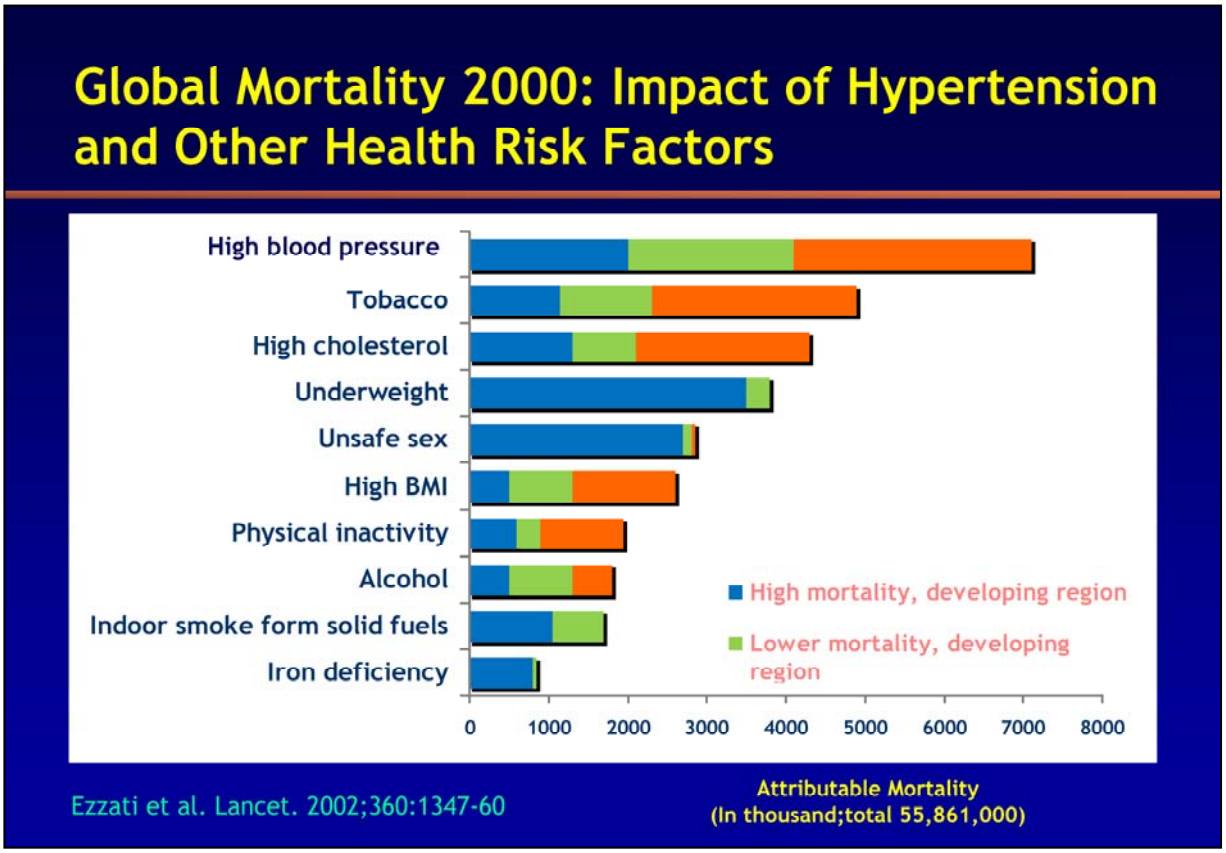
대한심장학회 춘계 심포지움
Apr 17th 2010

Paradigm Shift for Treatment of HYPERTENSION

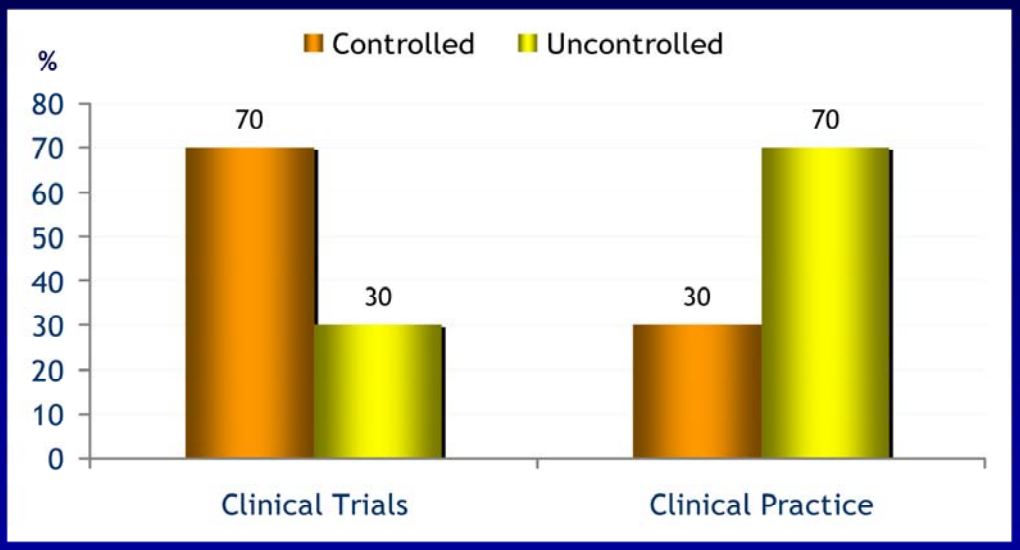
Myung Ho Jeong, MD, PhD, FACC, FAHA, FESC, FSCAI, FAPSIC

Professor, Principal Investigator of Korea Acute Myocardial Infarction Registry, Director of Heart Research Center Designated by Korea Ministry of Health and Welfare, Chonnam National University Hospital, Gwangju, Korea

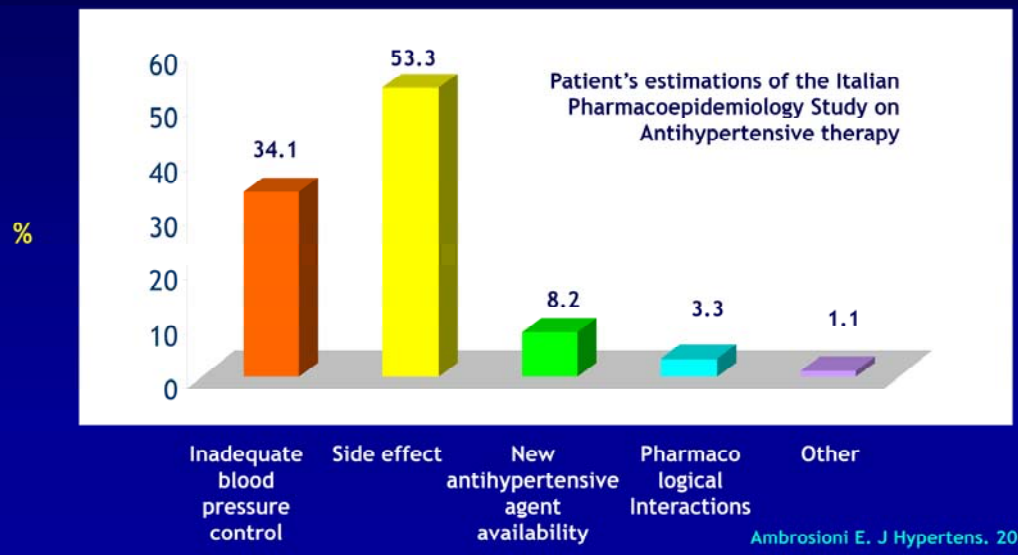


2000 년도의 5500 만 명의 전세계 global mortality 입니다. 고혈압이 가장 중요한 risk factor 이고 그외에 흡연, 고지혈증, underweight, AIDS, 비만, 비활동, 술 등입니다.

Blood Pressure Control in Hypertensive Patients



Reasons for Discontinuing Anti-Hypertensive Therapy



Ambrosioni E. J Hypertens. 2000;18:1691-9

Hazard Ratios versus Diuretics of Initial Treatment Discontinuation

Drug Class	Hazard ratio	95% CI	P
Alpha-blockers	0.91	0.83-1.00	0.070
Beta-blockers	0.70	0.65-0.75	<0.001
CCBs	0.56	0.52-0.60	<0.001
ACE-Inhibitors	0.50	0.47-0.54	<0.001
ARBs	0.44	0.41-0.48	<0.001

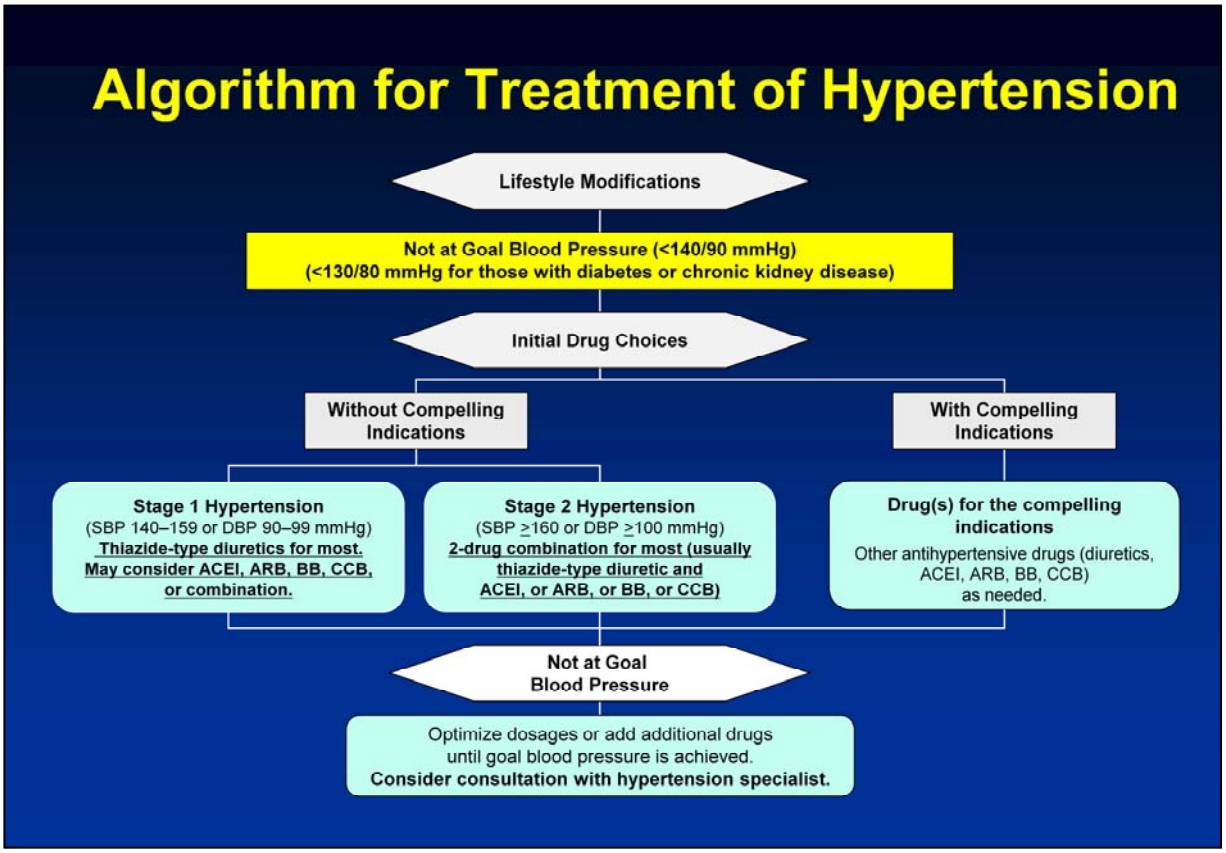
Mazzaglia G et al. J Hypertens. 2005;23:2093-100

Blood Pressure Classification

BP Classification	SBP mmHg		DBP mmHg
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Stage 1 Hypertension	140–159	or	90–99
Stage 2 Hypertension	≥160	or	≥100

Goals of Therapy

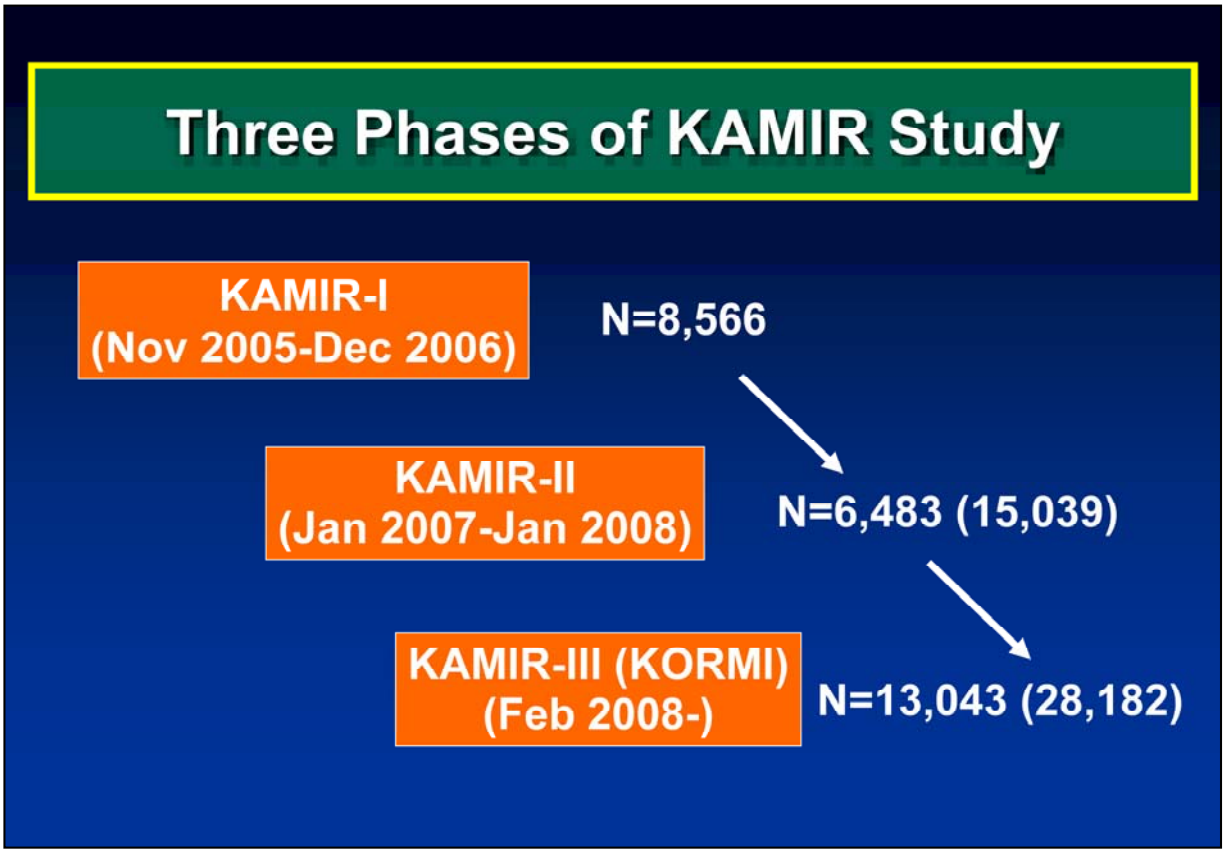
- Reduce CVD and renal morbidity and mortality
- Treat to BP <140/90 mmHg or BP <130/80 mmHg in patients with diabetes or CKD
- Achieve SBP goal especially in persons ≥50 years of age


Algorithm for Treatment of Hypertension
Lifestyle Modifications
Not at Goal Blood Pressure (<140/90 mmHg)
(<130/80 mmHg for those with diabetes or chronic kidney disease)
Initial Drug Choices
Without Compelling Indications
With Compelling Indications
Stage 1 Hypertension
(SBP 140–159 or DBP 90–99 mmHg)
Thiazide-type diuretics for most.
May consider ACEI, ARB, BB, CCB, or combination.
Stage 2 Hypertension
(SBP ≥160 or DBP ≥100 mmHg)
2-drug combination for most (usually thiazide-type diuretic and ACEI, or ARB, or BB, or CCB)
Drug(s) for the compelling indications
Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
Not at Goal Blood Pressure
Optimize dosages or add additional drugs until goal blood pressure is achieved.
Consider consultation with hypertension specialist.

