# Will Clinical Trials Tell Us the Vascular Protection Beyond Drug Properties?

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# Statins의 부가적 혈관보호효과

**LDL-Cholesterol Lowering Effect**

Beneficial Effects on Other Lipids
Normalization of Endothelial Dysfunction
Increased Nitric Oxide Bioavailability
Antioxidant Properties
Inhibition of Inflammatory Responses
Stabilization of Atherosclerotic Plaques

} Pleiotropic Effects

# 고혈압치료제의 부가적 혈관보호효과

**Reported pleiotropic effects on**

Vascular structure, vascular stiffness, vascular distensibility, endothelial function, proteinuria, albuminuria, chronic kidney disease, diabetes, insulin resistance, lipid profile, cognitive function, etc.

**Commonly reported drug classes**

Angiotensin-Converting Enzyme Inhibitor (ACEI)

Angiotensin Receptor Blocker (ARB)

Calcium-Channel Blocker (CCB)

# 부가적 혈관보호효과의 평가

1. 혈관의 구조적 기능적 변화

2. 동반질환의 예방 치료 효과

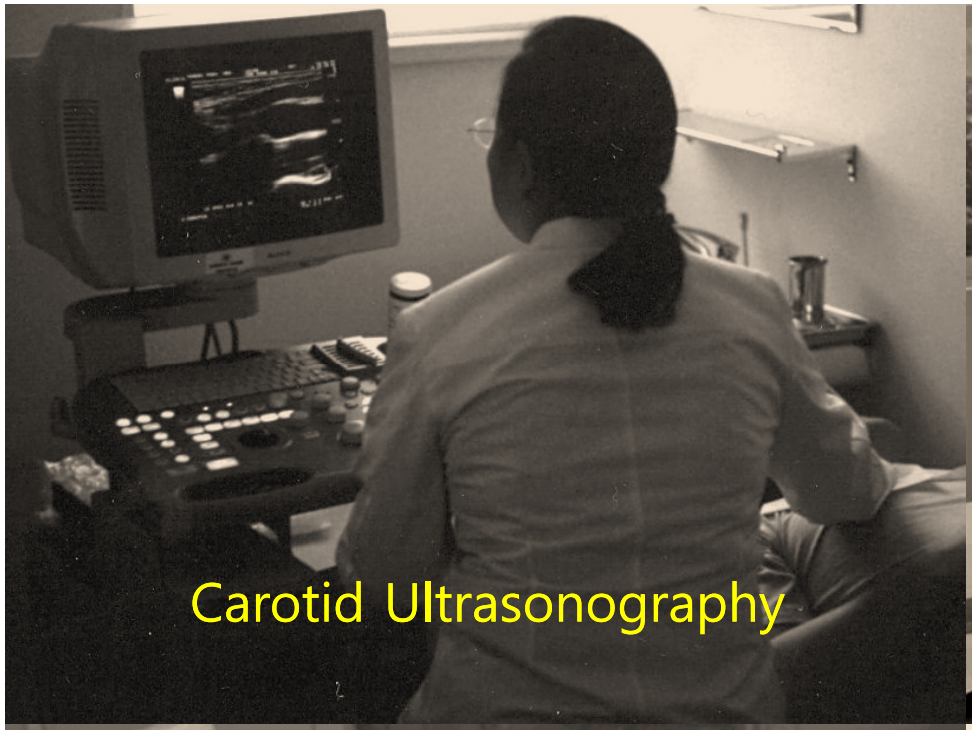
3. 임상적 혈관질환 예방 효과

# 부가적 혈관보호효과 (1)

- Structural and Functional Vascular Changes

- 혈관변성, 혈내피세포기능, 혈관확장능력, 혈관경직도 등 혈관의 구조적-기능적 변성을 예방하거나 정상화하는 효과가 보고되었음

- 고혈압치료제 복용 전후에 혈관의 구조적-기능적 변화를 검사실검사나 진단장비로 객관적으로 측정하여 혈관보호효과를 평가할 수 있음

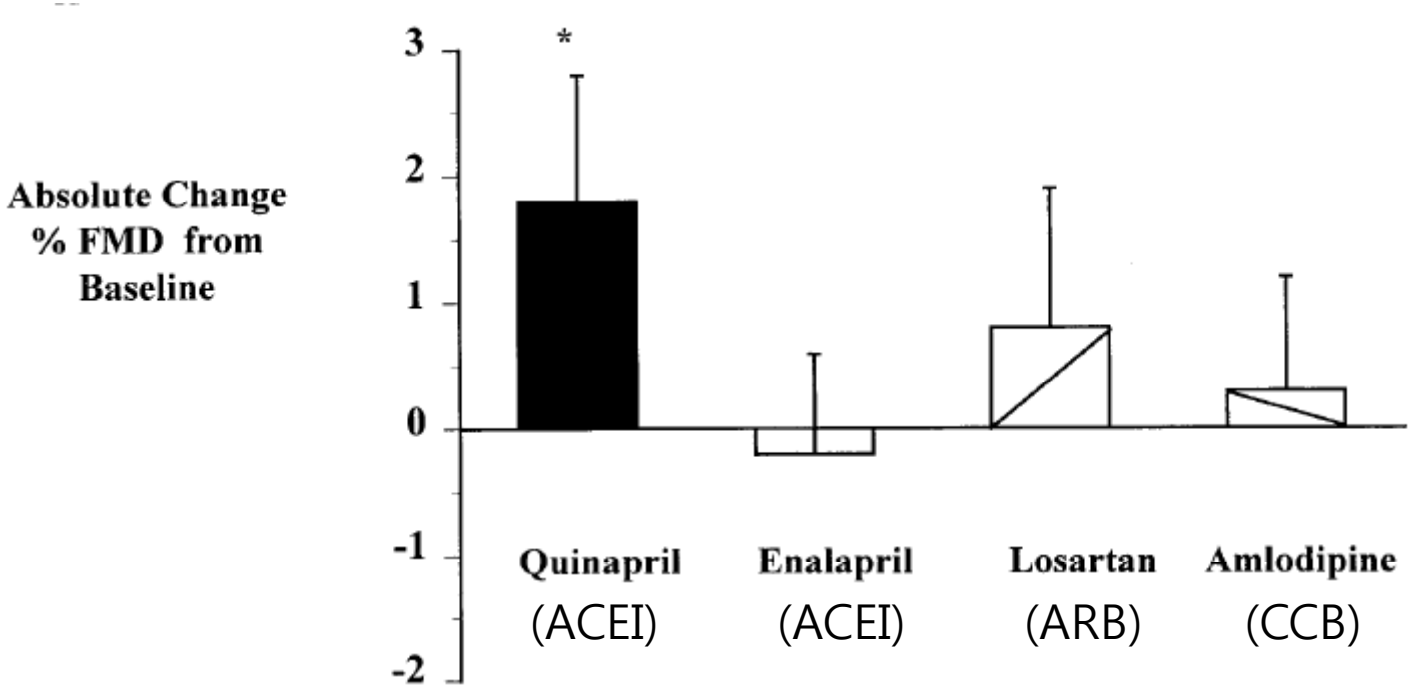

Carotid Ultrasonography


Pulse Wave Velocity


Flow Mediated Dilatation

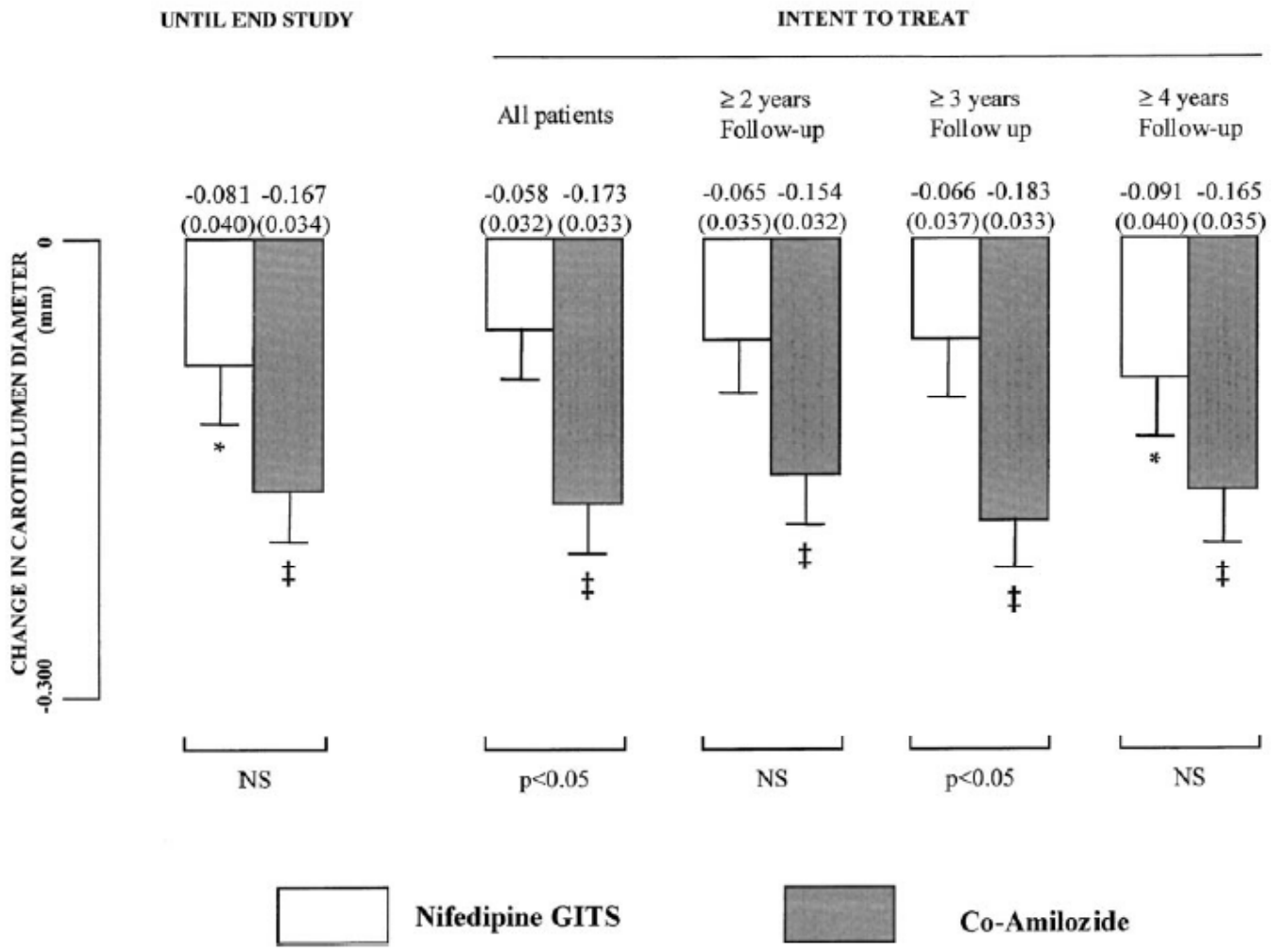

Pulse Wave Contour Analysis

# Comparative study of ACE-inhibition, angiotensin II antagonism, and calcium channel blockade on flow-mediated vasodilation in patients with coronary disease (BANFF study)




JACC Vol. 35, No. 1, 2000
January 2000:60–6

# Differential Effects of Nifedipine and Co-Amilozide on the Progression of Early Carotid Wall Changes




(CCB)

*Circulation* 2001;103;2949-2954

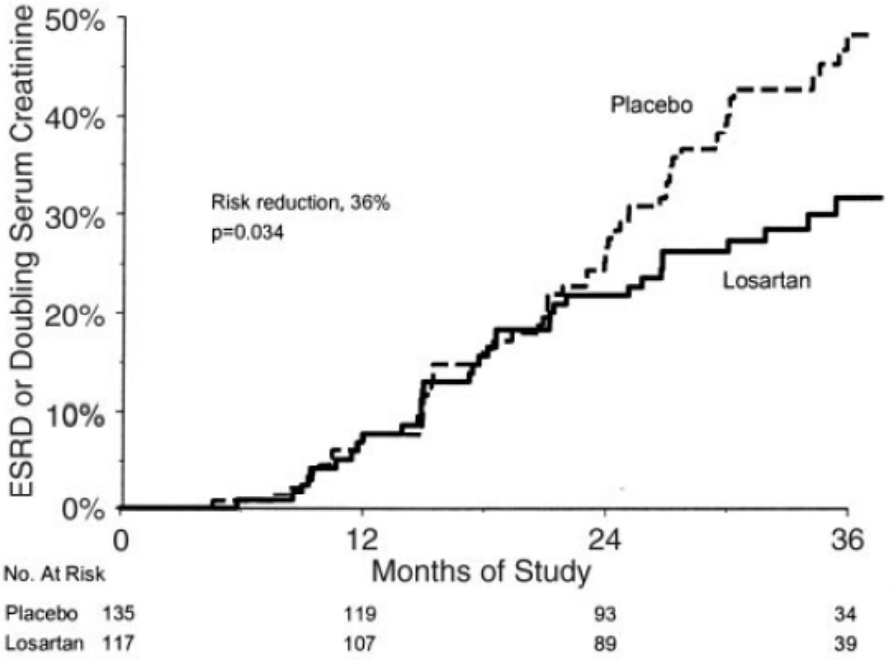
# 부가적 혈관보호효과 (2)

