EXONE-R (Val/Aml/Rosu)

FDC management of Hypertension and Dyslipidemia

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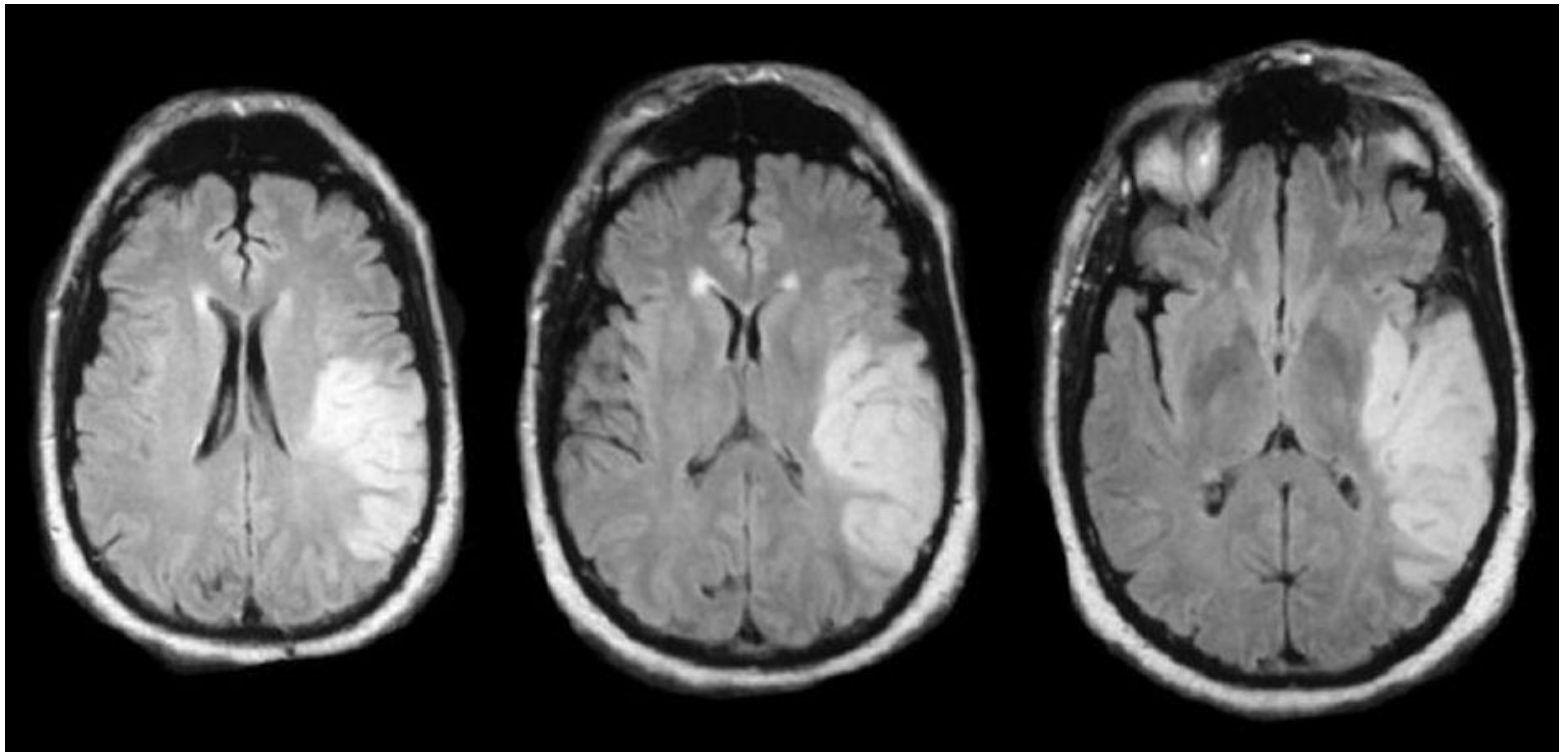
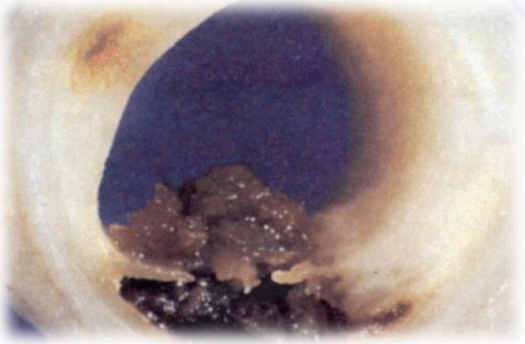
01 *Why Amlodipine ?*

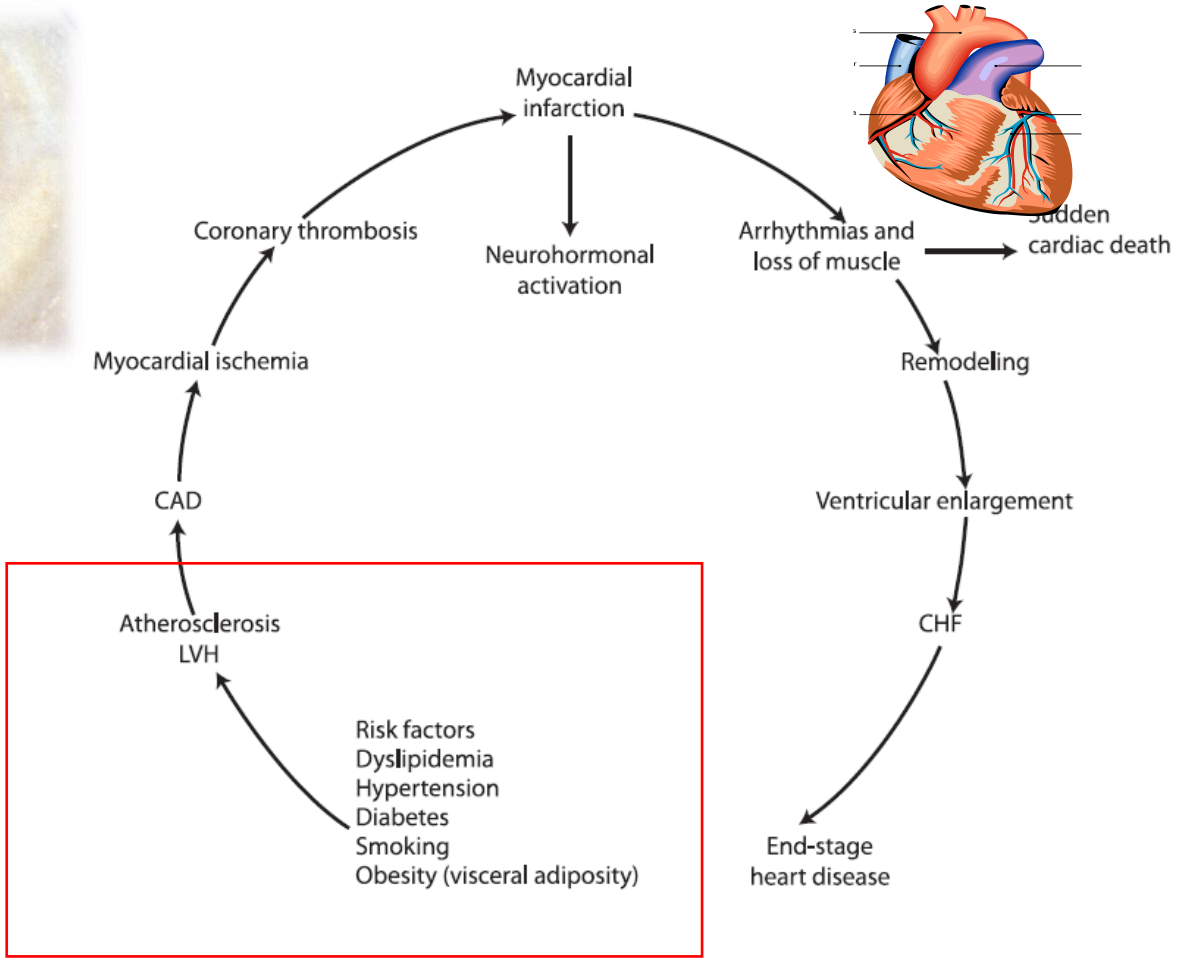
Case 2

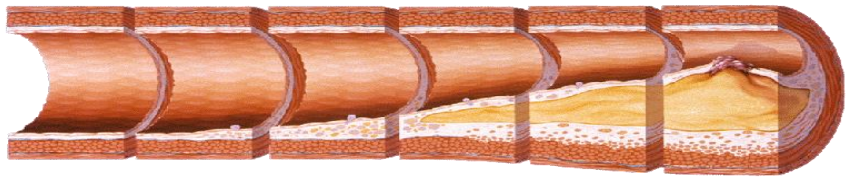
- 67-year old male with **known hypertension**, left for a wedding around noon but he did not return home until evening. When his wife called him around 7:00 PM, he gave **incoherent responses**. He was traced through the mobile phone's location and taken to the emergency room.



Cardiovascular disease continuum





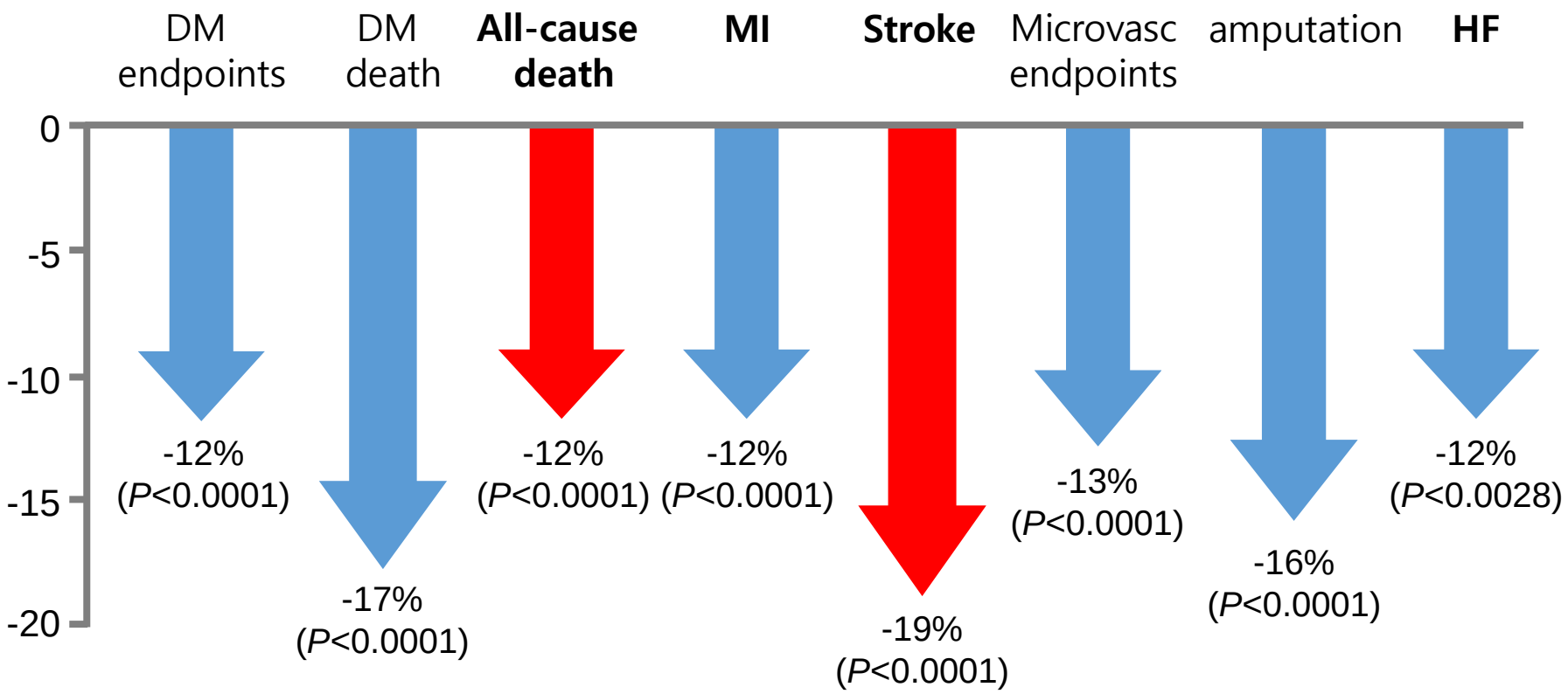


Dzau et al Circulation 2006;114:2850-2870

Cardiovascular Risk Factors

Non-modifiable	Modifiable-Medication	Modifiable-LSM
Age	**Hypertension**	Smoking
Gender	Diabetes mellitus	Exercise
Family history	**Hypercholesterolemia**	Obesity

Risk reduction with 10 mmHg BP drop

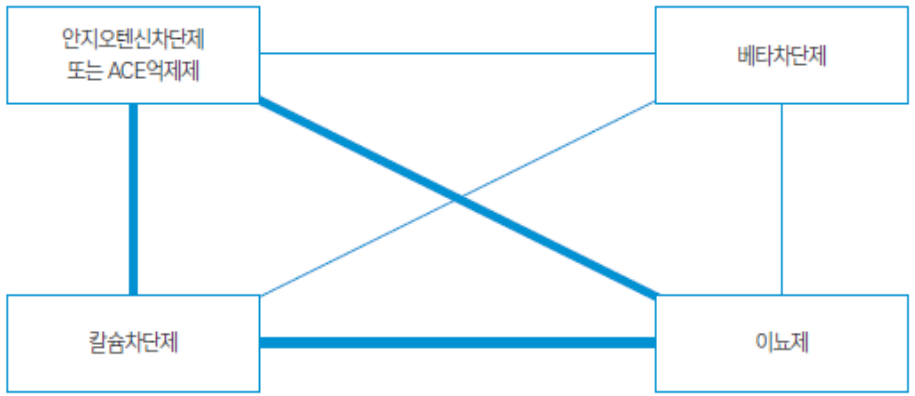


UKPDS Group 36 Adler A et al. *BMJ.* 2000;321:412–419.