CVD Risk Factors

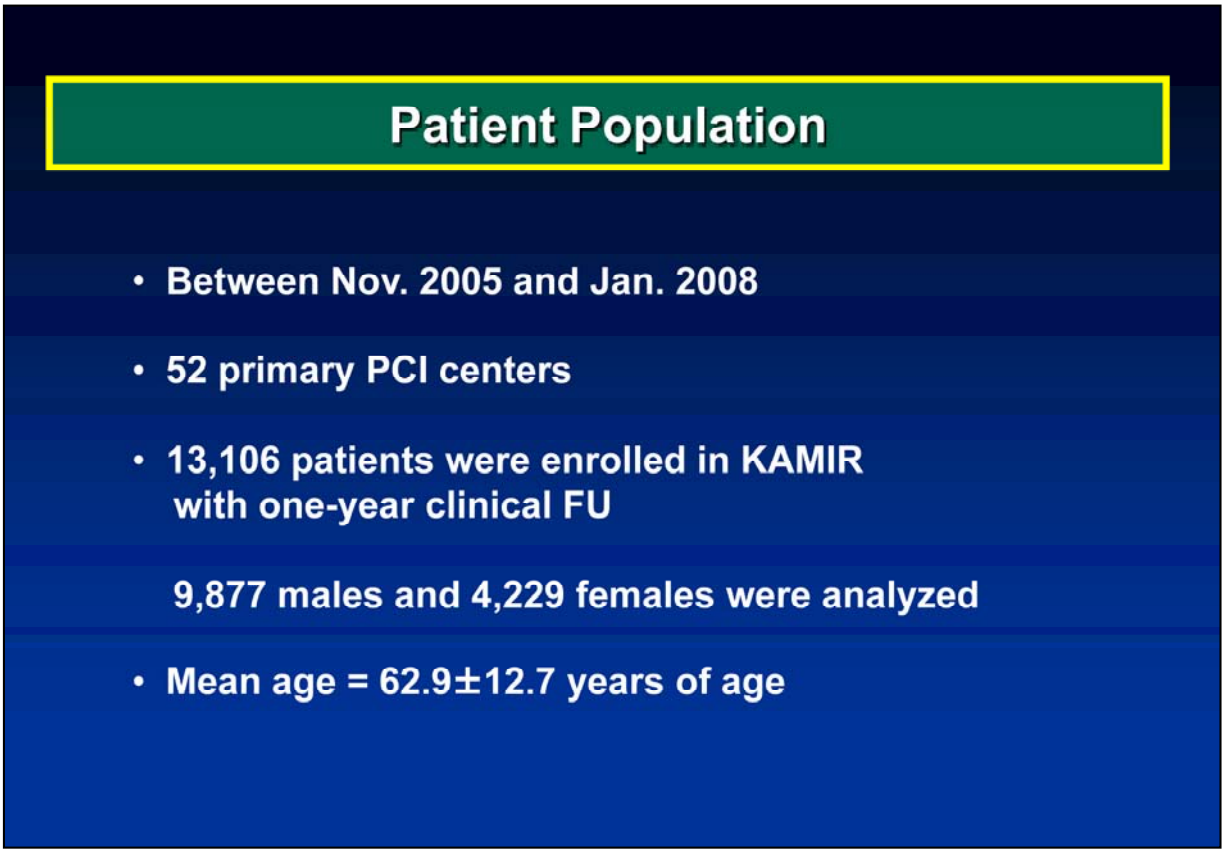
- Hypertension*
- Cigarette smoking
- Obesity* (BMI $\geq$30 kg/m^2)
- Physical inactivity
- Dyslipidemia*
- Diabetes mellitus*
- Microalbuminuria or estimated GFR <60 ml/min
- Age (older than 55 for men, 65 for women)
- Family history of premature CVD
  (men under age 55 or women under age 65)

KAMIR has been performed for the memorandum of the 50th anniversary of KCS.



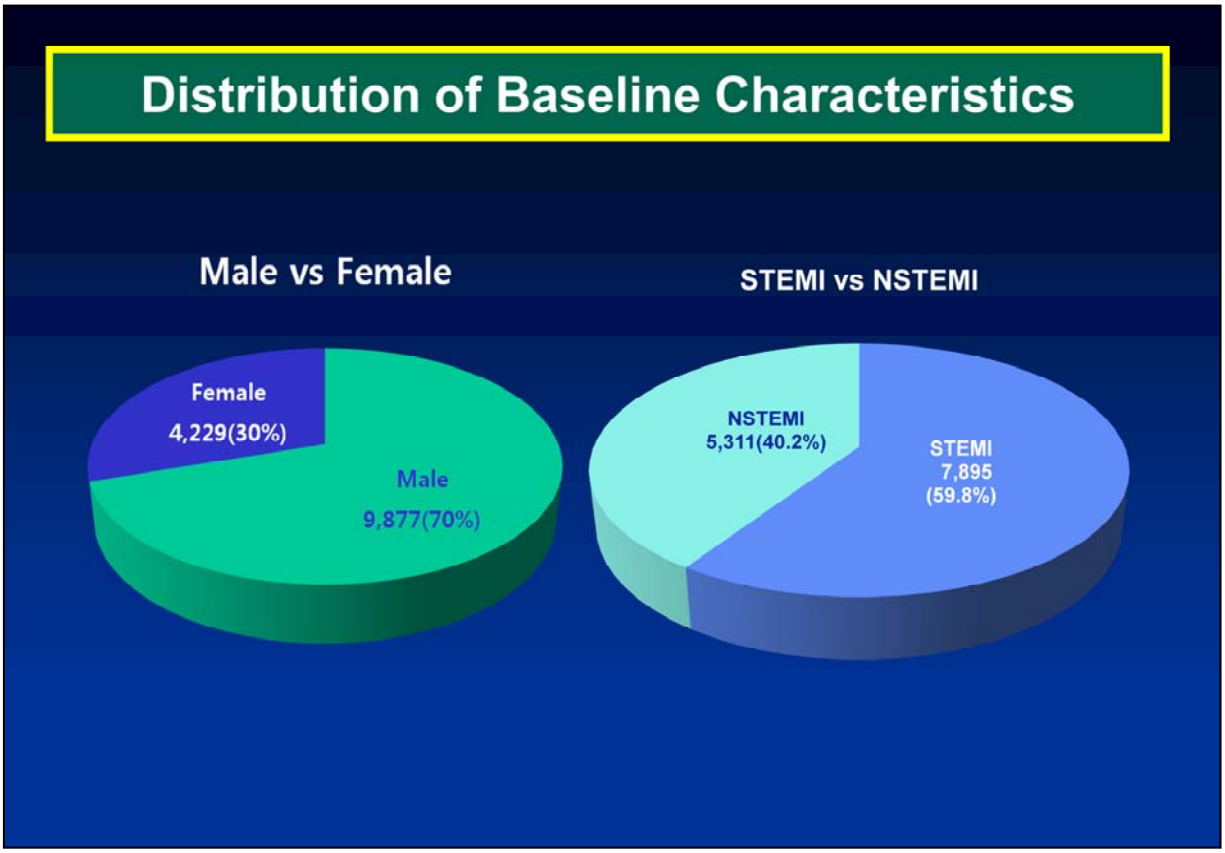
We have three phases of KAMIR.

We have registered more than 18 thousand patients since Nov 2005.



between Nov 2005 and Jan 2008, about13 thousand patients were enrolled in 52 primary PCI centers.

Nine thousand eight hundred patients were eligible for data analysis with one-year clinical FU.



The proportion of male patients were higher than female patients.
STEMI is more common in baseline characteristics.

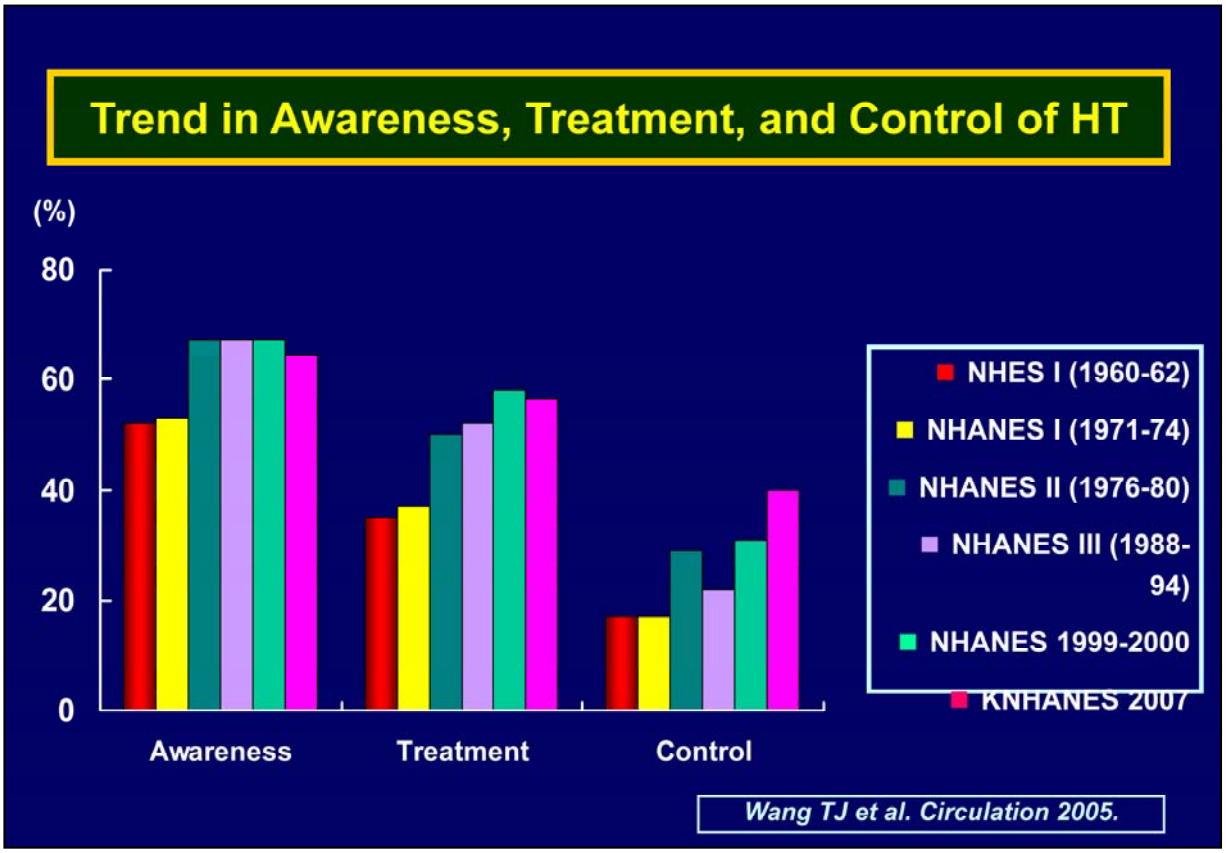
Baseline Characteristics of Patients According to Sex

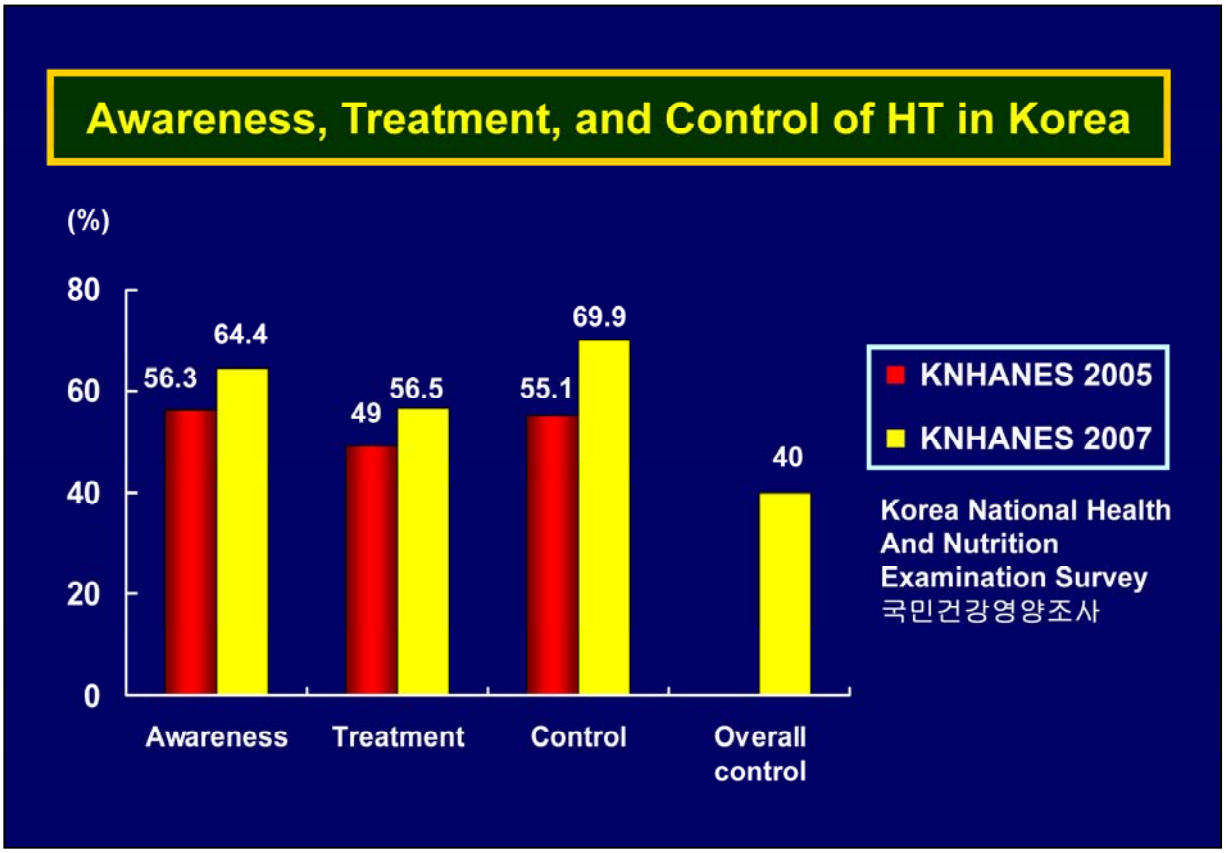
	Total	Male	Female	P-value
Age (yrs)	64.3±13.0	59.8±12.5	69.9±10.1	< 0.001
Height (cm)	163.5±8.8	167.5±6.1	153.6±6.2	< 0.001
Weight (cm)	64.1±11.4	67.6±10.4	55.6±9.1	< 0.001
BMI (kg/m^2)	23.9±3.2	24.1±3.1	23.5±3.3	< 0.001
Typical symptom (%)	84.1	85.9	79.6	< 0.001
Pain (%)	83.9	85.2	80.8	< 0.001
Dyspnea (%)	28.3	25.8	34.3	< 0.001
Past IHD (%)	16.9	16.8	17.0	0.828
Hypertension (%)	48.1	42.4	61.6	< 0.001
Diabetes (%)	27.3	24.9	33.1	< 0.001
Dyslipidemia (%)	8.5	8.1	9.3	0.096
Smoking (%)	58.2	76.4	14.5	< 0.001
Family History (%)	6.5	7.5	4.2	< 0.001

Int J Cardiol 2008;130:227-34, Prev Cardiol 2009;12:109-13

Mean age was higher in female patients, typical symptom of chest pain was common in male patients, female patient complained of dyspnea.

Hypertension and diabetes were important risk factor in male patients and smoking was important risk factor in male patients.


Trend in Awareness, Treatment, and Control of HT
(%)
80
60
40
20
0
Awareness
Treatment
Control
NHES I (1960-62)
NHANES I (1971-74)
NHANES II (1976-80)
NHANES III (1988-94)
NHANES 1999-2000
KNHANES 2007
Wang TJ et al. Circulation 2005.


