

Yesterday, Today and Tomorrow of ARB: Irbesartan



박광열

중앙대학교 신경과

Hypertension and Stroke

J curve in Stroke?

ACCORD

SPRINT

Renal protection of Irbesartan

Summary

Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble



Vassilis Kontis*, James E Bennett*, Colin D Mather, Guangguan Li, Kyle Foreman, Majid Ezzati

Summary

Background Projections of future mortality and life expectancy are needed to plan for health and social services and

Lancet 2012; 380: 1323–35

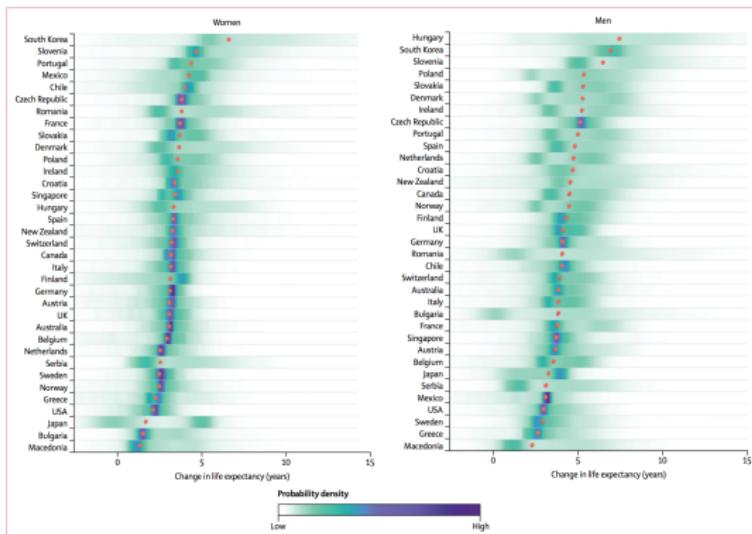
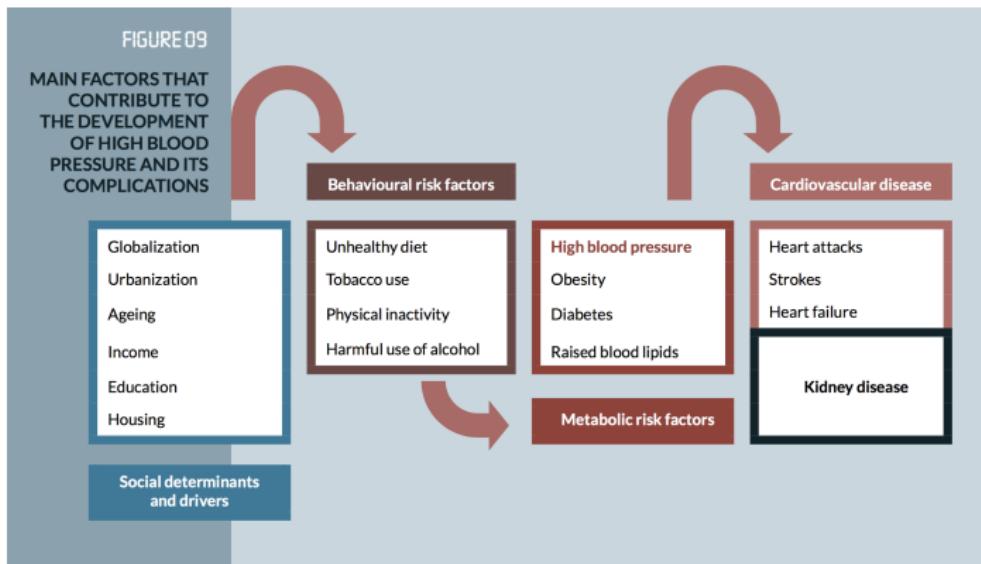


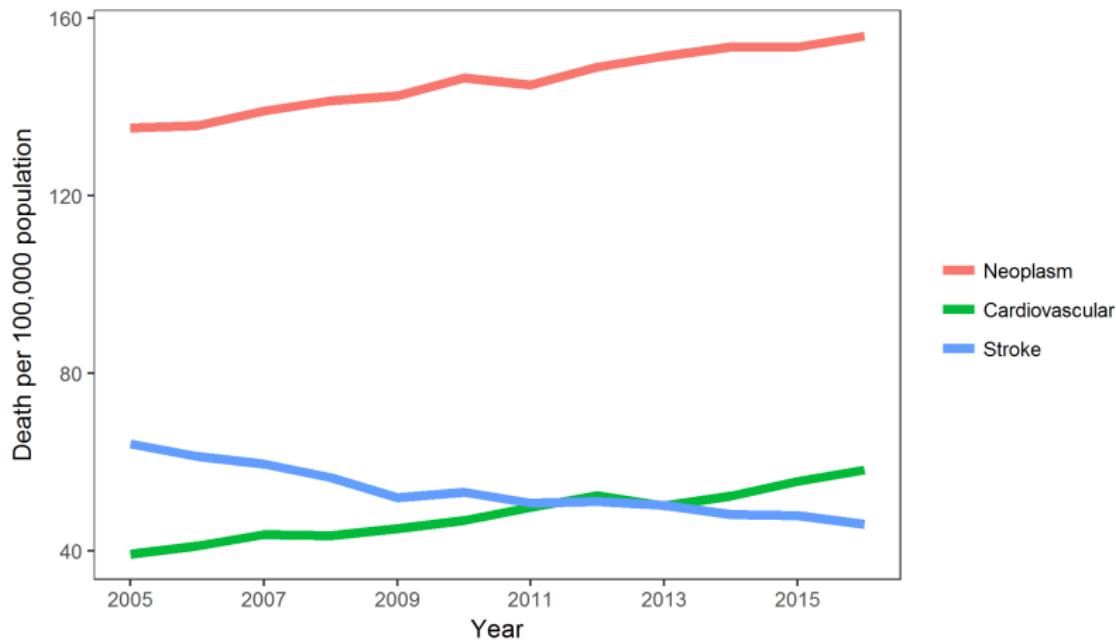
Figure 1: Posterior distribution of projected change in life expectancy at birth from 2010 to 2030
Red dots show the posterior medians. Countries are ordered vertically by median projected increase from largest (at the top) to smallest (at the bottom).

There is a 90% probability that life expectancy at birth among South Korean women in 2030 will be higher than 86 · 7 years, and a **57% probability that it will be higher than 90 years.**

There is a greater than 95% probability that life expectancy at birth among men in South Korea, Australia, and Switzerland will surpass 80 years in 2030, and a greater than 27% probability that it will surpass 85 years.



Secular trend of mortality in Korea



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

Stroke and HT

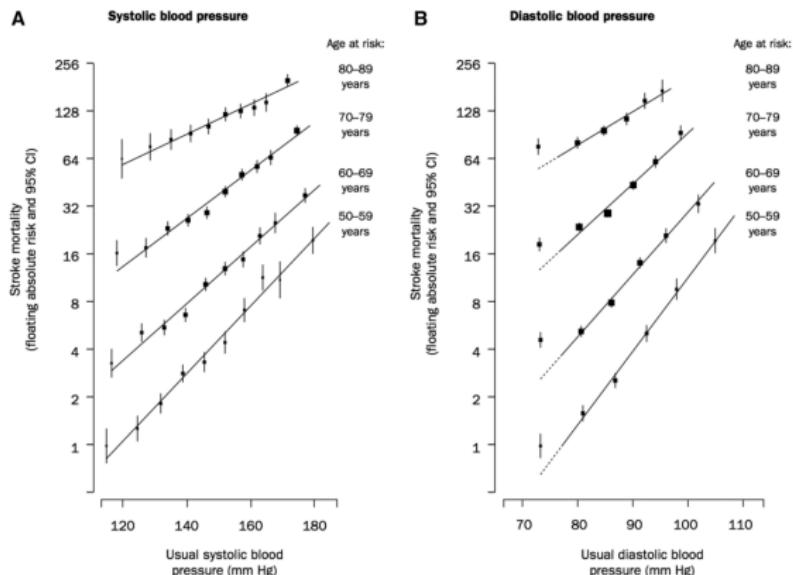


Figure 2. Stroke mortality in each decade of age vs usual blood pressure at the start of the decade. CI indicates confidence interval.
Adapted from the Prospective Studies Collaboration (Lewington et al¹²) with permission of the publisher. Copyright ©2002, Elsevier.