Drug classes for BP-lowering therapy

2022 KSH

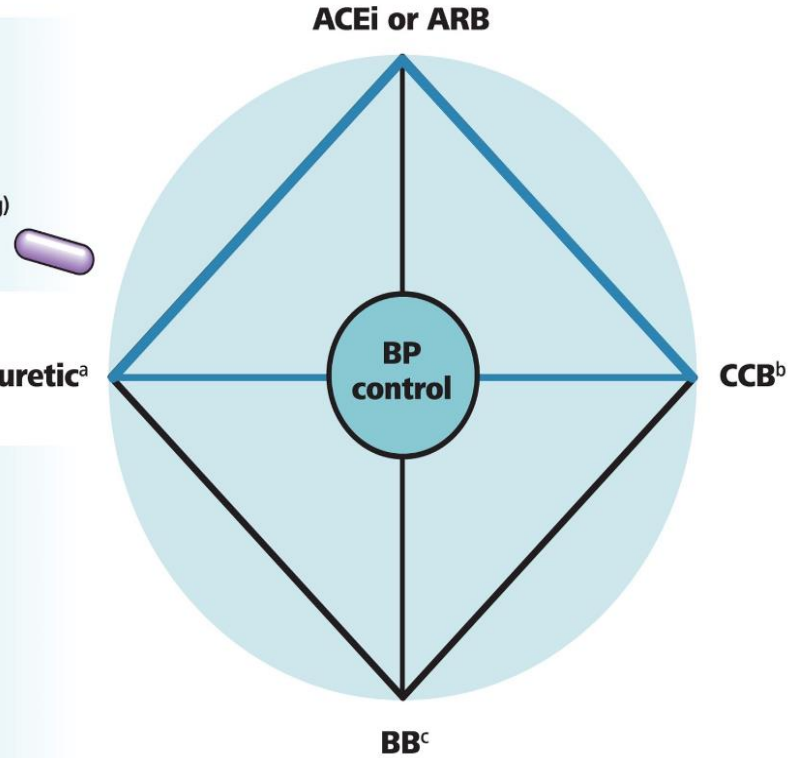
그림 9 권장되는 병용요법(굵은선: 우선 권장되는 병용요법, 가는선: 가능한 병용요법)



2023 ESH

Prescribing patterns:

- Start with dual combination therapy in most patients
- Uptitrate to maximum well tolerated doses and to triple therapy if needed
- **Once daily (preferred in the morning)**
- **Add further drugs if needed**
- **Preferred use of SPCs at any step**



Additional drug classes

General antihypertensive therapy:

- Steroidal MRA
- Loop Diuretic
- Alpha-1 Blocker
- Centrally acting agent
- Vasodilator

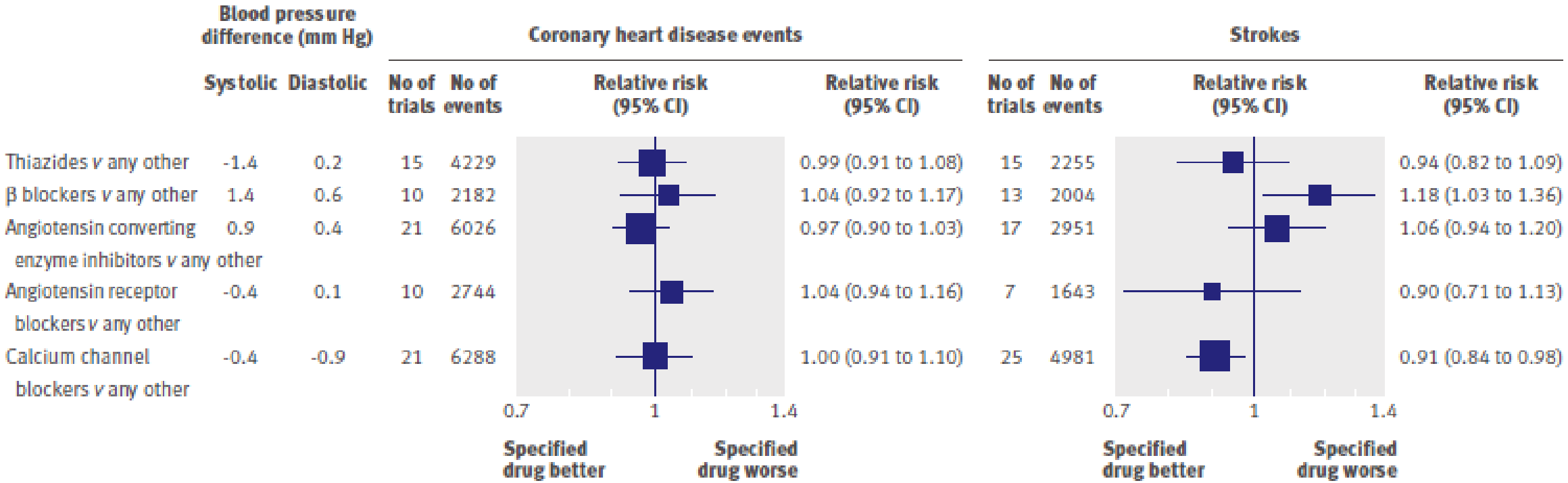
Special comorbidities:

- ARNi
- SGLT2i
- Non-Steroidal MRA

Drug classes for BP-lowering therapy. (a) Use of Diuretics: Consider transition to Loop Diuretic if eGFR is between 30 to 45 ml/min/1.73 m^2. If eGFR <30 ml/min/1.73 m^2 use Loop Diuretic. (b) Non-DHP CCB should not be combined with BB. (c) BB should be used as guideline directed medical therapy in respective indications or considered in several other conditions (Table 16). Start with dual combination therapy including a RAS-blocker (either ACEi or ARB) plus a $_{T/TL}$Diuretic or a CCB is recommended (thick blue lines). Triple therapy includes a combination of the three classes as indicated by the blue lines.

Ref) Journal of Hypertension41(12):1874-2071, December 2023, 대한고혈압학회 진료지침 2022

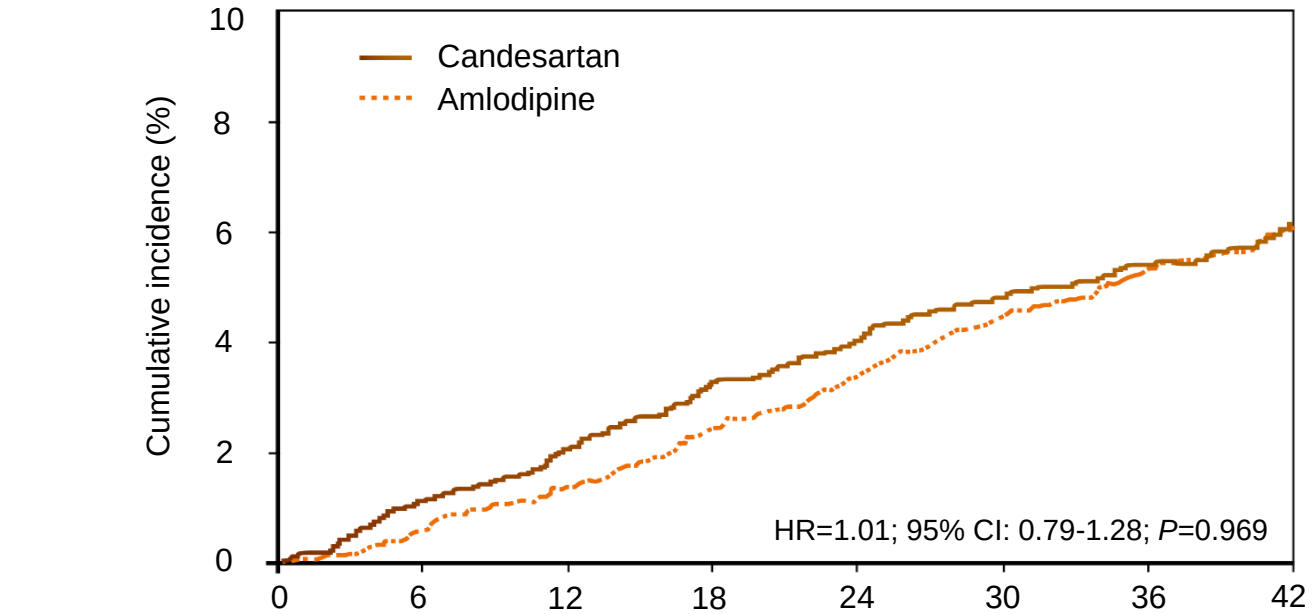
Comparison of the Antihypertensives



Law et al, BMJ 2009

ARB vs. CCB – CV morbidity and mortality

Patient:	prospective, randomized, open-label study (63.8 yr; BMI 24.6 kg/m2)
Intervention:	candesartan (n=2354)
Comparison:	amlodipine (n=2349)
Outcomes:	a composite of death and cerebral, cardiac, renal, vascular events, 3.2y

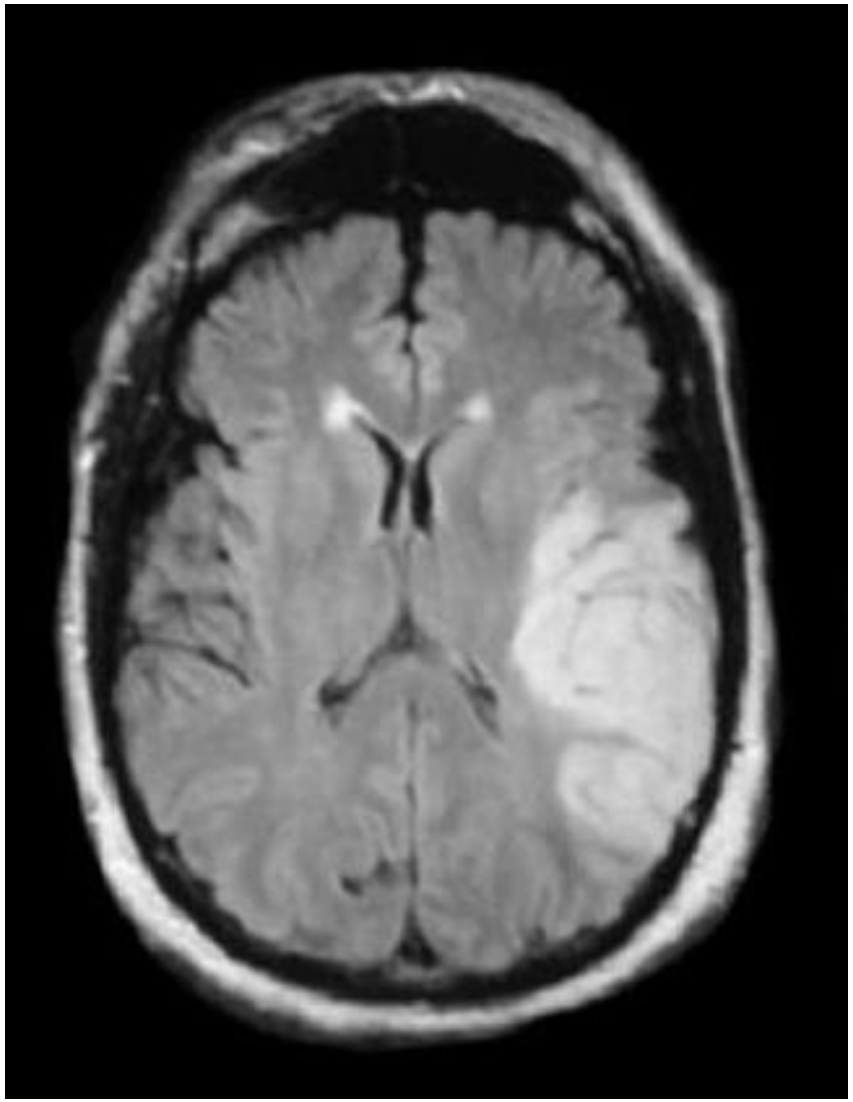


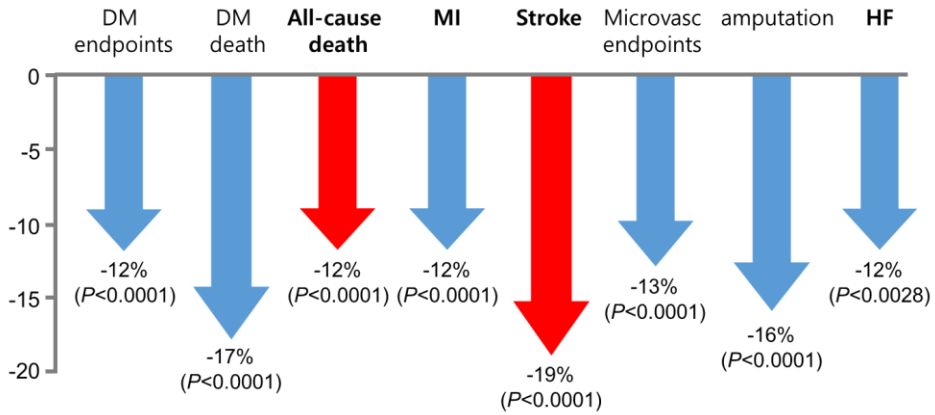
Number at Risk

Candesartan	2,354	2,273	2,221	2,157	2,101	2,058	1,977	964
Amlodipine	2,349	2,287	2,232	2,177	2,126	2,066	1,988	978

Ogihara T, et al. Hypertension 2008

Stroke is BP dependent outcome.





Circadian variation of stroke onset

Differences in circadian variation of cerebral infarction, intracerebral haemorrhage and subarachnoid haemorrhage by situation at onset

S Omama, Y Yoshida, A Ogawa, T Onoda, A Okayama

J Neurol Neurosurg Psychiatry 2006;**77**:1345–1349. doi: 10.1136/jnnp.2006.090373