- Prevention or Improvement of Co-morbidities

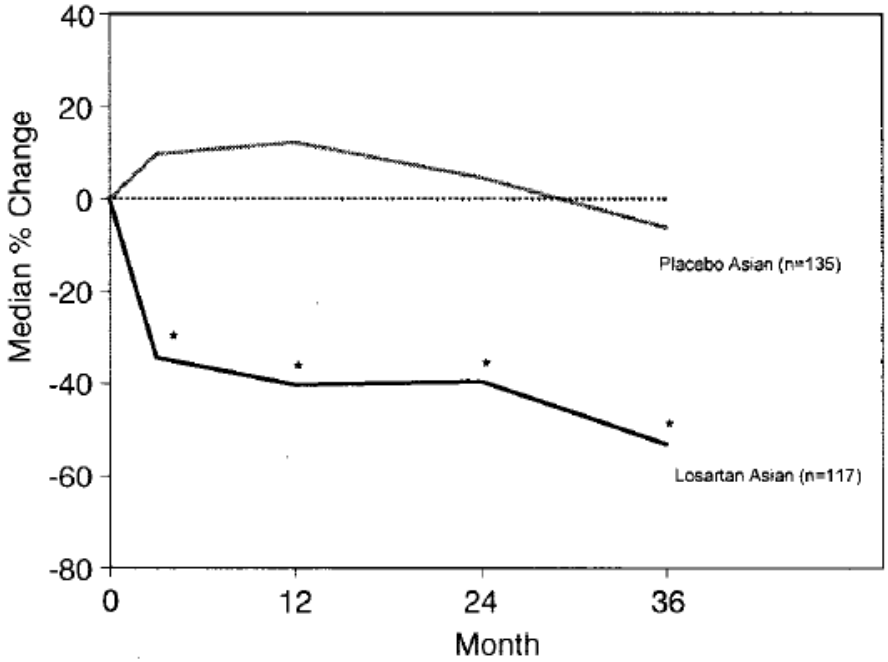
- 만성신장질환, 단백뇨, 당뇨병, 고지혈증, 인지기능장애 등 고혈압에 흔히 동반되는 질환을 예방하거나 개선시키는 효과가 보고되었음

- 이러한 동반질환을 결과변수(outcomes)로 측정하여 혈압 감소 이외의 예방효과를 평가할 수 있음

# Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study




ESRD or Doubling Serum Cr.

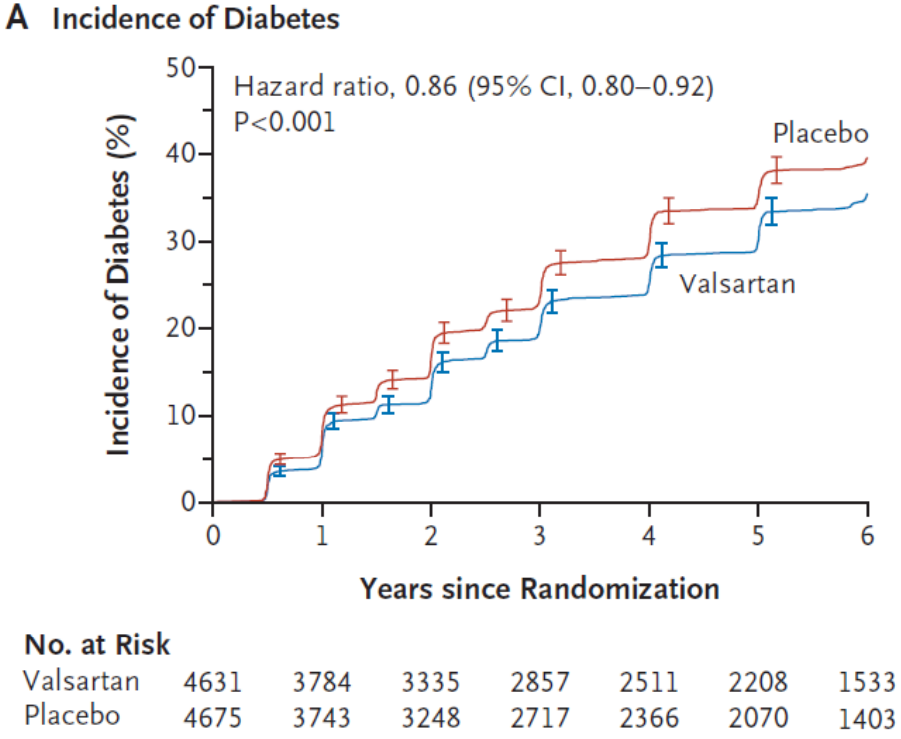



Change in Proteinuria

*Diabetes Care* 27:874–879, 2004

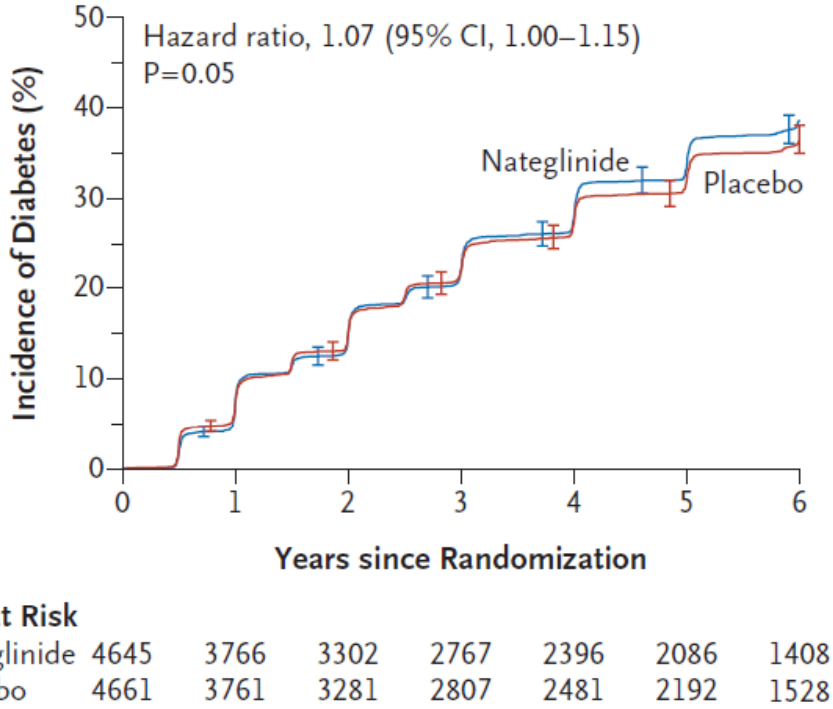
# Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Study Group