IHD and HT

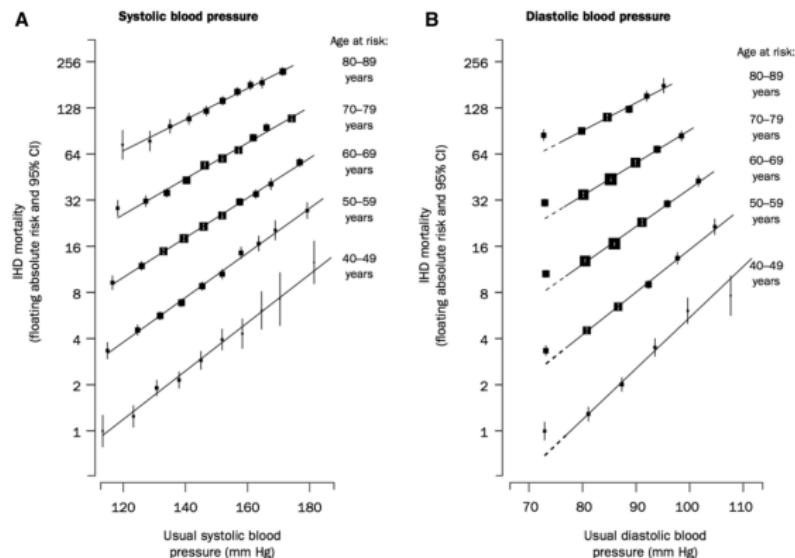


Figure 1. Ischemic heart disease (IHD) mortality in each decade of age vs usual blood pressure at the start of the decade.
CI indicates confidence interval. Adapted from the Prospective Studies Collaboration (Lewington et al¹⁷) with permission of the publisher.

IHD vs Stroke and SBP

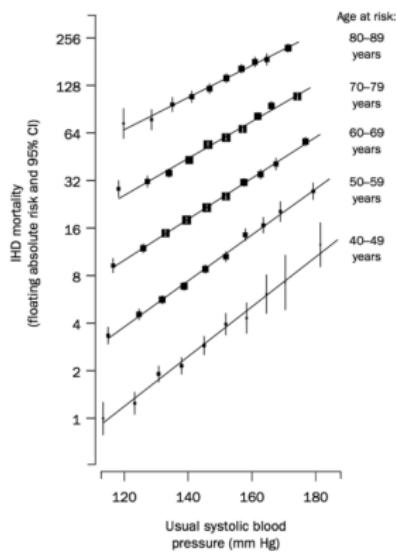


Figure 1. Ischemic heart disease (IHD) mortality

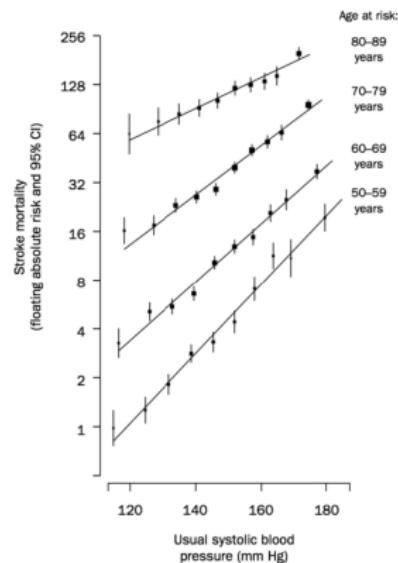
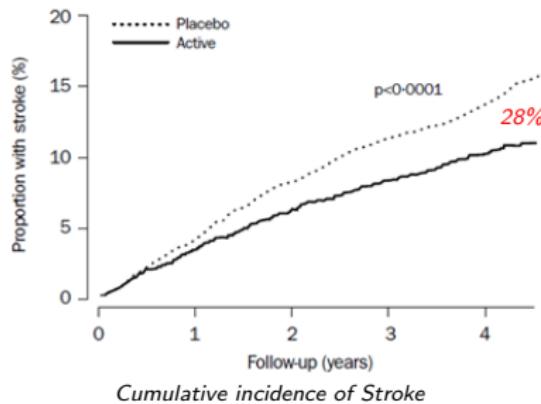
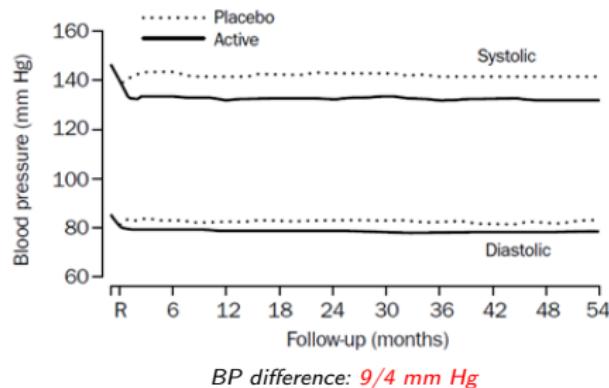