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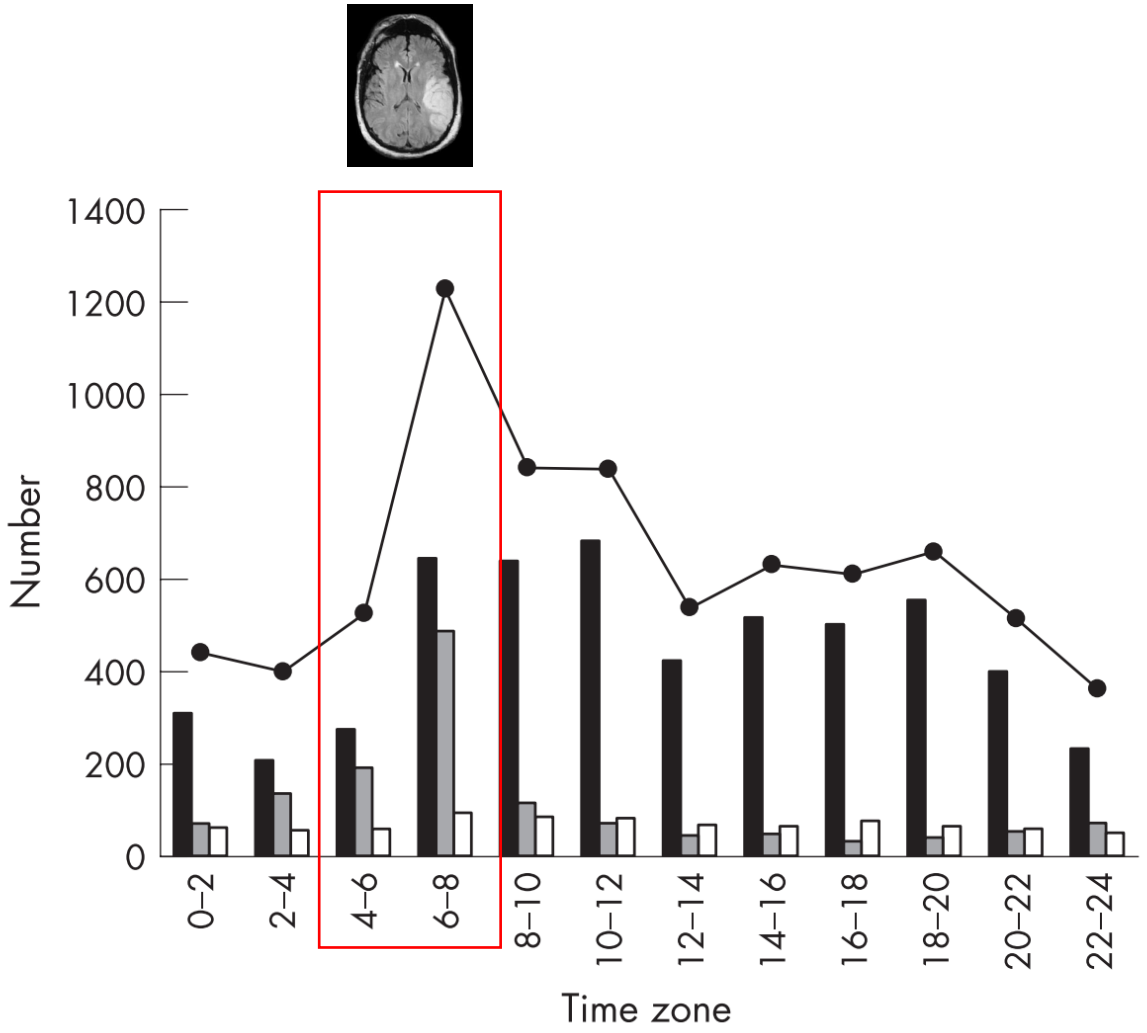
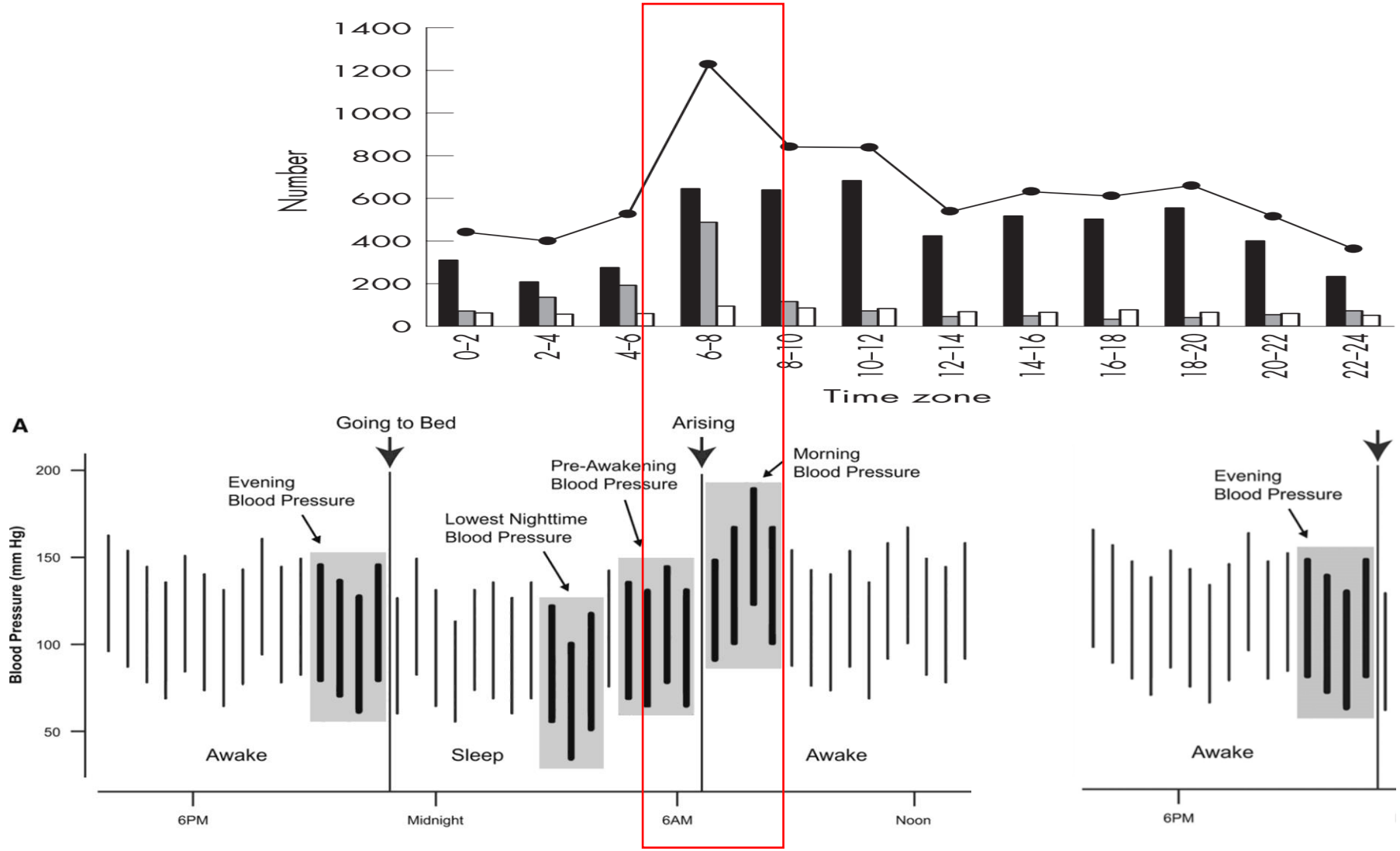
Published Online First 17 August 2006

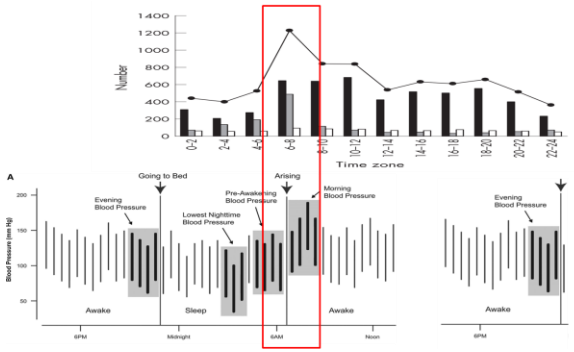
Background: The precise time of stroke onset during sleep is difficult to specify, but this has a considerable influence on circadian variations of stroke onset.
Aim: To investigate circadian variations in situations at stroke onset—that is, in the waking state or during sleep—and their differences among subtypes.
Methods: 12 957 cases of first-ever stroke onset diagnosed from the Iwate Stroke Registry between 1991 and 1996 by computed tomography or magnetic resonance imaging were analysed. Circadian variations were compared using onset number in 2-h periods with relative risk for the expected number of the average of 12 2-h intervals in the waking state or during sleep in cerebral infarction (CIF), intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH).
Results: ICH and SAH showed bimodal circadian variations and CIF had a single peak in all situations at onset, whereas all three subtypes showed bimodal circadian variations of stroke onset in the waking state only. These variations were different in that CIF showed a bimodal pattern with a higher peak in the morning and a lower peak in the afternoon, whereas ICH and SAH had the same bimodal pattern with lower and higher peaks in the morning and afternoon, respectively.
Conclusions: Sleep or status in sleep tends to promote ischaemic stroke and suppress haemorrhagic stroke. Some triggers or factors that promote ischaemic stroke and prevent haemorrhagic stroke in the morning cause different variations in the waking state between ischaemic and haemorrhagic stroke.



Peak time for stroke



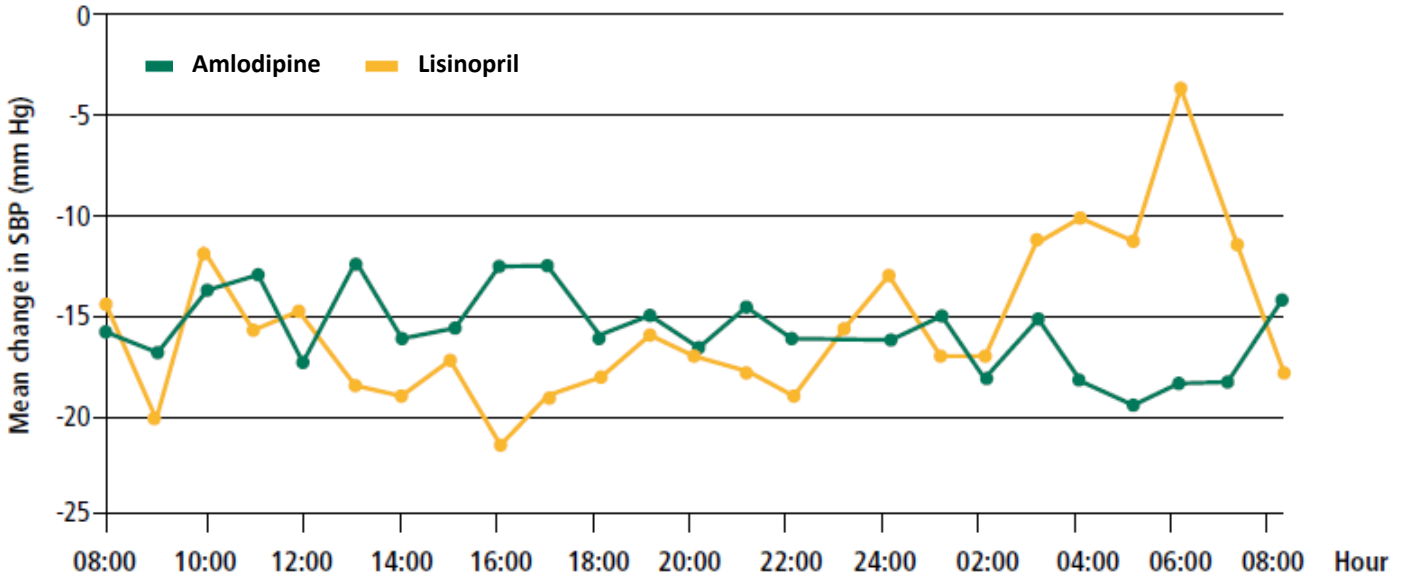
Amlodipine's long half-life and consistent BP control



Comparative pharmacokinetics of selected dihydropyridine calcium antagonists[1]

	Nifedipine	Nisoldipine	Felodipine	Amlodipine	Lacidipine
Oral absorption (%)	>90	>90	>90	**>90**	>90
Oral bioavailability (%)	30-50	5-15	10-25	**60-65**	5-15
Elimination half-life (h)	3-5	4-10	2-8	**35-50**	3-15

Mean changes in systolic BP from baseline[2]



Meredith PA, Elliott HL. J Hypertens 2004;22:1641-1648. Lorimer AR, et al. J Hum Hypertens 1998;12:411-416.

02 *Why Valsartan ?*

2018 Korean Society of HT guidelines

Comorbidities	ACE I or ARB	Beta blockers	CCB	Diuretic
Congestive heart failure	O	O		O
Left ventricular hypertrophy	O		O	
Coronary artery disease	O	O	O	
Chronic kidney disease	O			
Stroke	O		O	O
Elderly, isolated systolic hypertension	O		O	O
Post-myocardial infarction	O	O		
Prevention of atrial fibrillation	O			
Diabetes mellitus	O	O	O	O

Lee HY et al. Clin Hypertens. 2019 Aug 1;25:20.

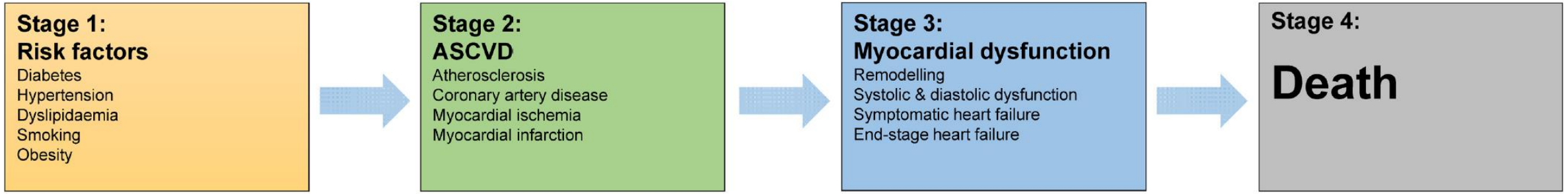
Valsartan

Approved Indications of ARBs

	Valsartan	Telmisartan	Olmesartan	Fimasartan	Candesartan	Irbesartan	Losartan
Hypertension	OK	OK	OK	OK	OK	OK	OK
HF	OK				OK		
Post-MI	OK						
DM Nephropathy						OK	OK
High Risk of MACE(≥ 55 years)		OK					

Valsartan is the only ARB Approved for Hypertension, HF & Post-MI Indication

Valsartan in cardiovascular disease continuum



VALUE[1]

Patients: High-risk HTN including DM

Outcome:

23% less risk of NODM compared to Amlodipine

23%

P<0.001, 95% CI 0.65-0.86

VALIANT[3]

Patients: Post MI

Outcome: All-cause mortality risk reduction

As effective as Captopril

P<0.001, 95% CI 0.39-0.81

Val-HeFT[2]

Patients: HF

Outcome:

reducing CV morbidity/mortal-ity rate by 44%

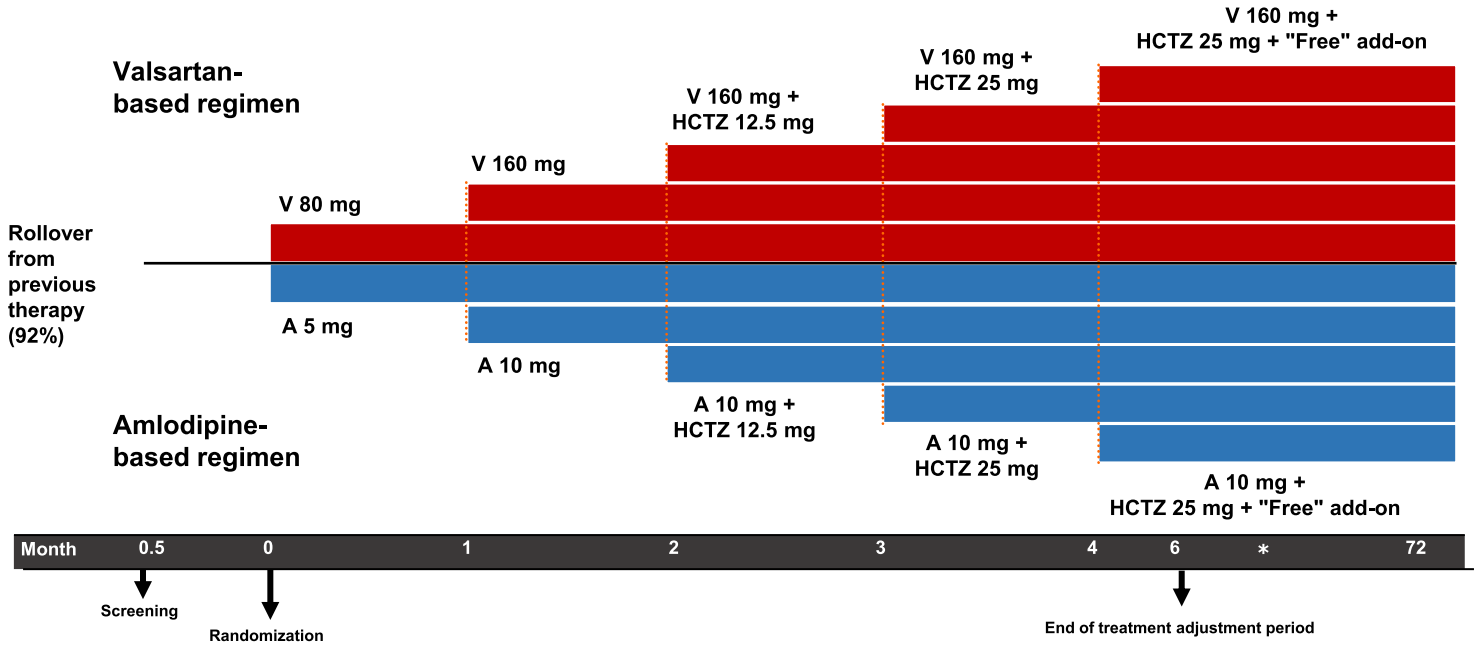
44%

P<0.001, 95% CI 0.39-0.81

1) Lancet 2004;363(9426):2022-31, 2) N Engl J Med 2001;34:1677-75, 3) N Engl J Med 2003;349:1893-906

VALUE STUDY

Patients	15,245 patients with hypertension over 50 years of age with high cardiovascular risk or disease
Design	Randomized, double-blind, parallel-group trial
Primary Outcome	First cardiac event*
Medication	Valsartan group (n=7649) vs Amlodipine group (n=7596), Median F/U 4.2years

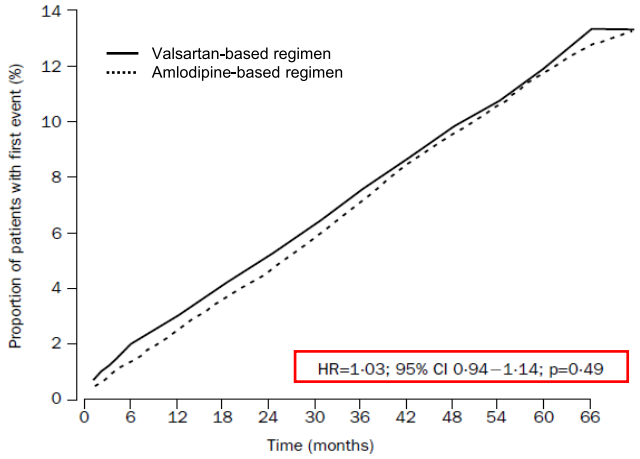


Julius S et al. Lancet . 2004 Jun 19;363(9426):2022-31.

