

# 초청 강연 I

죽상동맥경화증의 지표 : 기능적, 형태적 지표

- 좌장 | KAIST 장근식
- 건양의대 배장호
- 표준(연) 김원식

# 죽상동맥경화증의 지표 :기능적, 형태적지표

배장호<sup>1</sup>, 김원식<sup>2</sup>

<sup>1</sup>건양의대, <sup>2</sup>표준과학연구원

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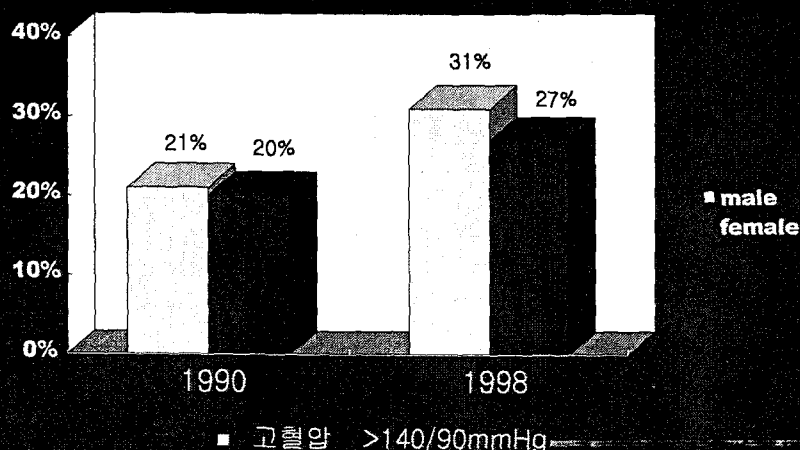
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- Introduction
- Arterial wall structure  
Technique  
Clinical significance
- Endothelial function  
Technique  
Clinical significance

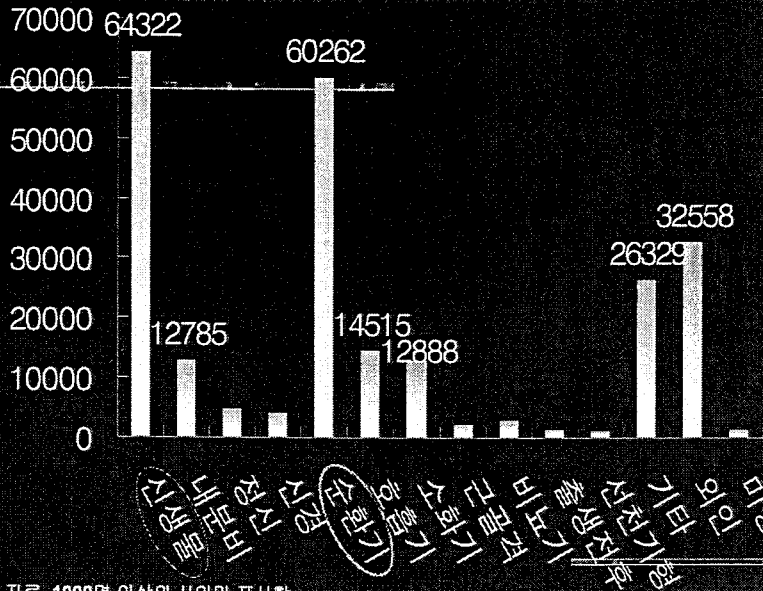
## 왜 죽상동맥경화증에 관심을?

- 죽상동맥 경화증의 위험(유발)인자의 급격한 증가.
- 죽상동맥경화증 관련질환의 높은 사인
- 순환기질환의 사망; 선진국 1위, 국내 2위

## 우리나라 고혈압의 유병률

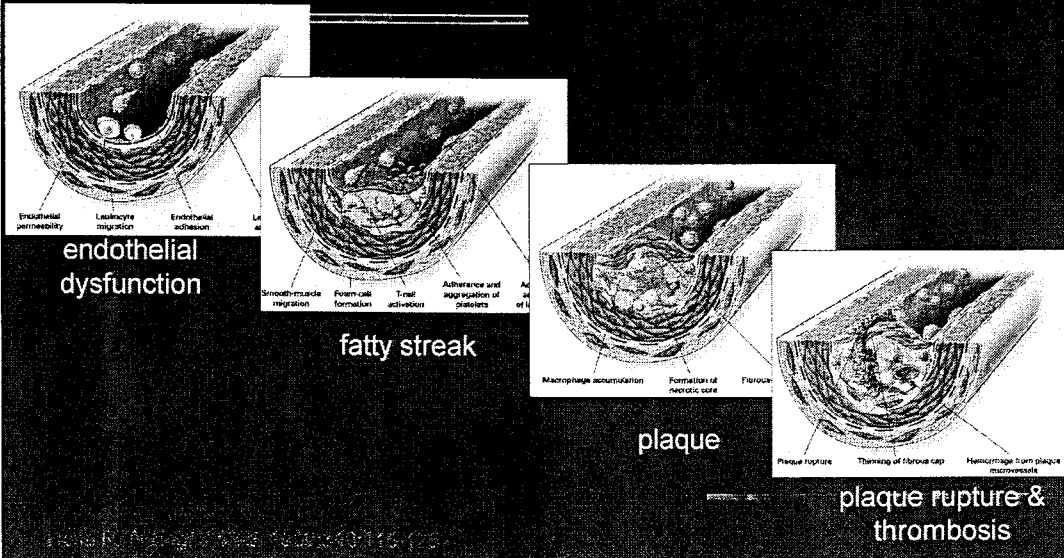


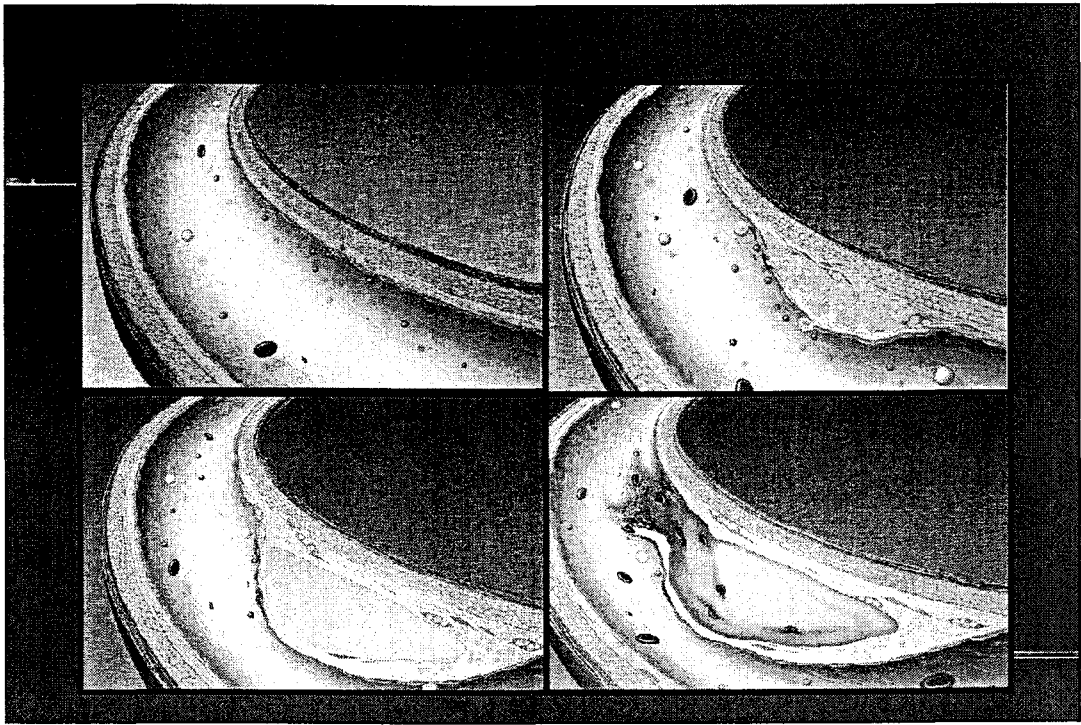
# 2003년 사인별 사망자수



2003 통계청 자료, 1000명 이상의 사인만 표시함.

# Pathophysiology of Atherosclerosis





대표적순환기  
질환의 종류

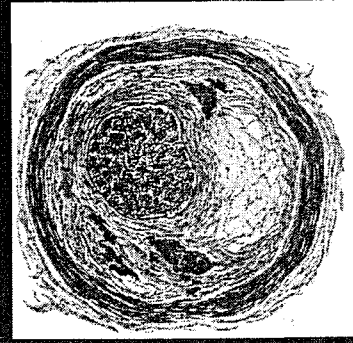
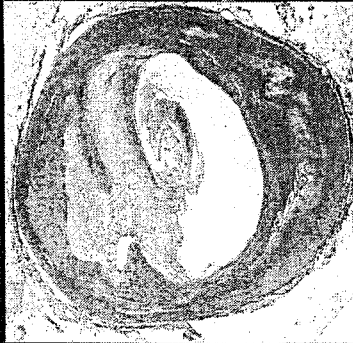
협심증