## Valsartan (ARB)



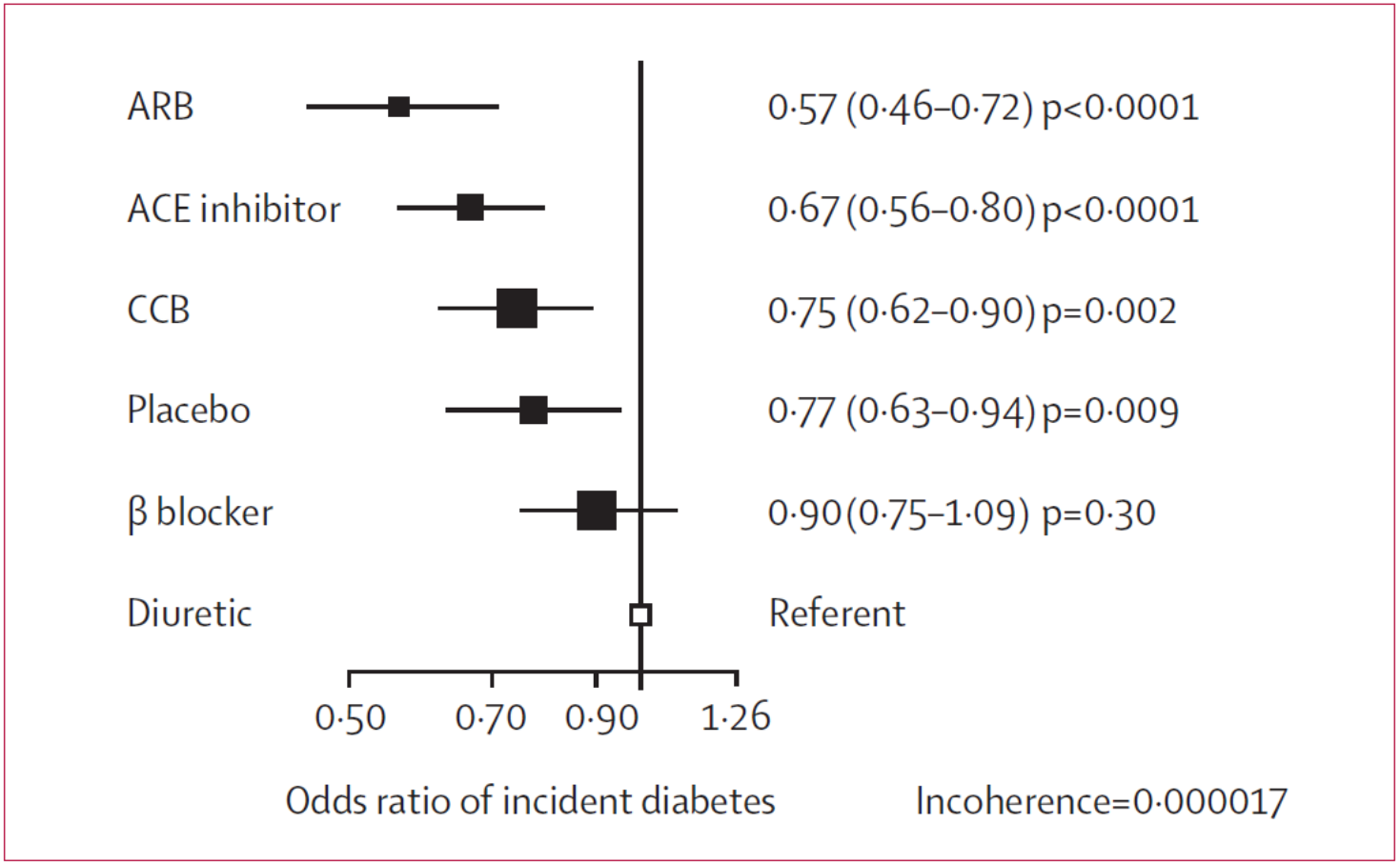

***NEJM***. 2010 Mar 14.

## Nateglinide (insulin secretagogue)




***NEJM.*** 2010 Mar 24

# Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis




*Lancet* 2007; 369: 201–07

# 부가적 혈관보호효과 (3)

- Going beyond the numbers
- 관상동맥질환, 뇌졸중, 심부전, 심혈관질환 사망 등 ultimate outcomes의 예방효과를 평가

1. Observed CVD prevention
   > Expected CVD prevention based on lowered BP

2. BP lowering: drug A < drug B
   CVD prevention: drug A > drug B

3. BP lowering: drug A < drug B
   CVD prevention: drug A = drug B

# 부가적 혈관보호효과 (3)

- Australian National Blood Pressure Trial 2 (ANBP-2)
- European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA)
- Heart Outcomes Protection Evaluation (HOPE)
- Losartan Intervention for End-Points (LIFE)
- Mortality after Stroke: Eprosartan Compared with Nitrendipine in Secondary Preventions (MOSES)
- Nordic Diltiazem Study (NORDIL)
- Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE)
- Perindopril Protection Against Recurrent Stroke Study (PROGRESS)

BMJ

RESEARCH

# Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies

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**ABSTRACT**

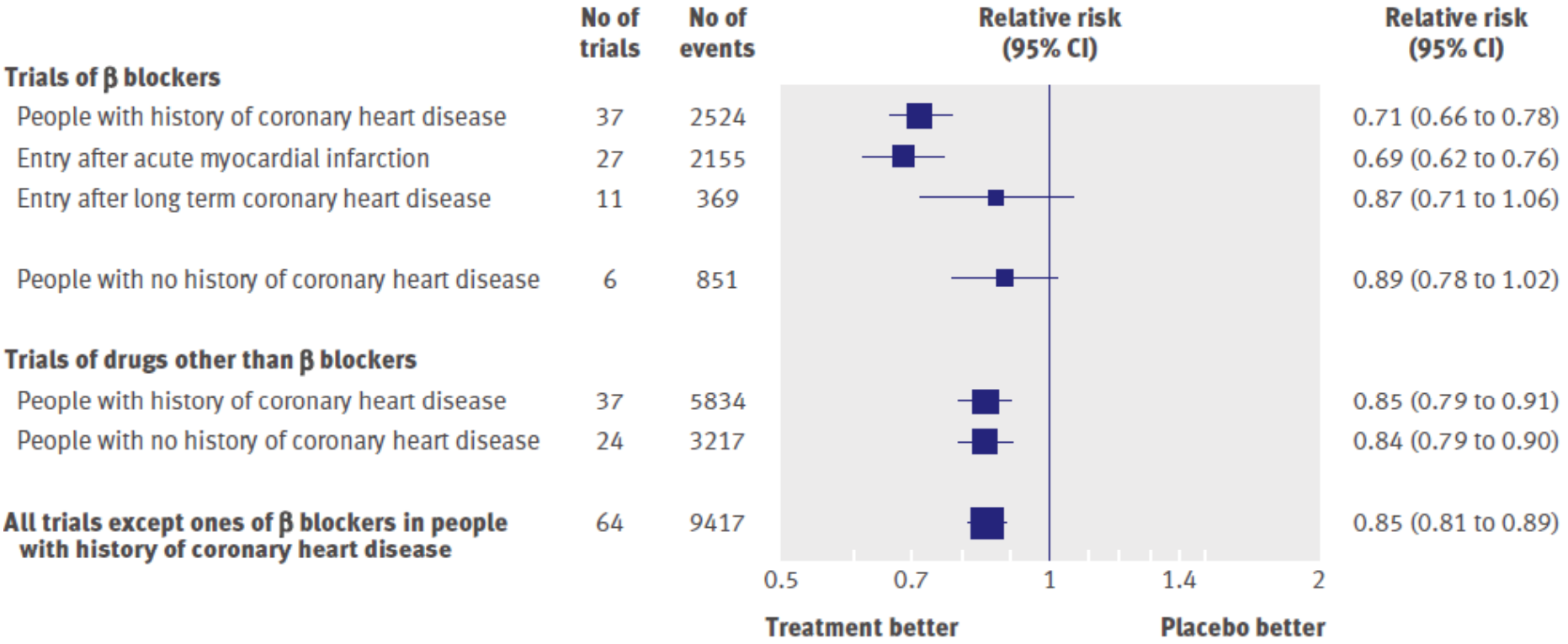
**Objectives** To determine the quantitative efficacy of different classes of blood pressure lowering drugs in preventing coronary heart disease (CHD) and stroke, and who should receive treatment.