Awareness, Treatment, and Control of HT in Korea
(%)
80
60
40
20
0
56.3
64.4
49
56.5
55.1
69.9
40
Awareness
Treatment
Control
Overall control
KNHANES 2005
KNHANES 2007
Korea National Health And Nutrition Examination Survey
국민건강영양조사

Results of 2007 KNHEANES

	30대	40대	50대	60대	>70대
유병율	7.6%	16.8%	33.9%	45.9%	58.9%
인지율	67.8%		69.8%	74.9%	71.2%
치료율	46.4%		66.9%	73.9%	62.6%
조절율	36.9%		54.9%	69.3%	64.2%

그럼 이와 같은 복합제를 사용한다면 어떤 실제적인 잇점이 있을까요?

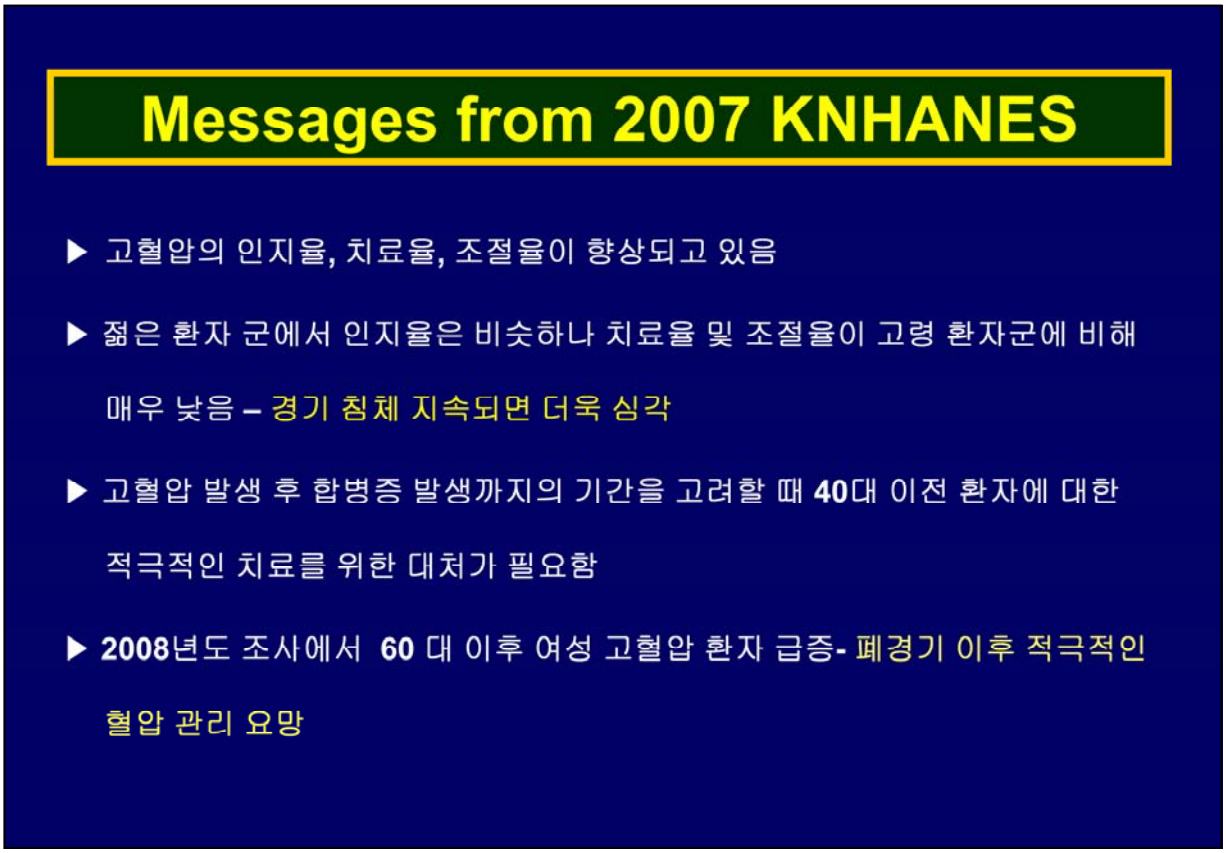
-강력한 BP 감소 효과

- 다른 기전의 약물을 사용함으로써 부작용 줄임

- 복약순응도의 향상

-Cost effectivess

마지막으로 고혈압 가이드라인(ESH/ESC & JNC-7)에서 recommendation을 말씀 드릴 수 있습니다.



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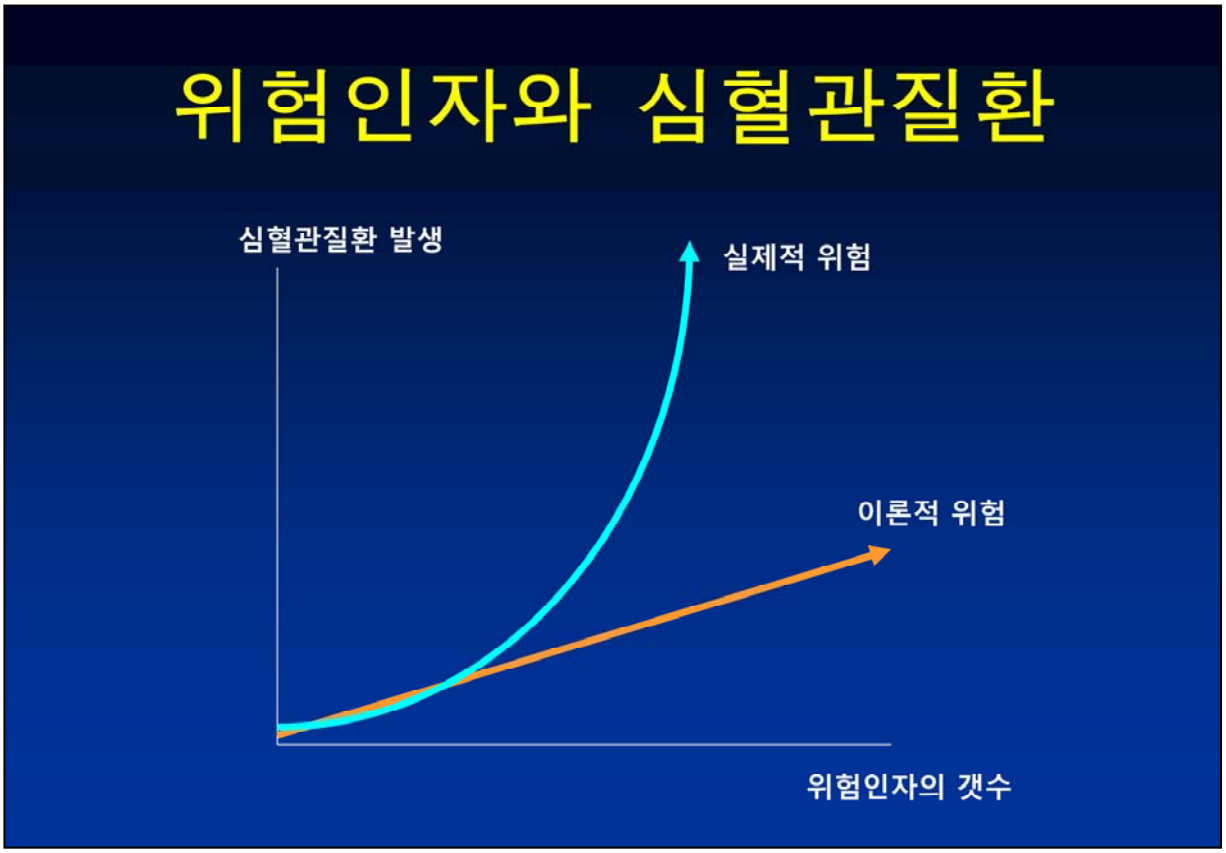
위험인자와 심혈관질환



J Korean Med Sci 2009; 24: 800-6
ISSN 1011-8934
DOI: 10.3346/jkms.2009.24.5.800

Clinical Effects of Hypertension on the Mortality of Patients with Acute Myocardial Infarction

The incidence of ischemic heart disease has been increased rapidly in Korea. However, the clinical effects of antecedent hypertension on acute myocardial infarction have not been identified. We assessed the relationship between antecedent hypertension and clinical outcomes in 7,784 patients with acute myocardial infarction in the Korea Acute Myocardial Infarction Registry during one-year follow-up. Diabetes mellitus, hyperlipidemia, cerebrovascular disease, heart failure, and peripheral artery disease were more prevalent in hypertensives (n=3,775) than nonhypertensives (n=4,009). During hospitalization, hypertensive patients suffered from acute renal failure, shock, and cerebrovascular event more frequently than in nonhypertensives. During follow-up of one-year, the incidence of major adverse cardiac events was higher in hypertensives. In multi-variate adjustment, old age, Killip class ≥ III, left ventricular ejection fraction <45%, systolic blood pressure <90 mmHg on admission, post procedural TIMI flow grade ≤ 2, female sex, and history of hypertension were independent predictors for in-hospital mortality. However antecedent hypertension was not significantly associated with one-year mortality. Hypertension at the time of acute myocardial infarction is associated with an increased rate of in-hospital mortality.

Dong Goo Kang[1], Myung Ho Jeong[2], Yongkeun Ahn[2], Shung Chull Chae[3], Seung Ho Hur[4], Taek Jong Hong[5], Young Jo Kim[6], In Whan Seong[7], Jei Keon Chae[8], Jay Young Rhew[9], In Ho Chae[10], Myeong Chan Cho[11], Jang Ho Bae[12], Seung Woon Rha[13], Chong Jin Kim[14], Yang Soo Jang[15], Junghan Yoon[16], Ki Bae Seung[17], Seung Jung Park[18], and other Korea Acute Myocardial Infarction Registry Investigators

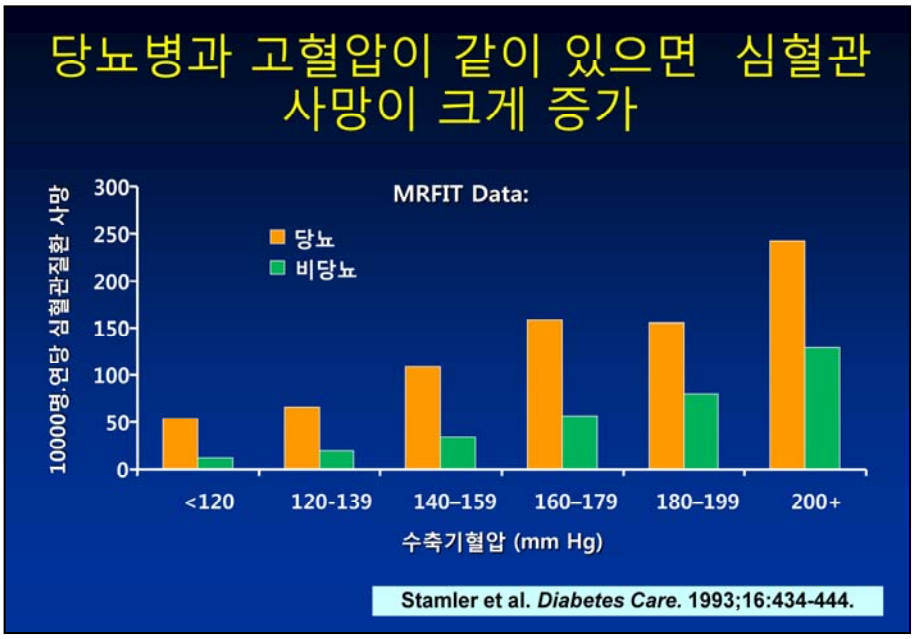
Kwangju Christian Hospital[1], Gwangju; Chonnam National University[2], Gwangju; Kyungpook National University[3], Daegu; Keimyung University Dongsan Medical Center[4], Daegu; Pusan National University Hospital[5], Busan; Yeungnam University Hospital[6], Daegu; Chungnam National University Hospital[7], Daejeon; Chonbuk National University Hospital[8], Jeonju; Jeonju Presbyterian Medical Center[9], Jeonju; Seoul National University Bundang Hospital[10], Seongam; Chungbuk National University[11], Cheongju; Konyang University[12], Daejon; Korea University Guro Hospital[13], Seoul; Kyunghee University Hospital[14], Seoul; Yonsei University Severance Hospital[15], Seoul; Wonju University Hospital[16], Wonju; Catholic University of Seoul St. Mary's Hospital[17], Seoul; Asan Medical Center, University of Ulsan[18], Seoul, Korea

KAMIR Investigators. J Korean Med Sci 2009;24:800-6

Table 3. In-hospital clinical outcomes

	Hypertensives (n=3,775)	Nonhypertensives (n=4,009)	*P*
Complications during admission, n (%)	550 (14.6)	488 (12.2)	0.002
Acute renal failure, n (%)	56 (1.5)	21 (0.5)	<0.001
Shock, n (%)	25 (0.7)	15 (0.4)	0.046
Major bleeding, n (%)	25 (0.7)	15 (0.4)	0.046
Cerebrovascular disease, n (%)	35 (0.9)	22 (0.5)	0.033
Heart failure, n (%)	37 (1.0)	32 (0.8)	0.153
Atrio-ventricular block, n (%)	83 (2.2)	81 (2.0)	0.190
Ventricular tachycardia or fibrillation, n (%)	120 (3.2)	152 (3.8)	0.069
In-hospital death, n (%)	222 (5.9)	159 (4.0)	<0.001

KAMIR Investigators. J Korean Med Sci 2009;24:800-6



Diabetes itself is an independent risk factor for CVD. Thus, persons with diabetes are particularly vulnerable to other risk factors for CVD.[39]

Data from MRFIT research demonstrated that diabetic men with elevated systolic BP are at a significantly greater risk for CVD death than those without diabetes.[39]

While systolic BP was related to risk for CVD in both groups, at every level of systolic BP, the CVD death rate was greater for diabetic than nondiabetic men. Moreover, CVD mortality rate increased more sharply for diabetic than nondiabetic men. It is thus particularly important to aggressively control BP and other modifiable CVD risk factors in the diabetic patient population.[39]

39. Stamler J, Vaccaro O, Neaton JD, Wentworth D, for the Multiple Risk Factor Intervention Trial Research Group. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care.* 1993;16:434-444.