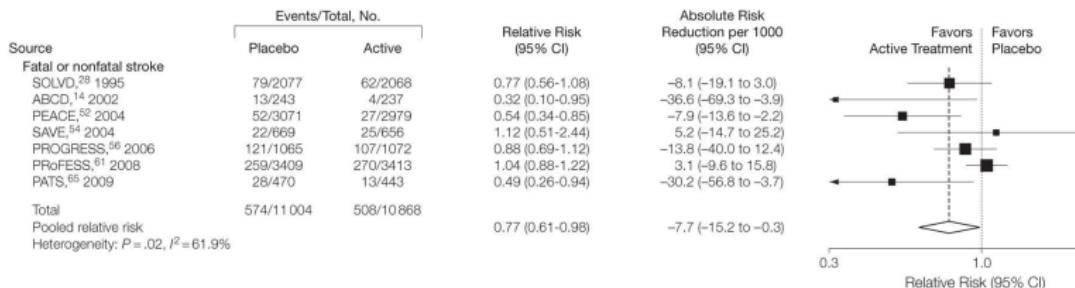
Figure 2. Stroke mortality

PROGRESS

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

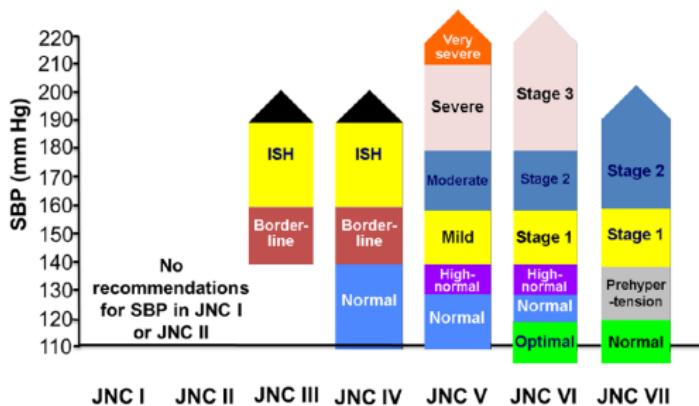


Anti-HT Tx. and stroke



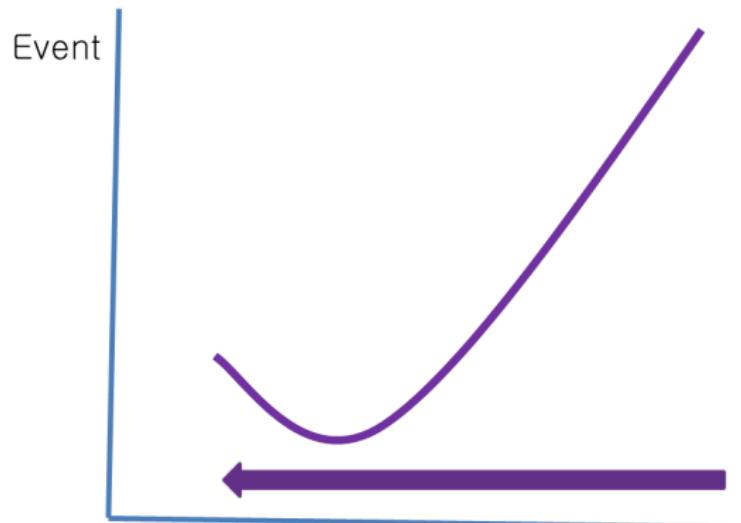
WASHINGTON, D.C.
April 9, 1944

9th	202/102	P.M.	196/96
10th	196/94	"	200/104
11th	192/96	"	204/100
12th	200/102	"	204/98
13th	196/100	"	202/96
14th	206/100	"	200/96
15th	206/102	"	196/100
16th	215/102	"	206/120
17th	216/120	"	206/116 (Dr.Bruen 6th sound)
18th	220/120	(4th sound)	Unicosp 1; XI \neq x t.i.d. ac.
19th	218/120	P.M.	204/104
20th	212/106	Noon	210/96 9:54 p.m. 190/100 (XI discontinued)
21st	9:05 a.m.	234/126; 10:15 a.m. (sitting)	210/116; 10:05 a.m. 218/120 (prone, both arms checked) 6:45 p.m. after outing 214/180; 9:50 p.m. 220/114.
22nd	9:30 a.m.	214/120; 11:30 a.m.	210/114; 6:30 p.m. (after boat trip) 206/110.
23rd	10:15 a.m.	214/118 (2 1/2 hr drive)	9:45 212/114.
24th	10:15 a.m.	222/122	10:30 p.m. 220/110
25th	10:05	224/116	10 p.m. 214/106 (after luncheon party).
26th	10. a.m.	214/112	10:30 p.m. 222/110
27th	10:15 a.m.	222/118;	9:45 p.m. 210/114
28th	224/124	P.M.	230/120 (one additional digit tablet Tuesday and Friday)
29th	9:15 a.m. (on swaying)	196/112; (sitting after breakfast)	10:10 226/120; (Prone, after E.E.) 220/118; 2:15 (after lunch) 226/112 (Thesodate discontinued) 9:30 p.m. 210/110
30th	8:45 (Prone, on swaying)	210/110; (after breakfast)	10:00 206/104; ; after lunch 206/114; 9:00 p.m. 224/120
May 1st.	Prone 9:15 a.m.	220/116; Noon	210/110; 2 p.m. (after lunch 210/ 106; 10:30 p.m. 210/118.

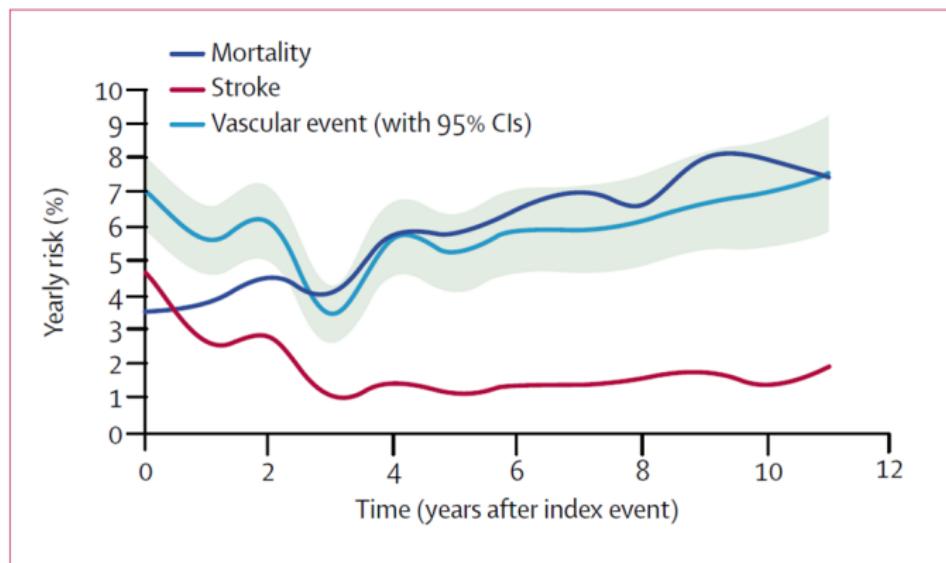


JNC I. *JAMA*. 1977;JNC II. *Arch Intern Med.* 1980; JNC III. *Arch Intern Med.* 1984; JNC IV. *Arch Intern Med.* 1988; JNC V. *Arch Intern Med.* 1993;JNC VI. *Arch Intern Med.* 1997;JNC 7 Express

Hypertension: J curve ?



Yearly Risk over Time in Dutch TIA trial



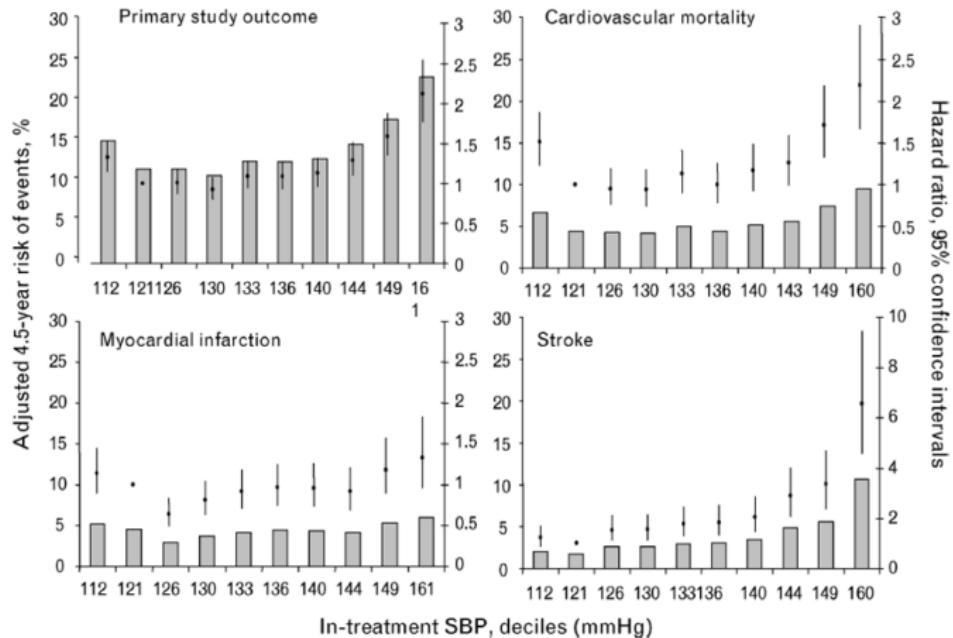
Vascular events after stroke

Risk of Myocardial Infarction and Vascular Death After Transient Ischemic Attack and Ischemic Stroke A Systematic Review and Meta-Analysis

Emmanuel Touzé, MD; Olivier Varenne, MD, PhD; Gilles Chatellier, MD, PhD;
Séverine Peyrard, MSc; Peter M. Rothwell, MD, PhD, FRCP; Jean-Louis Mas, MD

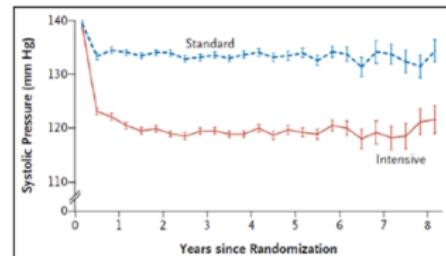
	Annual Risk
Nonstroke vascular death	2.1% (1.9 to 2.4)
Total MI	2.2% (1.7 to 2.7)
Nonfatal MI	0.9% (0.7 to 1.2)
Fatal MI	1.1% (0.8 to 1.5)