**Design** Meta-analysis.

**Data source** Medline (1966-2007).

**Study selection** Randomised trials of blood pressure lowering drugs recording CHD events and strokes. 108 trials studied differences in blood pressure between

points) in preventing CHD events and strokes, with the exception that calcium channel blockers had a greater preventive effect on stroke (relative risk 0.92, 95% confidence interval 0.85 to 0.98). The percentage reductions in CHD events and stroke were similar in people with and without cardiovascular disease and regardless of blood pressure before treatment (down to 110 mm Hg systolic and 70 mm Hg diastolic). Combining our results with those from two other studies (the meta-




**Extra protective effect of β blockers in people with CHD history**

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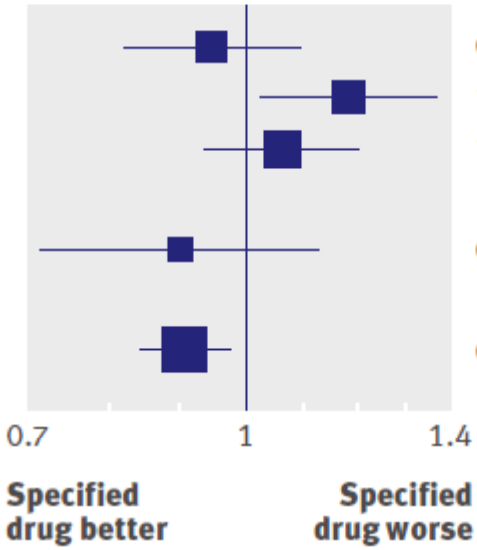
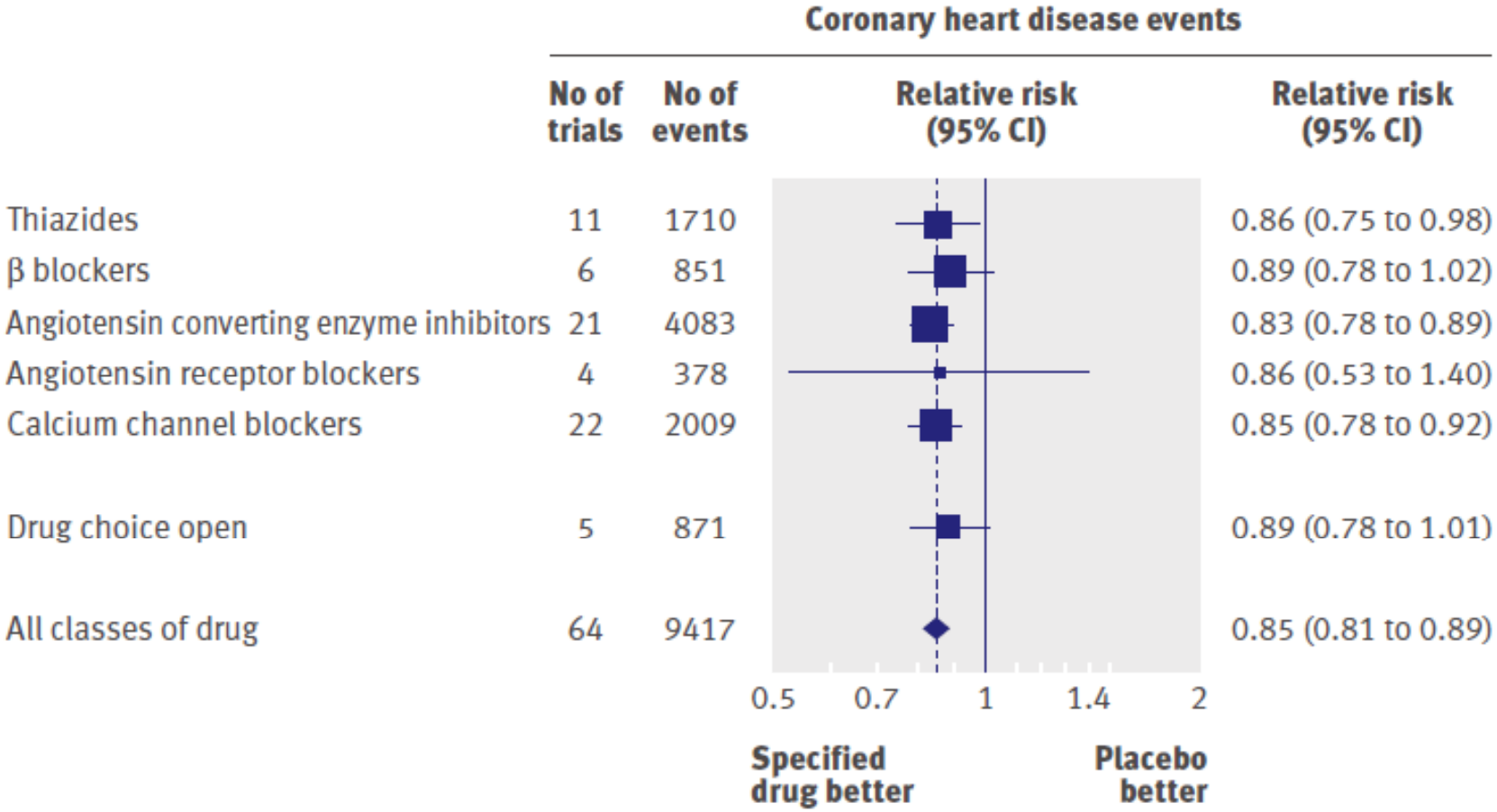
| | Blood pressure difference (mm Hg) | | Strokes | | | |
|---|---|---|---|---|---|---|
| | Systolic | Diastolic | No of trials | No of events | Relative risk (95% CI) | Relative risk (95% CI) |
| Thiazides *v* any other | -1.4 | 0.2 | 15 | 2255 | | 0.94 (0.82 to 1.09) |
| β blockers *v* any other | 1.4 | 0.6 | 13 | 2004 | | 1.18 (1.03 to 1.36) |
| Angiotensin converting enzyme inhibitors *v* any other | 0.9 | 0.4 | 17 | 2951 | | 1.06 (0.94 to 1.20) |
| Angiotensin receptor blockers *v* any other | -0.4 | 0.1 | 7 | 1643 | | 0.90 (0.71 to 1.13) |
| Calcium channel blockers *v* any other | -0.4 | -0.9 | 25 | 4981 | | 0.91 (0.84 to 0.98) |