ORIGINAL ARTICLE
DOI 10.4070/kcj.2009.39.6.243

Print ISSN 1738-5520 / On-line ISSN 1738-5555

Comparison of Clinical Outcomes Following Acute Myocardial Infarctions in Hypertensive Patients With or Without Diabetes

Min Goo Lee, MD[1], Myung Ho Jeong, MD[1], Youngkeun Ahn, MD[1], Shung Chull Chae, MD[2], Seung Ho Hur, MD[3], Taek Jong Hong, MD[4], Young Jo Kim, MD[5], In Whan Seong, MD[6], Jei Keon Chae, MD[7], Jay Young Rhew, MD[8], In Ho Chae, MD[9], Myeong Chan Cho, MD[10], Jang Ho Bae, MD[11], Seung Woon Rha, MD[12], Chong Jim Kim, MD[13], Donghoon Choi, MD[14], Yang Soo Jang, MD[14], Junghan Yoon, MD[15], Wook Sung Chung, MD[16], Jeong Gwan Cho, MD[1], Ki Bae Seung, MD[16], Seung Jung Park, MD[17] and Other Korea Acute Myocardial Infarction Registry Investigators

이민구 임상 조교수

34 세, 총각

KAMIR Investigators. Korean Circulation J 2009;39:243-50

ABSTRACT

Background and Objectives: It is thought that patients with diabetes mellitus (DM) have a poor prognosis after an acute myocardial infarction (AMI), but the effect of diabetes on the outcomes of hypertensive patients with AMIs has not been elucidated in the Korean population. The aim of this study was to investigate the effects of diabetes on long-term clinical outcomes following AMIs in patients with hypertension. **Subjects and Methods**: Using data from the Korea Acute Myocardial Infarction Registry (November 2005 to December 2006), 2,233 hypertensive patients with AMIs were grouped as follows based on the presence of DM: group I, diabetic hypertension (n=892, 544 men, mean age=66.2±10.9 years); and group II, non-diabetic hypertension (n=1341, 938 men, mean age=63.9±12.8 years). The primary study outcomes included in-hospital death and major adverse cardiac events (MACE; cardiac death, myocardial infarction (MI), repeat percutaneous coronary intervention, and coronary artery bypass surgery) at the 1 year follow-up. **Results**: Hypertensive patients with DM were older and more likely to be women. The diabetic group had lower blood pressure ($p<0.001$), a lower left ventricular ejection fraction ($p<0.001$), a more severe degree of heart failure ($p<0.001$), a longer duration of coronary care unit admission ($p<0.001$), and a higher incidence of hyperlipidemia ($p=0.007$). The N-terminal pro-brain natriuretic peptide level (4602.5±8710.6 pg/mL vs. 2320.8 ±5837.9 pg/mL, $p<0.001$) was higher and the creatinine clearance (62.4±29.9 mL/min vs. 73.0±40.8 mL/min, $p<0.001$) was lower in the diabetic group than the non-diabetic group. Coronary angiographic findings revealed more frequent involvement of the left main stem ($p=0.002$) and multiple vessels ($p<0.001$) in the diabetic group. The rate of in-hospital death was higher in the diabetic group ($p<0.001$). During follow-up, the rates of composite MACE at 1 month, 6 months, and 12 months were higher in the diabetic group ($p<0.001$). **Conclusion**: In hypertensive patients with AMI, DM was associated with worse clinical and angiographic features, with a higher risk of development of severe heart failure, and an increased risk of MACE on long-term clinical follow-up. **(Korean Circ J 2009; 39:243-250)**

KEY WORDS: Diabetes mellitus; Hypertension; Myocardial infarction.

KAMIR Investigators. Korean Circulation J 2009;39:243-50

Comparison of Clinical Outcomes Following AMI in Hypertensive Patients w/ DM or w/o DM

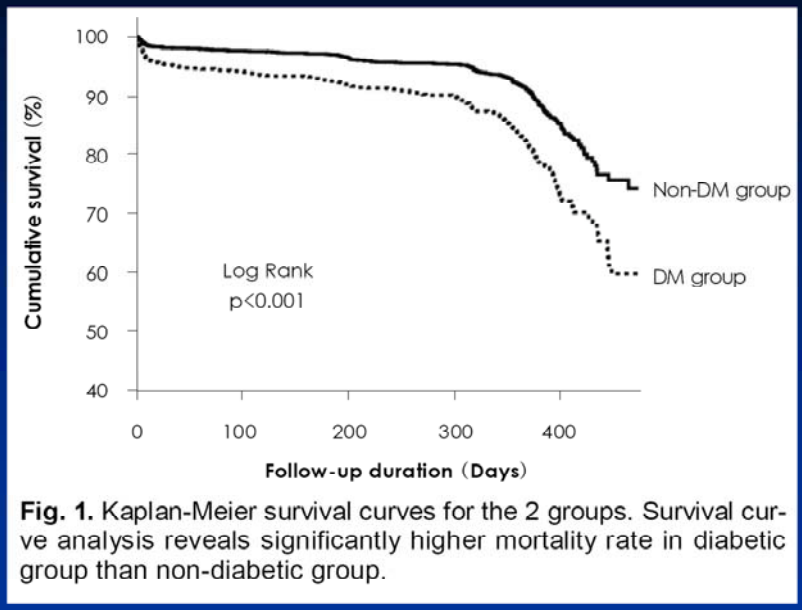


Fig. 1. Kaplan-Meier survival curves for the 2 groups. Survival curve analysis reveals significantly higher mortality rate in diabetic group than non-diabetic group.

KAMIR Investigators. Korean Circulation J 2009;39:243-50

Traditional CV risk perspective

'Silo' risk approach

질환에 대한 이해

고혈압, 이상 지질혈증, 당뇨병 등 위험인자들은 각각 독립적인 것으로 인식

" 고혈압, 혈압만 낮추면 되지…"

질환의 치료 가이드 라인

역시 각각의 독립적인 위험인자들을 구분하여 각 위험인자에 맞는 치료방법을 선택

New CV risk perspective

'Global' risk approach

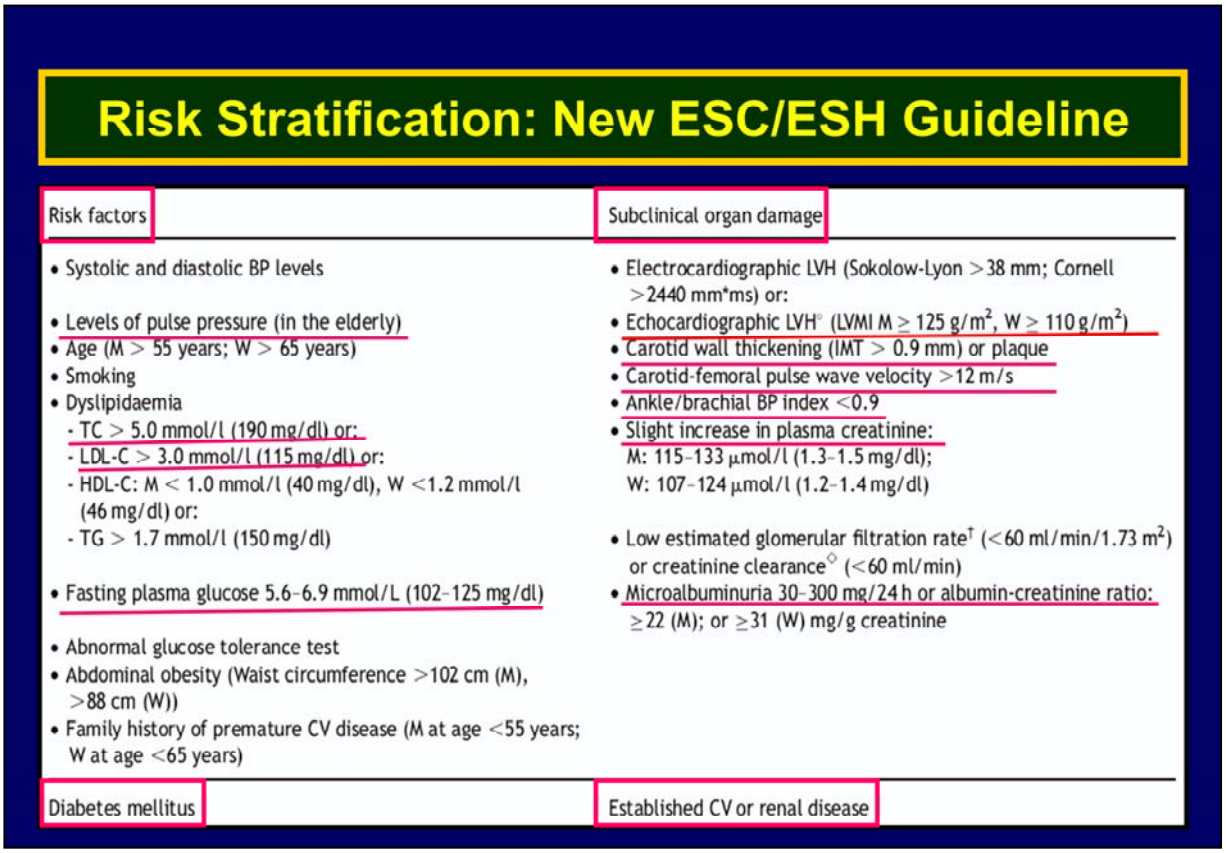
질환에 대한 이해

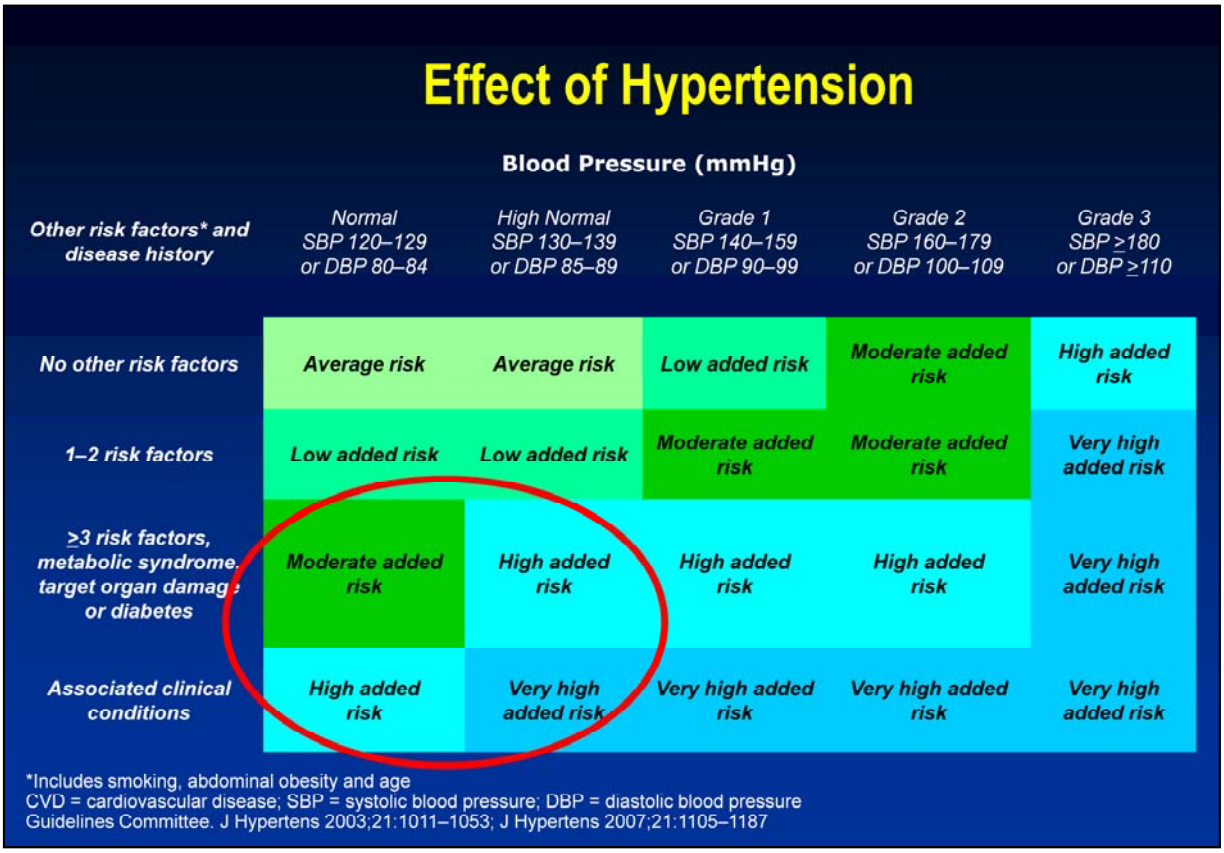
고혈압, 이상 지질혈증, 당뇨병,
비만,염증,흡연, 연령, 인종, 성별,
유전적인 요인 등의 다양한 위험인자들은
각각 독립적인 것이 아니라 모두 연관되어
있다는 인식

예시: 고혈압, 아직도 혈압만
관리하십니까?

질환의 치료 가이드 라인

어느 한 위험인자만 치료하는 것이 아니라
연관되어 있는 위험인자들을 통합적으로
치료하는 방법을 선택


Risk Stratification: New ESC/ESH Guideline
Risk factors
• Systolic and diastolic BP levels
• Levels of pulse pressure (in the elderly)
• Age (M > 55 years; W > 65 years)
• Smoking
• Dyslipidaemia
- TC > 5.0 mmol/l (190 mg/dl) or:
- LDL-C > 3.0 mmol/l (115 mg/dl) or:
- HDL-C: M < 1.0 mmol/l (40 mg/dl), W <1.2 mmol/l (46 mg/dl) or:
- TG > 1.7 mmol/l (150 mg/dl)
• Fasting plasma glucose 5.6–6.9 mmol/L (102–125 mg/dl)
• Abnormal glucose tolerance test
• Abdominal obesity (Waist circumference >102 cm (M), >88 cm (W))
• Family history of premature CV disease (M at age <55 years; W at age <65 years)
Subclinical organ damage
• Electrocardiographic LVH (Sokolow-Lyon >38 mm; Cornell >2440 mm*ms) or:
• Echocardiographic LVH° (LVMI M ≥ 125 g/m², W ≥ 110 g/m²)
• Carotid wall thickening (IMT > 0.9 mm) or plaque
• Carotid-femoral pulse wave velocity >12 m/s
• Ankle/brachial BP index <0.9
• Slight increase in plasma creatinine:
M: 115–133 µmol/l (1.3–1.5 mg/dl);
W: 107–124 µmol/l (1.2–1.4 mg/dl)
• Low estimated glomerular filtration rate† (<60 ml/min/1.73 m²) or creatinine clearance◇ (<60 ml/min)
• Microalbuminuria 30–300 mg/24 h or albumin-creatinine ratio: ≥22 (M); or ≥31 (W) mg/g creatinine
Diabetes mellitus
Established CV or renal disease



<u>Key point:</u> Hypertension or high blood pressure is one of the most significant CVD risk factors. The risk of CVD can be determined according to high blood pressure level, the presence of other risk factors and disease history.

The slide shows the stratification of total CV risk for European patients based on the updated 2007 European Society of Hypertension and European Society of Cardiology (ESH/ESC) combined guidelines.[1,2] It is derived from the scheme included in the 1999 World Health Organisation – International Society of Hypertension (WHO/ISH) guidelines, but extended to indicate the added risk in some groups of subjects with 'normal' or 'high normal' blood pressure (BP). The terms 'low', 'moderate', 'high' and 'very high' added risk are calibrated to indicate an approximate absolute 10-year risk of CVD of <15%, 15–20%, 20–30% and >30% in patients older than 60 years, according to Framingham criteria, or an approximate absolute risk of fatal CVD of <4%, 4–5%, 5–8% and >8% according to the SCORE chart.[3] These categories can also be used as indicators of relative risks in subjects less than 60 years old. The distinction between high and very high risk has been maintained, mostly in order to preserve a distinctive place for secondary prevention (patients with associated clinical conditions), although admittedly it does not significantly influence management decisions.