심근 경색증

심장혈관  
촬영



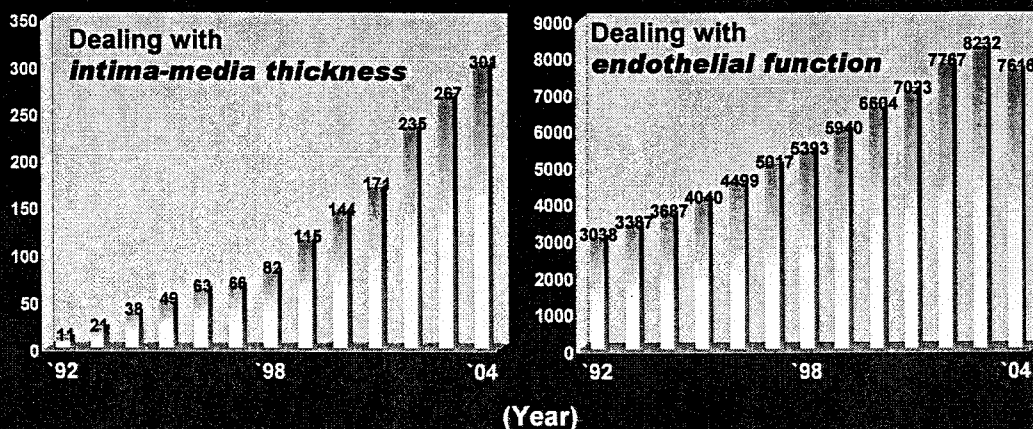
심장혈관  
조직소견



# Surrogates for Atherosclerosis

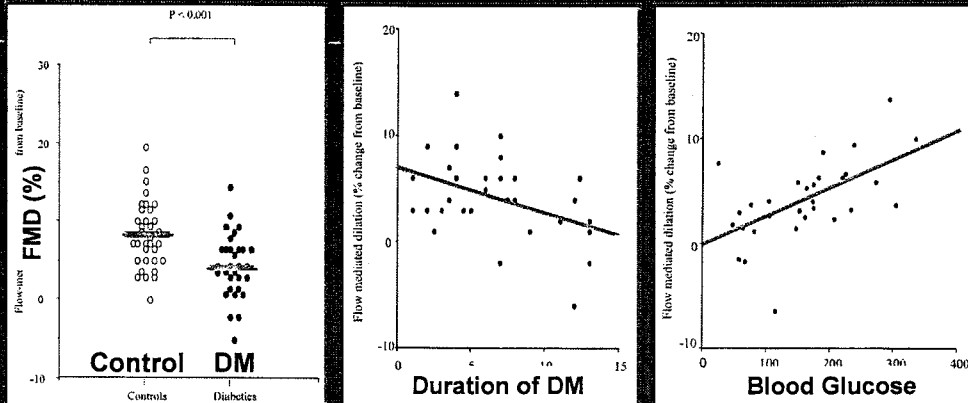
- Measures of endothelial function
- Measures of arterial wall structure
- Generalized measures of inflammation

## Numbers of publications in Pubmed



Searched at March 14, 2005

## Vascular Function and Carotid Intimal-Medial Thickness in Children With Insulin-Dependent Diabetes Mellitus



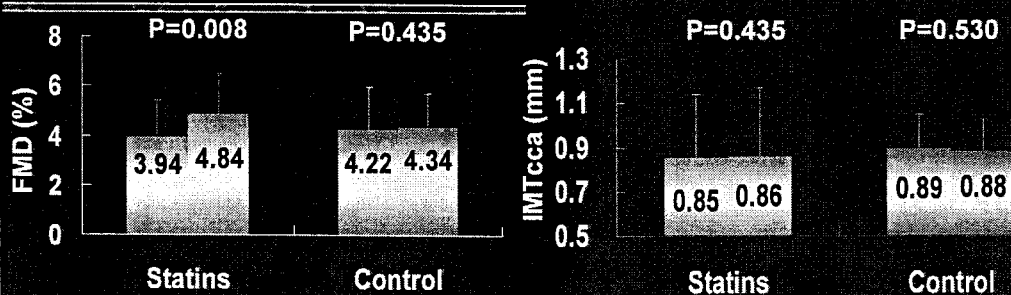
31 diabetic children (15 yrs old, 6.8 yrs DM duration), 35 age-matched healthy children

No difference in carotid IMT

Endothelial dysfunction precedes an increase in carotid IMT

Singh TP et al. J Am Coll Cardiol 2003;41:661-5

## Effects of low-dose atorvastatin on vascular responses in patients undergoing percutaneous coronary intervention with stenting



105 statin group and 100 control group undergoing stenting  
6 months follow up

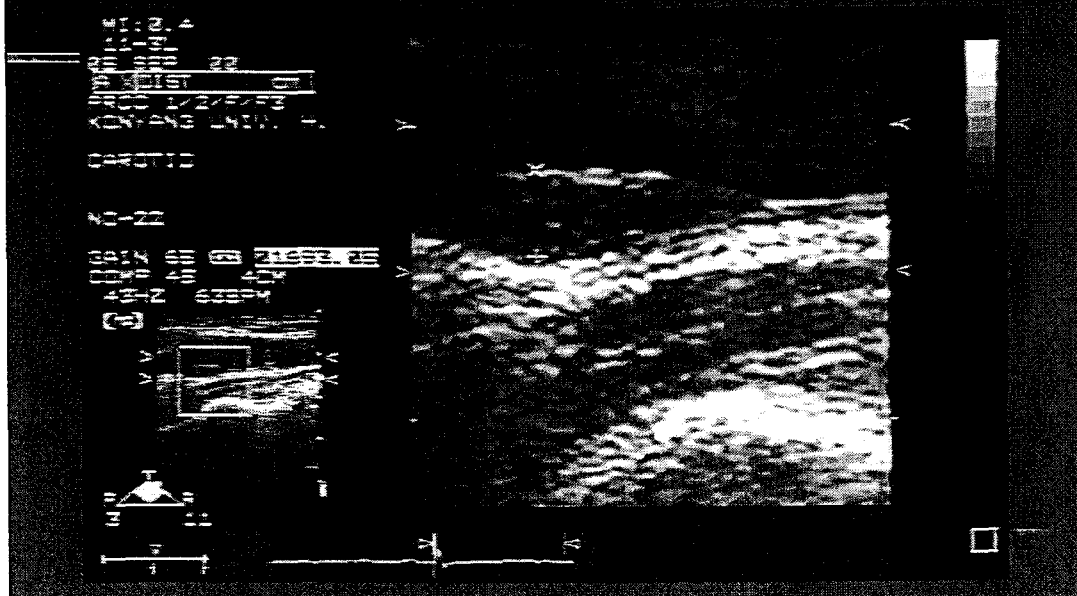
Statin improves endothelial dysfunction, not carotid IMT in patients undergoing stenting

Bae JH et al. J Cardiovasc Pharmacol Ther. 2004;9:185-92

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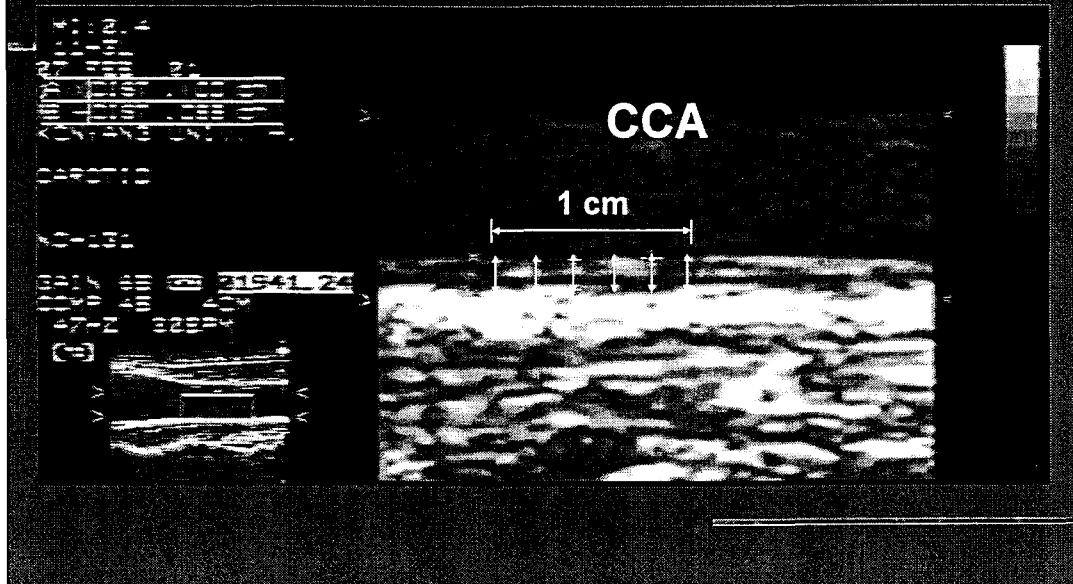
- Introduction
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  - Technique
  - Clinical significance
- Endothelial function
  - Technique
  - Clinical significance