**Minor additional effect of CCBs in preventing stroke**

*BMJ* 2009;338:b1665




**두 가지 경우를 제외하면**
**고혈압치료제의 심혈관질환 예방효과는 혈압 감소 정도와 비례한다.**

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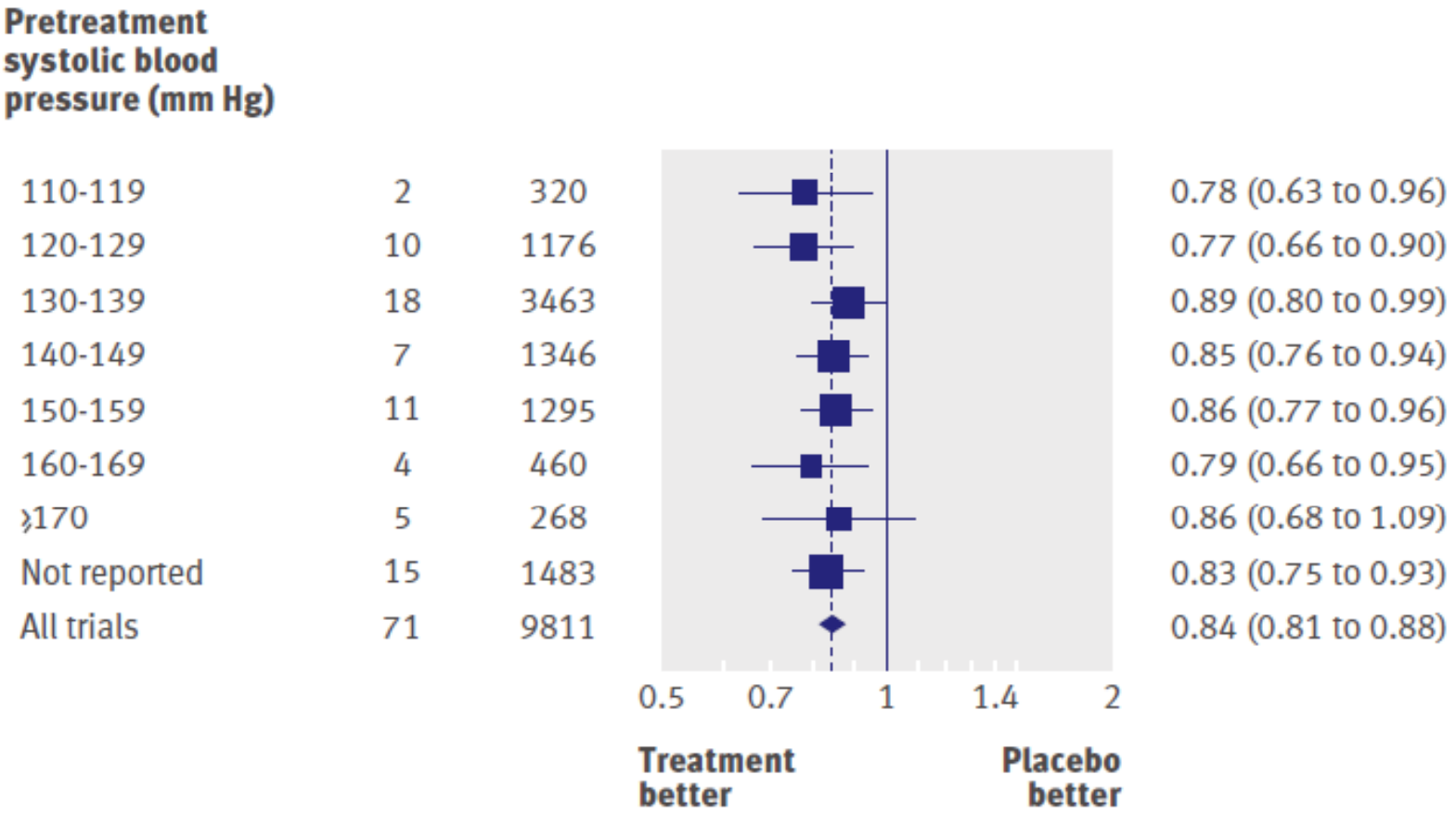