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

	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% *

Special Communication

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults

Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Paul A. James, MD; Suzanne Oparil, MD; Barry L. Carter, PharmD; William C. Cushman, MD;
Cheryl Dennison-Himmelfarb, RN, ANP, PhD; Joel Handler, MD; Daniel T. Lackland, DrPH;
Michael L. LeFevre, MD, MSPH; Thomas D. MacKenzie, MD, MSPH; Olugbenga Ogedegbe, MD, MPH, MS;
Sidney C. Smith Jr, MD; Laura P. Svetkey, MD, MHS; Sandra J. Taler, MD; Raymond R. Townsend, MD;
Jackson T. Wright Jr, MD, PhD; Andrew S. Narva, MD; Eduardo Ortiz, MD, MPH

Recommendation 1

In the general population aged ≥ 60 years, initiate pharmacologic treatment to lower blood pressure (BP) at systolic blood pressure (SBP) ≥ 150 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg and treat to a goal SBP < 150 mm Hg and goal DBP < 90 mm Hg. (Strong Recommendation – Grade A)

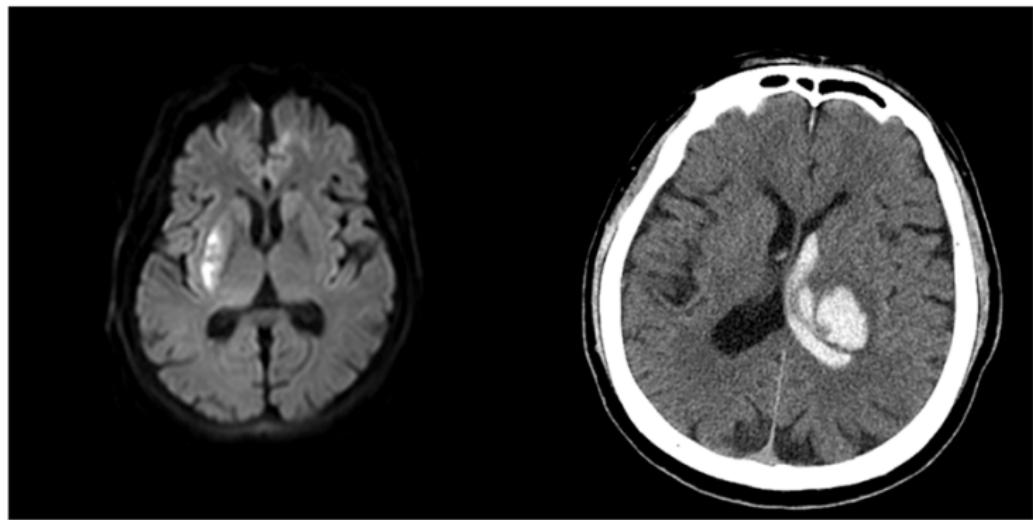
Corollary Recommendation

In the general population aged ≥ 60 years, if pharmacologic treatment for high BP results in lower achieved SBP (eg, < 140 mm Hg) and treatment is well tolerated and without adverse effects on health or quality of life, treatment does not need to be adjusted. (Expert Opinion – Grade E)

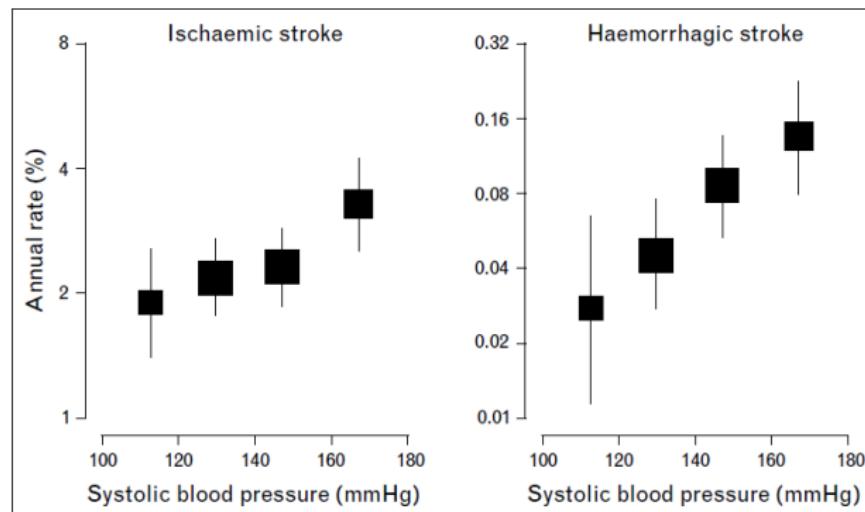
Irbesartan

└ J curve in Stroke?

└ ACCORD

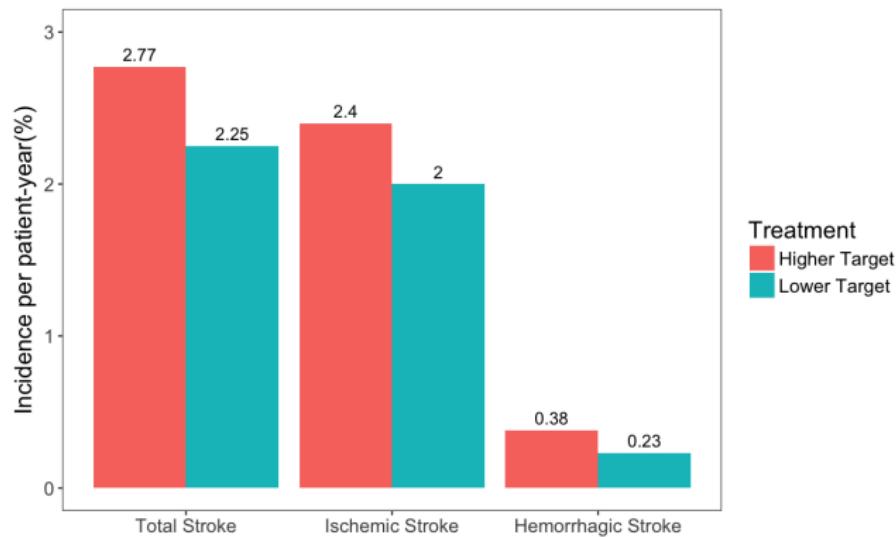


Lower target BP for stroke prevention: PROGRESS



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.



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)

Irbesartan

└ J curve in Stroke?

└ SPRINT

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

NOVEMBER 26, 2015

VOL. 373 NO. 22

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

ABSTRACT

BACKGROUND

The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among persons without diabetes remain uncertain.

METHODS

We randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

The members of the writing committee (Jackson T. Wright, Jr., M.D., Ph.D., Jeff D. Williamson, M.D., M.H.S., Paul K. Whelton, M.D., Joni K. Snyder, R.N., B.S.N., M.A., Kayce M. Sink, M.D., M.A.S., Michael V. Rocco, M.D., M.S.C.E., David M. Rebourdin, Ph.D., Mahboob Rahman, M.D., Suzanne Oparil, M.D., Cora E. Lewis, M.D., M.S.P.H., Paul L. Kimmel, M.D., Karen C. Johnson, M.D., M.P.H., David C. Goff, Jr., M.D., Ph.D., Lawrence J. Fine, M.D., Dr.P.H., Jeffrey A. Cutler, M.D., M.P.H., William C. Cush-

