

심혈관질환의 위험요인을 가지고 있는 폐경 여성의 호르몬 치료

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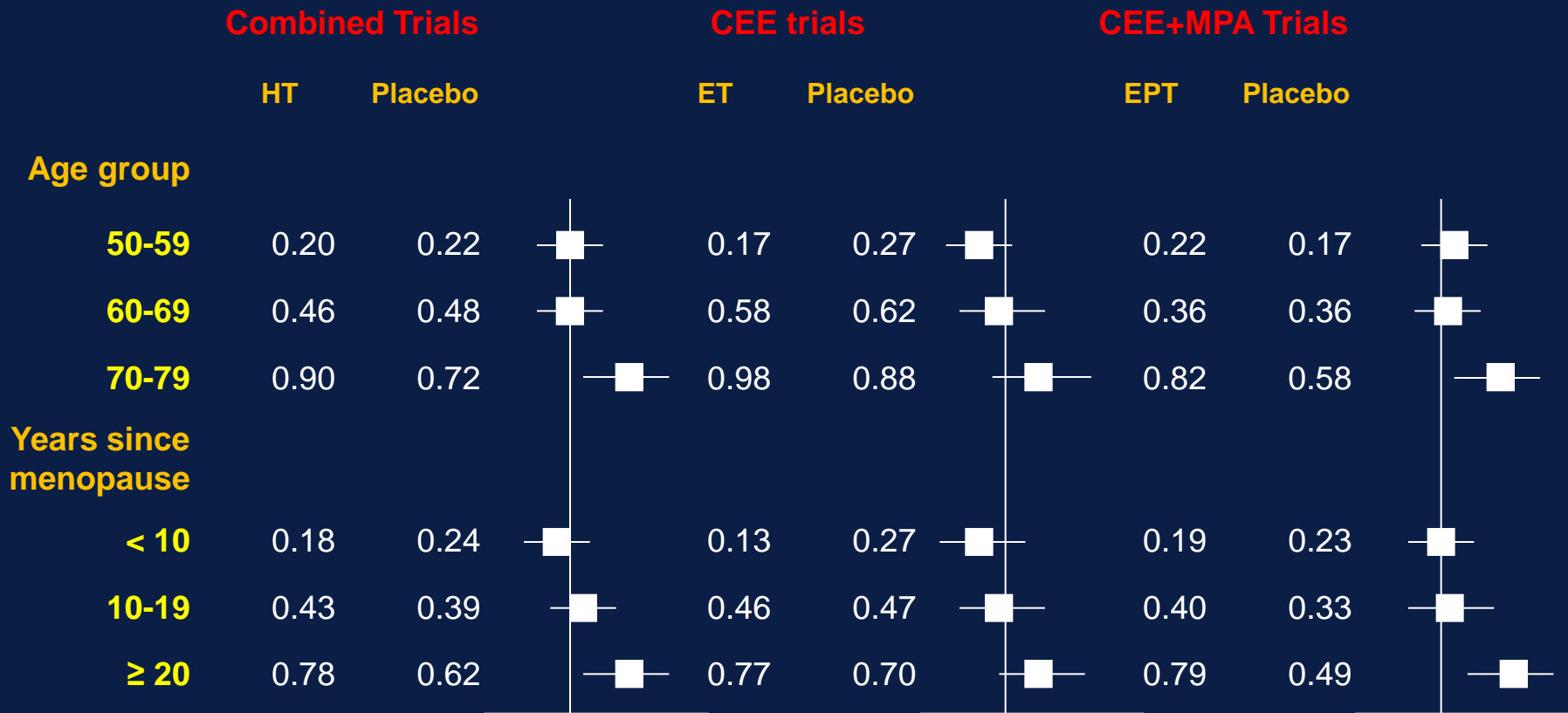
Women's Health Initiative study (2002)