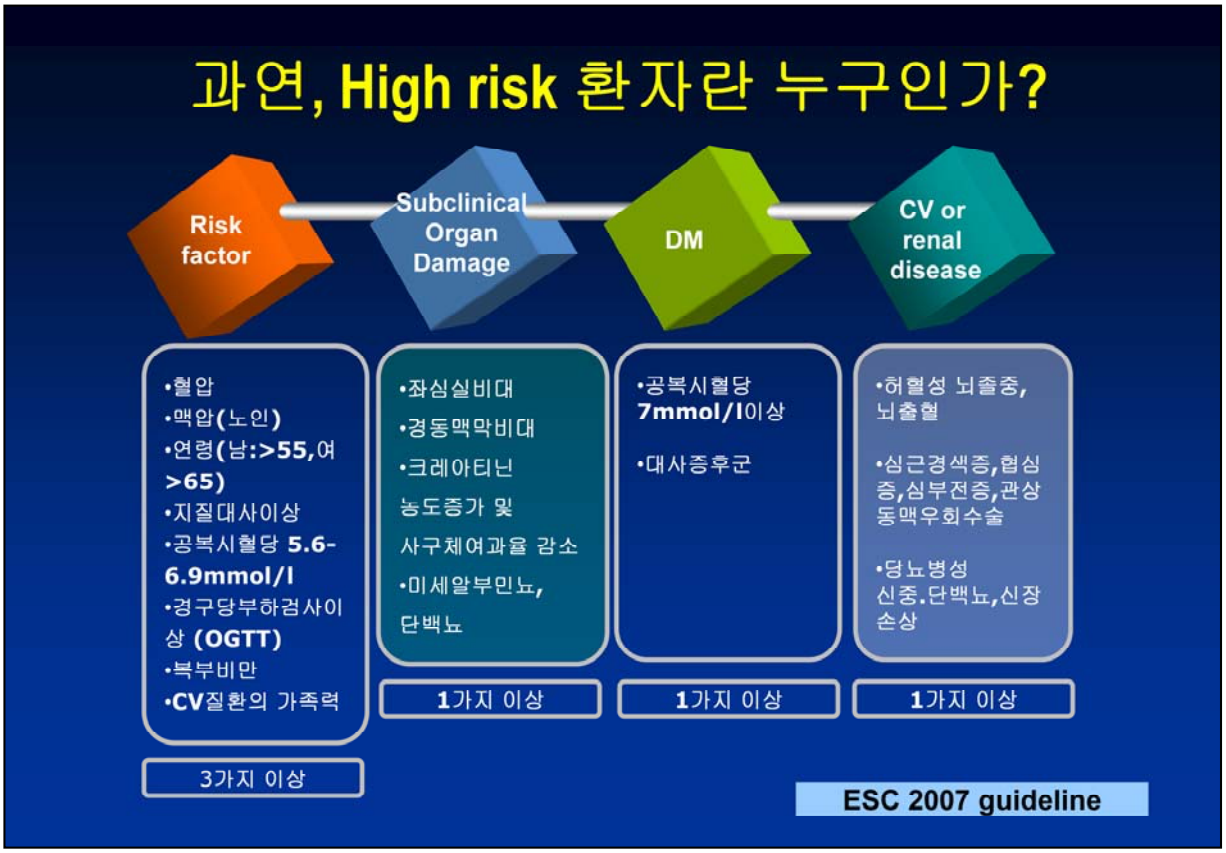
If we look in detail at the table, we see the initial BP of the subject. If this is normal and no other risk factors are present, the person is at low or low added absolute risk of a CV event within the next 10 years. Risk factors include smoking, abdominal obesity and increasing age. If diabetes or target-organ damage (e.g. left ventricular hypertrophy, microalbuminuria, increased serum creatinine) are present, the patient immediately moves into a higher risk category.

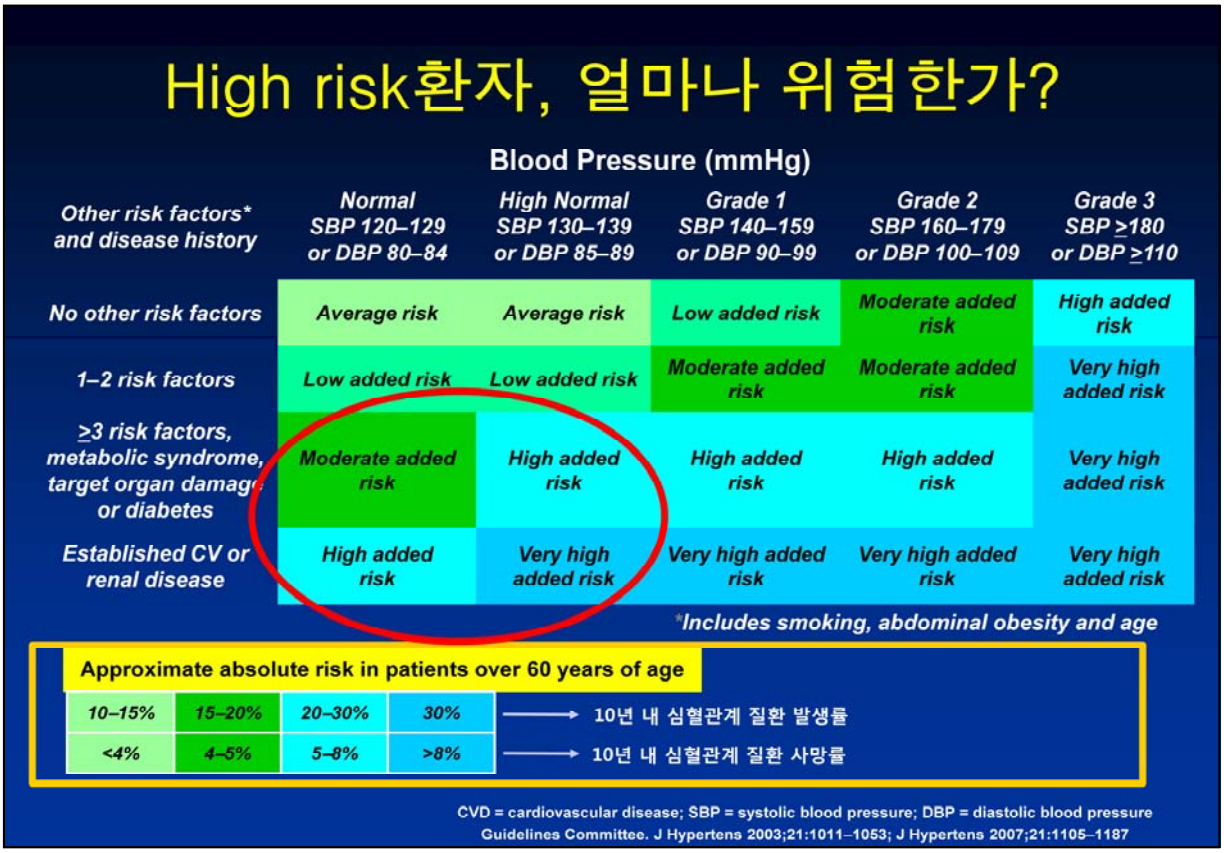
If the patient has an associated clinical condition, such as CV or renal disease, then they are considered to be at very high risk even if normotensive.

Patients at high risk or very high risk should have their BP treated if it is above 130/85 mmHg. Patients with BP that is consistently >140/90 mmHg should usually have it treated, regardless of the presence of other risk factors.

References

1. Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003;21:1011–1053.
2. Guidelines Committee. 2007 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2007;25:1105–1187.
3. Conroy RM, *et al.* Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987-1003.


과연, High risk 환자란 누구인가?
Risk factor
Subclinical Organ Damage
DM
CV or renal disease
•혈압
•맥압(노인)
•연령(남:>55,여 >65)
•지질대사이상
•공복시혈당 5.6-6.9mmol/l
•경구당부하검사이상 (OGTT)
•복부비만
•CV질환의 가족력
3가지 이상
•좌심실비대
•경동맥막비대
•크레아티닌 농도증가 및 사구체여과율 감소
•미세알부민뇨, 단백뇨
1가지 이상
•공복시혈당 7mmol/l이상
•대사증후군
1가지 이상
•허혈성 뇌졸중, 뇌출혈
•심근경색증,협심증,심부전증,관상동맥우회수술
•당뇨병성 신중.단백뇨,신장손상
1가지 이상
ESC 2007 guideline



<u>Key point:</u> Cardiovascular disease risk can be stratified according to blood pressure level and the presence of other risk factors and disease history.

The slide shows the stratification of total cardiovascular (CV) risk for European patients based on the updated 2007 European Society of Hypertension and European Society of Cardiology (ESH/ESC) combined guidelines.[1,2] It is derived from the scheme included in the 1999 WHO/ISH guidelines, but extended to indicate the added risk in some groups of subjects with 'normal' or 'high normal' blood pressure. The terms low, moderate, high and very high added risk are calibrated to indicate an approximate absolute 10-year risk of CV disease (CVD) of <15%, 15–20%, 20–30% and >30%, in patients older than 60 years, according to Framingham criteria, or an approximate absolute risk of fatal CVD of <4%, 4–5%, 5–8% and >8% according to the SCORE chart.[3] These categories can also be used as indicators of relative risks, in subjects less than 60 years old. The distinction between high and very high risk has been maintained, mostly in order to preserve a distinctive place for secondary prevention (patients with associated clinical conditions), although admittedly it does not influence management decisions significantly.
This table is designed for use in adult patients of either sex and any age.[1,2]
A disadvantage of other interventional tables that separate patients by age and gender is that younger adults (particularly women) are unlikely to reach treatment thresholds despite being at high risk relative to their peers, because they have more than one major risk factor. Whereas, on the other hand, most elderly men (e.g. >70 years) will often reach treatment thresholds while being at very little increased risk relative to their peers.
If we look in detail at the table, we see the initial blood pressure of the subject. If this is normal and no other risk factors are present, the person is at low or low added absolute risk of a CV event within the next 10 years. Risk factors include smoking, abdominal obesity and increasing age. If diabetes or target-organ damage (such as left ventricular hypertrophy, microalbuminuria or increased serum creatinine) are present, the patient immediately moves into a higher risk category.
If the patient has an associated clinical condition, such as CV or renal disease, then they are considered to be at

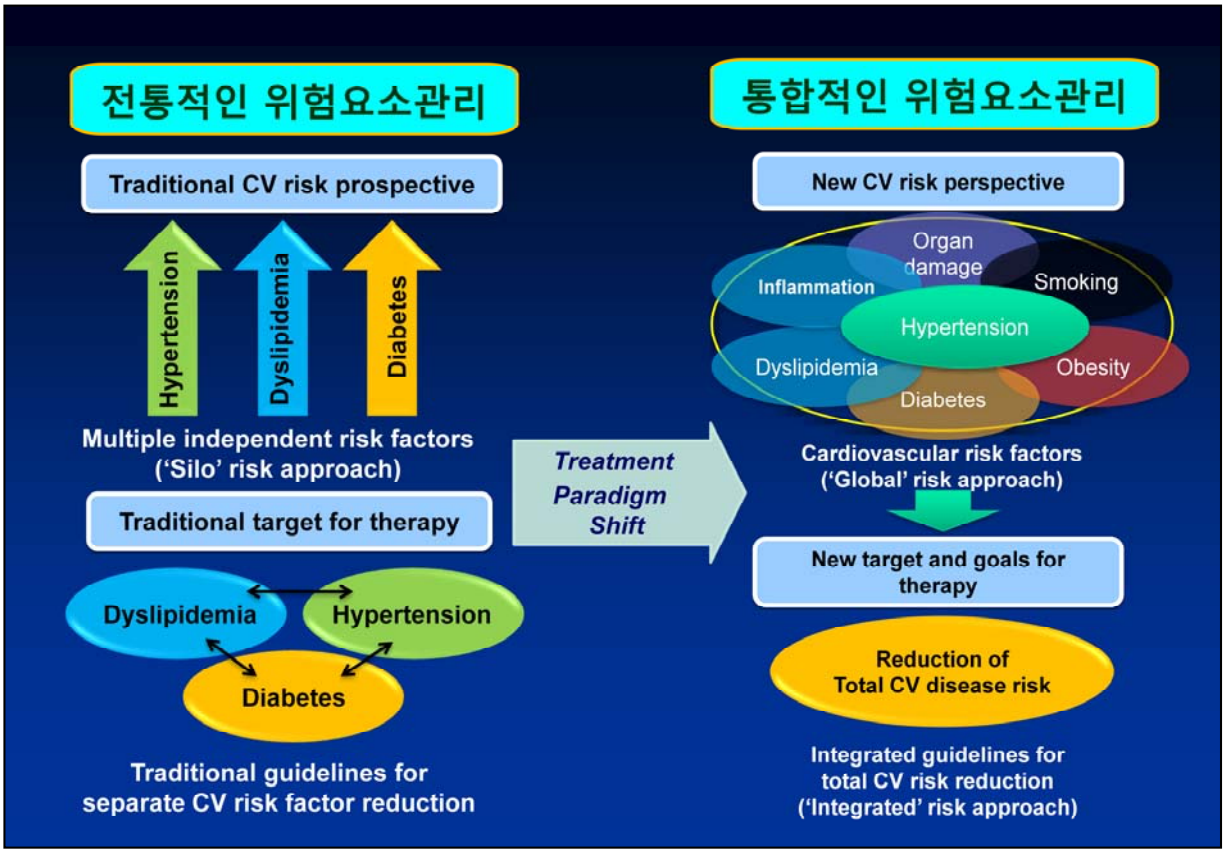
High Risk환자, 얼마나 위험한가?

10년 내 심혈관계질환 발생률

30%

10년 내 심혈관계질환 사망률

8%


전통적인 위험요소관리
Traditional CV risk prospective
Hypertension
Dyslipidemia
Diabetes
Multiple independent risk factors
('Silo' risk approach)
Traditional target for therapy
Dyslipidemia
Hypertension
Diabetes
Traditional guidelines for
separate CV risk factor reduction
Treatment
Paradigm
Shift
통합적인 위험요소관리
New CV risk perspective
Organ
damage
Inflammation
Smoking
Hypertension
Dyslipidemia
Obesity
Diabetes
Cardiovascular risk factors
('Global' risk approach)
New target and goals for
therapy
Reduction of
Total CV disease risk
Integrated guidelines for
total CV risk reduction
('Integrated' risk approach)

이상적 고혈압 관리

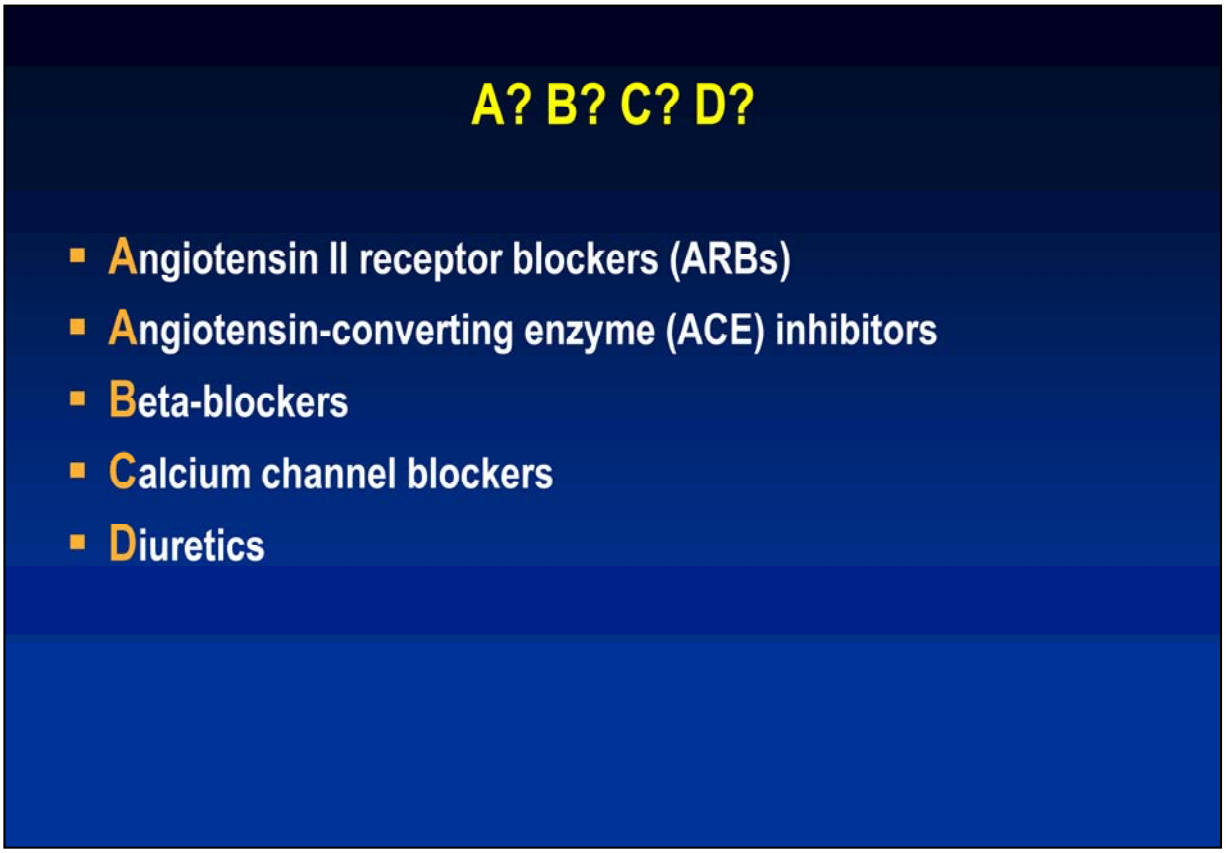
- 위험의 계층화/심혈관위험의 계산
- 위험이 높을 수록 낮은 혈압에서부터 치료를 시작하고 낮은 혈압을 유지
- 다른 위험인자들의 강력한 관리
- 효과적인 강압제의 선택

효과적인 강압제란?