**고혈압치료제의 심혈관질환 예방효과는 치료전 혈압수준과 무관하다.**

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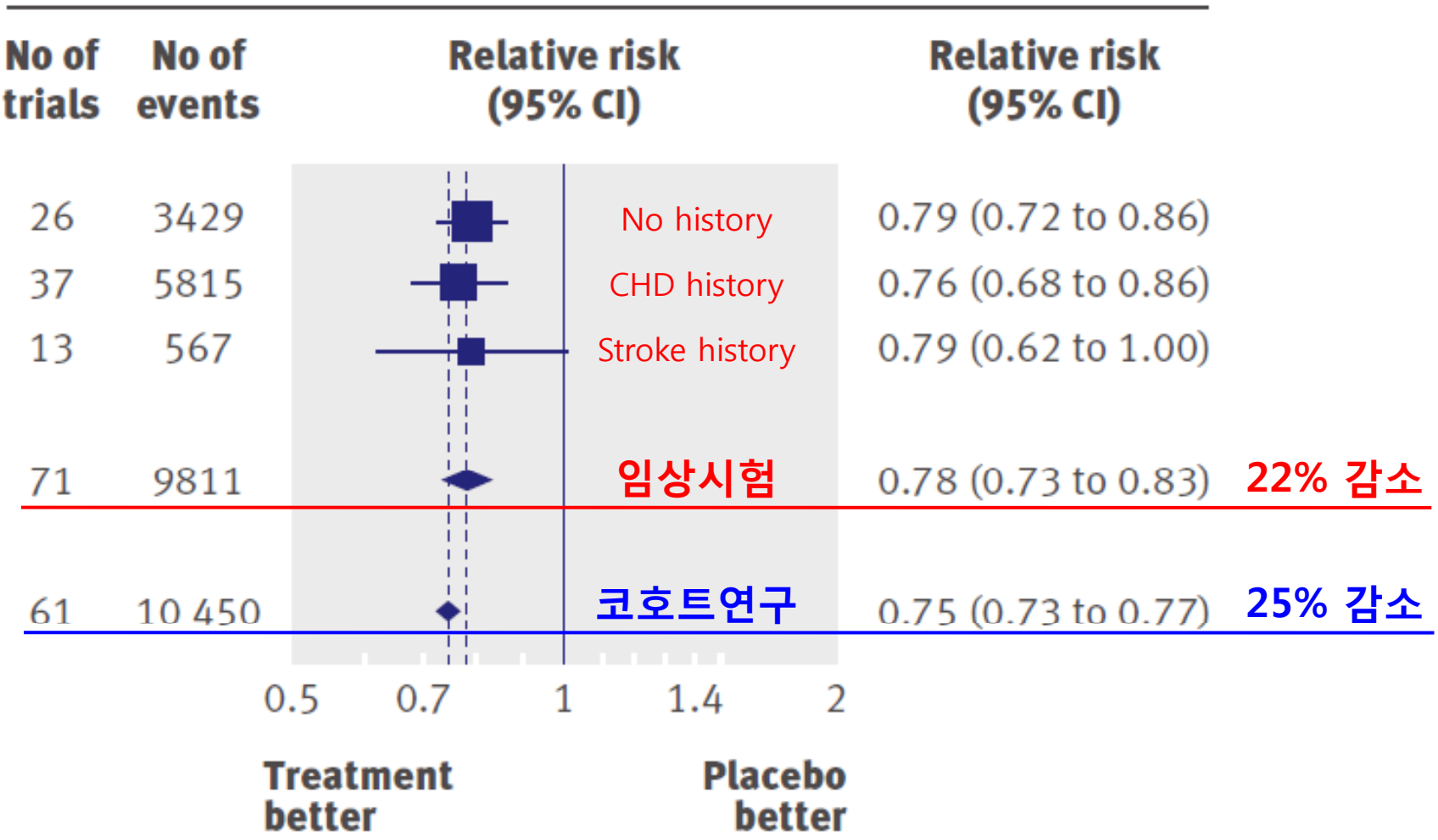
## Coronary heart disease events (SBP/DBP 10/5 mmHg↓)




**CHD reduction due to lowered BP in clinical trials**
**= CHD reduction related to lower BP in cohort studies**

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# 임상시험의 특성 (1)

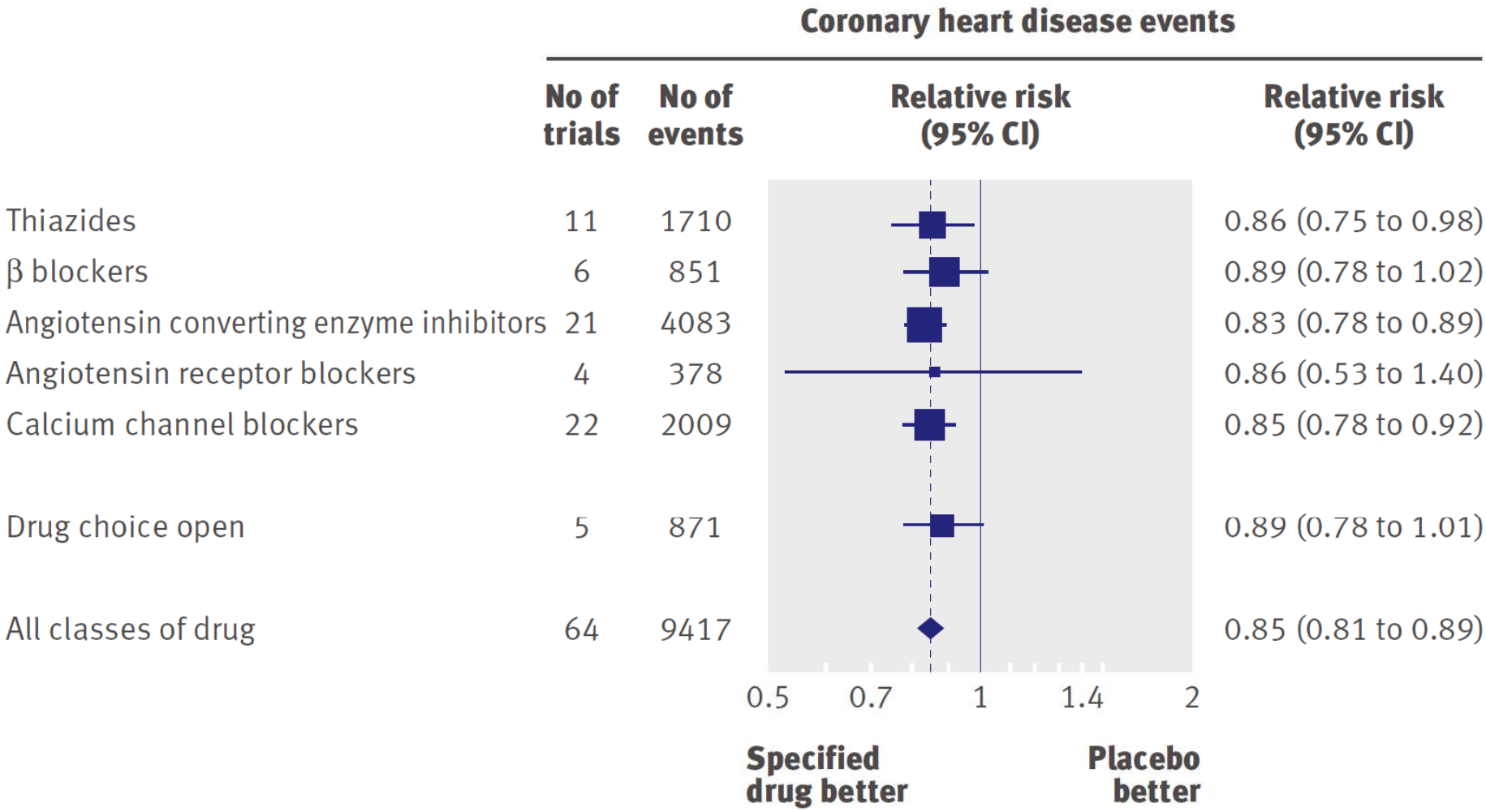
- Highly-selective homogeneous population
- Follow pre-determined strict protocol
  - 원인-결과 관계에 대한 가장 명확한 근거 제공
  - 결과의 일반화에는 제한점
  - 사전 정의된 가설 이외로 확대 해석에 주의