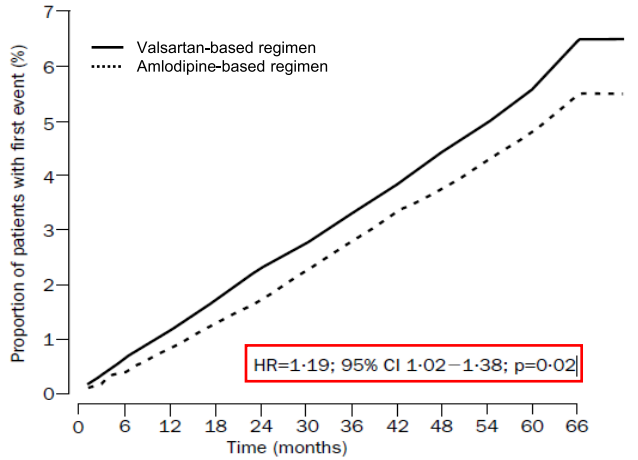
VALUE Results

- **Valsartan showed the same efficacy as amlodipine in the development of cardio-cerebrovascular disease.**

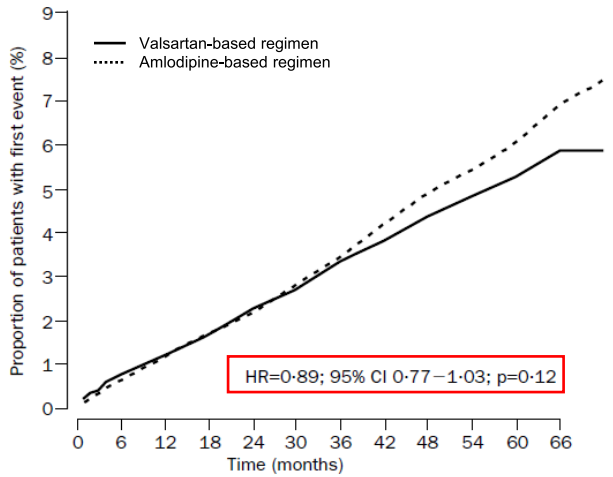
Primary composite endpoint



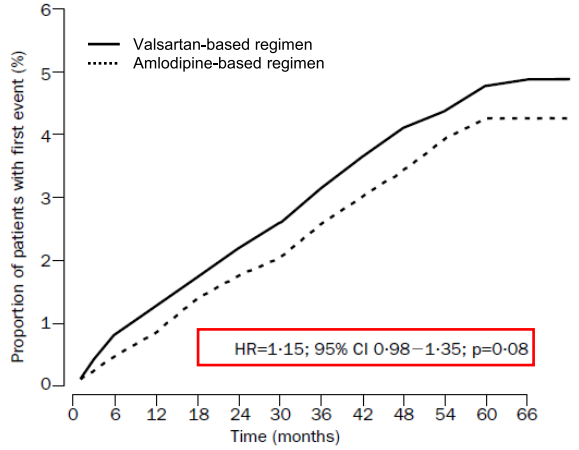
All Myocardial Infarction



All heart failure



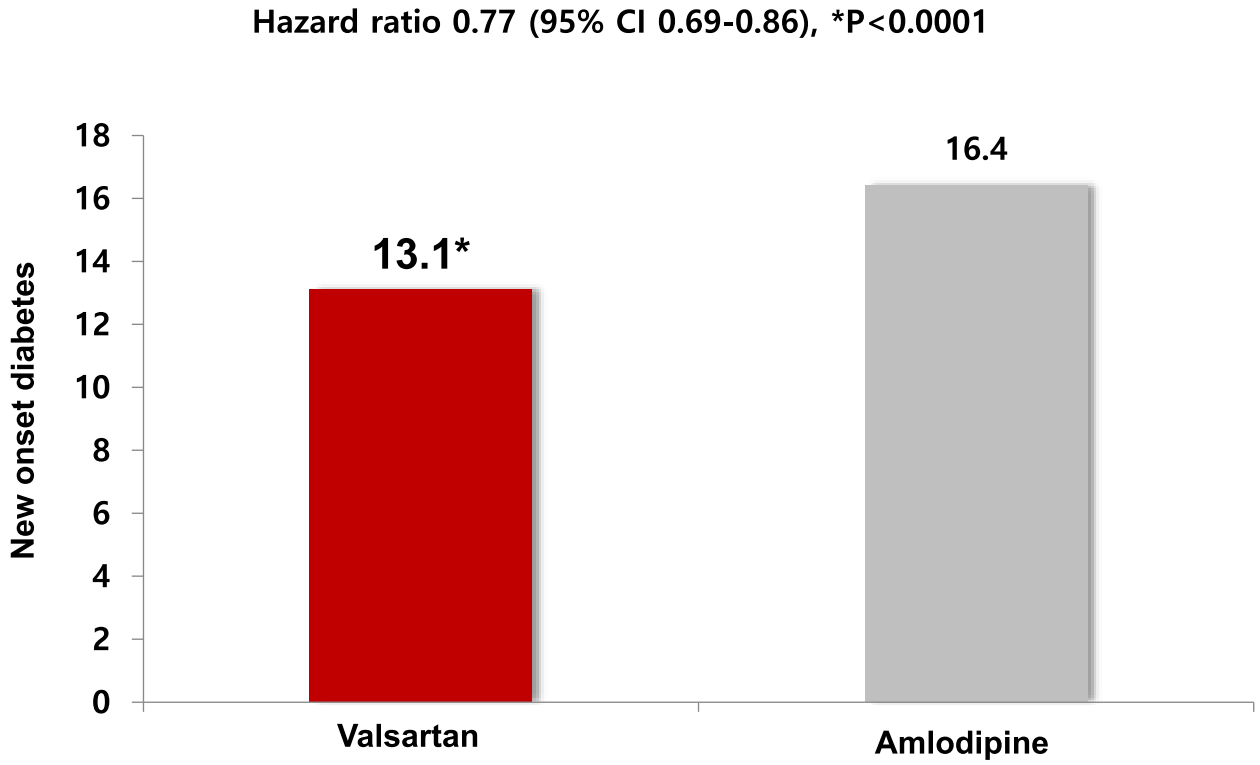
All stroke



Julius S et al. Lancet . 2004 Jun 19;363(9426):2022-31.

VALUE Results | NODM

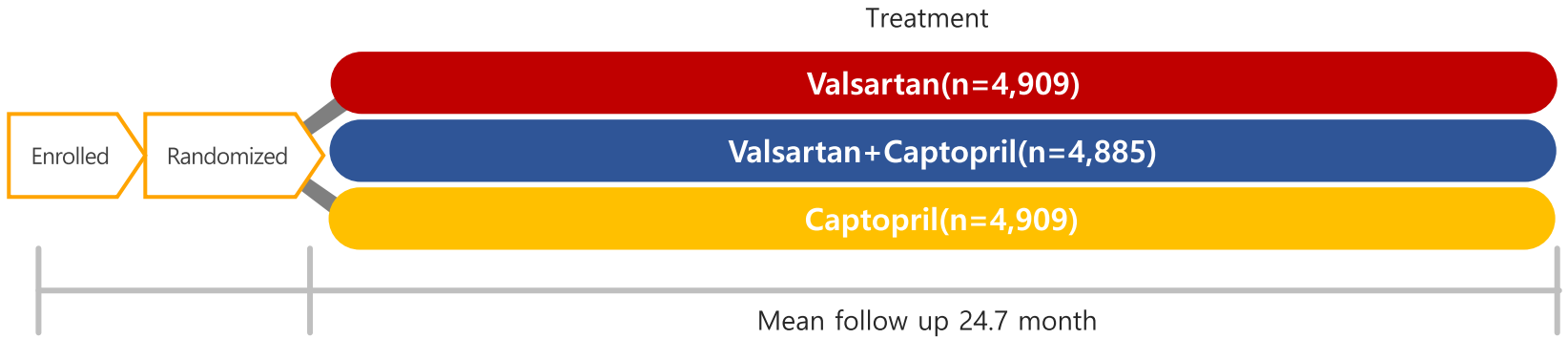
- The Valsartan group **reduced the incidence of diabetes by 23%** compared to the Amlodipine group.



Julius S et al. Lancet . 2004 Jun 19;363(9426):2022-31.

VALIANT (VALsartan In Acute myocardial iNfarcTion) study

Patients	**14,703 patients requiring additional treatment after AMI**
Design	**Randomized, double-blind trial**
Primay Outcome	**All cause Mortality**
Medication	**Valsartan(n=4,909), valsartan+captopril(n=4,885), captopril(n=4,909)**
Periods	To compare the mortality rate of patients with myocardial infarction by comparing valsartan (ARB) and captopril (ACEI), an average of 24.7 months



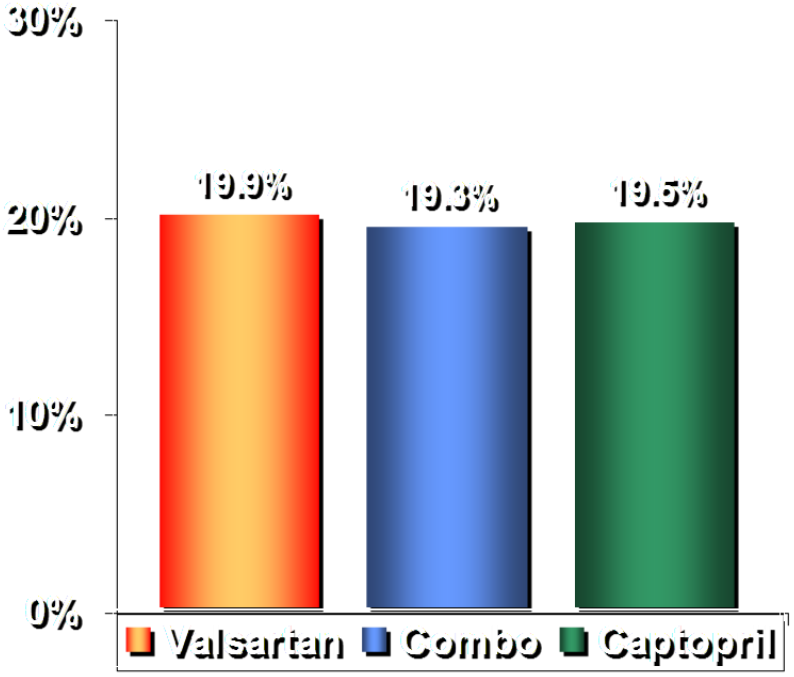
N Engl J Med 2003;349:1893-906

VALIANT Results

- **Valsartan showed an equivalent efficacy of captopril in reducing the risk of death in patients after myocardial infarction.**

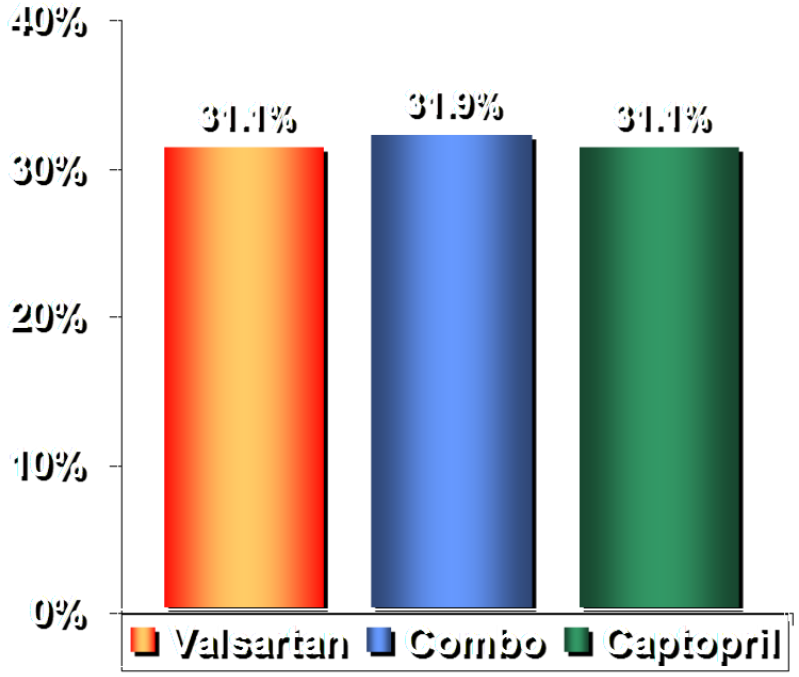
All-cause Mortality*

Valsartan vs captopril
HR 1.00, 97.5% CI 0.90-1.11, p=0.98
Combo vs captopril
HR 0.98, 97.5% CI 0.89-1.09, p=0.73