## Example of carotid plaque

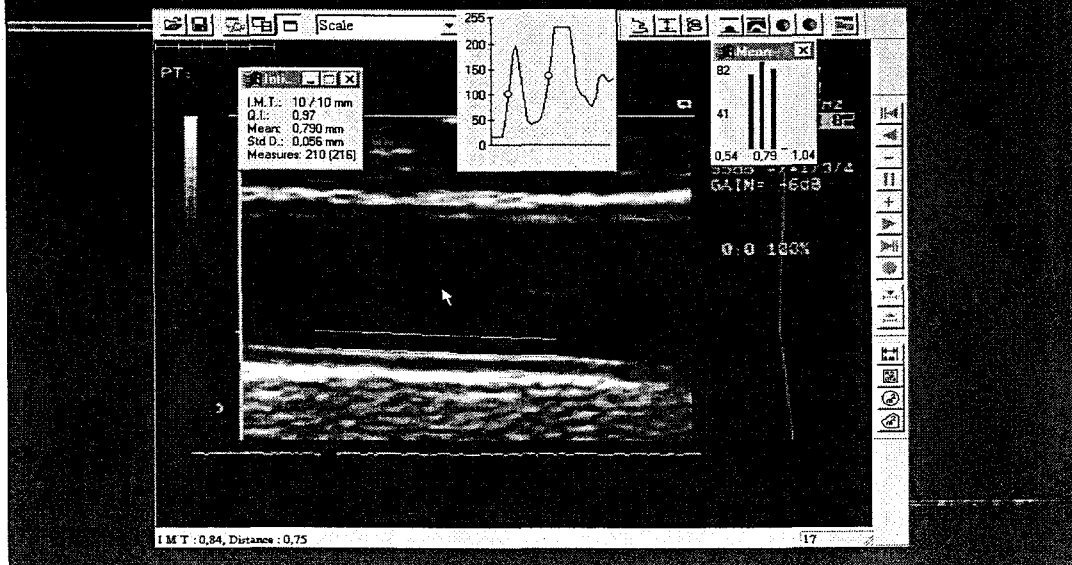




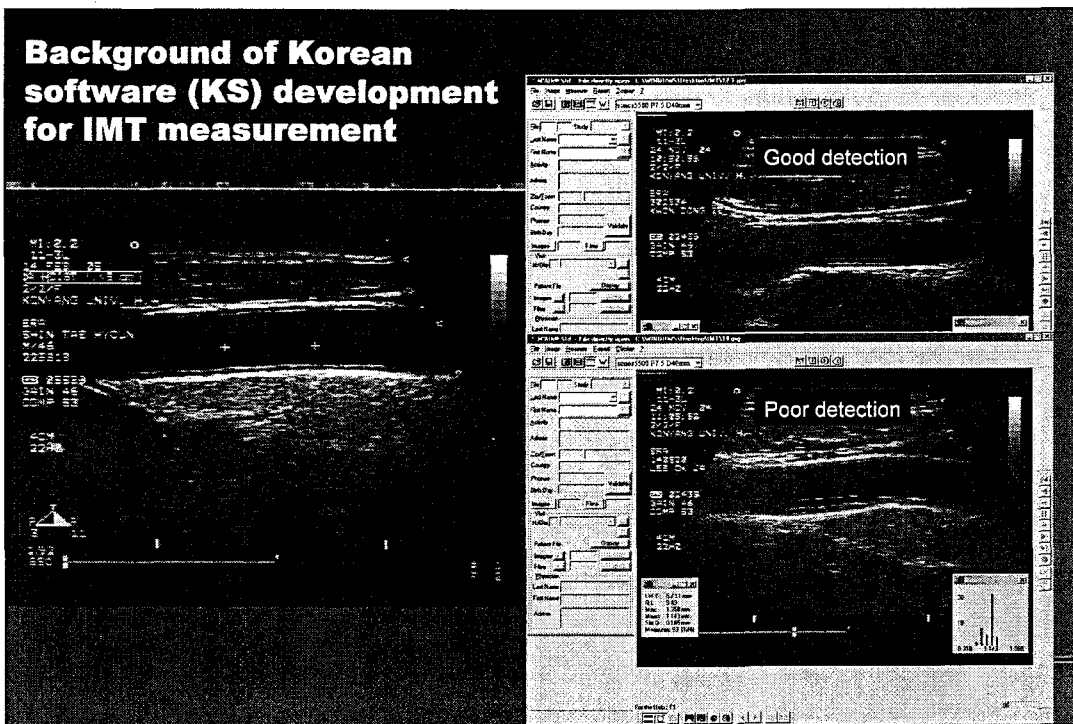
## Manual measurement of carotid IMT



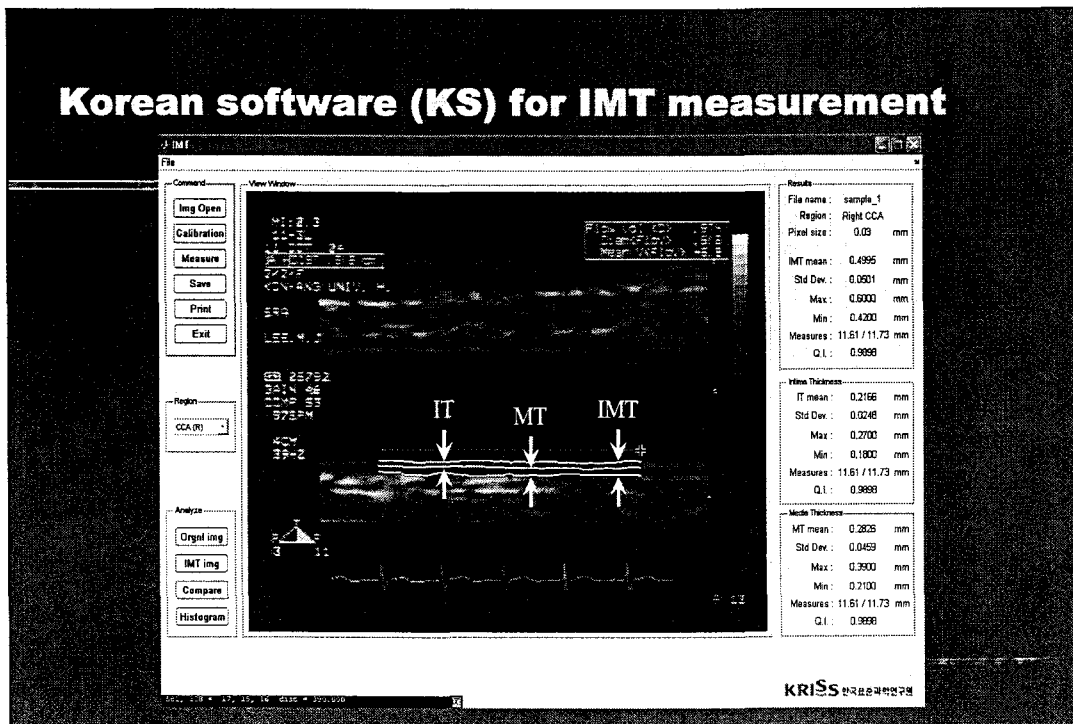
## IMT : Semi Automatic Measurement



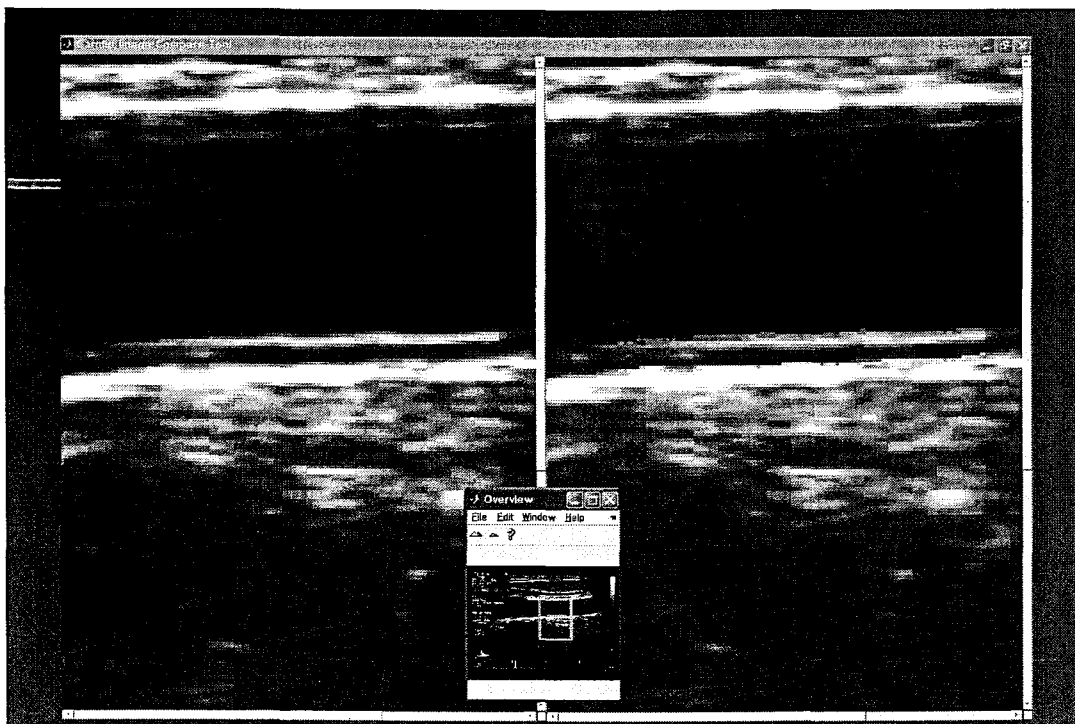
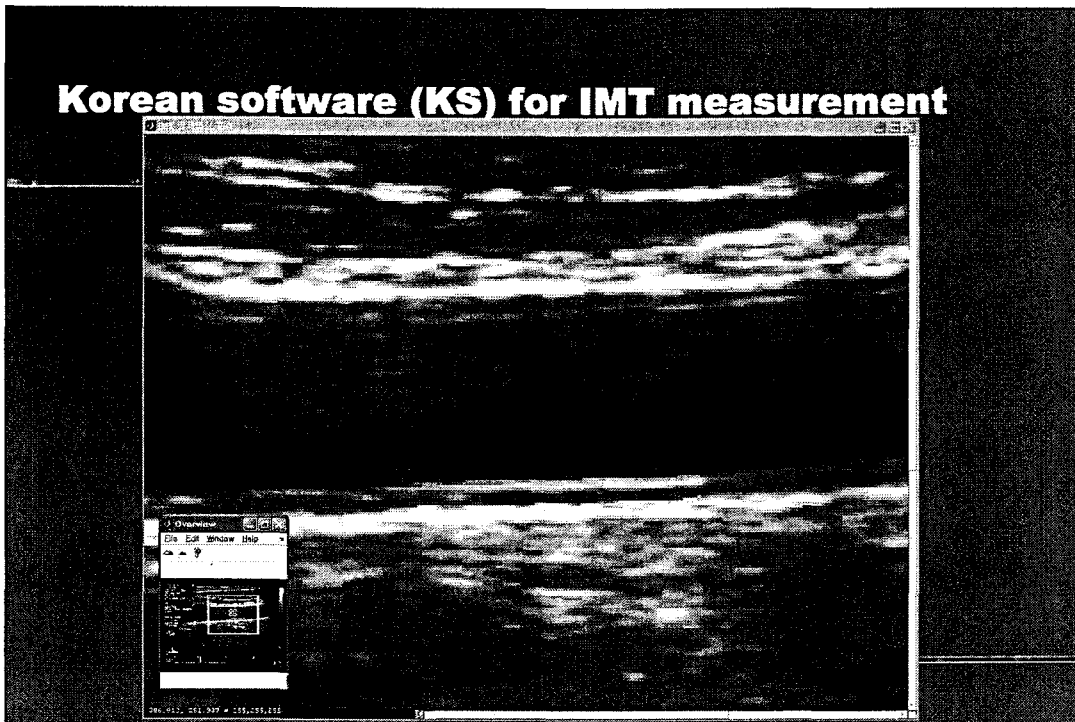
## Background of Korean software (KS) development for IMT measurement