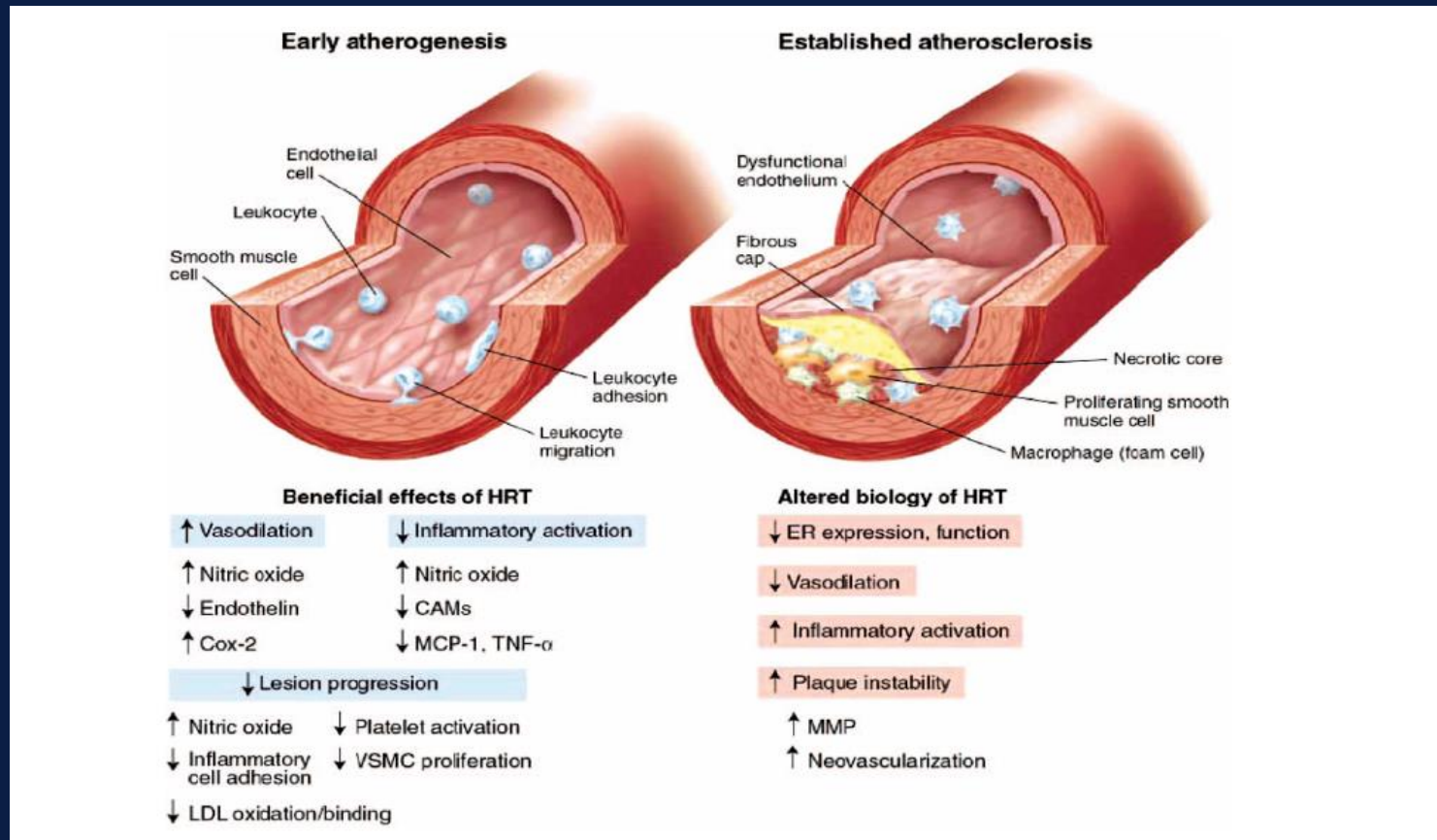
- Labeling revisions for both Prempro® & Premarin® (US FDA)
 - Boxed warning highlights the increased risk for **heart disease, myocardial infarction, stroke, and breast cancer**.
- 2011 Update guideline from the American Heart Association
 - HT is classified as a class III intervention
 - Not useful/effective and may be harmful