CV Death, re-MI, or hospitalization for HF*

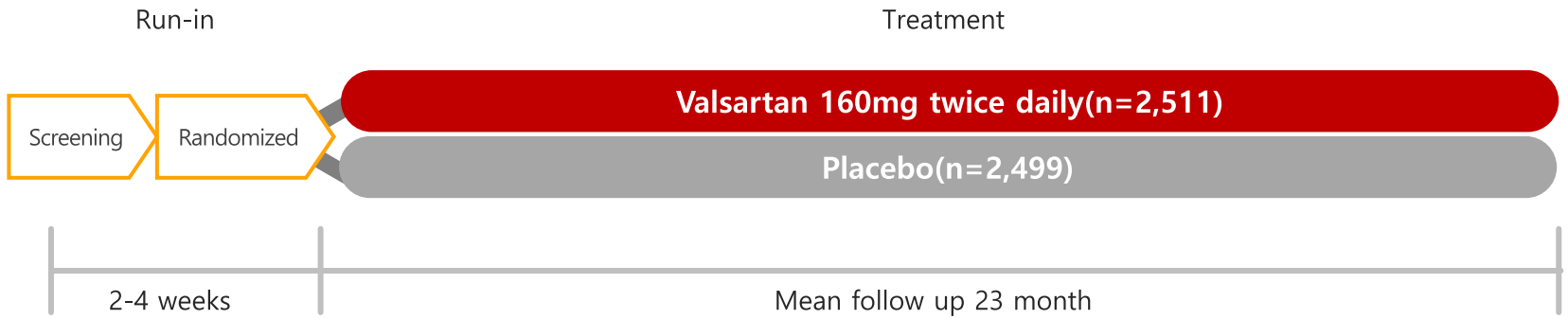
Valsartan vs captopril HR 0.95, p=0.20
Combo vs captopril HR 0.97, p=0.37



* Met criteria for non-inferiority of valsartan vs captopril

Val-HeFT Study (Valsartan in Heart Failure Trial)

Patients	**New York Heart Association (NYHA) class 2-4 heart failure patients (n=5,010), LVEF < 35%**
Design	**Double-blind, randomized, placebo-controlled trial**
Primary Outcome	Total of deaths due to other causes, cardiac arrest requiring CPR, hospitalization due to heart failure, and related heart failure medication into the intravenous vein for at least four hours other than hospitalization
Medication	Valsartan (up to 160 mg bid, n=2,511) vs Placebo (n=2,499) median f/u 23 months

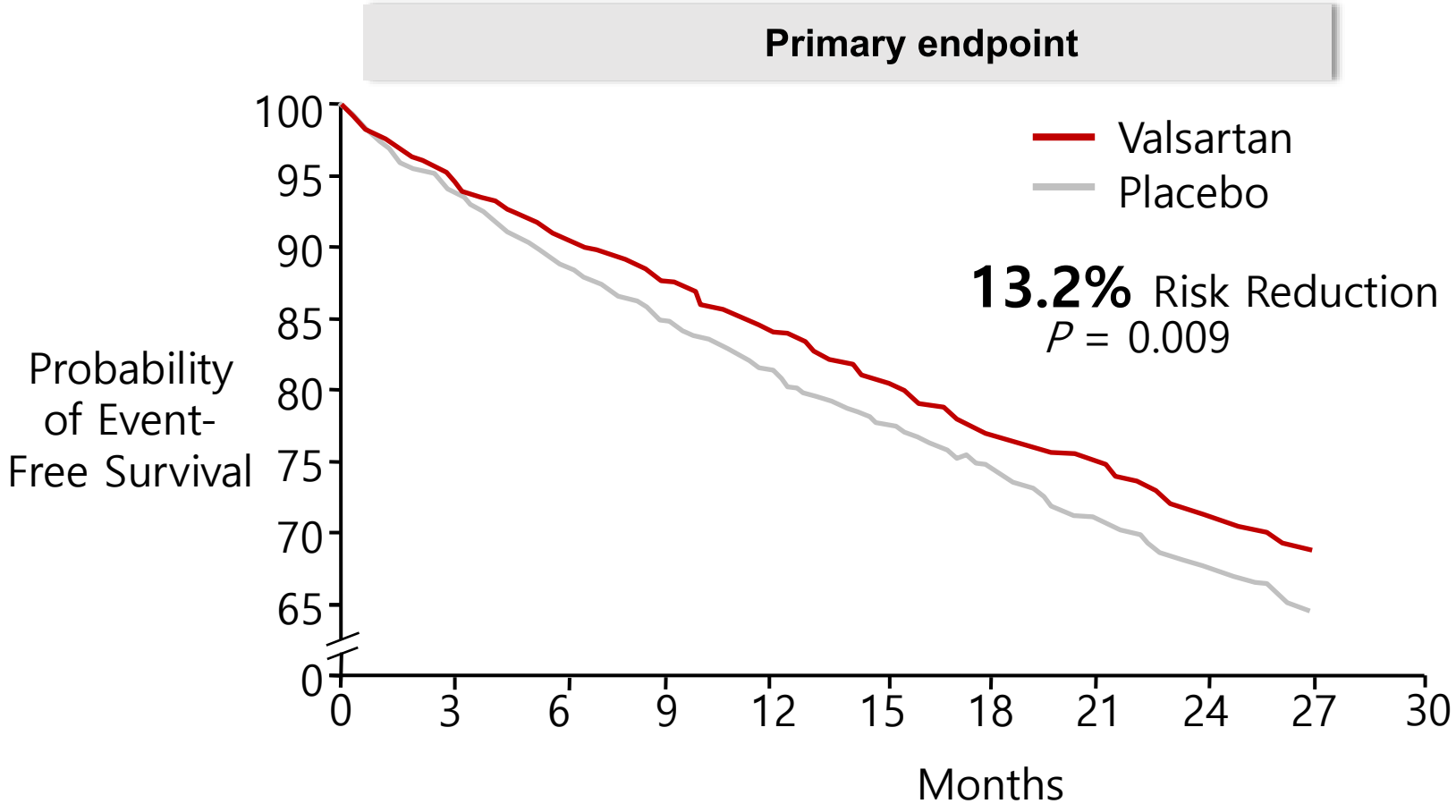


Cohn JN et al. Eur J Heart Fail. 2000;2:439-446

Val-HeFT Results

- **Valsartan significantly improved the incidence of first endpoint* compared to the placebo group in heart failure patients.**

*All-cause mortality, sudden death with resuscitation, hospitalization for worsening heart failure, or therapy with IV inotropes or vasodilators.

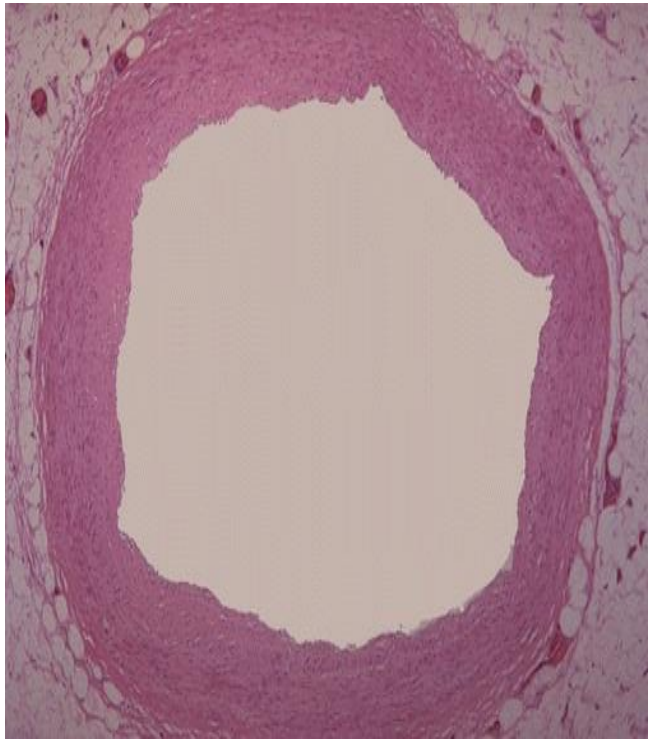


Cohn JN et al. N Engl J Med. 2001;345:1667-1675

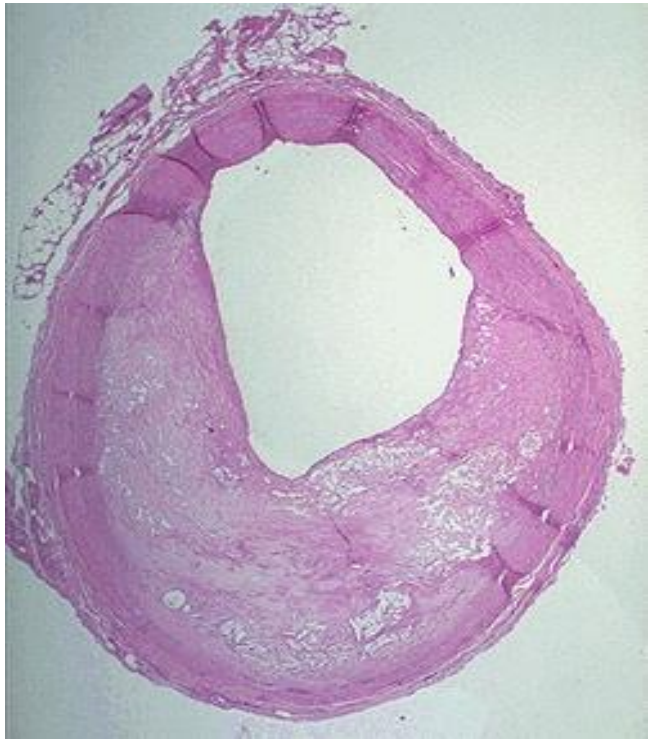
03 *Why rosuvastatin?*

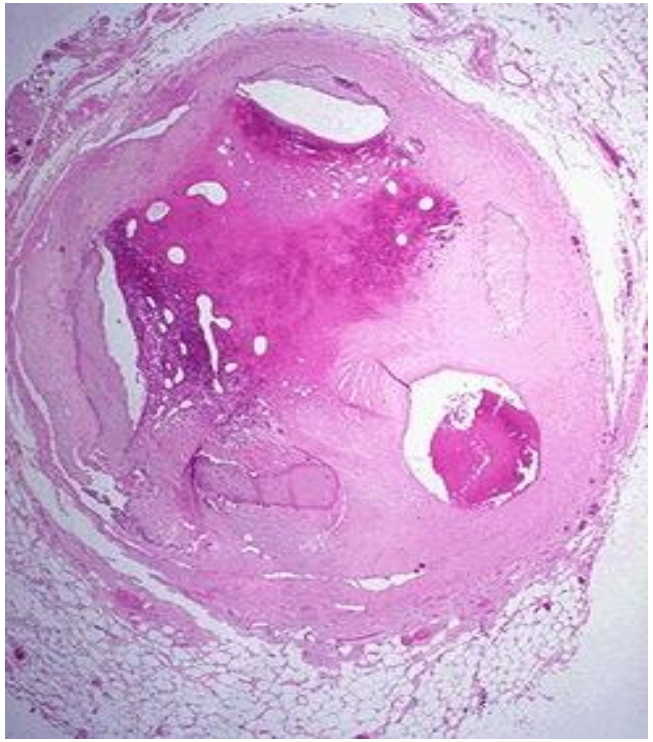
Atherosclerosis

Normal Coronary a.