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%

SPRINT and ACCORD

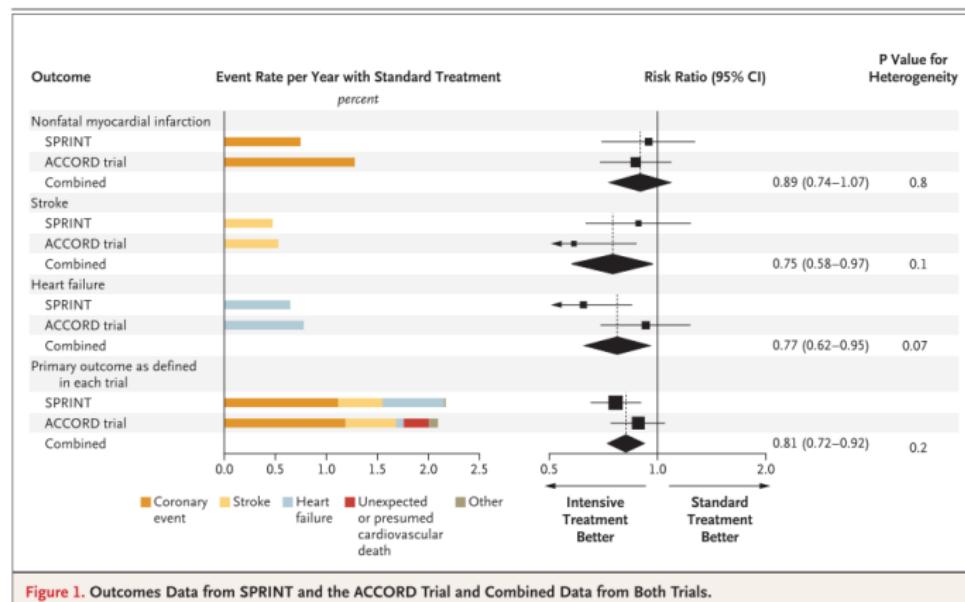
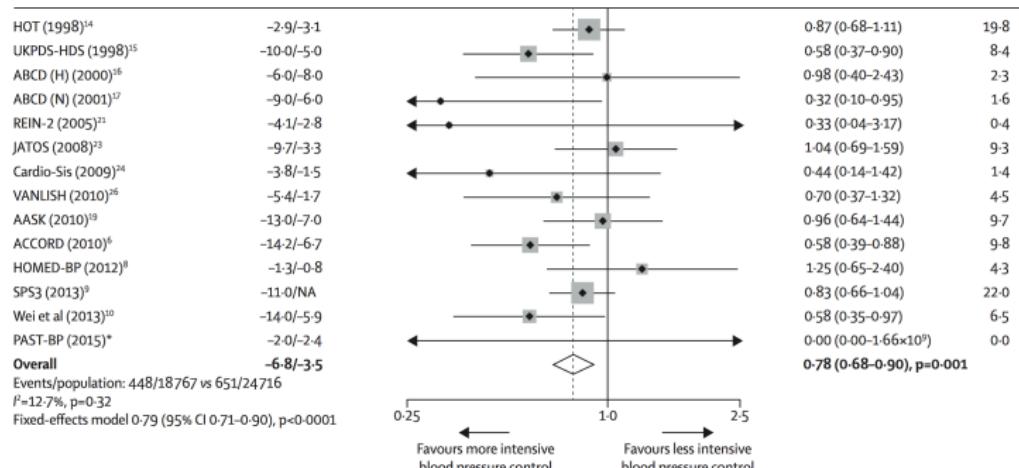


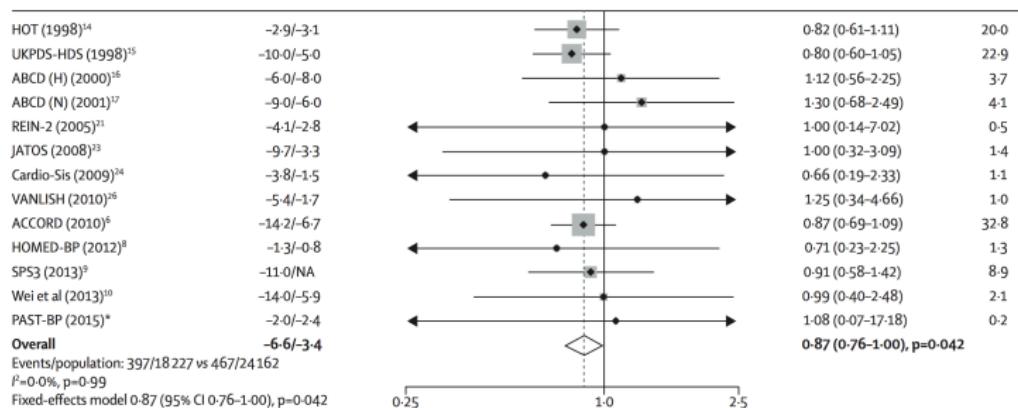
Figure 1. Outcomes Data from SPRINT and the ACCORD Trial and Combined Data from Both Trials.

Effect of intensive BP lowering on Stroke



133/76 mm Hg vs. 140/81 mm Hg

Effect of intensive BP lowering on MI



133/76 mm Hg vs. 140/81 mm Hg

Guidelines Debate

Is It Time to Reappraise Blood Pressure Thresholds and Targets?

A Statement From the International Society
of Hypertension—A Global Perspective

Michael A. Weber, Neil R. Poulter, Aletta E. Schutte, Louise M. Burrell, Masatsugu Horiuchi,
Dorairaj Prabhakaran, Agustin J. Ramirez, Ji-Guang Wang, Ernesto L. Schiffrin, Rhian M. Touyz

Taking into consideration the global target population of interest to the International Society of Hypertension, together with evidence derived from SPRINT and other recent meta-analyses and clinical trials, the practical message from the International Society of Hypertension is to strive for a systolic blood pressure target of 130 mmHg in most patients with hypertension. This is especially important considering that

Persistence with initial treatment in different studies

- Patients were more persistent on ARBs compared with other antihypertensive drugs including ACE-Is, CCBs, diuretics and BBs

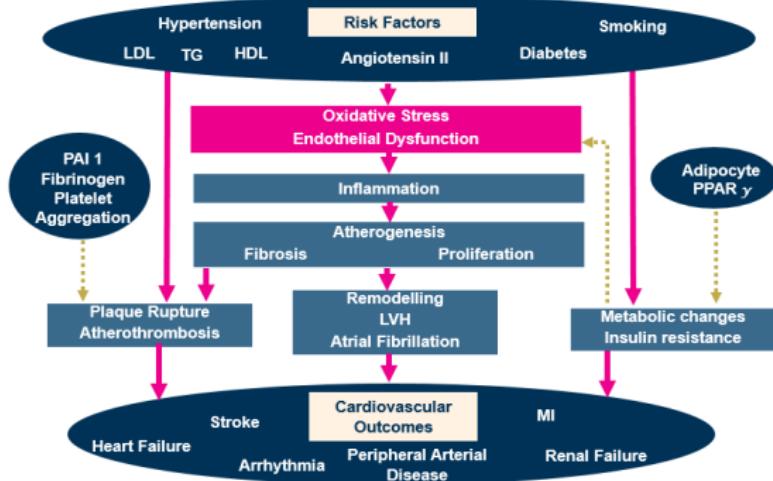
Study	Duration (months)	ARBs	ACE-Is	CCBs	BBs	Diuretics
Bloom	12	64%	58% [§]	50%	43%	38%
Conlin et al.	12	67.40%	60.7%*	54.1%*	45.6%*	20.8%*
Conlin et al.	48	50.90%	46.50%	40.7% [‡]	34.7% [‡]	16.4% [‡]
Hasford et al.	12	51.30%	42.00%	43.60%	49.70%	34.40%
Degli-Esposti et al.	12	41.70%	32.20%	26.70%	36.90%	25.90%
Erkens et al.	12	62.00%	59.70%	34.70%	35.00%	33.00%
Veronesi et al.	24	68.50%	64.50%	51.6% [‡]	44.8% [‡]	34.4%*
Hasford et al.	12	26.40%	28.20%	25.90%	25.80%	21.90%
Patel et al.	12	51.90%	48.00%	38.30%	40.30%	29.90%

*p < 0.01.

†p < 0.05.