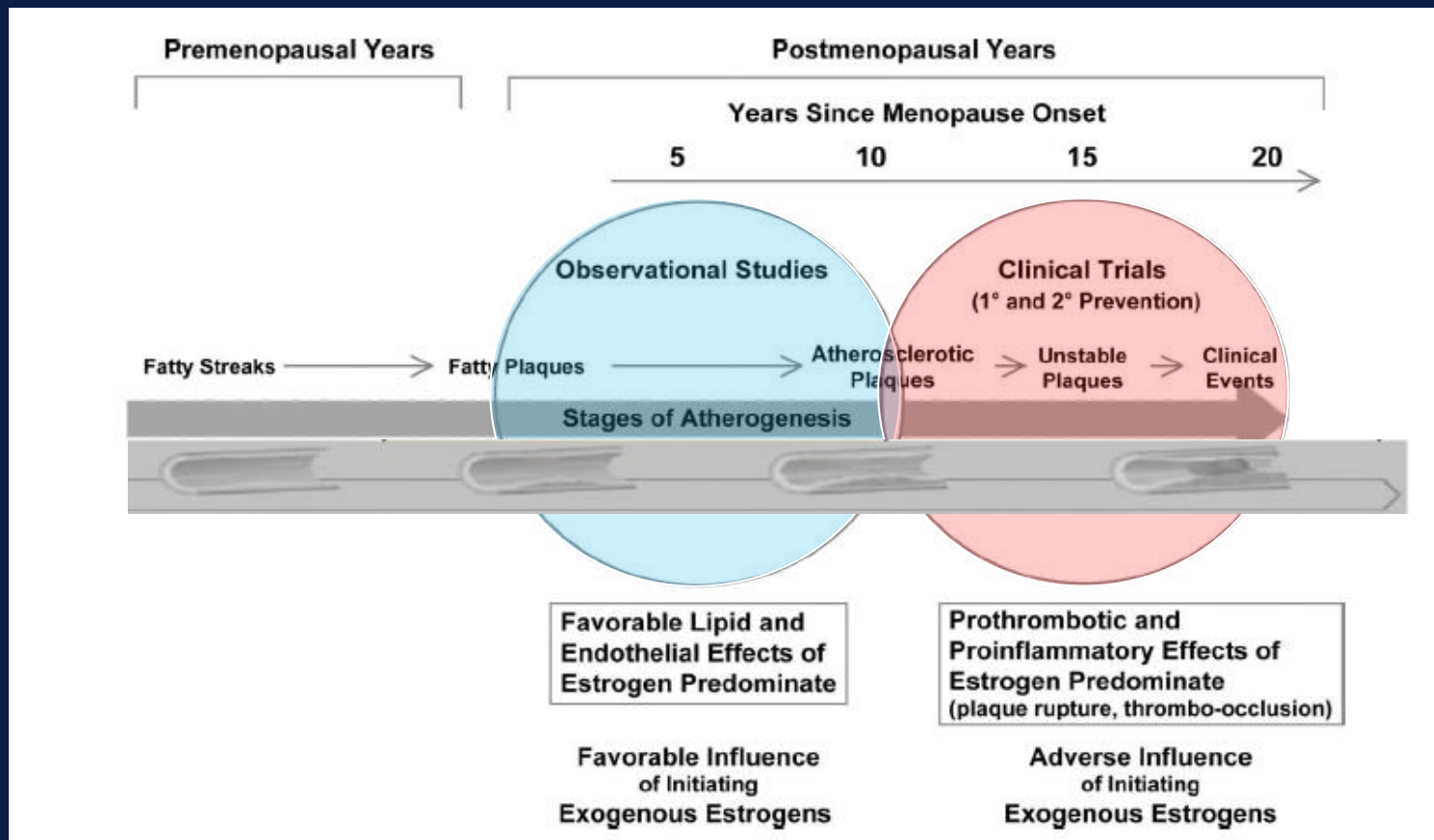
Hormone therapy and risk of cardiovascular disease by age and years since menopause