## Korean software (KS) for IMT measurement



## Korean software (KS) for IMT measurement



## Korean software for IMT measurement

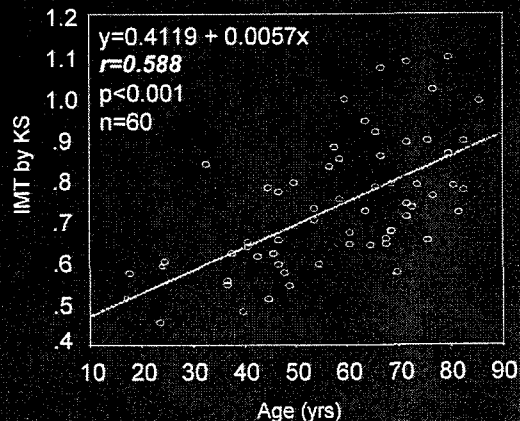
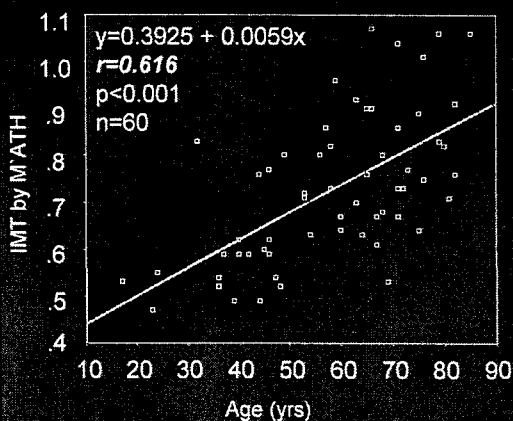
Number	60
Age	58.5±16
Sex (M/F)	
Height (cm)	
Weight (kg)	
BMI	
HBP	
DM	
Hyperlipidemia	
Smoking	
Diagnosis	
No atherosclerotic disease	
Patients with risk factors	
Atherosclerotic disease	
Total cholesterol (mg/dL)	183±42
Triglyceride (mg/dL)	140±77
HDL-cholesterol (mg/dL)	43.8±10.0
LDL-cholesterol (mg/dL)	106±30
Random glucose (mg/dL)	136±66
Uric acid (mg/dL)	4.63±1.98
BUN (mg/dL)	17.3±10.3
Creatinine (mg/dL)	1.03±0.58

Subjects: 60 consecutive subjects undergoing routine TTE

IMT: by M'ATH  
(blinded examiner)  
by Korean software  
(KRIS)

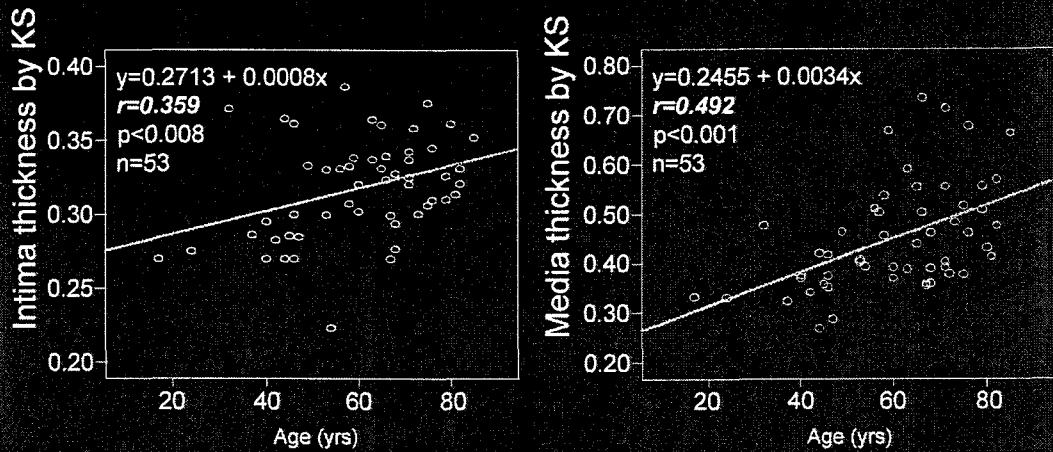
Compare Pearson correlation coefficients between age and the data of M'ATH and Korean software

## Korean software (KS) for IMT measurement



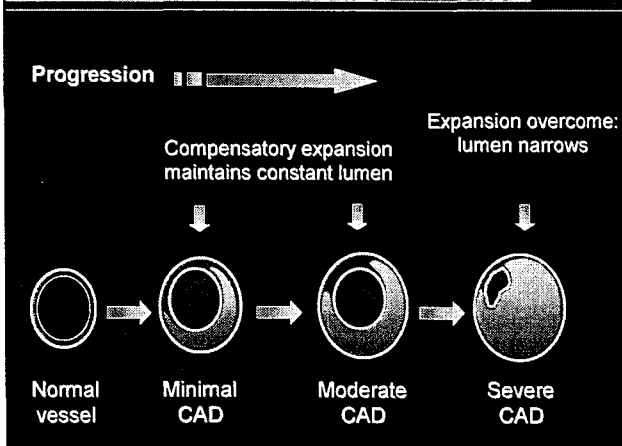
Comparison of Pearson correlation coefficients by both methods

## Korean software (KS) for IMT measurement



Correlation between age and intima or media thickness

## Measures of Arterial Wall

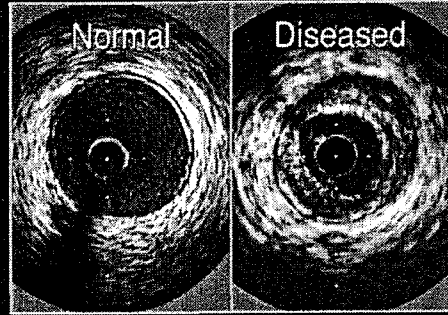


### ■ Angiography (QCA)

- Most early studies
- Invasive
- Glagov hypothesis  
→ angiographic change a late manifestation

## Measures of Arterial Wall

- Intra-vascular Ultrasound (IVUS)
  - Accurate impression of interior of coronaries
  - Can see atherosclerotic plaque
  - Invasive – only performed when CQA indicated
  - Only visualizes one artery at a time
  - Delineates thickness and echogenicity but not histology



## Measures of Arterial Wall

- Coronary Calcification Quantification
  - Electron Beam Computed Tomography
  - Expensive
  - Implications of increased calcification uncertain
  - Not a screening procedure

## Measures of Arterial Wall

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- **Magnetic Resonance Imaging**
    - Shows enormous promise
    - Can examine coronary or carotid arteries
    - Not refined for quantifying atherosclerosis
    - Non-invasive (relatively)
    - Expense precludes use as screening tool
- 

## Measures of Arterial Wall

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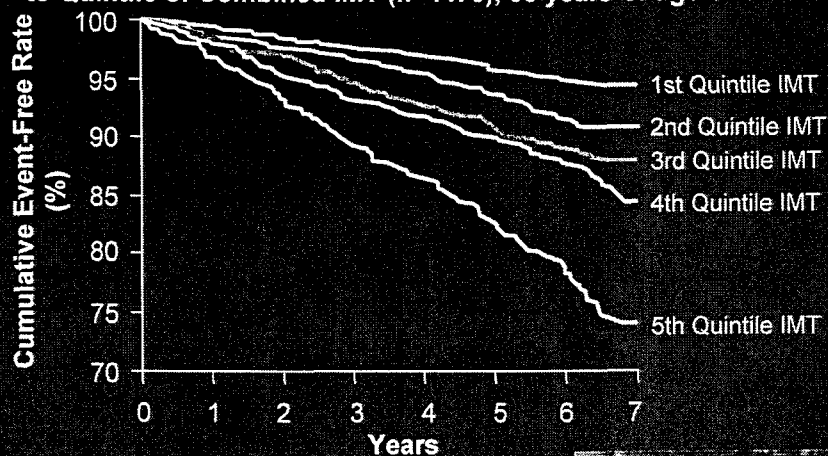
- **Intima Media Thickness (QIMT)**
    - Safe standardized and validated method
    - Direct assessment of disease
    - Reproducible
    - Easy to learn
    - Relatively inexpensive
-

## Measures of Arterial Wall

CLAS (1994)	colestipol and niacin	IMT 1cm below bulb is reproducible and has correlation with CV events
MARS (1994)	lovastatin	confirmed above
PLAC II (1995)	pravastatin	established that the most reliable part to measure is the far wall of the common carotid

## Systemic Atherosclerosis: Carotid Disease as a Marker of CV Risk

Cumulative Event-Free Rates for MI or Stroke, According to Quintile of Combined IMT (n=4476), 65 years of age or older.



O'Leary et al. *N. Engl. J. Med.* 1999;340:14-22.



