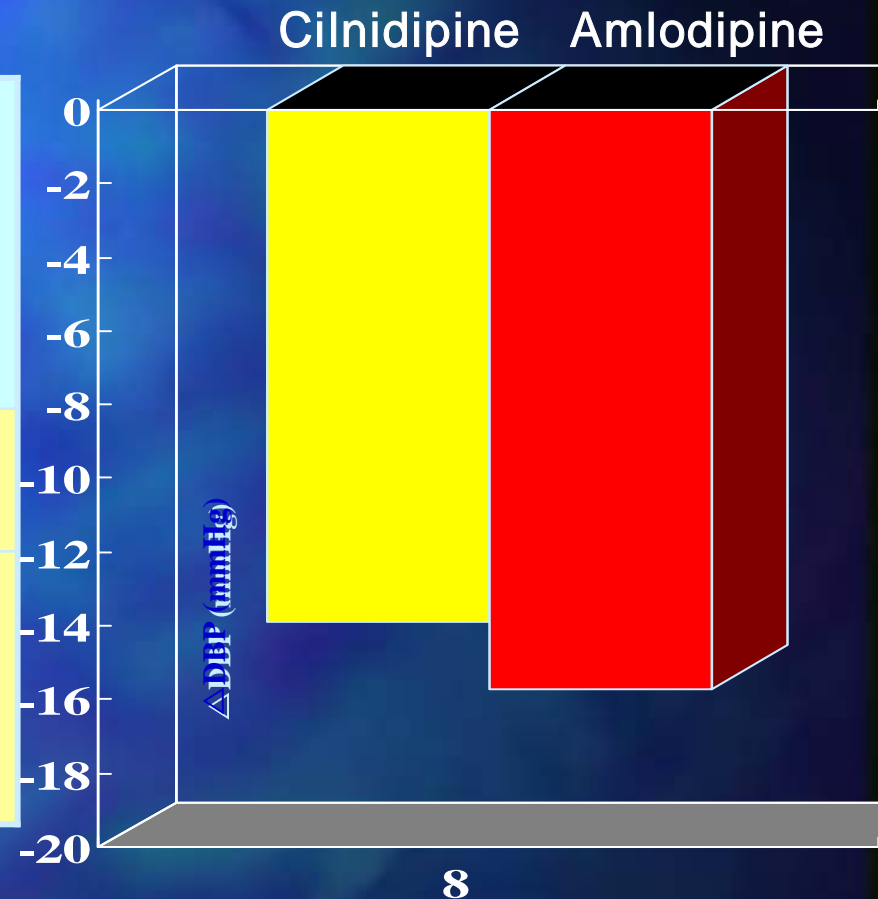
	Cilnidipine(n=38)			Amlodipine(n=46)		
	<u>Before</u>	<u>3months</u>	<u>P value</u>	<u>Before</u>	<u>3months</u>	<u>P value</u>
average SBP,mmHg	158 ±13	145 ±11	P<0.001	159 ± 12	143 ± 10	P<0.001
average DBP,mmHg	103 ±9	94 ±6	P<0.001	105 ± 9	93 ± 7	P<0.001
average Heart rate	74 ±8	76 ±8	NS	73 ± 7	77 ± 8	P<0.001

Night time Ambulatory Blood Pressure before and after 3-month treatment of cilnidipine or amlodipine

	Cilnidipine(n=38)			Amlodipine(n=46)		
	<u>Before</u>	<u>3months</u>	<u>P value</u>	<u>Before</u>	<u>3months</u>	<u>P value</u>
24h average SBP,mmHg	149 ±21	135 ±15	P< 0.001	146 ± 16	135 ± 13	P<0.001
24h average DBP,mmHg	96 ±13	86 ±10	P<0.001	95 ± 11	87 ± 9	P<0.001
24h average Heart rate	64 ±12	63 ±7	NS	61 ± 6	65 ± 9	P<0.05

Changes in Trough DBP at 8w

	Cilnidipine 군 (mean ±SD)	Amlodipine 군 (mean ±SD)	Mean Differe nce (95% CI)
N(명)	59	71	
8W DBP (mmHg)	-13.9 ±6.1	-15.7 ±6.1	1.77 (-3.90, 0.37)