Effect of hormone therapy in **early** and **established** atherosclerosis



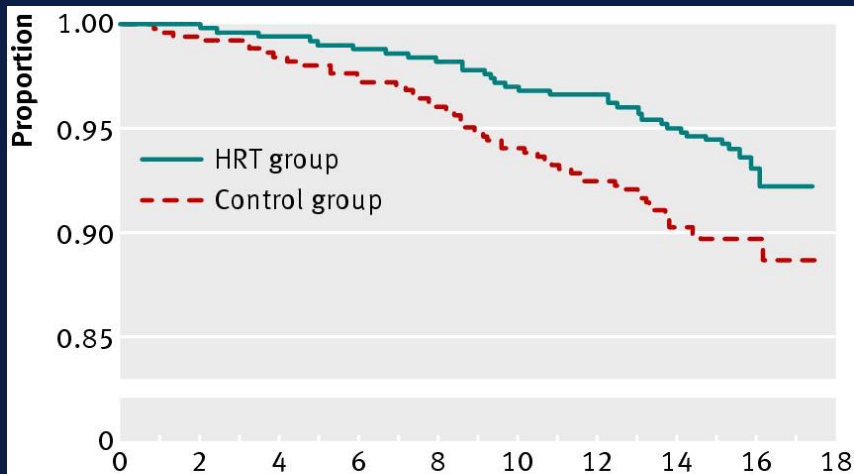
Timing of hormone therapy initiation in relation to stage of atherosclerosis



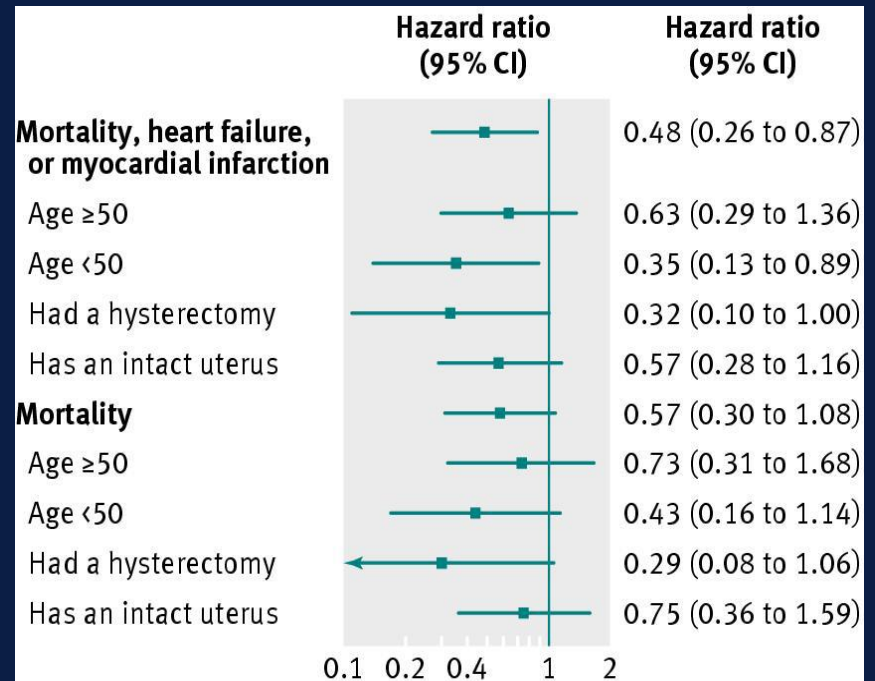
Effect of HT on cardiovascular events in recently postmenopausal women

Danish Osteoporosis Prevention Study (DOPS)

- 1006 healthy women aged 45-58 were enrolled.
- 502 women were randomly allocated to receive HT and 504 to receive no treatment
- Intervention was stopped after about 11 years.
- Participants were followed for up to 16 years.



Risk of death or admission to hospital due to heart failure or myocardial infarction



Atherosclerosis

- It progresses silently for a long time without any symptom.
- About 30-50% of these patients go through heart attack as their initial symptom.