# Carotid IMT

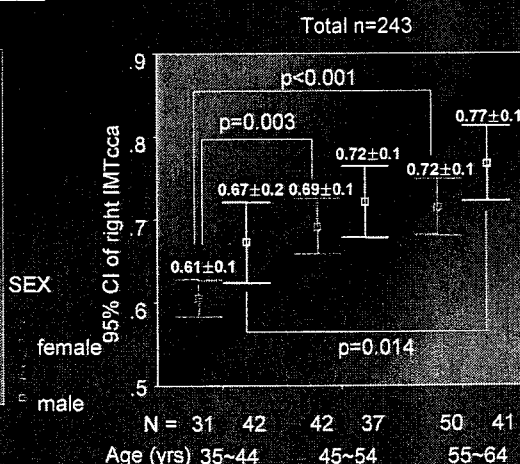
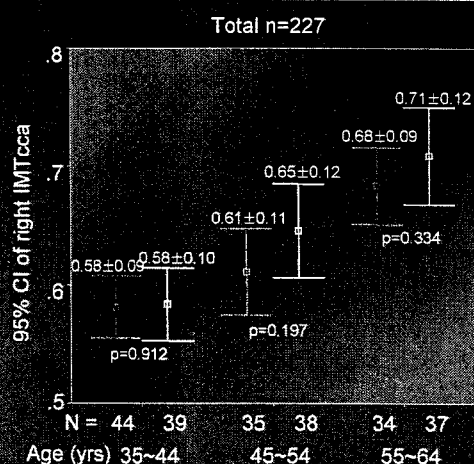
- AHA recommendation for evaluation of risk in primary prevention out of the various noninvasive imaging ; **Carotid intima-media thickness (IMT)**
- Carotid IMT
  - ; independent assessment of coronary risk
  - ; **independent predictor of coronary events in patients with CAD.**

Smith SC et al. AHA conference proceedings. 2000;101:111-116  
 Chan SY et al. J Am Coll Cardiol 2003;42:1037-43.

## Korean IMT Study

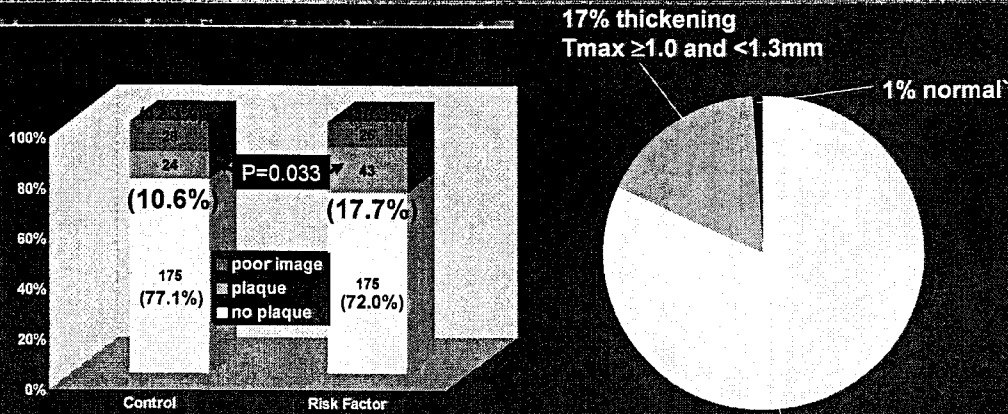
### Normal

### Risk Factor



Bae JH et al. Korean Society of Hypertension (supp) 2004:124-5

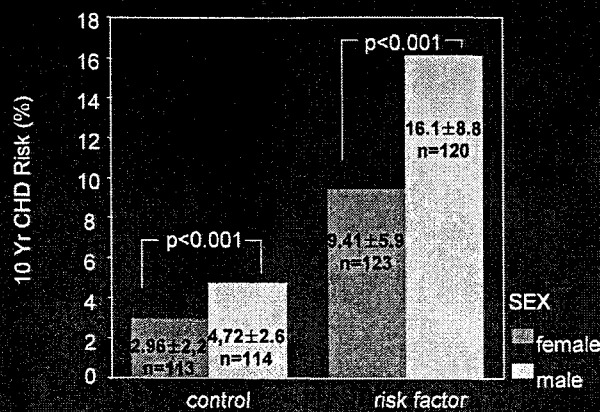
# Korean IMT Study Carotid artery plaque



Zanchetti et al, J Hypertens. 1998;16:949-61

Bae JH et al. Korean Society of Hypertension (supp) 2004;124-5

# Sex, Risk Factors, and 10 Year CHD Risk



Bae JH et al. Korean Society of Hypertension (supp) 2004;124-5

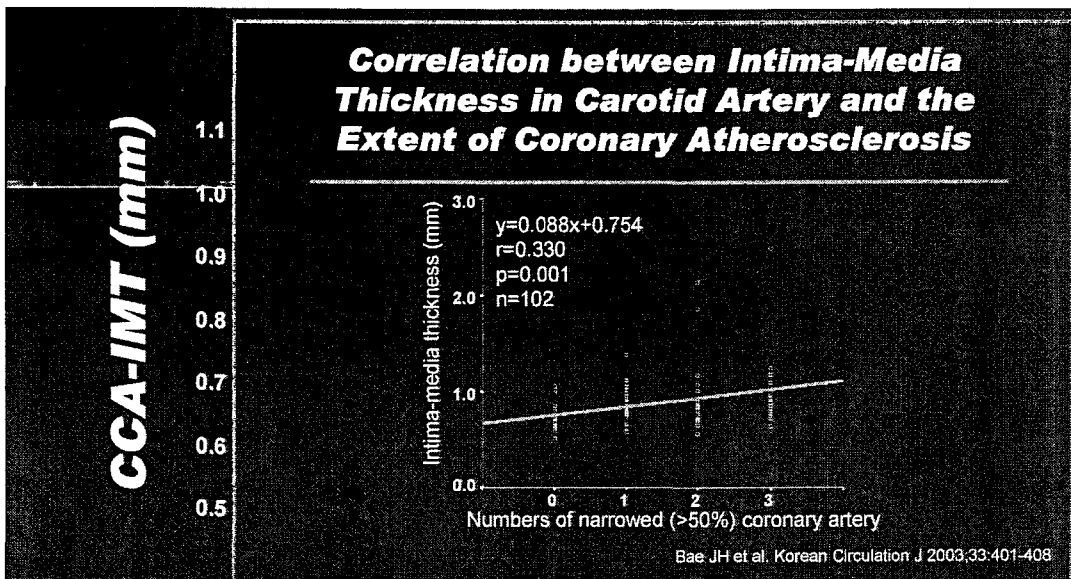
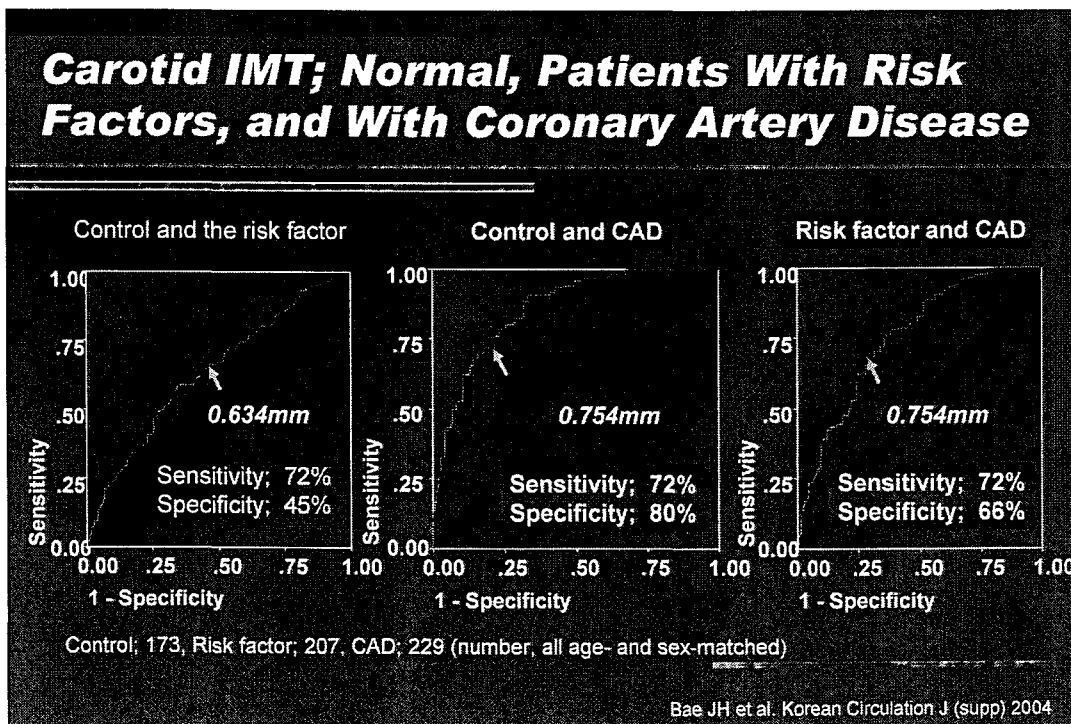
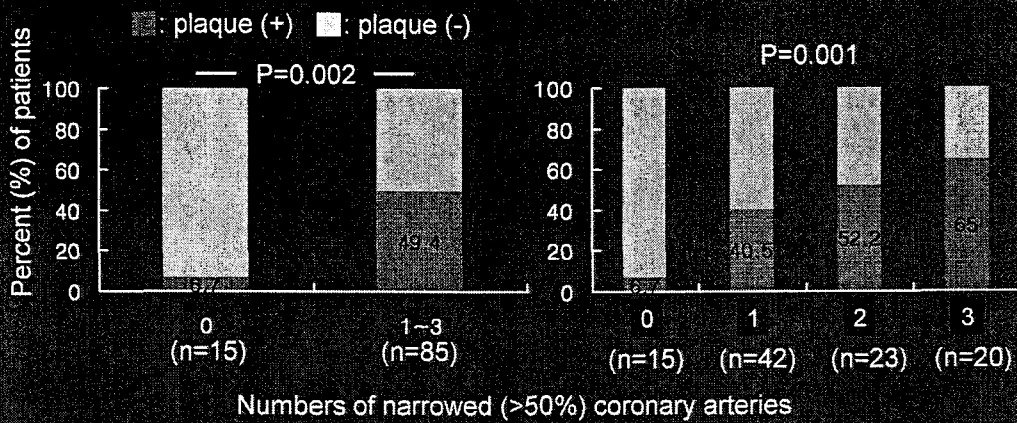


Figure. Comparison of intima-media thickness of the common carotid artery (CCA-IMT) among three groups. Data represent mean value.