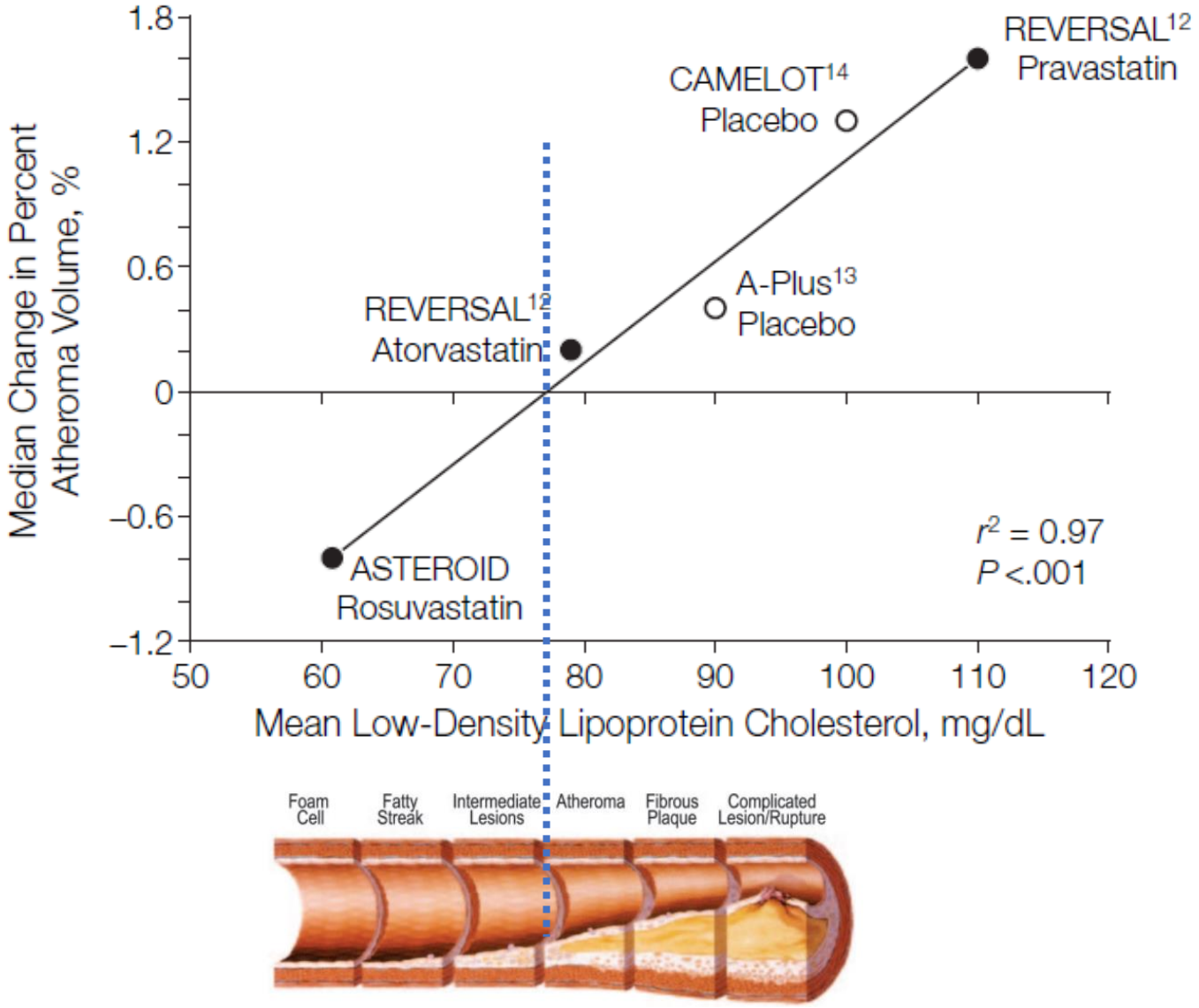


Atherosclerosis with plaque rupture



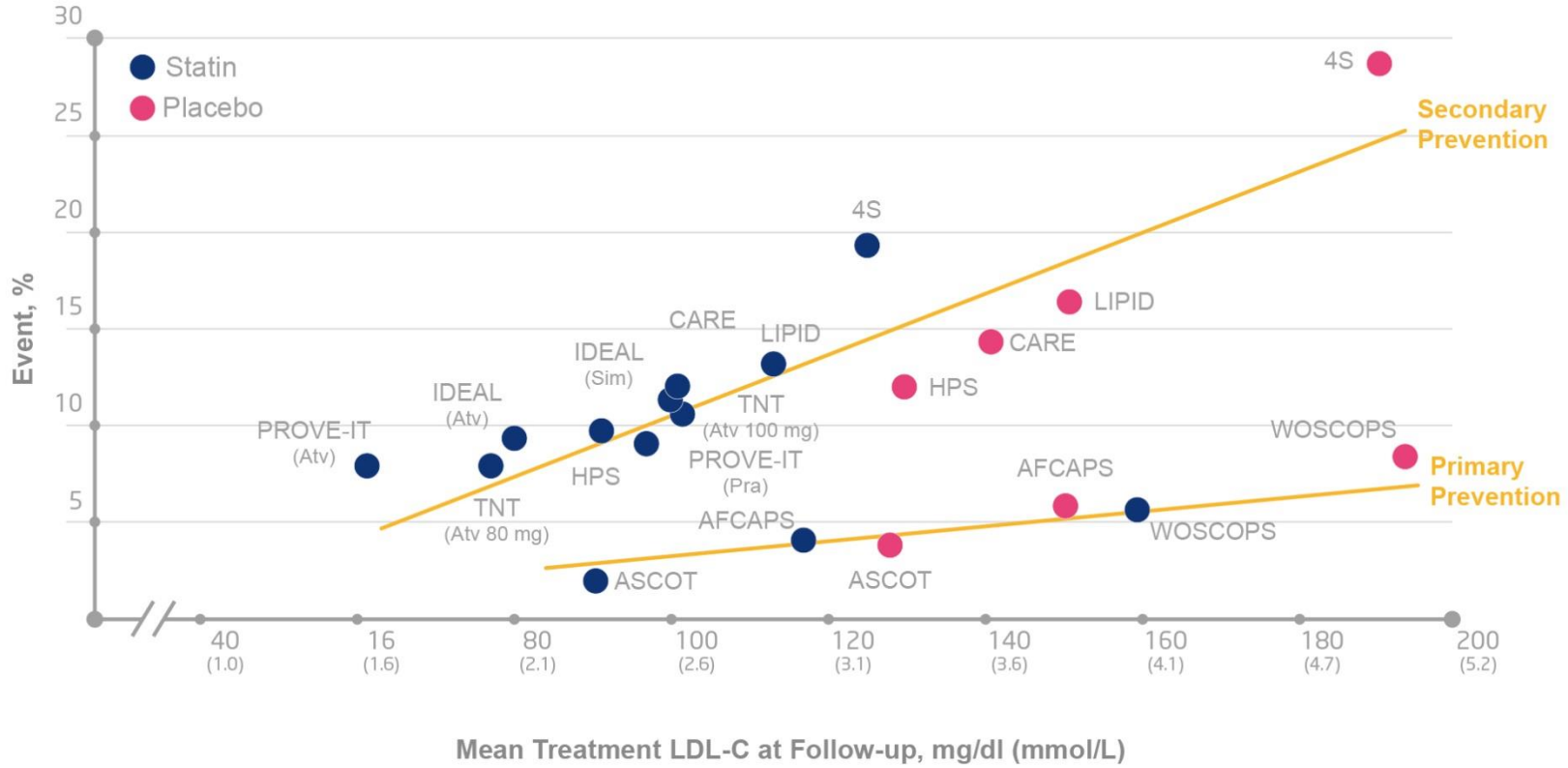


LDL-level and Plaque progression



Nissen et al, JAMA 2006

Why LDL < 70mg/dL



Atv=Atorvastatin, Pra=Pravastatin, Sim=Simvastatin, PROVE-IT=PRavastatin Or atorVastatin Evaluation and Infection Therapy, IDEAL=Incremental Decrease in Endpoints through Aggressive Lipid Lowering, ASCOT=Anglo-Scandinavian Cardiac Outcomes Trial, AFCAPS=Air Force Coronary Atherosclerosis Prevention Study, WOSCOPS=West Of Scotland COronary Prevention Study

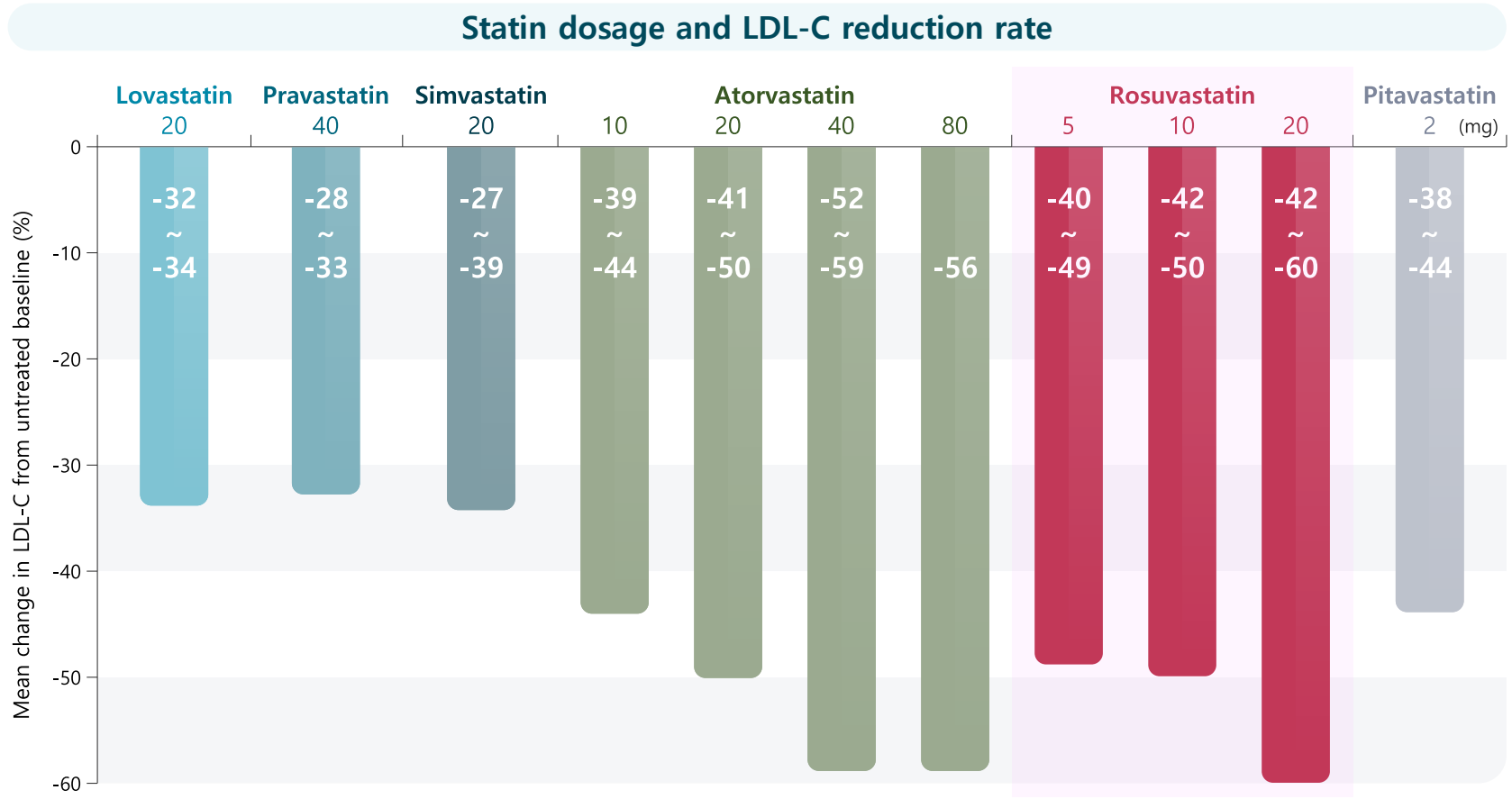
1. Expert Opin Emerg Drugs. 2004;9:269–279. 2. N Engl J Med. 2005;352:1425–1435. 3. JAMA. 2005;294:2437–2445

High-intensity and moderate-intensity statin therapy

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy
Lowers LDL Cholesterol by **≥50%**	Lowers LDL Cholesterol by **30% to <50%**
Atorvastatin 40–80mg **Rosuvastatin 20-40mg**	Atorvastatin 10-20mg **Rosuvastatin 5-10mg** Simvastatin 20-40mg Pravastatin 40-80mg Lovastatin 40mg Fluvastatin XL 80mg Pitavastatin 2-4mg

Potent lipid lowering efficacy of rosuvastatin

- **Rosuvastatin has -40 ~ -60% LDL-C mean change percentage, which can be controlled by dosage.**



The Korean Society of Lipid & Atherosclerosis. 2018 Korean Guidelines for the Management of Dyslipidemia 4th Ed.

JUPITER (high dose statin, primary prevention)

Patient:	no history of CVD, LDL < 130mg/dL, CRP ≥ 2mg/L
Intervention:	Rosuvastatin 20mg (n=8901)
Comparison:	Placebo (n=8901)
Outcomes:	MACE (MI, stroke, hospitalization of UA, or CV death)

HR, 0.56 [0.46 -0.69]; P<0.00001

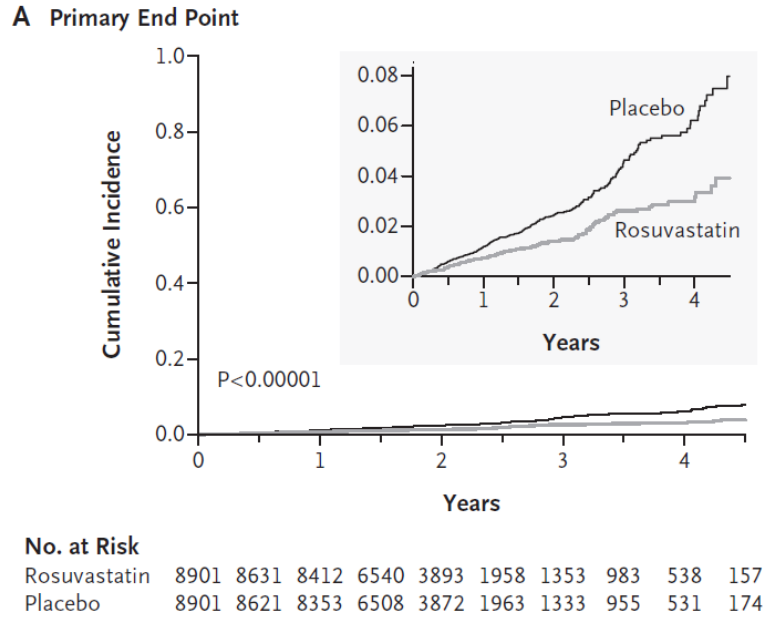


Table 4. Monitored Adverse Events, Measured Laboratory Values, and Other Reported Events of Interest during the Follow-up Period.*

Event	Rosuvastatin (N=8901)	Placebo (N=8901)	P Value
Monitored adverse events			
Any serious adverse event — no. (%)	1352 (15.2)	1377 (15.5)	0.60
Muscular weakness, stiffness, or pain — no. (%)	1421 (16.0)	1375 (15.4)	0.34
Myopathy — no. (%)	10 (0.1)	9 (0.1)	0.82
Rhabdomyolysis — no. (%)†	1 (<0.1)	0	—
Newly diagnosed cancer — no. (%)	298 (3.4)	314 (3.5)	0.51
Death from cancer — no. (%)	35 (0.4)	58 (0.7)	0.02
Gastrointestinal disorder — no. (%)	1753 (19.7)	1711 (19.2)	0.43
Renal disorder — no. (%)	535 (6.0)	480 (5.4)	0.08
Bleeding — no. (%)	258 (2.9)	275 (3.1)	0.45
Hepatic disorder — no. (%)	216 (2.4)	186 (2.1)	0.13
Laboratory values‡			
Creatinine, >100% increase from baseline — no. (%)	16 (0.2)	10 (0.1)	0.24
Glomerular filtration rate at 12 mo — ml/min/1.73 m²			0.02
Median	66.8	66.6	
Interquartile range	59.1–76.5	58.8–76.2	
Alanine aminotransferase >3× ULN on consecutive visits — no. (%)	23 (0.3)	17 (0.2)	0.34
Glycated hemoglobin at 24 mo — %			0.001
Median	5.9	5.8	
Interquartile range	5.7–6.1	5.6–6.1	
Fasting glucose at 24 mo — mg/dl			0.12
Median	98	98	
Interquartile range	91–107	90–106	
>Trace of glucose in urine at 12 mo — no. (%)	36 (0.5)	32 (0.4)	0.64
Other events			
Newly diagnosed diabetes (physician-reported) — no. (%)	270 (3.0)	216 (2.4)	0.01
Hemorrhagic stroke — no. (%)	6 (0.1)	9 (0.1)	0.44

Ridker et al , NEJM 2008

HOPE-3 (low lose statin in primary prevention)

Patient: Patients at intermediate risk (1%/year) (n=12705)
Intervention: Rosuvastatin 10mg (n=6361)
Comparison: Placebo (n=6344)
Outcomes: Co-primary endpoints