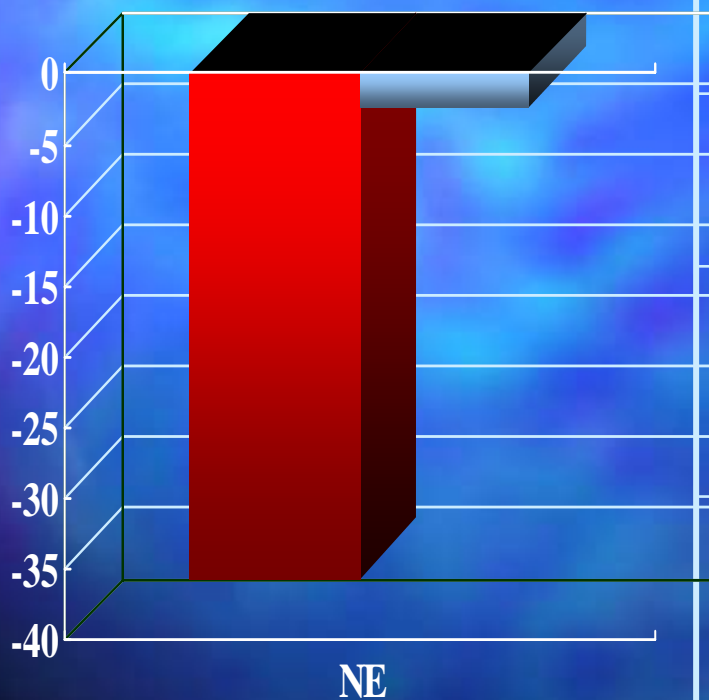
» Cilnidipine군과 Amlodipine군의 혈압강하효과의 차이가 4mmHg이내에 존재한다는 가설을 만족함.

Autonomic function and CRP before and after 3-month treatment of cilnidipine or amlodipine

	Cilnidipine			Amlodipine		
	<u>Before</u>	<u>3months</u>	<u>P</u>	<u>Before</u>	<u>3months</u>	<u>P</u>
Norepinephrine, pg/ml	181 ±148	148 ±96	NS	167 ±110	174 ±122	NS
24H urinary NE*(µg/L)	29.4 ± 21.4	32.3 ±27.6	NS	30.3 ±19.0	35.6 ±26.6	NS
24H urinary EP**(µg/L)	3.5 ±2.8	3.5 ±5.8	NS	3.2 ±2.2	3.7 ±5.5	NS
CRP(ng/ml)	0.601 ±1.276	0.380 ±0.688	NS	0.768 ±1.656	0.751 ± 1.312	NS

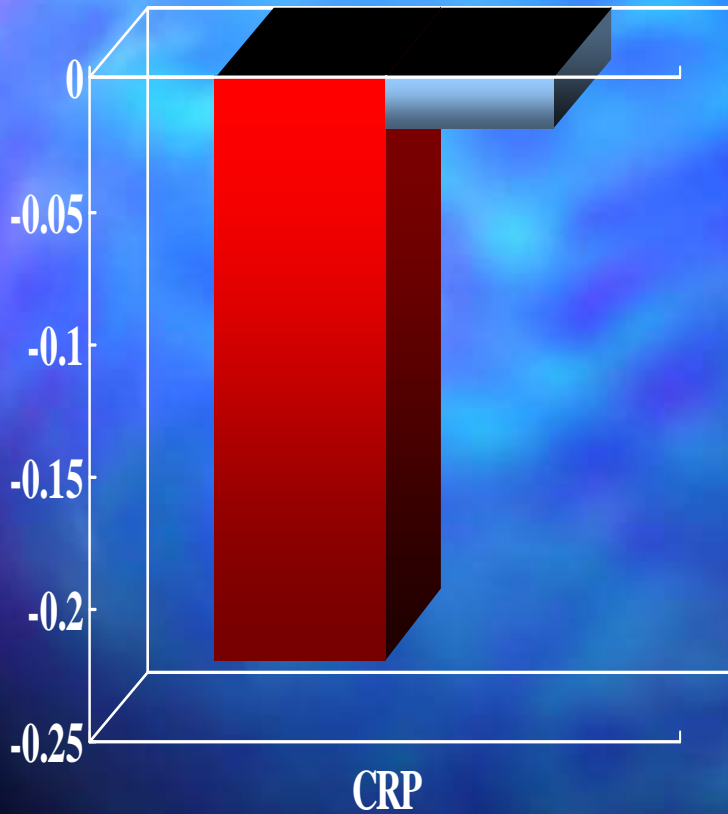
* NE:Norepinephrine, **EP:Epinephrine, p***:p value