Foam Cells

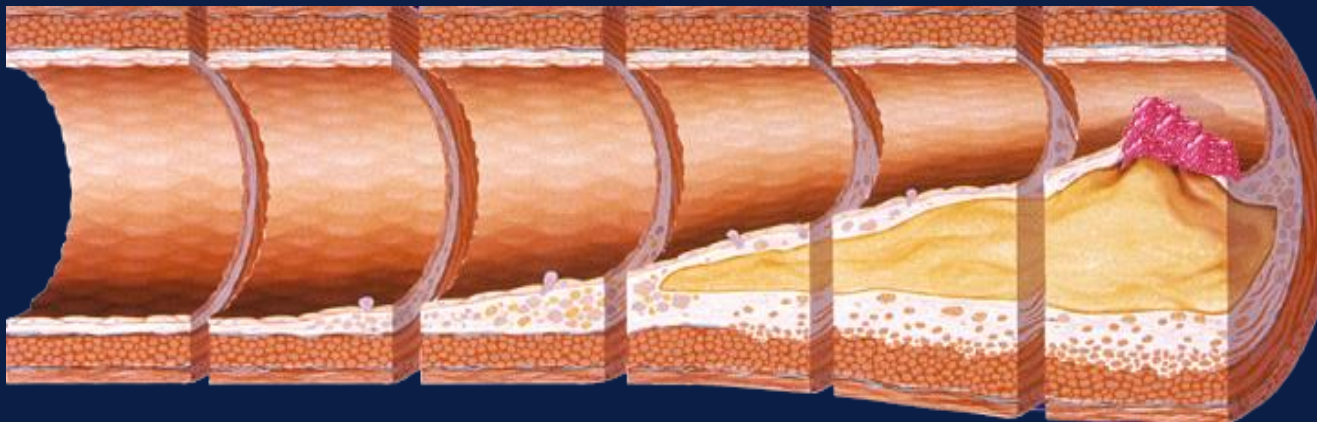
Fatty Streak

Intermediate Lesion

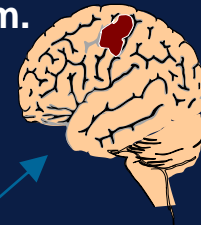
Atheroma

Fibrous Plaque

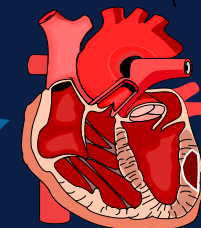
Complicated Lesion/Rupture



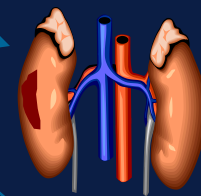
Endothelial Dysfunction



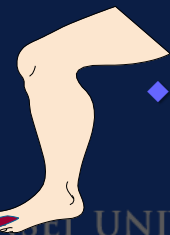
◆ Stroke
◆ TIA



◆ MI
◆ Angina




◆ High BP
◆ Renal failure



◆ PAD



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Presumptive clinical benefits of screening for atherosclerosis in postmenopausal women

- Earlier detection of atherosclerosis
 - May be a helpful to decide the initiation of MHT.
 - May lead to decreases in CVD associated morbidity and mortality.



Framingham risk score



NATIONAL CHOLESTEROL EDUCATION PROGRAM

Third Report of the Expert Panel on

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)

The [risk assessment tool](#) below uses recent data from the Framingham Heart Study to estimate 10-year risk for “hard” coronary heart disease outcomes (myocardial infarction and coronary death). This tool is designed to estimate risk in adults aged 20 and older who do not have heart disease or diabetes. Use the calculator below to estimate 10-year risk.

Age:

years

Gender:

☐ Female ☐ Male

[Total Cholesterol:](#)

mg/dL

[HDL Cholesterol:](#)

mg/dL

[Smoker:](#)

☐ No ☐ Yes

[Systolic Blood Pressure:](#)

mm/Hg

Currently on any medication to treat high blood pressure.

☐ No ☐ Yes

Calculate 10-Year Risk



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Framingham risk score



NATIONAL CHOLESTEROL EDUCATION PROGRAM

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| | |
|---------------------------------|------------------|
| Age: | 55 |
| Gender: | female |
| Total Cholesterol: | 220 mg/dL |
| HDL Cholesterol: | 55 mg/dL |
| Smoker: | Yes |
| Systolic Blood Pressure: | 135 mm Hg |
| On medication for HBP: | Yes |
| Risk Score* | 7% |

Low Risk: Framingham 10-year risk <5%

Intermediate Risk: 6-20%

High Risk: >20% (or diabetes)



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Prevalence of conventional risk factors among women with CHD

Risk “paradox”