Bae JH et al. Korean Circulation J (suppl) 2004

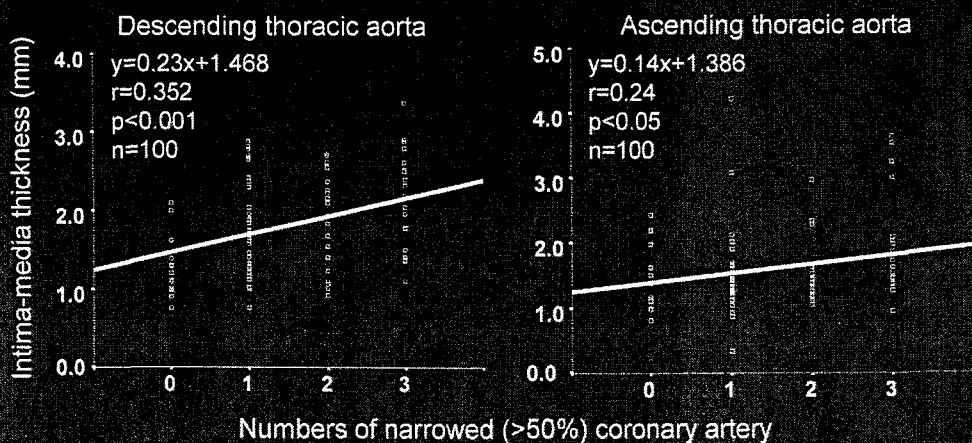


## Significance of the Intima-Media Thickness of the Thoracic Aorta in Patients With Coronary Atherosclerosis



Bae JH et al 2002 JACC, Suppl. Clinical Cardiology 2003;26:574

## Significance of the Intima-Media Thickness of the Thoracic Aorta in Patients With Coronary Atherosclerosis



Bae JH et al 2002 JACC, Suppl. Clinical Cardiology 2003;26:574

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    - Clinical significance
- 

## **Methods assessing endothelial function**

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### **Invasive**

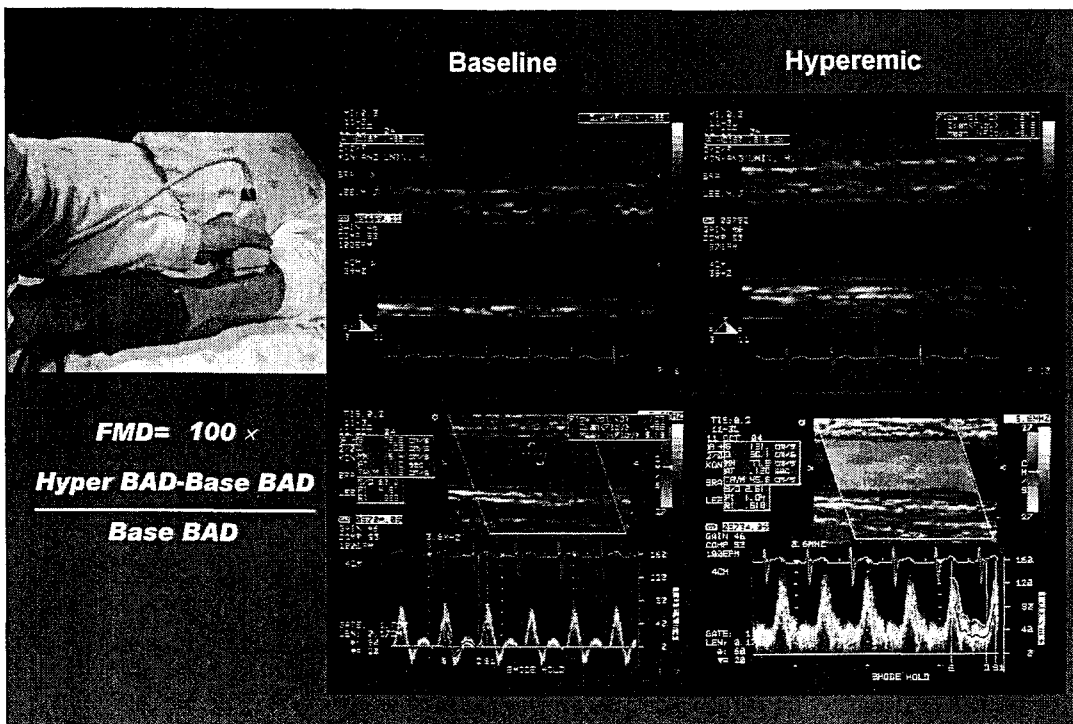
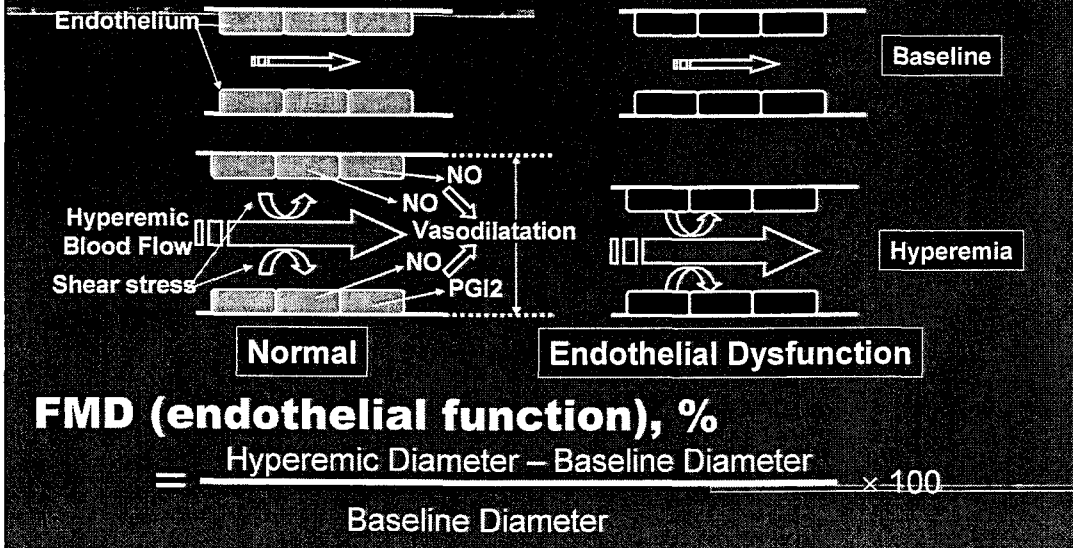
Coronary angiography using Doppler wire  
Strain gauge plethysmography

### **Noninvasive**

Flow-Mediated brachial artery Dilation  
*first introduced in 1992 by Dr. Celermajer.*

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## Basic principle of Flow-Mediated BA Dilation for measuring endothelial function



## 실제 FMD 측정 (동영상)

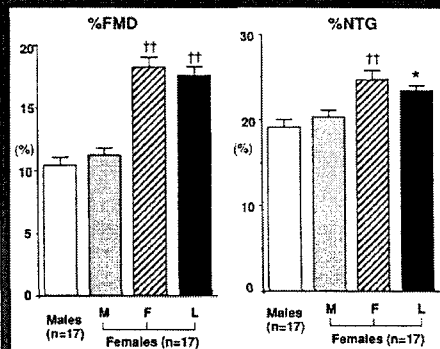
Measurement of  
Brachial Artery  
Vasoactivity

### ***Guidelines for FMD of the Brachial Artery (Subject preparation)***

- Overnight fasting (8~12 hrs)
- A quiet, temperature-controlled room
- Medicine withheld for at least four half-lives, if possible
- Consider the subject's menstrual cycle
  
- Affecting factors; temperature, food, drugs, sympathetic stimuli

Corretti MC et al. JACC 2002;39:257-65

## Menstrual Cycle on FMD



Phase	...	M	F	L
Age, y	24.8±0.6	25.1±0.8	...	...
Body mass index, kg/m <sup>2</sup>	22.4±0.4 <sup>†</sup>	20.5±0.5	...	...
Total cholesterol, mmol/L	4.37±0.19	4.45±0.17	4.50±0.17	4.22±0.19
HDL cholesterol, mmol/L	1.63±0.15	1.68±0.08	1.78±0.09	1.70±0.08
LDL cholesterol, mmol/L	2.35±0.15	2.63±0.11	2.49±0.13	2.26±0.13
Triglyceride, mmol/L	1.94±0.18 <sup>†</sup>	1.24±0.07	1.20±0.09	1.29±0.10
Estradiol, pmol/L	114.5±9.9	121.9±12.5	632.1±74.5 <sup>§</sup>	533.8±33.4 <sup>§</sup>
Progesterone, nmol/L	1.6±0.16	1.6±0.19	3.2±0.60	48.7±4.8 <sup>¶</sup>

*Endothelium-dependent vasodilatation varies during the menstrual cycle. The endogenous estradiol may be involved in this menstrual cycle-related vasodilatation.*

Gokce N et al. JACC 2002;40:761-5

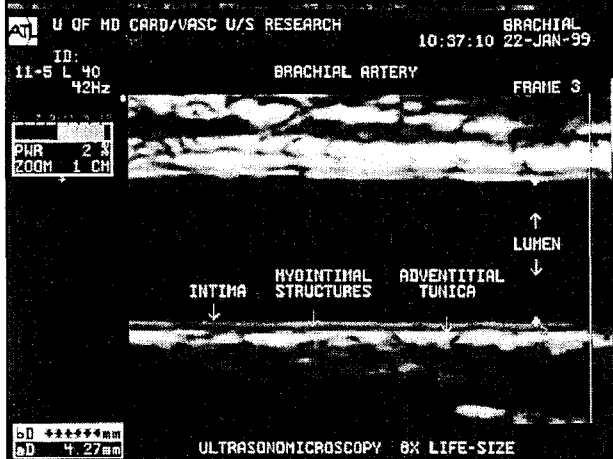
## Guidelines for FMD of the Brachial Artery (Equipment)

- Vascular software (2D-imaging, color and spectral Doppler, an internal ECG monitor) and a high-frequency vascular transducer)
- For sufficient resolution, a minimum frequency of 7 MHz
- Image resolution is enhanced with broad-band (7 to 12 MHz)