Plasma Norepinephrine



	Cilnidipine		Amlodipine	
N(명)	54		62	
NE \pm SD	-35.78 \pm 168.01		-2.42 \pm 169.35	
mean NE (pg/ml)	Before	After	Before	After
	185.4	149.6	173.5	171.1

Plasma CRP



	Cilnidipine		Amlodipine	
N (명)	56		64	
CRP \pm SD	-0.22 \pm 1.28		-0.02 \pm 1.89	
mean CRP (ng/ml)	Before	After	Before	After
	0.61	0.38	0.80	0.78

	<u>Cilnidipine</u>	<u>Amlodipine</u>
BP(SBP/DBP), mmHg	두 군 모두 유의적인 혈압강하 효과를 보였으며, 그 효과가 4mmHg 이내로 동등하다고 판단됨.	
Heart rate, bpm	Cilnidipine군에서 Heart rate 가 투여 전에 비하여 2bpm 감소하였고, Amlodipine군에서는 1bpm이 감소하였으나 통계적 의미는 없음.	
Norepinephrine, pg/ml	Cilnidipine군에서의 Plasma NE 값이 감소경향을 보임	Amlodipine군에서의 Plasma NE 값이 증가 경향을 보임
12H urinary NE*(µg/L)	12시간 Urinary NE값이 두 군에서 투여 전후에 거의 변동이 없음 (소폭 증가했으나, 통계적 유의성은 없음)	
CRP	Cilnidipine군에서의 CRP 값이 감소경향을 보임	Amlodipine군에서의 CRP 값이 증가경향을 보임

HRV parameter

	Cilnidipine(n=50)			Amlodipine(n=46)		
	<u>Before</u>	<u>3months</u>	<u>P value</u>	<u>Before</u>	<u>3months</u>	<u>P value</u>
SDNN(ms)	135 ±29	141 ±39	P<0.05	143 ±32	133 ±30	NS
SDANN(ms)	121 ±29	130 ±30	P<0.05	129 ±30	122 ±29	NS
LF(ms)	19.78 ±10.18	21.08 ±27.26	NS	20.14 ±12.20	17.55 ±11.35	NS
HF(ms)	12.52 ±6.74	11.56 ±7.34	NS	11.68 ±5.55	10.72 ±8.50	NS
LF/HF ratio	1.62 ± 0.40	1.69 ±0.46	NS	1.75 ±0.40	1.73 ±0.41	NS

	<u>Cilnidipine</u>	<u>Amlodipine</u>
Time domain Method	SDNN, SDANN, Rmssd, pNN50 등 Heart rate variability 가 증가하는 경향을 나타냄. (일부항목에서 통계적 유의)	SDNN, SDANN, Rmssd, pNN50 등 Heart rate variability 가 감소하는 경향을 나타냄. (일부항목에서 통계적 유의)
Frequency domain Method	LF, HF, LF/HF ratio는 투여 전 후 거의 변화가 없음 (통계적 유의성 없음)	LF, HF, LF/HF ratio는 투여 전 후 거의 변화가 없음 (통계적 유의성 없음)

» Heart rate variability parameter를 통한 Autonomic function을 검토하고자 함

» Time domain method, frequency domain method 를 통해 판단된 HRV parameter 는 특이한 변동사항을 보여주지 않음.

Conclusion

- 고혈압 환자에 있어서 cilnidipine 과 amlodipine 투여 후 모두 유의한 혈압 강하 효과를 보였으며, 양 군간의 강압효과의 차이는 없었다.
- Cilnidipine은 심박수의 증가가 없었으나 amlodipine은 심박수의 증가를 보였다.
- Cilnidipine군에서 교감신경의 과활성을 억제시키면서, 동시에 Heart rate variability와 CRP를 개선시켰다.



Thirsty?
Summer
Softly



특이 407182 | 특이 0403888 | 외장음복 298274
not prefer | prefer