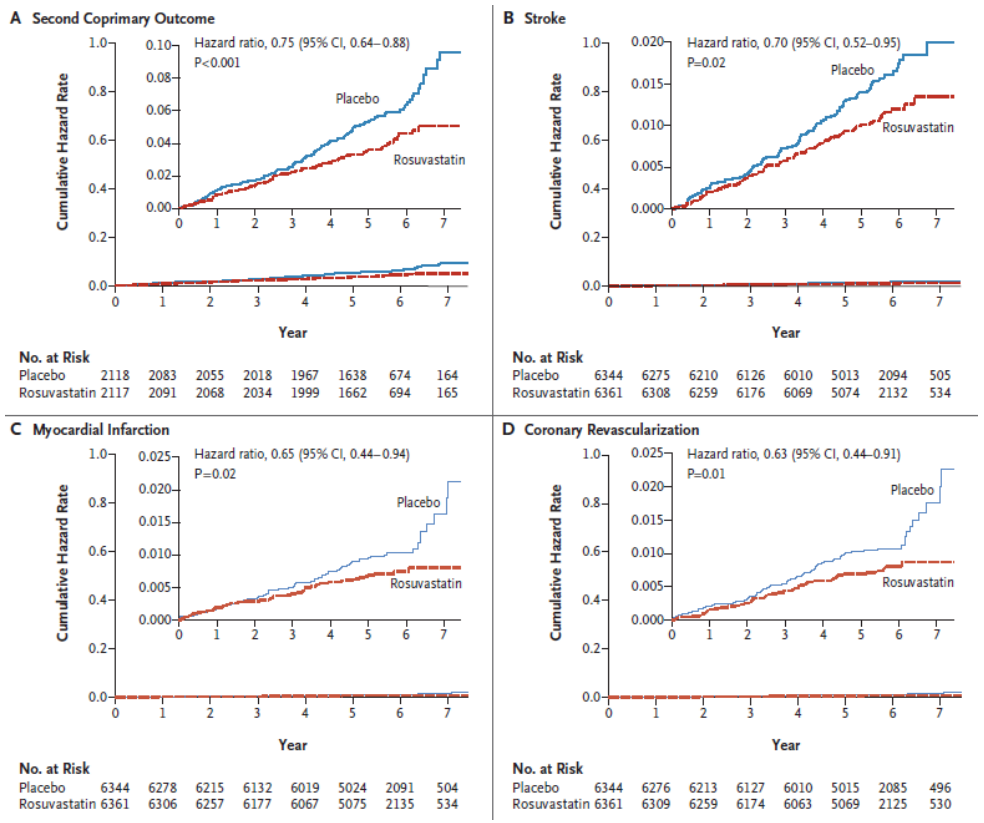


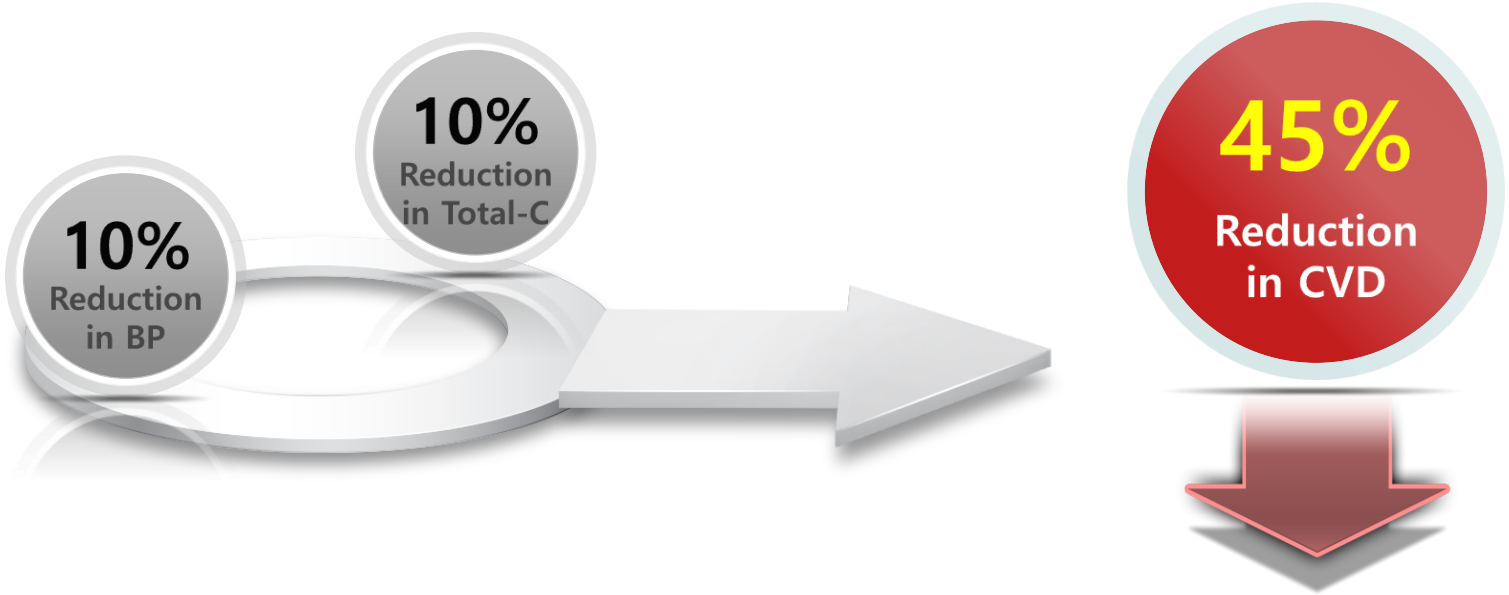
Table 2. Primary, Secondary, and Other Outcomes.*

Outcome	Rosuvastatin Group (N=6361)	Placebo Group (N=6344)	Hazard Ratio (95% CI)	P Value
Coprimary outcomes — no. (%)				
First coprimary outcome	235 (3.7)	304 (4.8)	0.76 (0.64–0.91)	0.002
Second coprimary outcome	277 (4.4)	363 (5.7)	0.75 (0.64–0.88)	<0.001
Secondary outcome — no. (%)	306 (4.8)	393 (6.2)	0.77 (0.66–0.89)	<0.001
Components of the coprimary and secondary outcomes — no. (%)				
Death from cardiovascular causes	154 (2.4)	171 (2.7)	0.89 (0.72–1.11)	
Myocardial infarction	45 (0.7)	69 (1.1)	0.65 (0.44–0.94)	
Stroke	70 (1.1)	99 (1.6)	0.70 (0.52–0.95)	
Resuscitated cardiac arrest	4 (0.1)	4 (0.1)	0.99 (0.25–3.97)	
Revascularization	56 (0.9)	82 (1.3)	0.68 (0.48–0.95)	
Heart failure	21 (0.3)	29 (0.5)	0.72 (0.41–1.26)	
Angina with evidence of ischemia	56 (0.9)	64 (1.0)	0.87 (0.61–1.24)	
Death from any cause — no. (%)	334 (5.3)	357 (5.6)	0.93 (0.80–1.08)	0.32
New-onset diabetes — no. (%)	232 (3.9)	226 (3.8)	1.02 (0.85–1.23)	0.82
Coronary heart disease — no. (%)†	105 (1.7)	140 (2.2)	0.74 (0.58–0.96)	0.02
First and recurrent events of the second coprimary outcome‡				
No. of participants with ≥1 event	277	363		
No. of participants with ≥2 events	68	89		
No. of participants with ≥3 events	6	16		
Total no. of events	353	473	0.75 (0.64–0.89)	0.001
Hospitalizations — no. (%)§				
For cardiovascular causes	281 (4.4)	369 (5.8)	0.75 (0.64–0.88)	<0.001
For noncardiovascular causes	881 (13.9)	879 (13.9)	1.00 (0.91–1.10)	0.99

04 *Why Exone R?*

Combined Effect of Reductions in CV Risk Factors

10% reductions in long-term mean blood cholesterol and blood pressure could have reduced major CVD by 45%



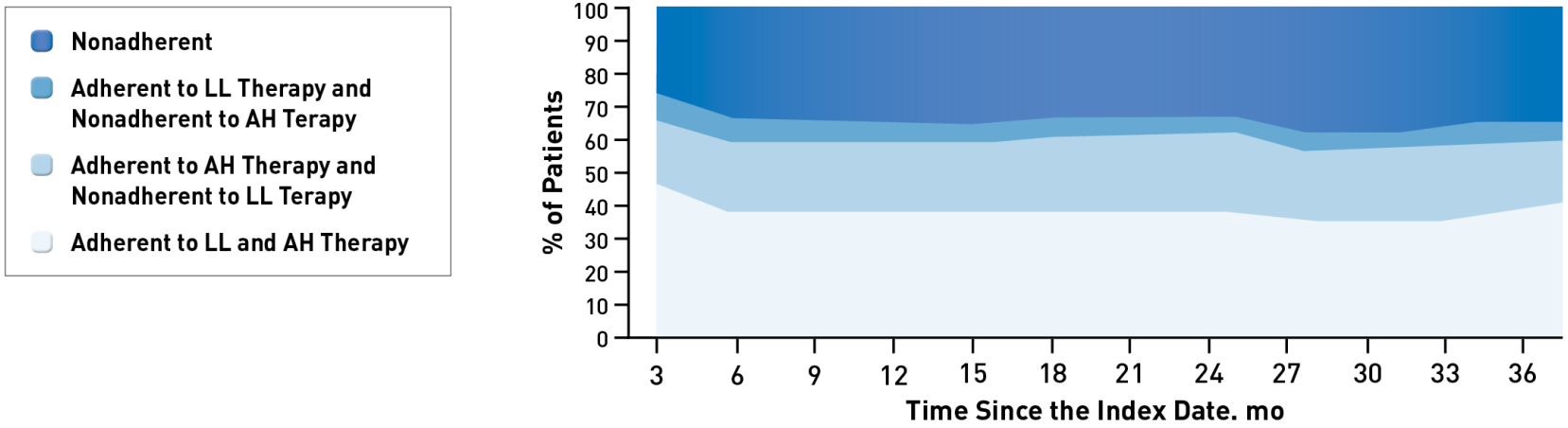
* CV=Cardiovascular, CVD=Cardiovascular Disease

Eur Heart J. 2004;25:484-491.

Adherence with concomitant therapy is poor

Adherence with concomitant antihypertensive (AH) and lipid-lowering (LL) therapy is poor, with only 1 in 3 patients adherent with both medications at 6 months.

Patterns of patient adherence to concomitant therapy over 3 years.



Total No. of Patients	8406	7439	6655	5759	4997	4204	3358	2495	1501	1200	926	691
Nonadherent	27.4	35.0	35.9	35.3	36.1	33.8	34.3	34.2	39.0	38.5	36.3	36.5
Adherent to LL Therapy and Nonadherent to AH Terapy	8.5	7.2	6.5	6.5	5.7	5.9	5.8	5.7	5.7	5.3	5.9	5.2
Adherent to AH Therapy and Nonadherent to LL Terapy	19.4	21.9	21.0	22.4	22.6	23.4	23.3	23.9	21.3	23.0	22.6	20.1
Adherent to LL and AH Therapy	44.7	35.9	36.6	35.8	35.6	36.9	36.5	36.2	34.0	33.2	35.2	38.2

The index date was defined as the date concomitant therapy (ie, second drug) was initiated. Percentages at each date may not total 100 because of rounding. AH indicates antihypertensive; LL, lipid-lowering.

Methods: This retrospective cohort study examined 8406 enrollees in a US managed care plan who initiated treatment with AH and LL therapy within a 90-day period. Adherence was measured as the proportion of days covered in each 3-month interval following initiation of concomitant therapy (mean follow-up, 12.9 months). Patients were considered adherent if they had filled prescriptions sufficient to cover at least 80% of days with both classes of medications. A multivariate regression model evaluated potential predictors of adherence.

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Chapman, et al. *Arch Intern Med*. 2005;165:1147-1152

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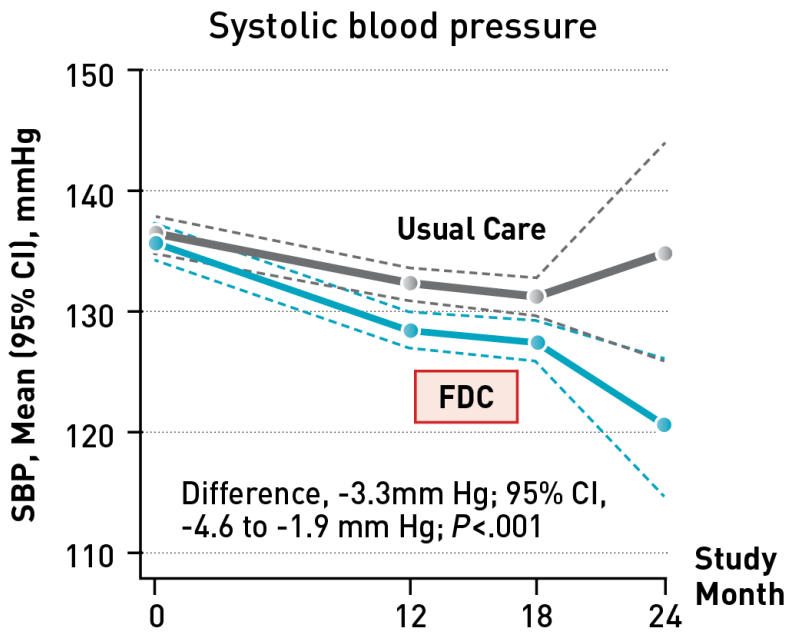
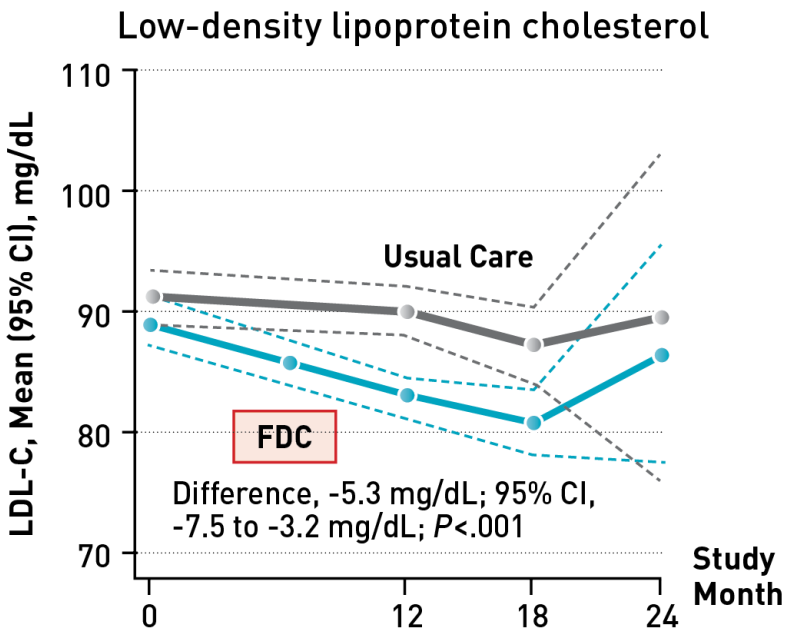
Fixed-Dose Combination Strategy for the patients with or at High Risk of CVD

The FDC group had improved adherence vs usual care (86%vs 65%; relative risk [RR] of being adherent, 1.33; 95%CI, 1.26-1.41; $p < 0.001$) with concurrent reductions in SBP and LDL-C

SBP and LDL-C Levels by Treatment Group During Follow-up





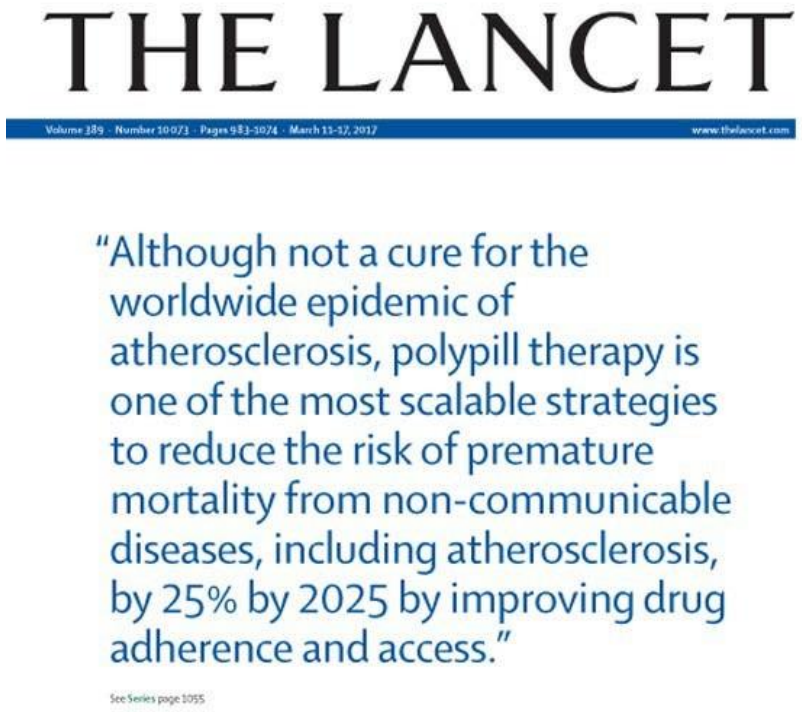
No.				
FDC	1002	917	479	32
Usual Care	1002	892	475	31

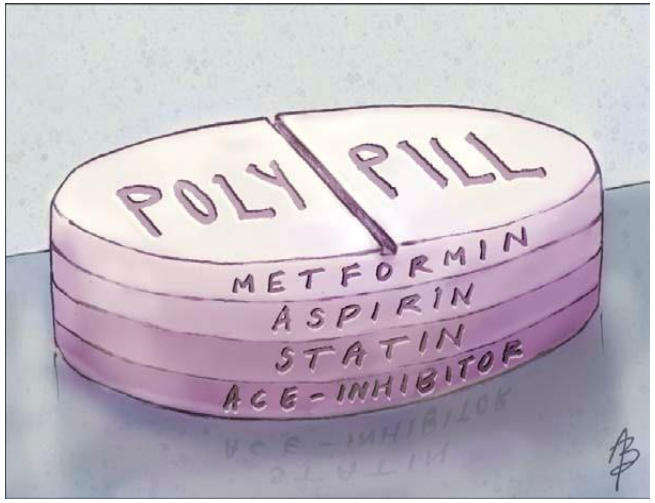
No.				
FDC	985	904	467	32
Usual Care	991	876	458	30

Thom S, et al. *JAMA*. 2013;310(9):918-929.