# 임상시험의 특성 (2)

- 임상시험들이 서로 다른 결과를 제시하기도 함

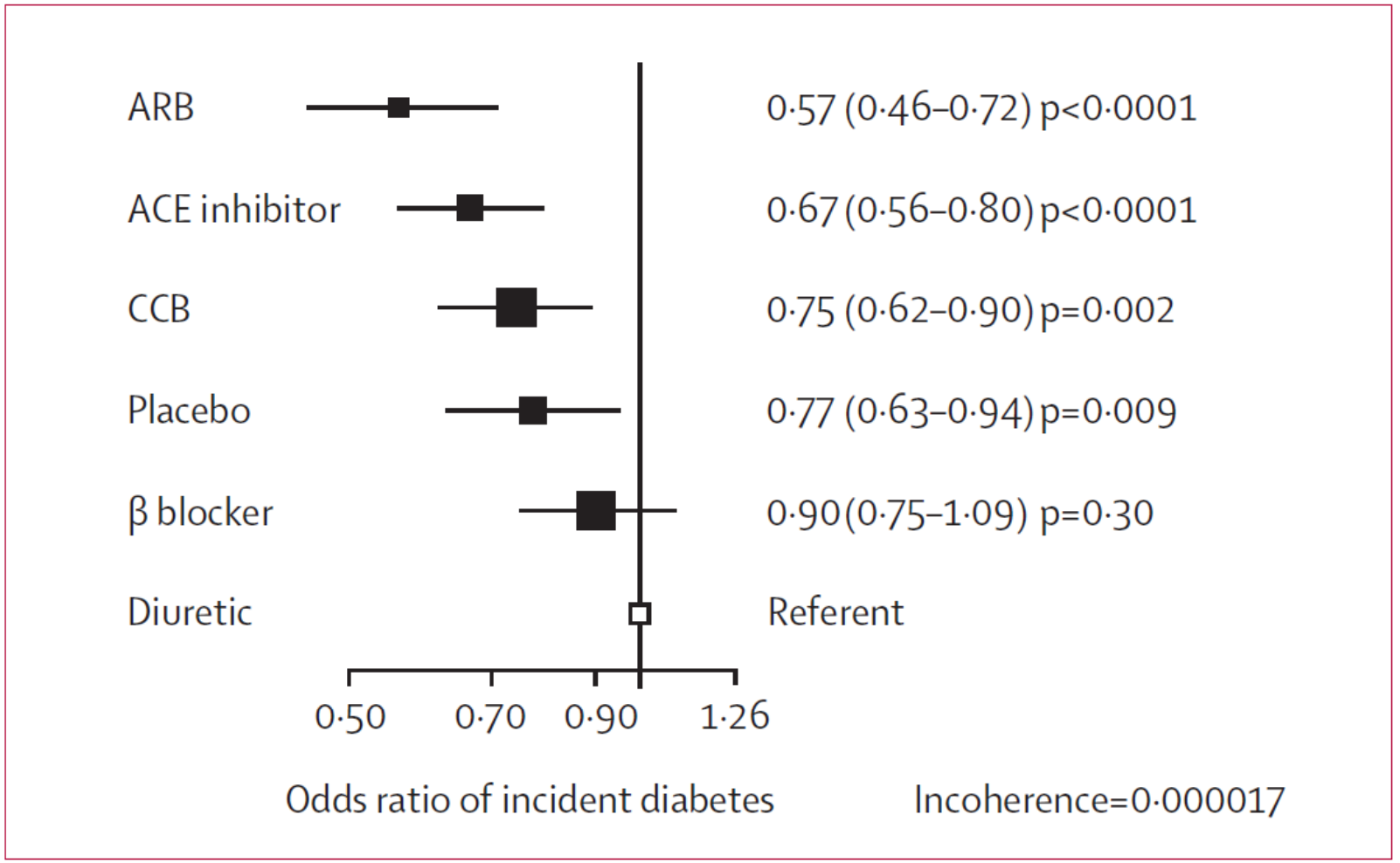
- Meta-analysis of clinical trials
  - 여러 임상시험 결과들을 종합하여 summary estimate 산출 가능
  - 비교적 유사한 결과들을 통합하는 데에는 매우 유용
  - 차이가 큰 연구결과들을 통합하는 데에는 부적절

# 유사한 연구결과의 메타분석




*BMJ* 2009;338:b1665

# 차이가 큰 연구결과의 메타분석




*Lancet* 2007; 369: 201–07

# 임상시험의 특성 (3)

- **Provide direct evidence on causal relationships**
  - 고혈압치료제의 부가적 혈관보호효과 평가에서도 임상시험은 중요함

- **Do not provide information regarding underlying biological mechanism**
  - 부가적 혈관보호효과가 입증되더라도 기전을 이해하기 위한 기초연구와 후속 임상연구가 필요함

  - 부가적 혈관보호효과를 outcomes으로 직접 평가하는 보다 많은 임상시험 결과가 필요

# *www.ClinicalTrials.gov*

| Project title | Drugs | Effects on |
|---|---|---|
| The Antihypertensives and Vascular, Endothelial and Cognitive Function Trial (AVEC) | ARB<br>ACEI<br>Diuretics | Vascular function<br>Endothelial function<br>Cognitive function |
| Antiproteinuric Effect of Valsartan and Lisinopril | Valsartan (ARB)<br>Lisinopril (ACEI) | Proteinuria |
| Antialbuminuric Effects of Valsartan and Lisinoprol | Valsartan (ARB)<br>Lisinopril (ACEI) | Albuminuria<br>Lt. ventricular mass index |
| COREG MR versus TOPROL-XL on reduction of Microalbuminuria in Patients with Hypertension and Microalbuminuria | Metoprolol (β blocker)<br>Carvedilol (α,β blocker)<br>Lisinopril (ACEI) | Microalbuminuria |
| Efficacy of Coreg CR and Lisinopril on Markers for Cardiovascular Functional and Structural Disease (DETECT) | Coreg CR (β blocker)<br>Lisinopril (ACEI) | Vascular function & structure: Rasmussen Disease Score |
| Cognitive/Cerebrovascular Consequences of HTN Treatment | Atenolol (β blocker)<br>Lisinopril (ACEI) | Brain blood flow<br>Cognitive function |
| The Effect of Amlodipine and Lisinopril on Retinal Auto-regulation in Type I Diabetes | Amlodipine (CCB)<br>Lisinopril (ACEI) | Retinal vessel diameter |
| ALLOGRAFT, A study to Evaluate the Renalprotective Effects on Losartan | Losartan (ARB) | Renal protective effects |
| Vascular function,Endothelin, and Inflammation in Pre-diabetic Obesity versus Lean Healthy Controls | Lisinopril (ACEI) with NSAIDS | Vascular function<br>Endothelin level<br>Inflammatory markers |

# 임상시험의 특성 (4)

- **관찰연구**와 **임상시험**의 비교
  - **Lower BP** and **CVD risk reduction** in cohort studies
  - **Lowered BP** and **CVD risk reduction** in clinical trials
  - 고혈압치료제의 부가적 혈관보호효과 유무 평가

- **임상시험의 후속연구**
  - 임상시험 동안 확보한 임상정보와 생체시료를 추가 분석
  - Intervention이 종료후에 코호트연구로 전환하여 추적 관찰

**To Understand Pleiotropic Effects of Antihypertensive Medications,**

**Clinical Trials are Required but Not Sufficient.**