- 우수한 강압효과
- 적은 부작용
- 간편한 복용
- 심혈관계 및 신장 질환의 예방 혹은 감소
- 저렴한 가격

강압 효과란?

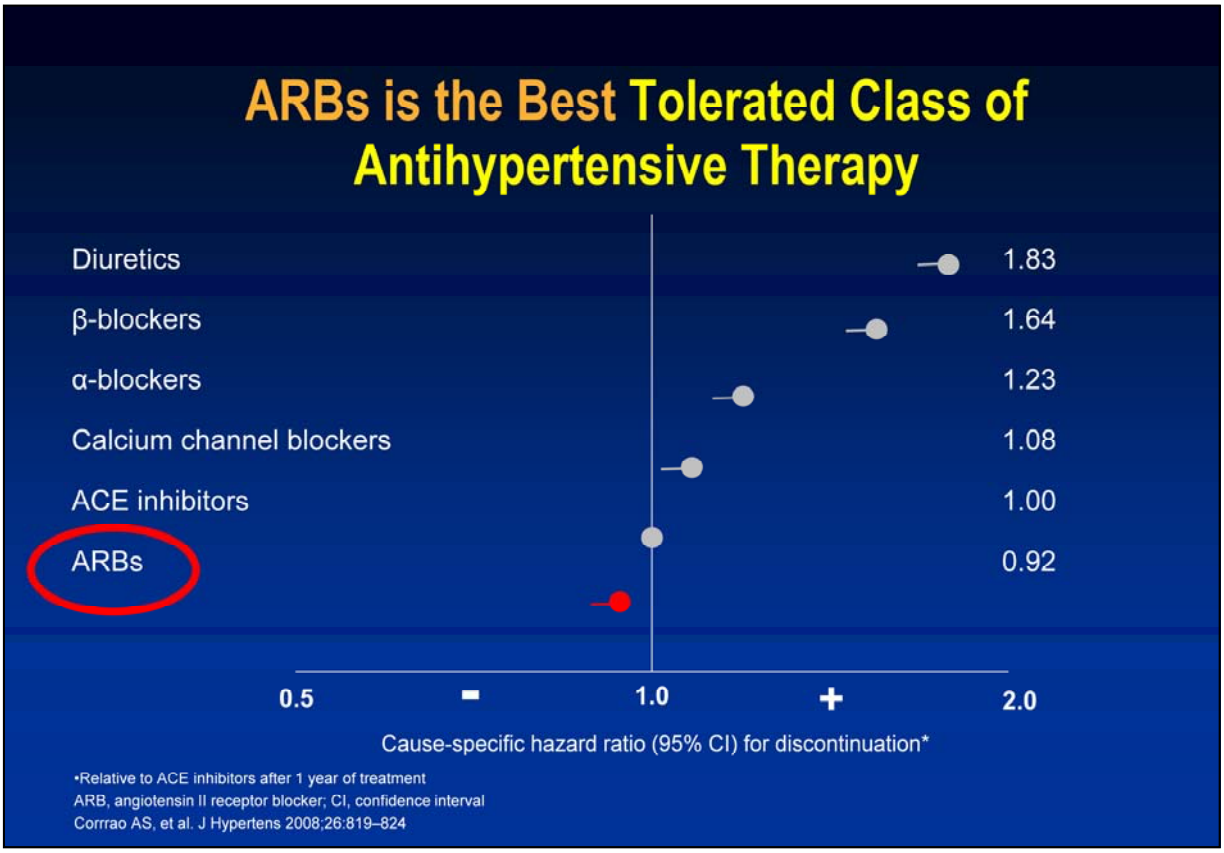
- 일차적으로 혈압 강하이지만, 궁극적인 목표는 심혈관계 질환 감소
- 일반적으로 강압효과와 심혈관 질환의 감소는 비례
- 약제에 따라 강압효과보다 심혈관 질환의 감소가 큰 약제도 있음 - **beyond BP lowering effect**



Key point: **The goal of hypertension treatment is to lower high blood pressure and protect important organs, like the brain, heart and kidneys from damage.**

In today's treatment landscape there are a number of difficult treatment options – ARBs are the most recent class to be developed, and ARBs are effective, well-tolerated and representing valuable alternative to often prescribed ACE-inhibitors.

Current treatment guidelines recommend individualised approach to patient management, and also recognise that often more than one therapy is required to achieve BP goals.



<u>Key point:</u> Adherence to ARBs is superior to that of other classes of anti-hypertensives followed by ACE inhibitors

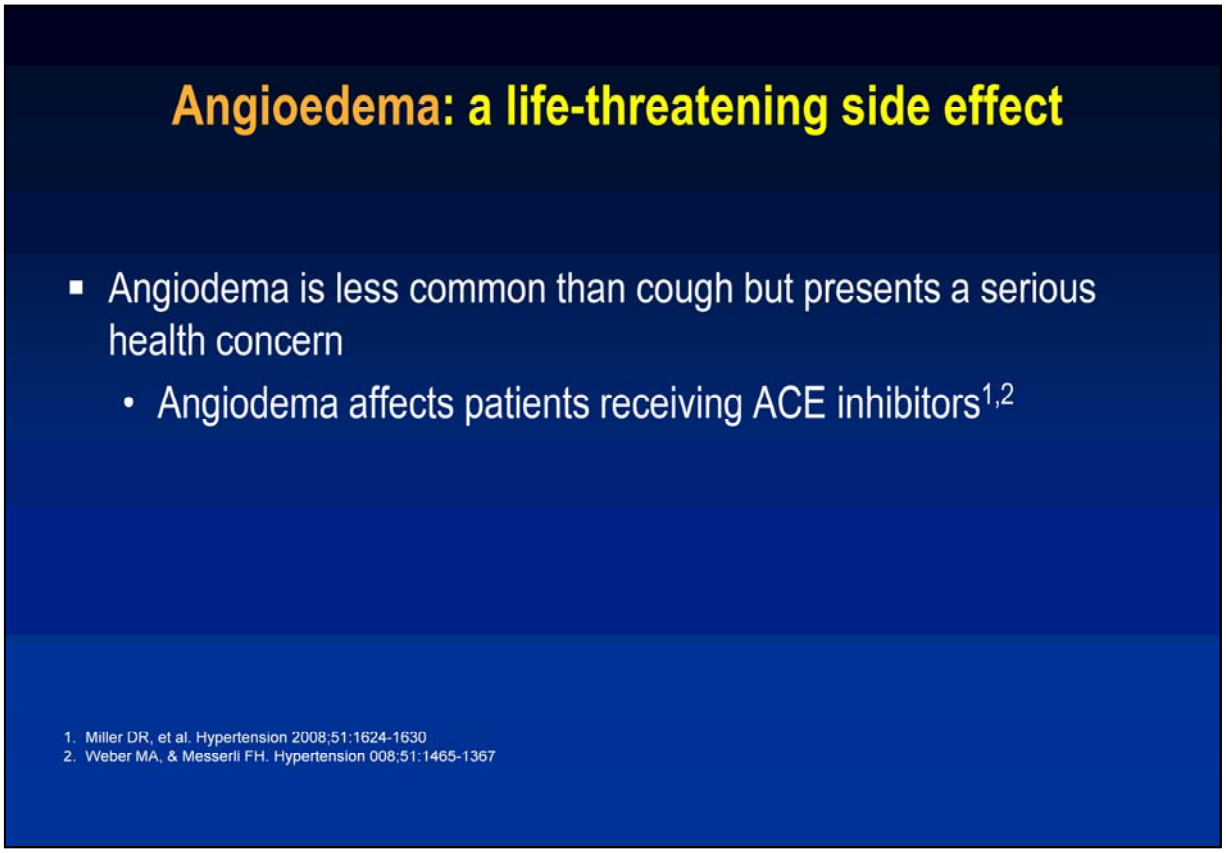
Adherence to different classes of antihypertensive agents

Clearly, overall adherence to antihypertensive therapy is poor. This large cohort study conducted in Lombardia, Italy assessed the rates of treatment discontinuation of, or changes in, initial antihypertensive drug monotherapy in 445,356 subjects aged 40–80 years.[1] Discontinuation was defined as the absence of any antihypertensive prescription during a 90-day period following the end of the latest prescription. Changing was defined as the addition of an antihypertensive agent of a different class (as a result of lack of efficacy) or the replacement of the initially prescribed drug with an alternative (largely due to reported side effects).

Compared with the addition of second antihypertensive or switching to an alternative drug, discontinuation occurred more than twice as frequently. After 1 year, 18% of patients had changed to combination therapy and 17% to an alternative agent, but 41% had completely discontinued treatment. Discontinuation was cumulative and after 5 years had risen to 50%. Treatment discontinuation rates differed for different classes of antihypertensive. The best stay-on treatment rate was observed with blockers of the RAS, and the hazard ratio was lowest for ARBs. Many patients, therefore appear to make a conscious decision to stop their medication.

Reference

1. Corrao AS, *et al.* Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: a population-based study in Italy. J Hypertens 2008; 26: 819–824.



<u>Key point:</u> ACE inhibitors are also associated with angioedema, a potentially life-threatening side effect.

ACE inhibitors and angioedema

Despite having a much lower prevalence compared with cough in ACE inhibitor treated patients,[1,2] angioedema is an adverse effect that must never be ignored. Discontinuation of treatment is essential in all patients experiencing facial swelling after initiation of ACE inhibitor therapy.

Angioedema induced by ACE inhibitors poses a serious health concern. Currently, very large numbers are treated worldwide for hypertension or heart failure with ACE inhibitors.[3] Nussberger et al. calculated. A recent report suggests that nearly one-third of patients presenting to emergency departments appear to cause by ACE inhibitor therapy.[4]

As well as the face becoming swollen, the mouth, tongue and pharynx may be affected. The consequent airway obstruction can be life-threatening due to suffocation.

References

1. Miller DR, *et al*. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. Hypertension 2008;51:1624-1630.
2. Weber MA, & Messerli FH. Angiotensin-converting enzyme inhibitors and angioedema: estimating the risk. Hypertension 2008;51:1465-1367.
3. Nussberger J, *et al*. Bradykinin-mediated angioedema. N Engl J Med 2002;347:621-2
4. Banerji A, *et al*. Multicenter study of patients with angiotensin-converting enzyme inhibitor-induced angioedema who present to the emergency department. Ann Allergy Asthma Immunol 2008;100:327-332.

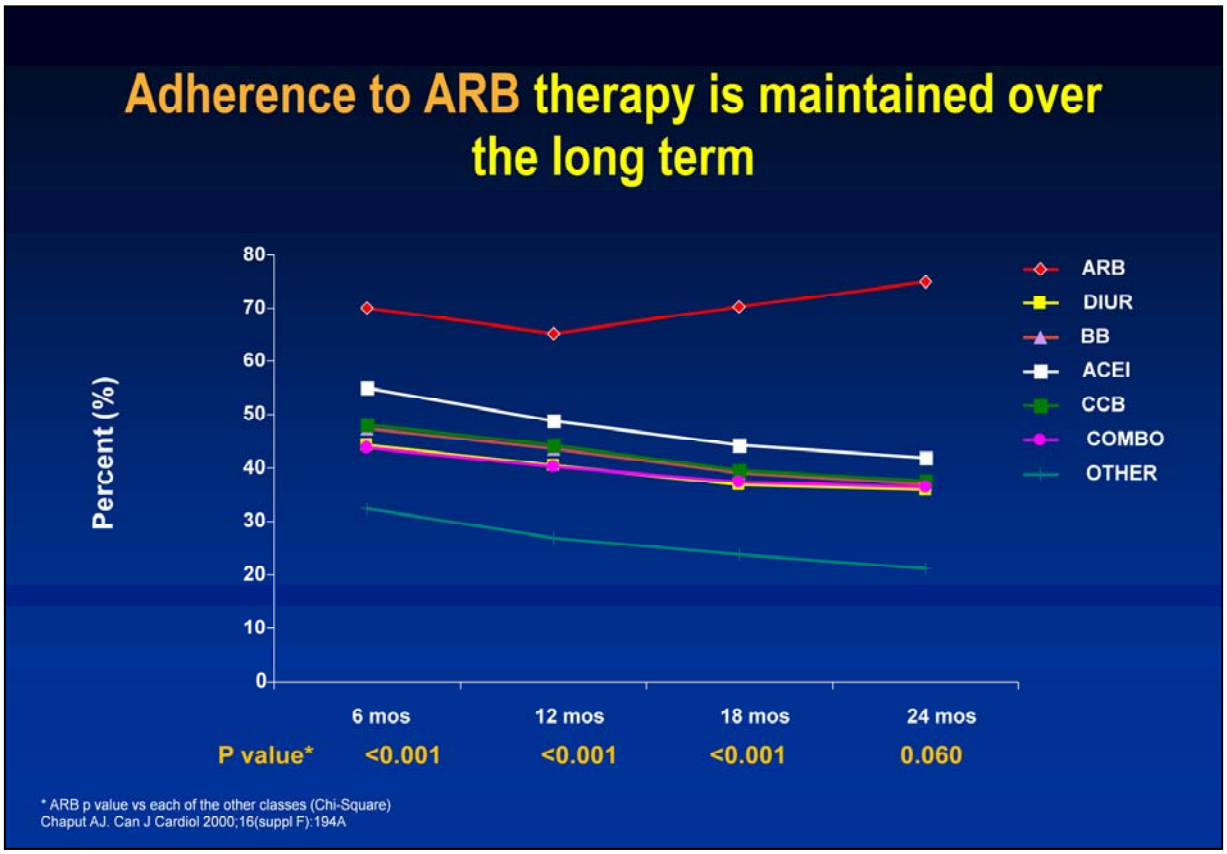

ONTARGET
Tolerance of Telmisartan and Ramipril among Asians
Antonio L. Dans MD
Steering Committee
ONTARGET Program

Permanent Withdrawals (Ramipril vs Telmisartan)

	Overall		Asians		Non-Asians	
	R	T	R	T	R	T
Discontinued	24.7%	23.4%	19.9%*	14.4%ϕ	25.5%*	24.8%ϕ
Hypotension	1.5%	2.1%	1.0%	0.8%ϕ	1.6%	2.3%ϕ
Syncope	0.2%	0.2%	0.1%	0.3%	0.2%	0.2%
Cough	4.1%	1.0%	5.9%*	1.4%	3.8%*	1.0%
Diarrhea	0.1%	0.2%	--	0.2%	0.2%	0.2%
Angioedema	0.3%	0.1%	0.2%	--	0.3%	0.1%
Renal impairment	0.6%	0.6%	0.3%	0.4%	0.6%	0.6%

* p< 0.0001 (asians vs non-asians)
ϕ p< 0.0001 (asians vs non-asians)

Overall telmisartan was better tolerated,
and this was consistent among asians as well as non-asians
In fact, if you compare across the table, there were more discontinuations among non-asians than asians (exept for cough)
The difference in tolerability was greater among asians



<u>Key point:</u> Persistence with ARB therapy is maintained in the long term.

Adherence to different classes of antihypertensive agents

Analysis of patient behaviour over 2 years has shown that ARBs are the therapy with higher treatment persistence over 2 years. These data are derived from hypertensive patients listed in the Saskatchewan Database. Adherence for each class was measured at 6, 12, 18, and 24 months. Patients were defined as adherent if the original prescription was refilled within 21 days of the target months.

Persistence with ARB treatment was significantly greater than with other therapies at all time points. Furthermore, whereas adherence declined with time for other anithypertensive classes, it remained high for ARBs.

Tolerability is likely to be a major cause of the increased treatment persistence with ARBs. Efficacy advantages may also have contributed, with doctors switching patients if blood pressure goals were not achieved.