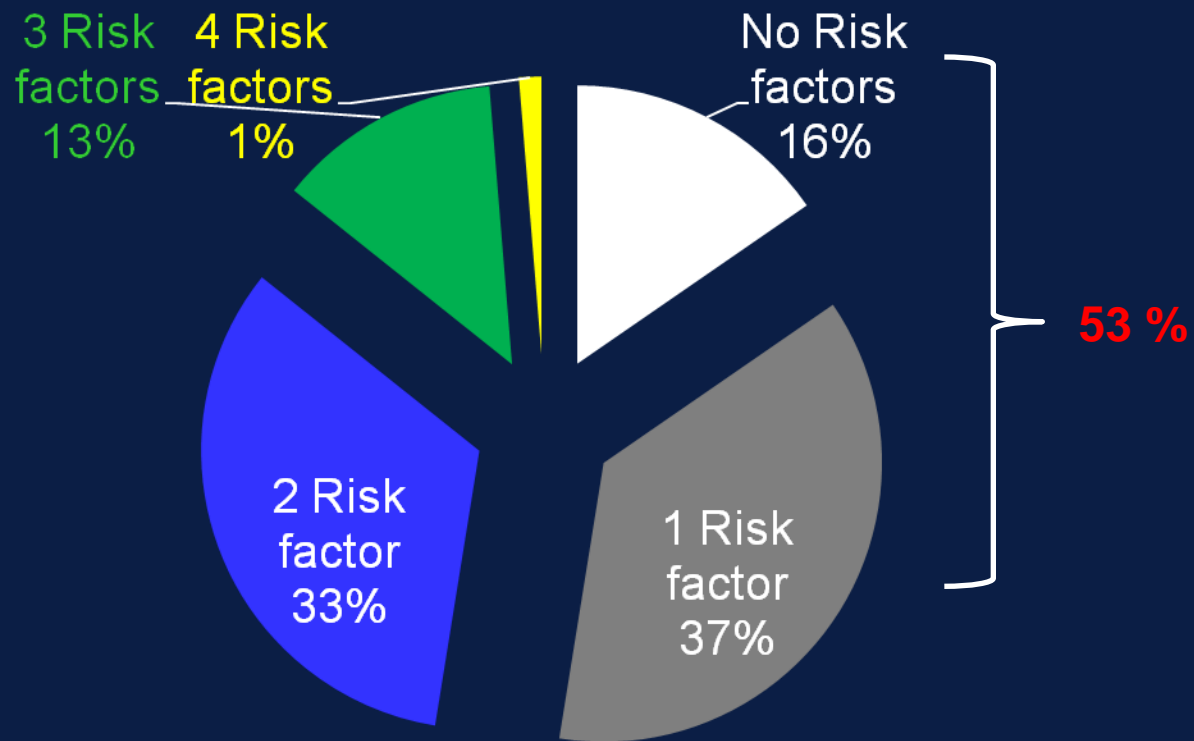
N = 34,859

Smoking

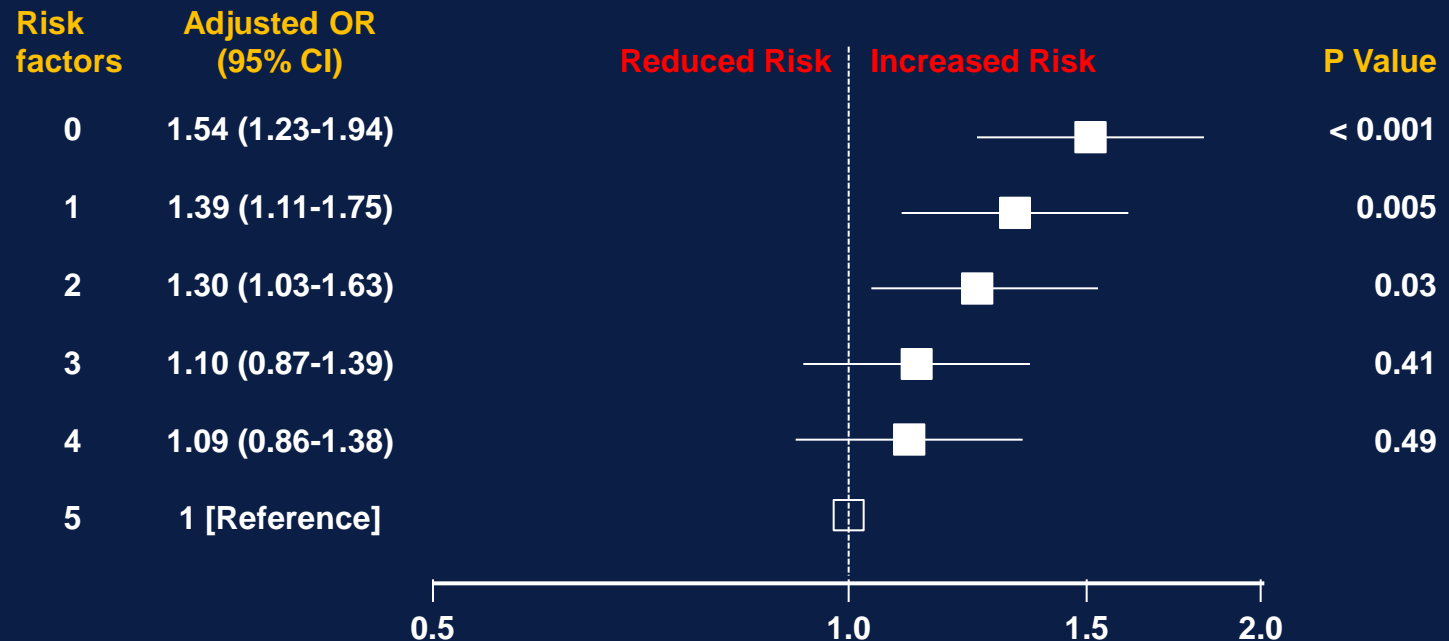
HTN

DM

Dyslipidemia



Mortality risk of patients with and without cardiovascular risk factors and first myocardial infarction



After adjusting for age and other important outcome-associated factors at presentation, there was a significant inverse relationship between adjusted mortality and number of CHD risk factors present at hospitalization (P for trend .001)





SCREENING METHODS FOR ATHEROSCLEROSIS



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Screening for Atherosclerosis

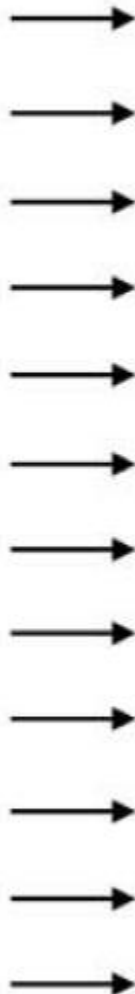
Risk Factors vs Disease

Numerous Risk Factors

High LDL
Low HDL
High BP
Diabetes
Smoking
CRP
Metabolic Syn
Lp(a)
Homocysteine
Dense LDL
Lp-PLA2
ApoB/ApoA
Family History
Sedentary Life
Obesity
Stress

...
?

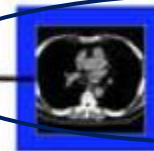
Over 200 risk factors have been reported.