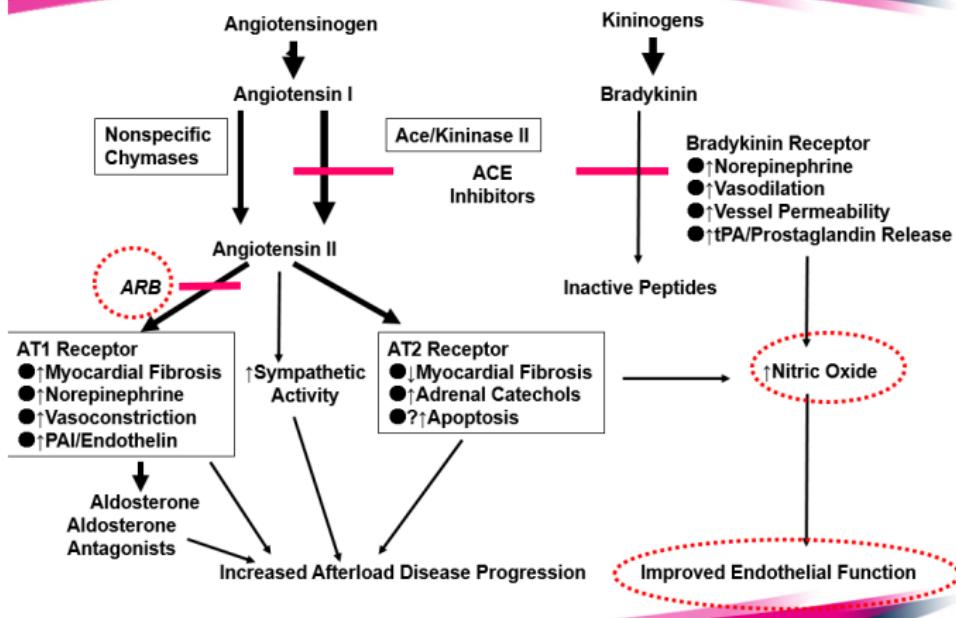
§ p < 0.007 versus ACE-Is.

Atherogenesis – origins and outcomes

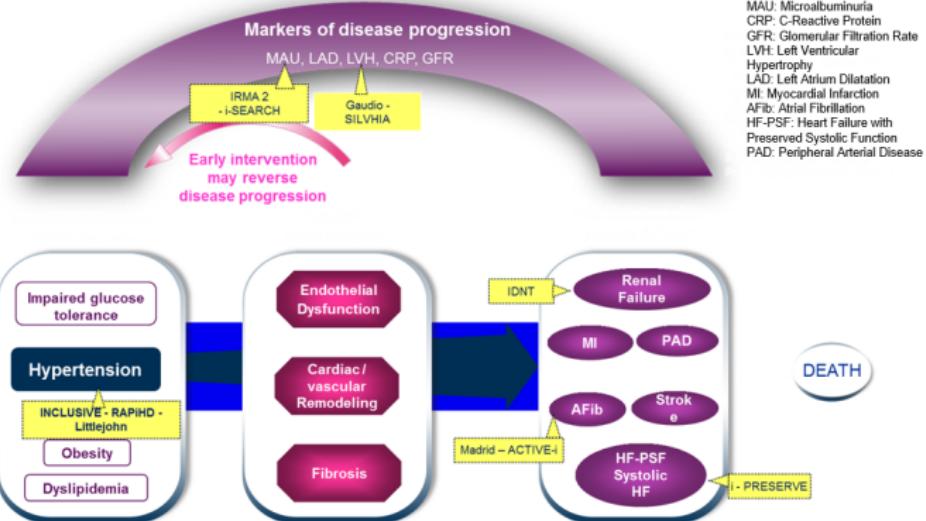


Harrison D et al. *Am J Cardiol* 2003; 91(3A): 7A-11A. Munger MA et al. *J Am Pharm Assoc (Wash DC)* 2004; 44(2 Suppl 1): S5-12 3. Murtagh BM et al. *J Invasive Cardiol* 2004; 16(7): 377-384 4. Shishehbor MH et al. *Curr Atheroscler Rep* 2004; 6(3): 243-250

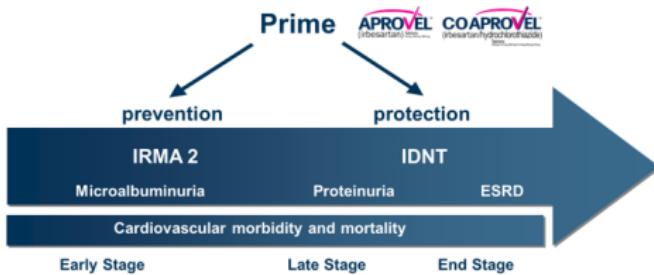
Relationships between angiotension and kinin cascades



Aprovel (irbesartan) fit within the CV continuum



Protection of Aprovel, Coaprovel In diabetic nephropathy



Program for Irbesartan Mortality and Morbidity Evaluations
Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria
Irbesartan Diabetic Nephropathy Trial
End-stage renal disease

Renoprotection (IRMA-2)

The New England Journal of Medicine

THE EFFECT OF IRBESARTAN ON THE DEVELOPMENT OF DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES

HANS-HENRIK PARVING, M.D., D.M.Sc., HENDRIK LEHNERT, M.D., JENS BRÖCHNER-MORTENSEN, M.D., D.M.Sc.,

RAMON GOMIS, M.D., STEEN ANDERSEN, M.D., AND PETER ARNER, M.D., D.M.Sc.,

FOR THE IRBESARTAN IN PATIENTS WITH TYPE 2 DIABETES AND MICROALBUMINURIA STUDY GROUP*

•TITLE: 미세알부민뇨 및 제2형 당뇨병을 동반한 고혈압 환자의 명백한 신증으로의 진행에 있어 대조군(위약과 제외 범주의의 항고혈압제 병용)과 Irbesartan의 효과 비교

•AUTHOR: Parving H-H, et al

•JOURNAL: N Engl J Med 2001;345:870-878

>SUMMARY: 아프로벨 300mg은 미세알부민뇨에서 당뇨병성 신증으로의 진행에 있어서 대조군에 비해 위험도를 70% 감소시켰다.

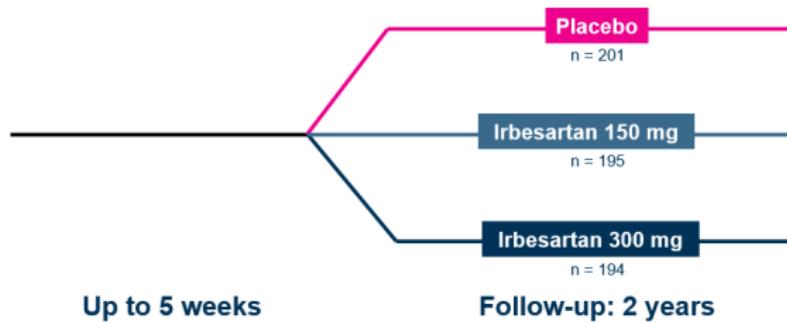
IRMA-2 Study Design : Irbesartan in Patients with Early Renal Disease

IRMA-2 study

590 patients (mean age 58 years) with type 2 diabetes, microalbuminuria (albumin excretion rate 20–200 µg/min), normal renal function, and hypertension