Polypills: an essential medicine for CVD

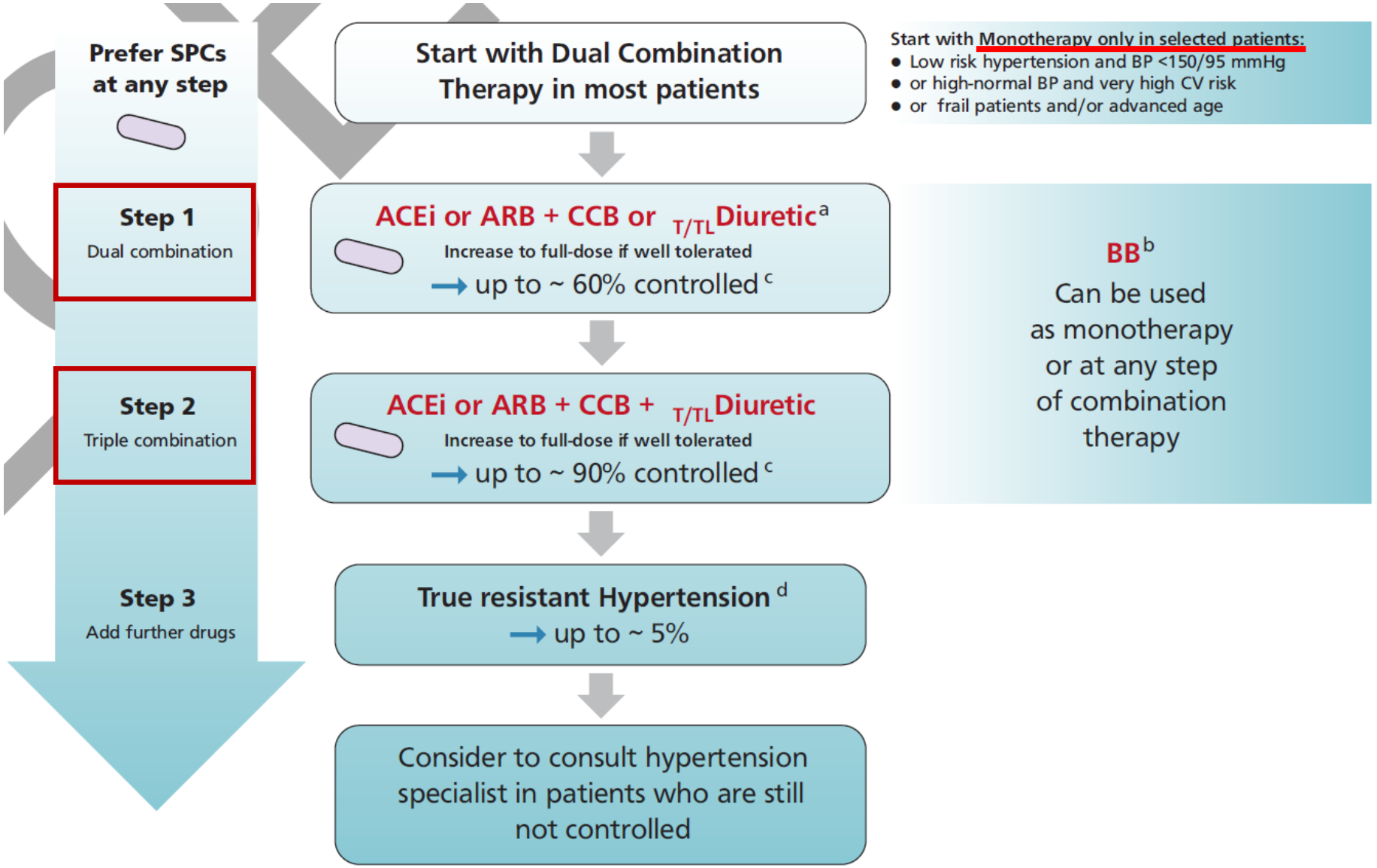
- **Polypills combining Statin with one or more antihypertensive drugs and aspirin**
  → improve treatment adherence rates
  → safely reduce cardiovascular risk factors in patients with established CVD.





Lancet. 2017;389(10073):984.

Treatment Algorithm (ESC/ESH)

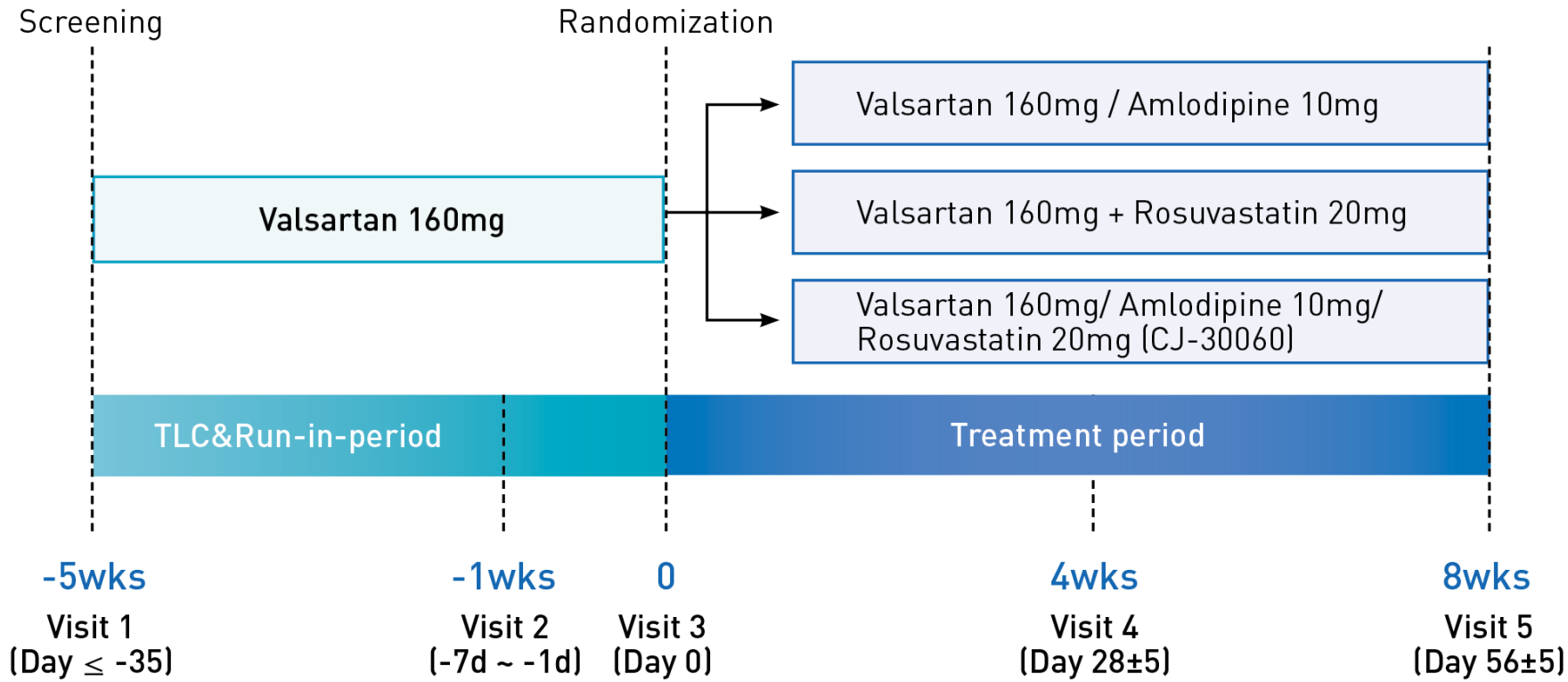


J Hypertens. 2023 Jun 21. Online

EXONE-R

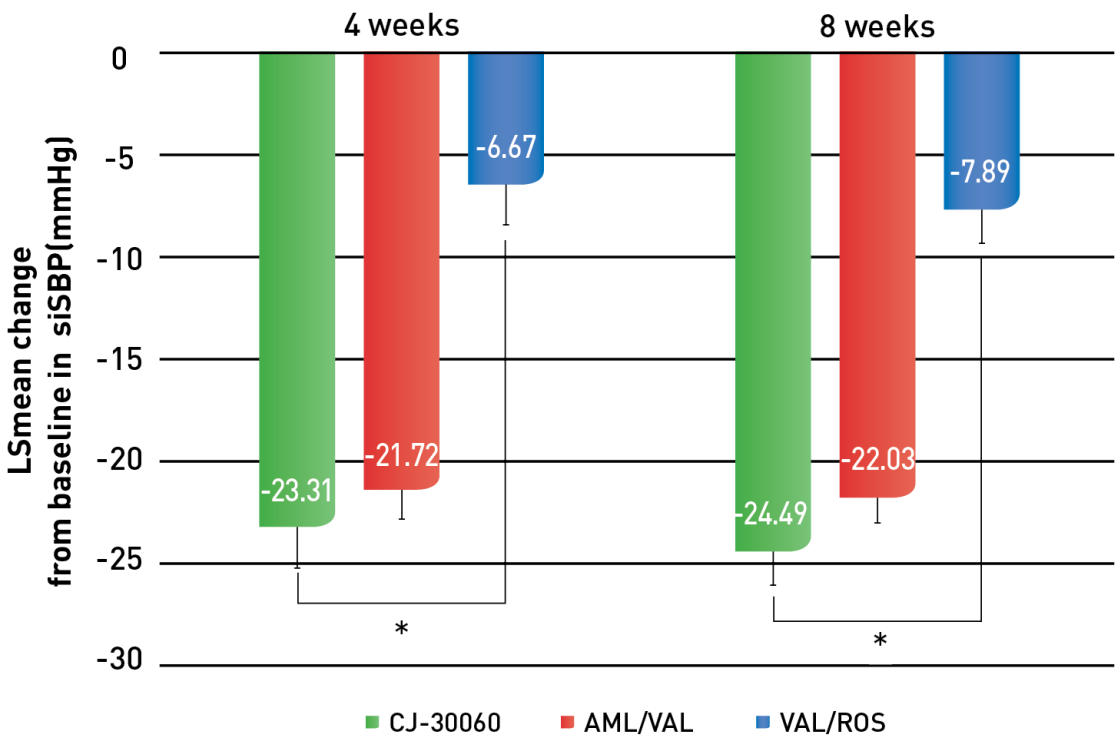
제품명	엑스원-R (EXONE-R tab.)
분류	전문의약품
성분명	Amlodipine / Valsartan/ Rosuvastatin
함량,제형	Amlodipine 5mg/ Valsartan 80 mg / Rosuvastatin 2.5 mg (5월 1일 출시) Amlodipine 5mg/ Valsartan 160 mg / Rosuvastatin 2.5 mg (5월 1일 출시) Amlodipine 5mg/ Valsartan 80 mg / Rosuvastatin 5 mg Amlodipine 5mg/ Valsartan 80 mg / Rosuvastatin 10 mg Amlodipine 5mg/ Valsartan 160 mg / Rosuvastatin 5 mg Amlodipine 5mg/ Valsartan 160 mg / Rosuvastatin 10 mg
적응증	암로디핀 또는 발사르탄 단독요법으로 혈압이 적절하게 조절되지 않는 본태성 고혈압
용법, 용량	• 1일 1회 1정을 물과 함께 복용한다. • 가능하면 매일 같은 시간(예: 아침)에 복용하는 것이 권장

Study Design (Phase Ⅲ trial)

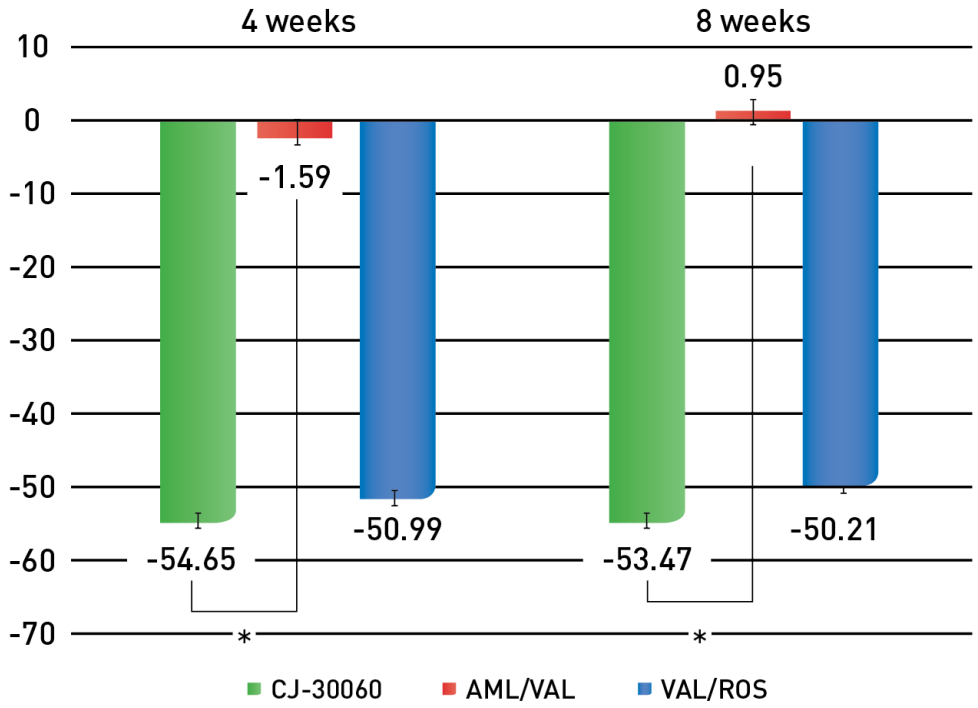


LS mean change from baseline

siSBP change



LDL-C change



Summary

- **Fixed Dose Combination-based care** not only improves adherence but also decrease **more BP and LDL-C**, reduce cardiovascular risk factors in patients with established cardiovascular disease.
- **Valsartan** is the only ARB with HF & Post MI indication with the highest AT1 receptor selectivity among ARBs.
- **Amlodipine** provided stable **SBP reduction**.
- **Rosuvastatin** is high intensity statin that is effective in high risk and intermediate risk patints.
- Proven benefits of **Rosuvastatin and Amlodipine/Valsartan** combined, **EXONE-R** can be a optimal choice for patients with vHypertension and Dyslipidemia.