Corretti MC et al. JACC 2002;39:257-65



## Guidelines for FMD of the Brachial Artery (Image Acquisition)



Cross-sectional imaging  
 ; can not be used  
 ; inadequate lat wall definition  
 ; skew artifact

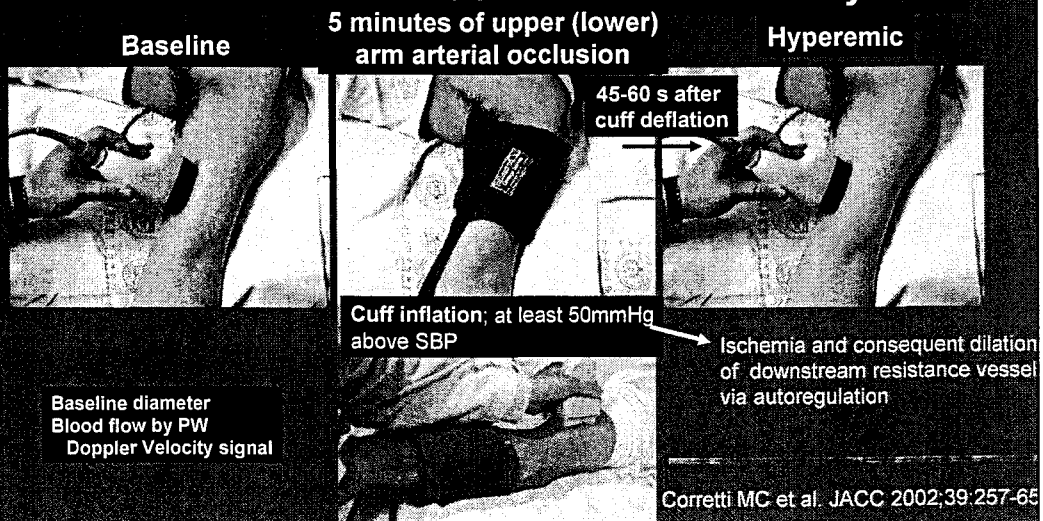
M mode and A mode (wall tracking)  
 ; more error owing to tracking drift

Anatomic landmarks  
 ; veins and fascial planes

Corretti MC et al. JACC 2002;39:257-65

## Guidelines for FMD of the Brachial Artery (Endothelium-dependent FMD)

■ To create a flow stimulus in the brachial artery



## Guidelines for FMD of the Brachial Artery (Endothelium-dependent FMD)

### ■ Measurement of BA diameter in hyperemic phase

5 minutes of upper (lower)  
arm arterial occlusion

Hyperemic

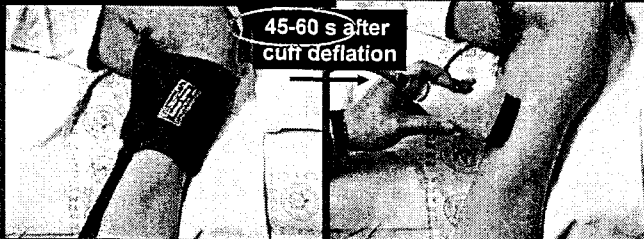
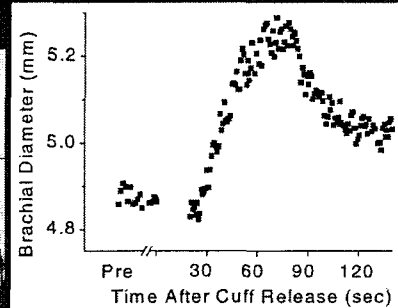


Image of BA in hyperemic phase;  
recording continuously  
from 30 s before to 2 min after deflation

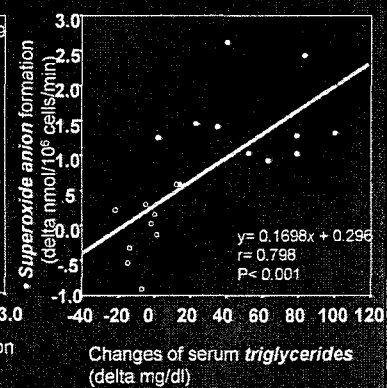
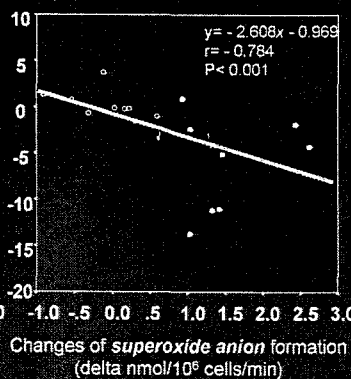
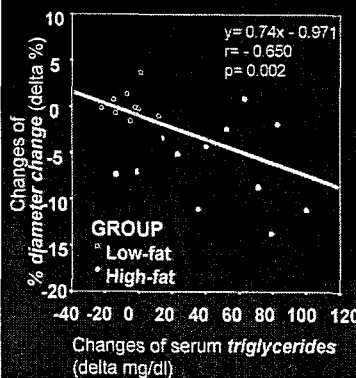
Why 45-60 s after cuff deflation



Most studies; 1 min after cuff deflation

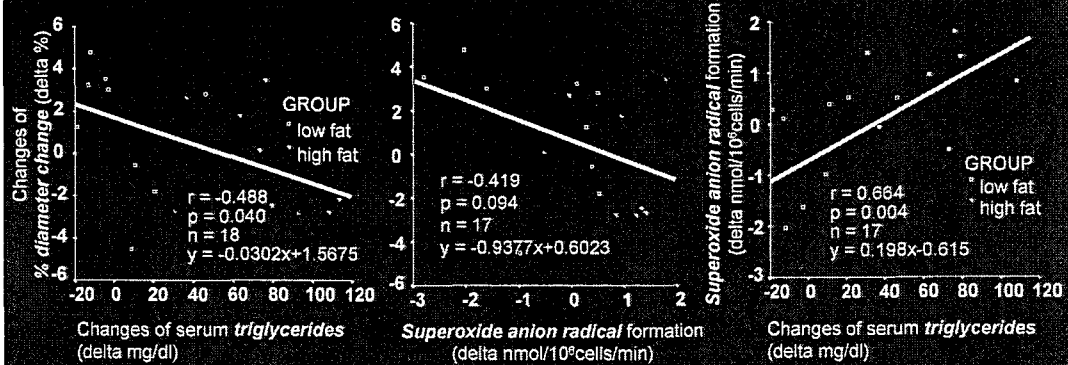
Corretti MC et al. JACC 2002;39:257-65

## Endothelial Function, Oxidative Stress, and Lipid



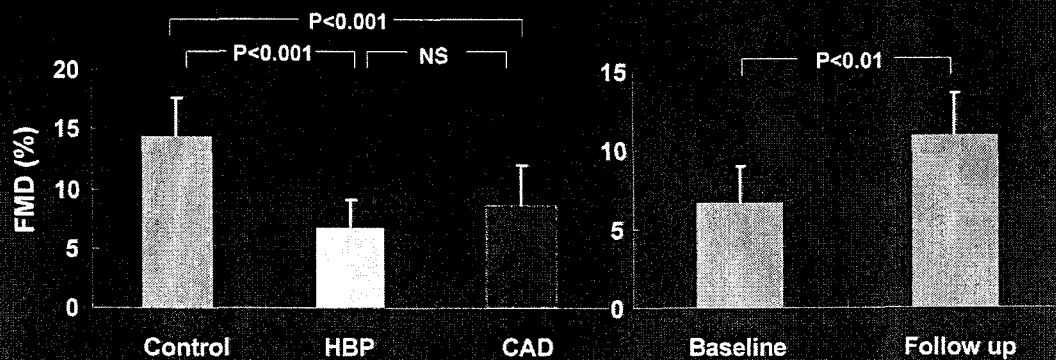
Bae JH et al. Atherosclerosis 2001;155:517-523