Screening/Enrollment

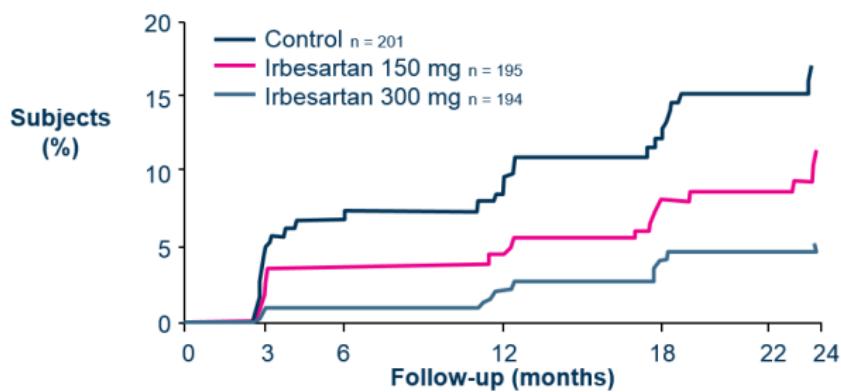
Double-blind Treatment



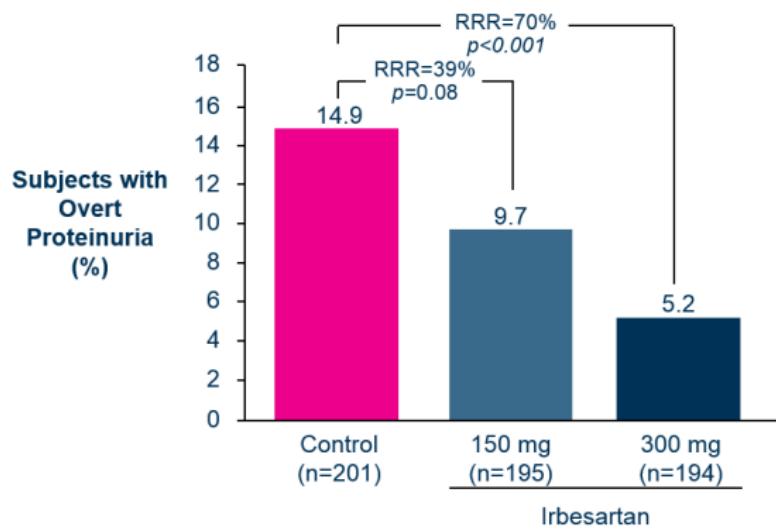
Parving H-H et al. *N Engl J Med* 2001;345: 870-8.

IRMA-2 Results: Irbesartan Significantly Delays Progression To Overt Proteinuria

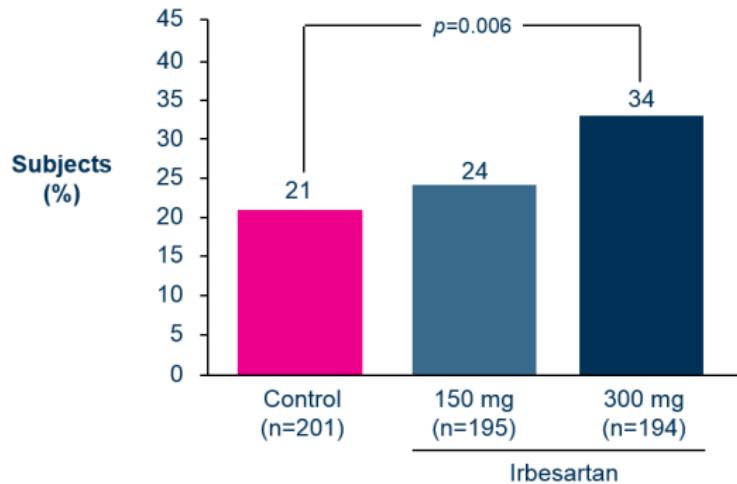
Primary endpoint: Time to overt proteinuria



IRMA-2 Results: Irbesartan Reduces Incidence of Overt Proteinuria



IRMA-2 Results: Irbesartan Normalizes Urinary Albumin Excretion



Parving H-H et al. *N Engl J Med* 2001;345: 870-8.

Effects of Angiotensin Receptor Blocker on Phenotypic Alterations of Podocytes in Early Diabetic Nephropathy

- Early irbesartan intervention attenuates the podocyte damage and ameliorates phenotypic alterations of podocytes, which provides a novel insight for the early application of angiotensin receptor blocker to prevent the development of DN.

Am J Med Sci. 2011 Mar;341(3):207-14

IRMA-2: Early Use of Irbesartan is Renoprotective in Hypertensive Type 2 Diabetes Patients with Microalbuminuria

- Irbesartan is renoprotective in hypertensive patients with type 2 diabetes and microalbuminuria,
 - Regression to normoalbuminuria was more frequent with irbesartan 300 mg
- The renoprotective effect of irbesartan is independent of its blood pressure-lowering effect
- Irbesartan has a good safety/tolerability profile
 - Fewer non-fatal CV events, serious AEs, and discontinuations due to AEs in the irbesartan groups

70% risk reduction in the progression from microalbuminuria to overt proteinuria with irbesartan 300 mg

Renoprotection (IDNT)

The New England Journal of Medicine

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VOLUME 345

SEPTEMBER 20, 2001

NUMBER 12



RENOPROTECTIVE EFFECT OF THE ANGIOTENSIN-RECEPTOR ANTAGONIST IRBESARTAN IN PATIENTS WITH NEPHROPATHY DUE TO TYPE 2 DIABETES

EDMUND J. LEWIS, M.D., LAWRENCE G. HUNSICKER, M.D., WILLIAM R. CLARKE, PH.D., TOMAS BERL, M.D.,
MARC A. POHL, M.D., JULIA B. LEWIS, M.D., EBERHARD RITZ, M.D., ROBERT C. ATKINS, M.D., RICHARD RONDE, B.S.,
AND ITAMAR RAZ, M.D., FOR THE COLLABORATIVE STUDY GROUP*

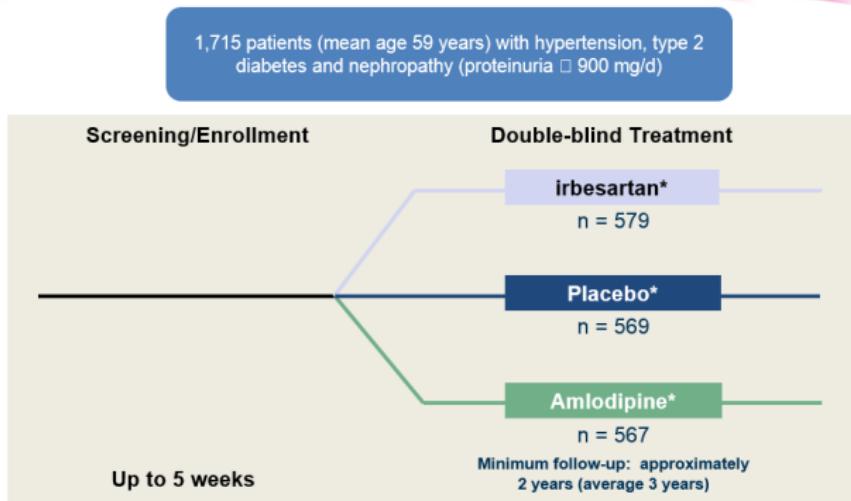
•TITLE: 제2형 당뇨병과 말기 당뇨병성 신질환을 가지고 있는 고혈압환자에서
신질환의 진행에 대해 Irbesartan과 amlodipine 및 대조군과의 비교

•AUTHER: Lewis EJ et al

•JOURNAL: N Engl J Med 2001;345:851-860

>SUMMARY: 1차 종료점에서 아프로벨은 혈압강하효과와는
독립적으로 Amlodipine 투여군에 비해 말기신질환의 위험을 23% 감소시켰다.