Reference

- Chaput AJ. Persistence with angiotensin receptor blockers (ARB) versus other antihypertensives (AHT) using the Saskatchewan database.Can J Cardiol 2000;16(suppl F):194A

The 53rd Annual Scientific Meeting of The Korean Society of Cardiology 2009

Effect of ACEI, ARB, and Combination of Both Drugs on Long-Term Clinical Outcomes in AMI Patients, Who Underwent PCI, According to Renal Function

Korea Acute Myocardial Infarction Investigators

Background (I) ACE Inhibition: ACEI vs. ARB?

- ACE inhibition by ACEI or ARB
  - : Play in the treatment of HT and HF
  - : Provide added benefits beyond BP lowering in hypertensive patients with co-morbidities, such as, HF, MI, DM, chronic kidney disease, and stroke
- ACEI vs. ARB (Which one is better?)
  - : Lack of head to head comparative data between ACEI and ARB

Brunner et al. J Hypertens 2005;23:233-46

Background (I) ACE Inhibition: ACEI vs. ARB?

ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult

4.3. Patients With Current or Prior Symptoms of HF (Stage C)

4.3.1. Patients With Reduced LVEF

RECOMMENDATIONS

Class I

3. Angiotensin converting enzyme inhibitors are recommended for all patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (see Table 3 and text). *(Level of Evidence: A)*

5. Angiotensin II receptor blockers approved for the treatment of HF (see Table 3) are recommended in patients with current or prior symptoms of HF and reduced LVEF who are ACEI-intolerant (see text for information regarding patients with angioedema). *(Level of Evidence: A)*

ACC/AHA 2002 Guideline Update for the Management of Patients With Chronic Stable Angina

Recommendations for Pharmacotherapy to Prevent MI and Death in Asymptomatic Patients

Class I

4. ACE inhibitor in patients with CAD who also have diabetes and/or systolic dysfunction. *(Level of Evidence: A)*

Class IIa

4. Angiotensin converting enzyme inhibitor in all patients with diabetes who do not have contraindications due to severe renal disease. *(Level of Evidence: B)*

ARB: No comments

Background (I) ACE Inhibition: ACEI vs. ARB?

Study Population	Agents studied	Comments
Treatment of HT in patients with DM	Enalapril vs telmisartan[1]	No difference between ACEI and ARB May be additional benefits from combination of ACEI and ARB
Prevention of the progression of nephropathy	Trandolapril vs losartan vs combination[2]	Combination of ACEI and ARB showed additional benefit
Reduction of stroke in patients with HT	No head to head data between ACEI and ARB	
Prevention of new onset DM	No head to head data between ACEI and ARB	

1. Barnett et al. N Engl J Med 2004
2. Parving HH et al. Semin Nephrol 2004

Background (I) ACE Inhibition: ACEI vs. ARB?

Study Population	Agents studied	Comments
Prevention of AF in patients with HT or HF	No head to head data between ACEI and ARB	
Benefits in systolic HF	Captopril vs losartan[3,4] Captopril vs valsartan[5] Captopril vs candesartan[6]	No difference between ACEI and ARB in all-cause mortality and hospitalization for HF[3] Potential trend toward a reduction in mortality with captopril[4] No difference between ACEI and ARB in cardiovascular mortality and hospitalization for HF[6]

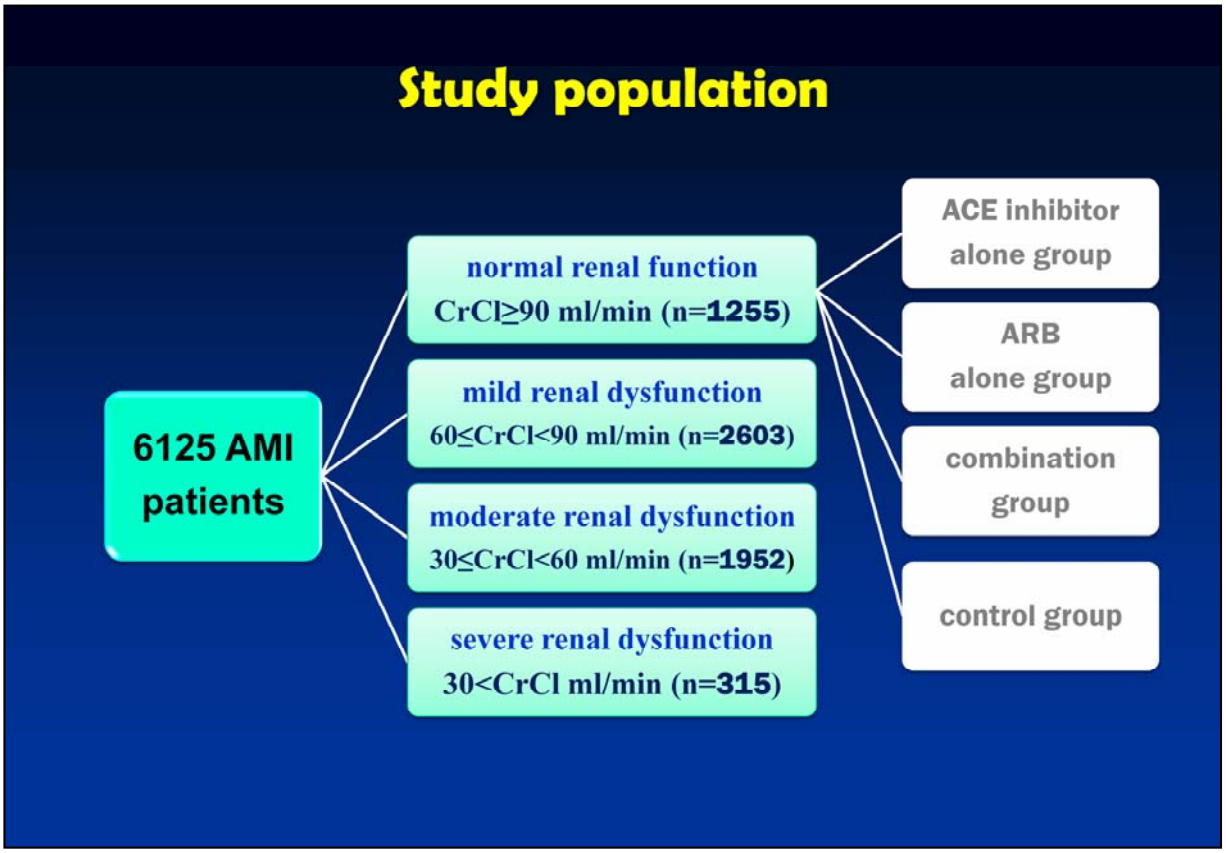
3. Pitt B et al. Lancet 2000. 4. Dickstein K et al.Lancet 2002.
5. Pfeffer MA et al. New Engl J Med 2003. 6. Granger CB et al. Lancet 2003

Objectives

- To assess the beneficial effect of ARB, ACE inhibitor, and combination of both drugs for the improvement of long term clinical outcomes in Korean acute myocardial infarction patients according to renal dysfunction

Study Population

- 6125 AMI patients (65.2 ± 12.0 years, 4461 males)
- between Nov. 2005 and Dec. 2007
- enrolled KAMIR
- who underwent successful PCI
- Survived in hospital period
- Same medication during in hospital period and discharge
- Followed-up during one year after discharge



Methods

- Creatinine clearance (CrCl)

  → calculated using the Cockcroft–Gault formula

$$\text{CrCl} = \frac{(140\text{-age}) \times \text{body weight}}{\text{serum creatinine} \times 72} \quad (\times 0.85, \text{ if female})$$

Methods

ACEi

- Ramipril (Tritace®)
- Imidapril (Tanatril®)
- Captopril (Capril®)
- Cilazapril (Inhibace®)
- Lisinopril (Zestril®)
- Perindopril (Acertil®)
- Enalapril (Renipril®)
- Fosinopril(Monopril®)
- Moexipril (Univasc®)

ARB

- Telmisartan (Pritor®, Micardis®)
- Candesartan (Atacand®)
- Ibesartan (Aprovel®)
- Olmesartan (Olmetec®)
- Valsartan (Diovan®)
- Losartan (Cozaar®)
- Eprosartan (Teveten®)

Methods

- Primary end points
  - MACE during one-year clinical follow up
    - Cardiac death
    - Non-cardiac death
    - Re-infarction
    - Coronary artery bypass grafting
    - Target lesion revascularization

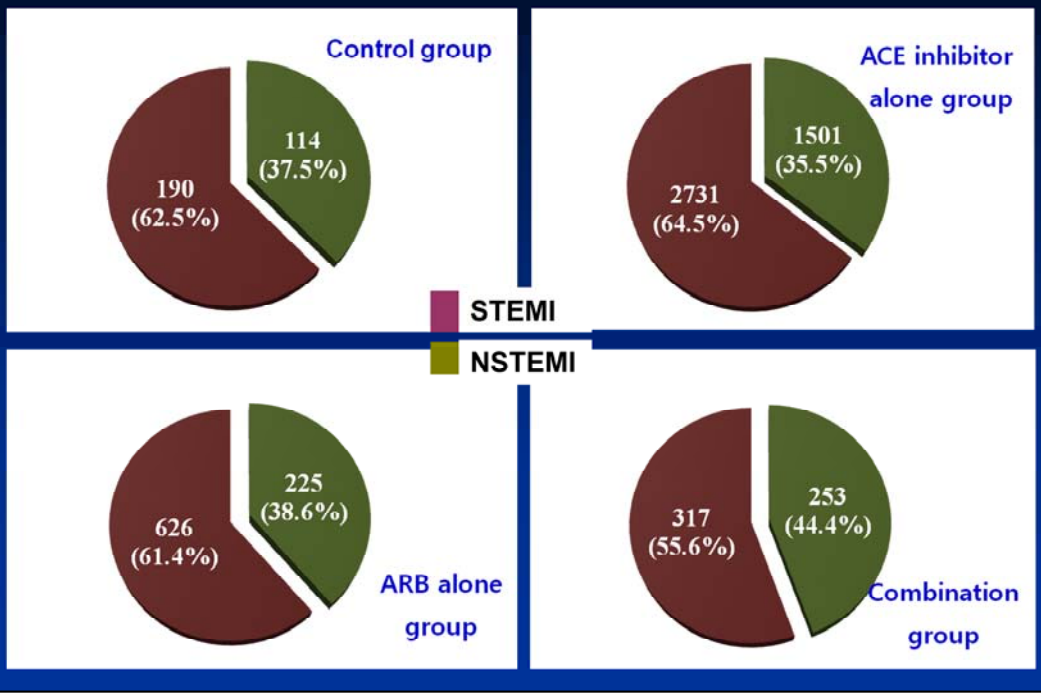
Results- baseline clinical characteristics

Variable	Control group (N=1019)	ACE inhibitor alone group (N=4232)	ARB alone group (N=570)	Combination group (N=304)	*P*
Age (years)	65.7±12.6	63.1±12.6	63.4±13.1	66.2±11.9	0.082
Male (%)	732(71.8)	3125(73.9)	401(70.4)	203(66.8)	0.062
Hypertension (%)	464(45.5)	1918(45.3)	338(59.3)	184(60.5)	<0.001
Diabetes mellitus (%)	254(24.9)	1086(25.7)	193(33.9)	109(35.9)	<0.001
Smoking (%)	588(58.3)	2632(62.4)	306(54.1)	167(55.1)	<0.001
Hyperlipidemia (%)	97(9.5)	439(10.4)	74(13.0)	24(7.9)	0.072
Family history (%)	55(5.4)	313(7.4)	43(7.5)	20(6.6)	0.148

Results- Symptoms and hemodynamics on admission

Variable	Control group (N=1019)	ACE inhibitor alone group (N=4232)	ARB alone group (N=570)	Combination group (N=304)	*P*
Systolic blood pressure (mmHg)	131.3±29.5	130.4±28.3	137.0±35.2	135.4±34.0	0.118
Heart rate (n/min)	78.9±21.2	78.0±22.5	81.9±24.7	27.2±41.6	0.120
Shock (%)	70(6.9)	185(4.4)	29(5.1)	22(7.2)	0.003
Killip class (%)					<0.001
I or II	906(88.9)	3860(91.2)	521(91.4)	243(79.9)	
III or IV	113(11.1)	372(8.8)	49(8.6)	61(20.1)	

Results- Final Diagnosis



Results- ECG and echocardiogram findings

Variable	Control group (N=1019)	ACE inhibitor alone group (N=4232)	ARB alone group (N=570)	Combination group (N=304)	*P*
ECG finding					
LBBB	20(2.0)	76(1.8)	12(2.1)	5(1.6)	0.146
AV block	15(1.5)	55(1.3)	3(1.2)	5(1.5)	0.819
Atrial fibrillation	67(6.6)	262(6.2)	34(6.0)	6(6.9)	0.717
Ventricular tachycardia and fibrillation	21(2.1)	66(1.8)	72(1.7)	7(2.2)	0.454
Echocardiogram findings					
Left ventricular ejection fraction (%)	53.4±31.6	51.6±12.4	51.3±13.0	51.8±37.4	0.298
Total wall motion score	18.86±11.4	19.6±10.6	19.5±10.0	18.2±10.7	0.637

Results- Laboratory finding

Variable	Control group (N=1019)	ACE inhibitor alone group (N=4232)	ARB alone group (N=570)	Combination group (N=304)	*P*
Creatine kinase-MB (U/L)	124.4±20.4	135.8±20.8	126.8±12.6	151.4±29.3	0.797
Troponin I (ng/ml)	35.4±6.1	53.0±18.7	48.1±8.2	56.7±19.2	0.372
Troponin T (ng/ml)	8.9±7.0	16.9±10.3	11.1±7.8	20.9±12.4	0.837
Triglyceride (mg/dl)	132.4±86.3	130.4±108.2	118.1±68.7	120.6±94.6	0.428
HDL-cholesterol (mg/dl)	45.4±27.2	46.3±28.1	44.6±12.2	47.6±63.7	0.967
LDL-cholesterol (mg/dl)	116.9±46.4	119.6±46.1	116.2±35.4	114.4±77.5	0.498
High sensitivity-CRP (mg/dl)	3.8±1.2	3.4±1.2	3.3±6.7	3.0±1.3	0.445
N-terminal pro-BNP (pg/ml)	4501.1±898.3	4526.3±603.6	5492.9±927.0	4246.1±882.0	0.009