## Endothelial Function, Oxidative Stress, and Lipid in Patients with CAD

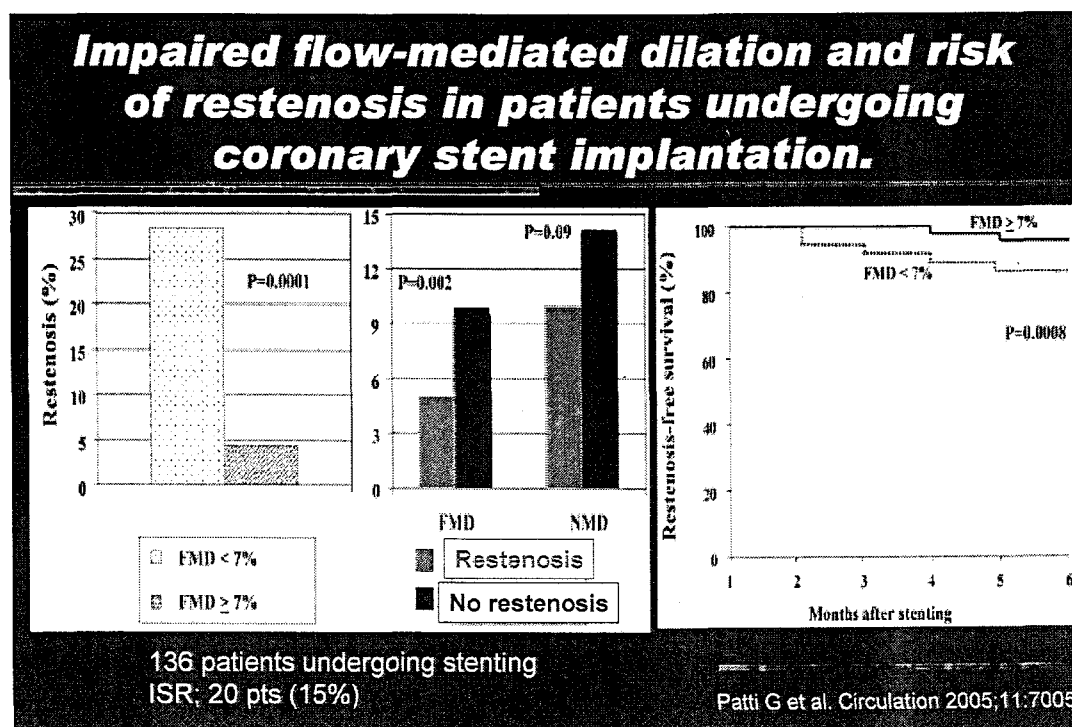
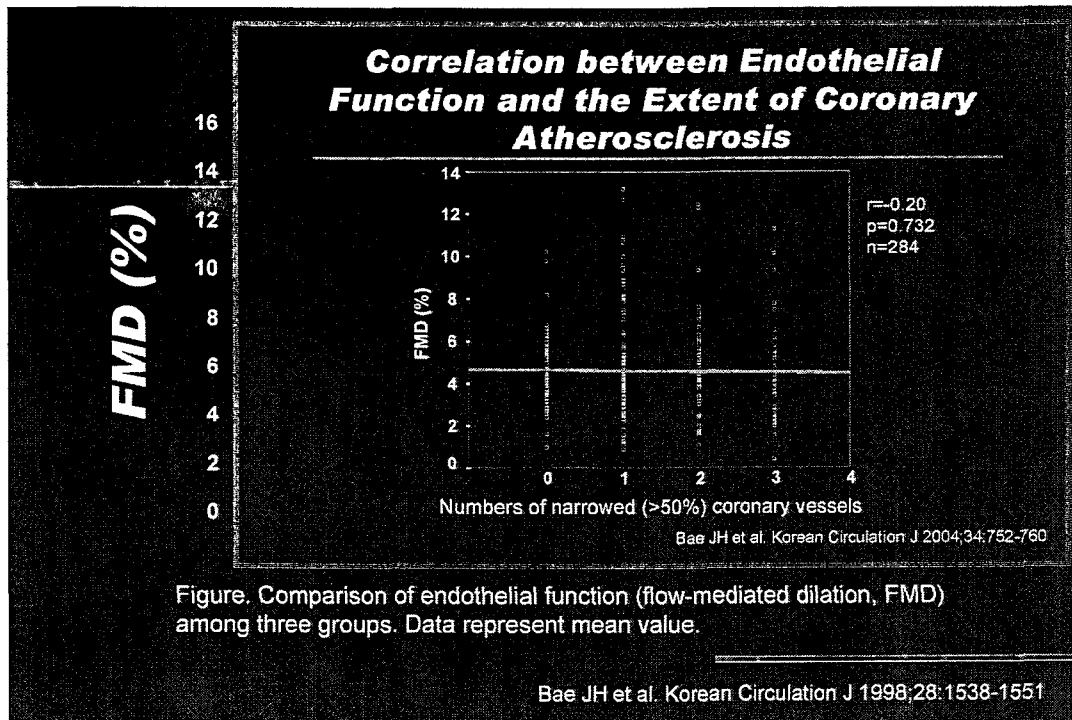


Bae JH et al. Atherosclerosis 2001;158:165-171

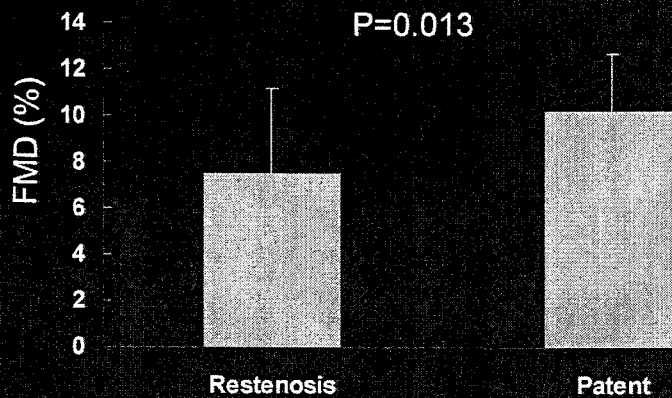
## Can We Restore the Endothelial Dysfunction in Patients with Essential Hypertension with Calcium Channel Blockers?



Bae JH et al. Korean Circulation J 2000;30:1010-6

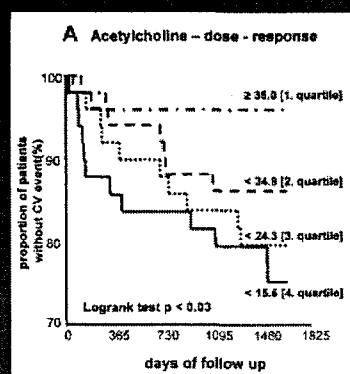
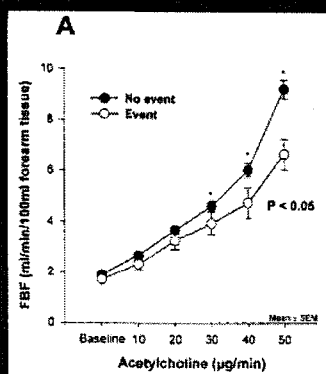


## The Difference of Endothelial Function According to the Presence of Restenosis in Patients Undergoing PCI



Bae JH et al. Korean Circulation J 2001;31:1117-1122

## Prognostic Value of Systemic Endothelial Dysfunction in Patients With Acute Coronary Syndromes



198 patients with ACS

Cardiovascular events  
cardiovascular death  
myocardial infarction  
ischemic stroke

Assessment of systemic vasoreactivity provides important prognostic information

Fichtischerer S et al. Circulation. 2004;110:1926-1932

## Impact of Left Ventricular Ejection Fraction on Endothelial Function in Patients With Coronary Artery Disease

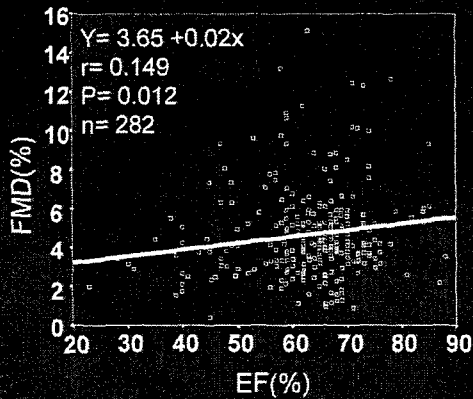


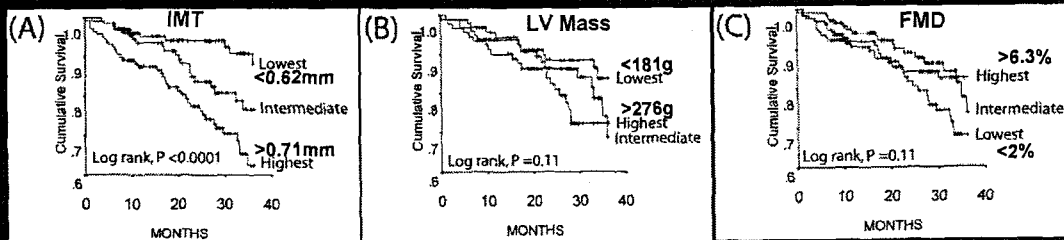
Table. Logistic regression analysis on FMD

Variables	B	P-value	Exp (B)
Age	0.49	0.058	1.63
Sex	-0.39	0.136	0.68
DM	0.33	0.325	1.39
MI	-0.53	0.146	0.59
Vessel No.	0.12	0.751	1.13
EF	0.83	0.043	2.31

Bae JH et al. Clin Cardiol 2004;27:333-3337

## The Relative Importance of Vascular Structure and Function in Predicting Cardiovascular Events

### Kaplan-Meier curves for event-free survival



CV events; death, MI, admission with ACS, stroke, revascularization

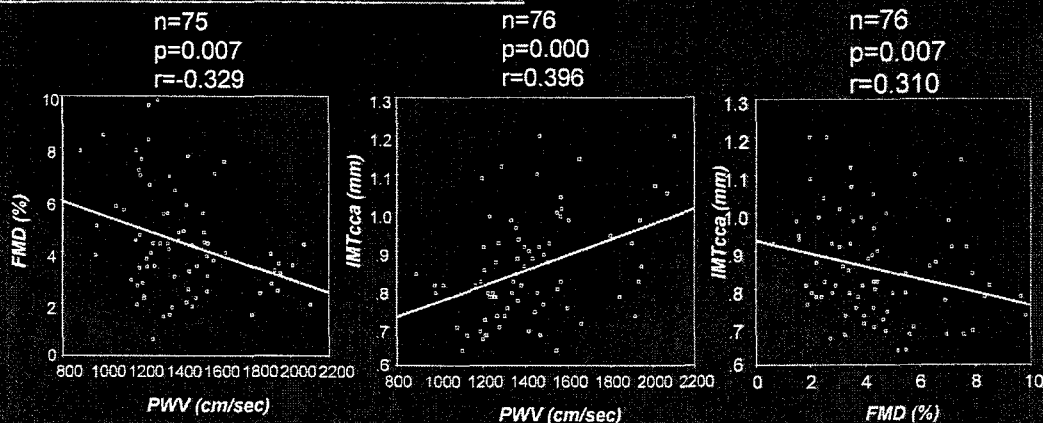
444 patients with CAD, dialysis, or multiple risk factors

Follow-up; 24 months

**IMT was the independent vascular factor for mortality, even in the subgroup with no CAD and low risk.**

Fathi R et al. J Am Coll Cardiol 2004;43:616-23

## FMD, IMT, and PWV



These are related to each other,  
the combination of these measurement will be of stronger clinical relevance

Bae JH et al. Korean Circulation J 2004;34:845-55

## In Conclusion

- FMD, IMT, and PWV are functional and structural surrogates of the atherosclerotic process.
- Limitations of FMD; variable reproducibility, influenced by exogenous factors.
- Future; need to reveal an association of improvement in response to treatment with improvement in prognosis