IDNT study: irbesartan in patients with late renal disease study design

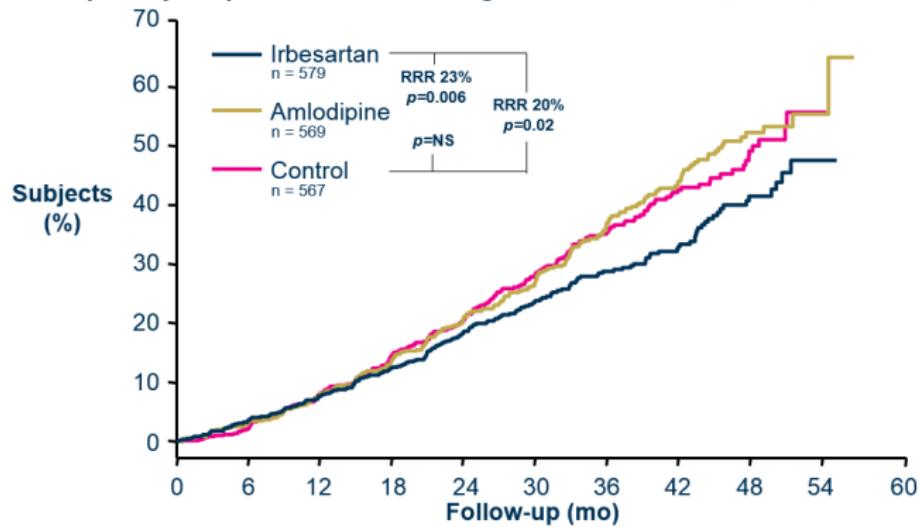


* Adjunctive antihypertensive therapies (excluding ACE inhibitors, angiotensin II receptor antagonists, and calcium channel blockers) added to each arm to achieve equal blood pressure reduction

Source: Lewis EJ et al. *N Engl J Med* 2001; **345**: 851 – 860

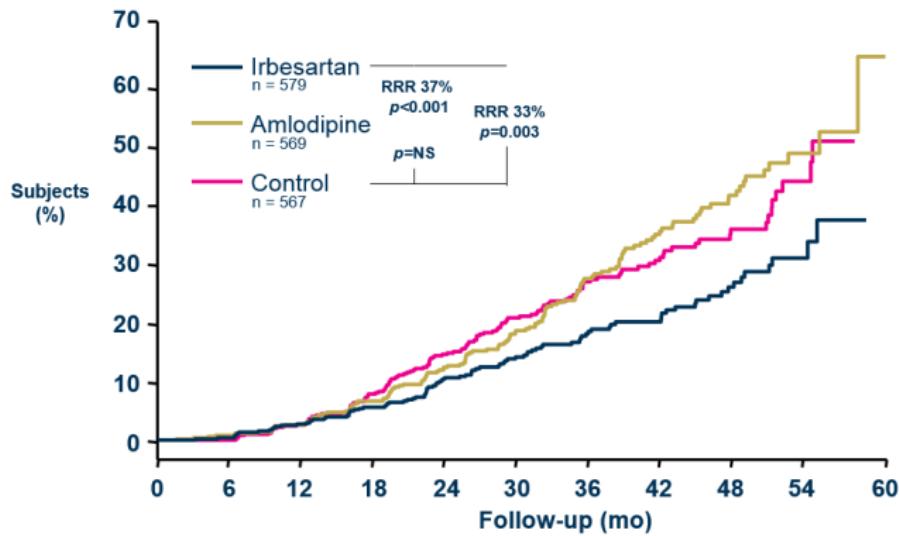
IDNT Results: Irbesartan Reduces the Progression of Diabetic Nephropathy (Combined Endpoint)

IDNT primary endpoint: Time to doubling of serum creatinine, ESRD, or death



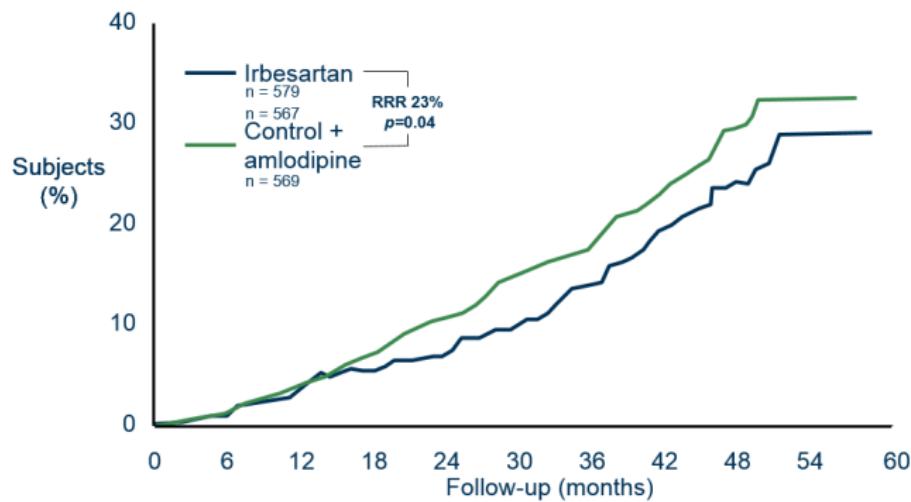
Lewis EJ et al. *N Engl J Med* 2001; **345**: 851-860.

IDNT Results: Irbesartan Significantly Reduces the Time to Doubling of Serum Creatinine



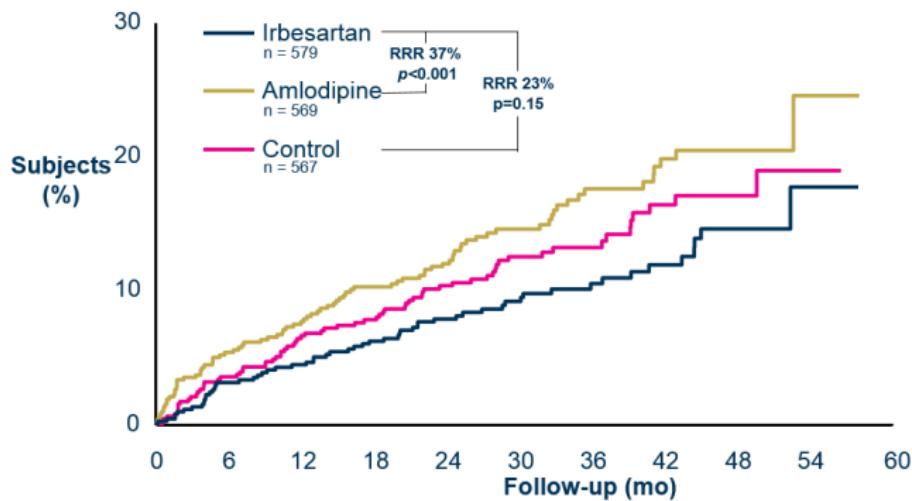
Lewis EJ et al. *N Engl J Med* 2001; **345**: 851–860.

IDNT Results: Irbesartan Significantly Reduces the Time to ESRD



IDNT Results: Irbesartan Reduces the Incidence of Heart Failure

For internal use only. Out of label results



Berl, et al. Ann Intern Med. 2003; 138: 542-549.

IDNT: Irbesartan Has a Good Safety/Tolerability Profile

	Number of Adverse Outcomes (%)		
	Irbesartan	Amlodipine	Control
Early serum creatinine rise	0	0	1
D/C due to hyperkalemia	11 (1.9)	3 (0.5)	2 (0.4)
Stopped study medicine	134 (23)	133 (23)	140 (25)
SAEs / 1000 days on drug	2.0	2.5	2.3

IDNT: Irbesartan is Renoprotective in Hypertensive Type 2 Diabetes Patients with Nephropathy

- Irbesartan resulted in a reduction in the primary composite endpoint (a doubling of the base-line serum creatinine concentration, the development of end-stage renal disease, or death) of:
 - 20% compared with placebo
 - 23% compared with amlodipine
- The benefit associated with irbesartan was independent of its blood pressure-lowering effects
- There were no difference between groups for cardiovascular outcomes
- Irbesartan has a good safety/tolerability profile
- Lower rate of SAEs in the irbesartan group than in the placebo and amlodipine groups

Take-Home Message

- ▶ Stroke and Hypertension are big health issues in rapidly aging societies like Korea.
- ▶ Therapeutic target of BP in patients with stroke should be individualized.
- ▶ Irbesartan has an indication in hypertensive patients with early and late stage diabetic nephropathy .