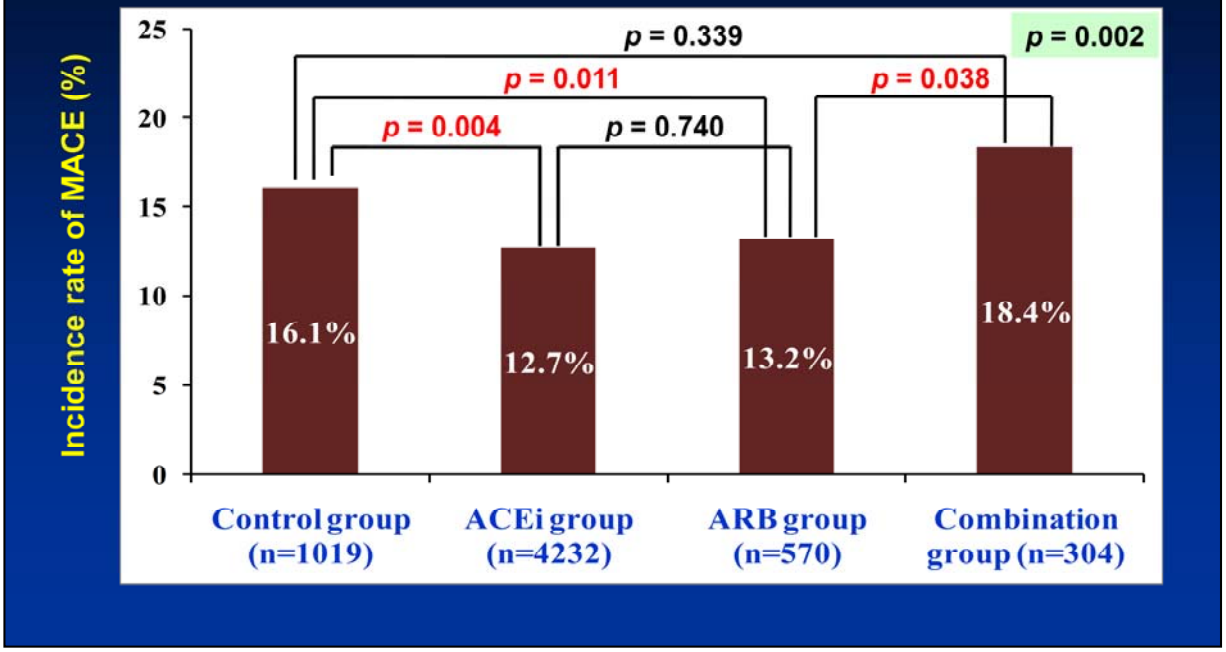
Results- Medical therapy on admission

Variable	Control group (N=1019)	ACE inhibitor alone group (N=4232)	ARB alone group (N=570)	Combination group (N=304)	*P*
Aspirin	997(97.8)	4219(99.7)	568(99.6)	302(99.3)	0.453
Clopidogrel	979(96.1)	4195(99.1)	560(98.2)	300(98.7)	0.525
Cilostazol	383(37.6)	1623(38.4)	192(33.7)	120(39.5)	0.442
Unfractionated heparin	561(55.1)	2746(64.9)	319(56.0)	205(67.4)	<0.001
Low molecular weight heparin	505(49.6)	1486(35.1)	307(53.9)	162(53.3)	<0.001
Abciximab	70(6.9)	457(10.8)	44(7.7)	49(16.1)	<0.001
Beta blocker	857(84.1)	3659(86.5)	493(86.5)	264(86.8)	0.904
Nitrate	676(66.3)	3249(76.8)	420(73.7)	261(85.9)	<0.001
Statin	813(79.8)	3364(79.5)	453(79.5)	242(79.6)	0.196

Results- Medical therapy at discharge

Variable	Control group (N=1019)	ACE inhibitor alone group (N=4232)	ARB alone group (N=570)	Combination group (N=304)	*P*
Aspirin	994(97.5)	4162(98.3)	548(96.1)	295(97.0)	0.146
Clopidogrel	979(96.1)	4099(96.9)	539(94.6)	291(95.7)	0.131
Cilostazol	310(30.4)	1679(39.7)	198(34.7)	114(37.5)	<0.001
Beta blocker	810(79.5)	3426(81.0)	458(80.3)	241(79.3)	0.260
Nitrate	472(46.3)	2043(48.3)	296(47.2)	147(48.4)	0.707
statin	788(77.3)	3273(77.3)	446(78.2)	234(77.0)	0.217

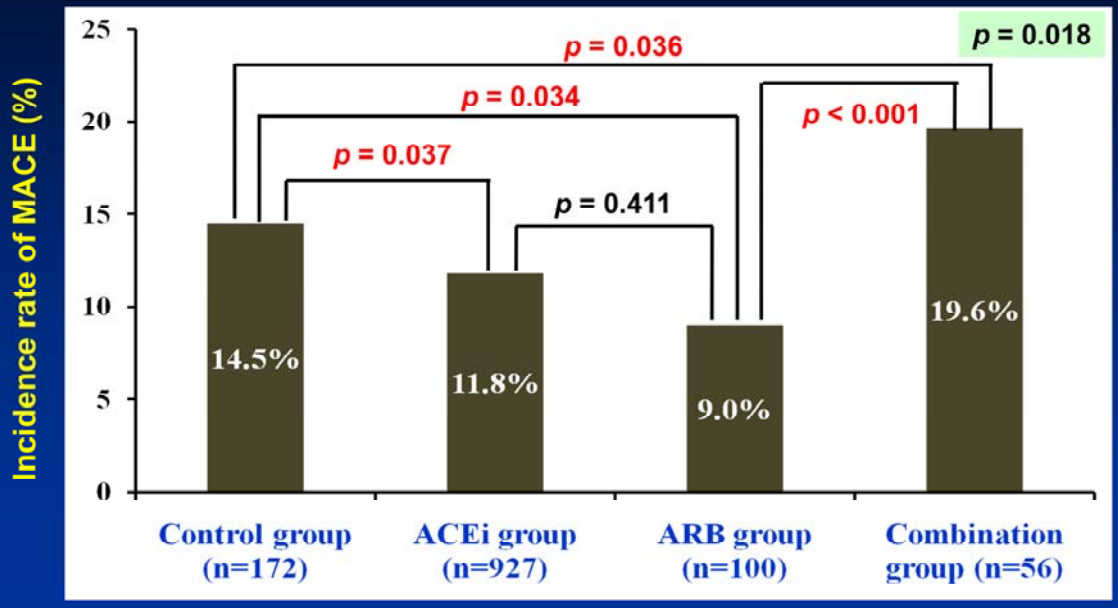
Results - Overall patients (n=6,125)



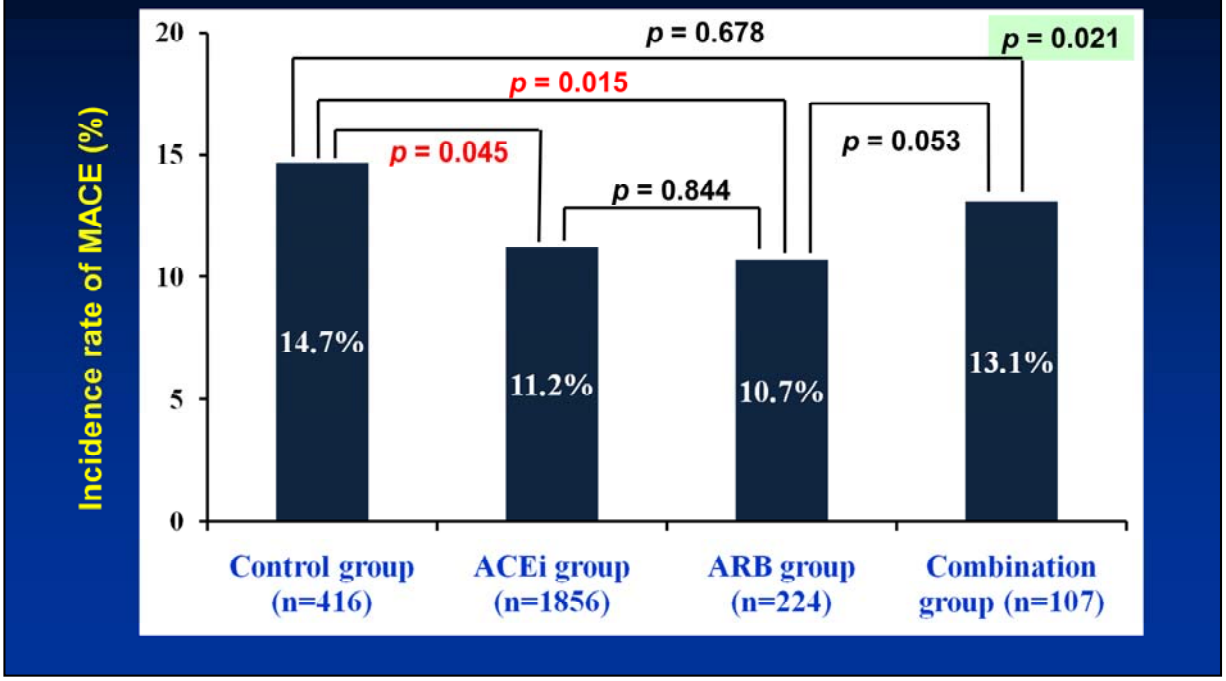
Results - Composite of primary end points
Overall patients (n=6,125)

Variable	Control group (N=1019)	ACE inhibitor alone group (N=4232)	ARB alone group (N=570)	Combination group (N=304)	*P*
Composite of MACE (%)	164 (16.1)	536 (12.7)	75 (13.2)	56 (18.4)	0.002
Cardiac death (%)	29 (2.8)	75 (1.8)	12 (2.1)	17 (5.6)	<0.001
Non cardiac death (%)	20 (2.0)	53 (1.3)	6 (1.1)	8 (2.6)	0.081
Re-infarction (%)	11 (1.1)	47 (1.1)	5 (0.9)	3 (1.0)	0.963
CABG (%)	7 (0.7)	15 (0.4)	3 (0.5)	0 (0.0)	0.297
Re PCI (%)	99 (9.7)	359 (8.5)	49 (8.6)	28 (9.2)	0.645
TLR	24 (2.4)	138 (3.3)	22 (3.9)	15 (4.9)	0.111
TVR	10 (1.0)	61 (1.4)	6 (1.1)	4 (1.3)	0.640
Non-TVR	66 (6.5)	162 (3.8)	21 (3.7)	8 (2.6)	<0.001

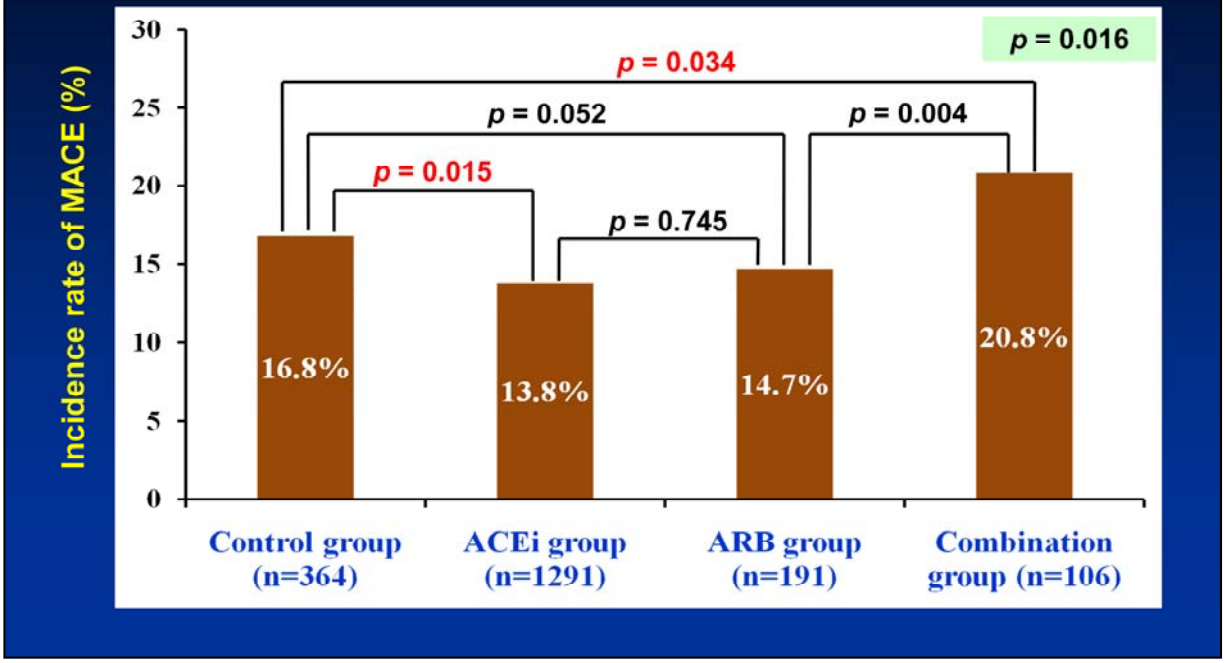
Results - Normal renal function group (n=1,255)



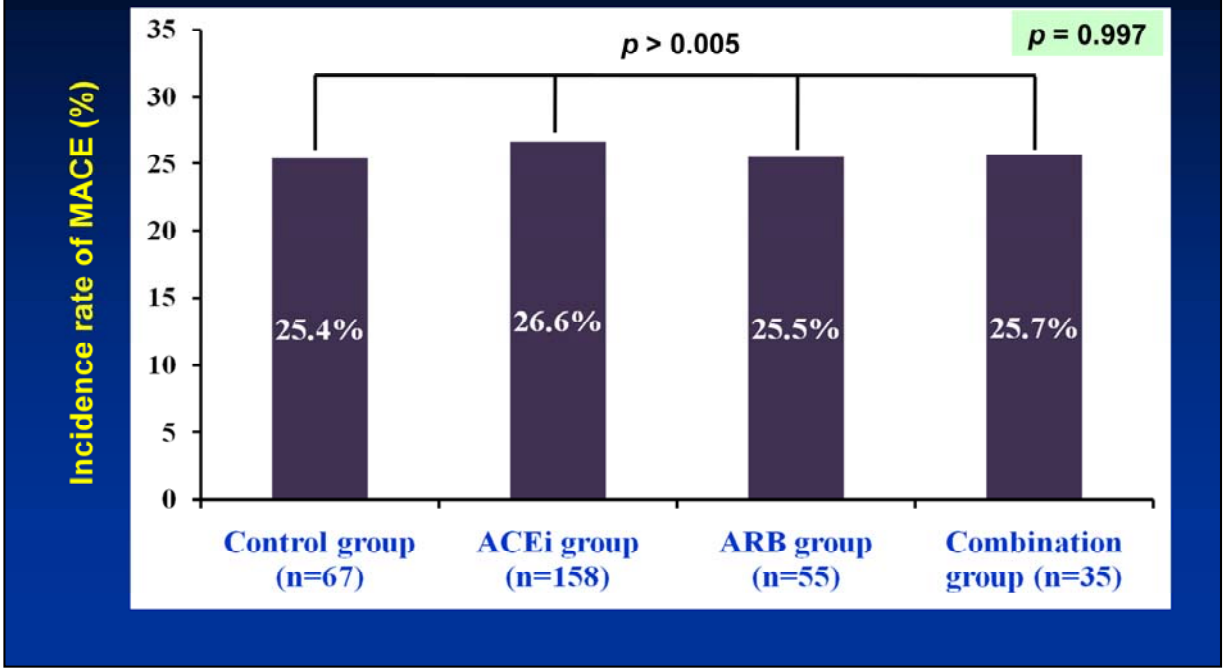
Results - Mild renal insufficiency group (n=2,603)



Results - Moderate renal insufficiency group (n=1,952)



Results - Severe renal insufficiency group (n=315)



Results : Multivariate analysis of primary end points

	Odd ratio	95% confidence interval		p
		Lower	Upper	
Low creatinine clearance	1.009	1.005	1.011	<0.001
Angiotensin receptor blocker treatment	0.971	0.964	0.978	<0.001
Old age	1.019	1.012	1.027	<0.001
Angiotensin converting enzyme inhibitor treatment	0.779	0.628	0.966	0.023
ST segment elevation myocardial infarction	1.141	0.953	1.366	0.152
Beta blocker treatment	0.864	0.704	1.061	0.164
Statin treatment	0.909	0.762	1.085	0.291

Conclusion of KAMIR Study

- The beneficial effects of ARB were equivalent to those of ACE inhibitor, esp. in Korean AMI patients with normal renal function and mild renal dysfunction
- Considering side effects of ACE inhibitor, ARB is better in high-risk CV Korean patients
- The combination of the two drugs was associated with more adverse events without an increase in benefit in AMI patients

Telmisartan Approved by FDA
For Myocardial Infarction and Stroke
For Risk Reduction in High Risk CV Patients

결 론

- 국내의 고혈압관리는 크게 향상되어 선진국수준에 도달하였지만 심근경색증 환자의 가장 중요한 위험 인자
- 고령화에 따라서 고혈압 환자 급증
- 심혈관질환의 최소화를 위해서 이상지질혈증, 비만, 당뇨병, 신장질환 등의 위험인자의 전체적 관리 및 심혈관계 위험도의 계층화가 필요
- 이상적인 강압제는 강압효과와 함께 심혈관계 질환을 감소시킬 수 있는 **Beyond BP Lowering Effect** 가 있어야 함, 특히 심근경색증과 같은 고위험군에서 효과적이어야 함
- 한국인 고위험 환자군에서 ARB 가 우수한 임상효과를 보임


여러분 모두 행복하고
평화로운 봄을 맞이
하시길 기원합니다