Carotid IMT and Plaque Measured by Ultrasound



Aortic and Carotid Plaque Detected by MRI



Coronary Calcium Score Measured by CT



Ankle Brachial Index



Brachial Vasoreactivity Measured by Ultrasound



Vascular Compliance Measured by Radial Tonometry

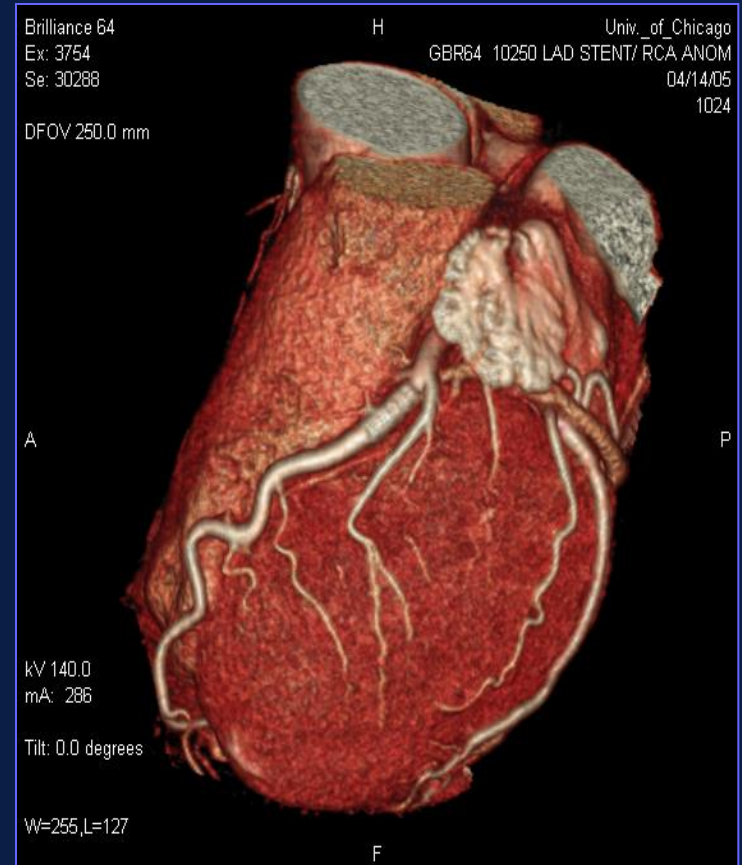
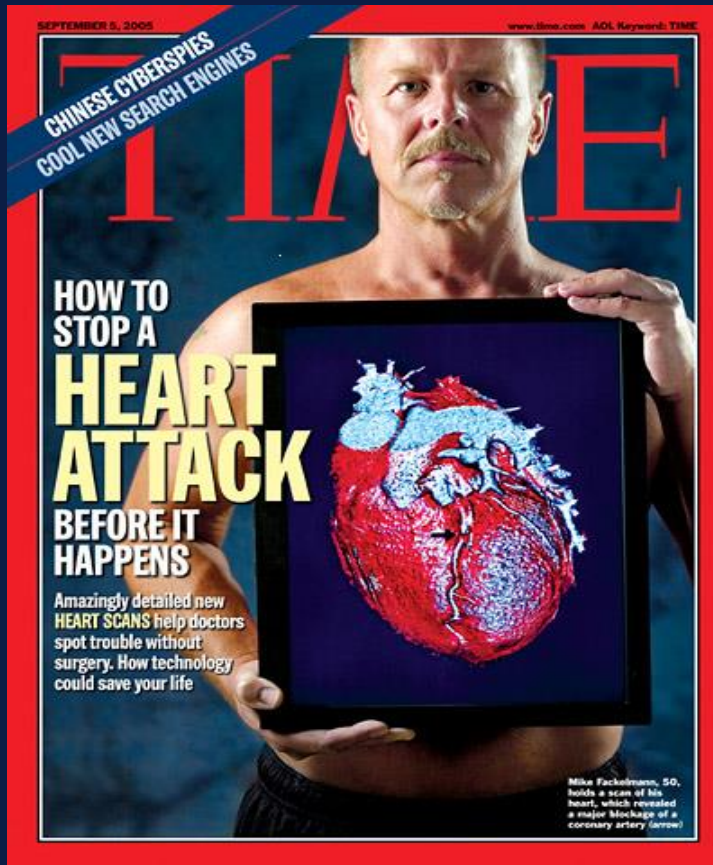


Microvascular Reactivity Measured by Fingertip Tonometry

Examples of Arterial Structure Tests

Examples of Arterial Function Tests

Coronary CT angiography



● ● ● | CT of coronary artery disease

- Compared with invasive coronary catheterization, coronary CT angiography has high accuracy for stenosis detection.
- The available evidence suggests that the use of electrocardiographically synchronized CT for the assessment of patients with acute chest pain is accurate and safe.
- Coronary CT angiography enables the noninvasive assessment of the calcified and noncalcified atherosclerotic plaque burden and may play an increasing future role for cardiac risk stratification and therapeutic monitoring.
- Coronary CT angiography, if used according to established guidelines, is cost-effective.



Current technical limitations

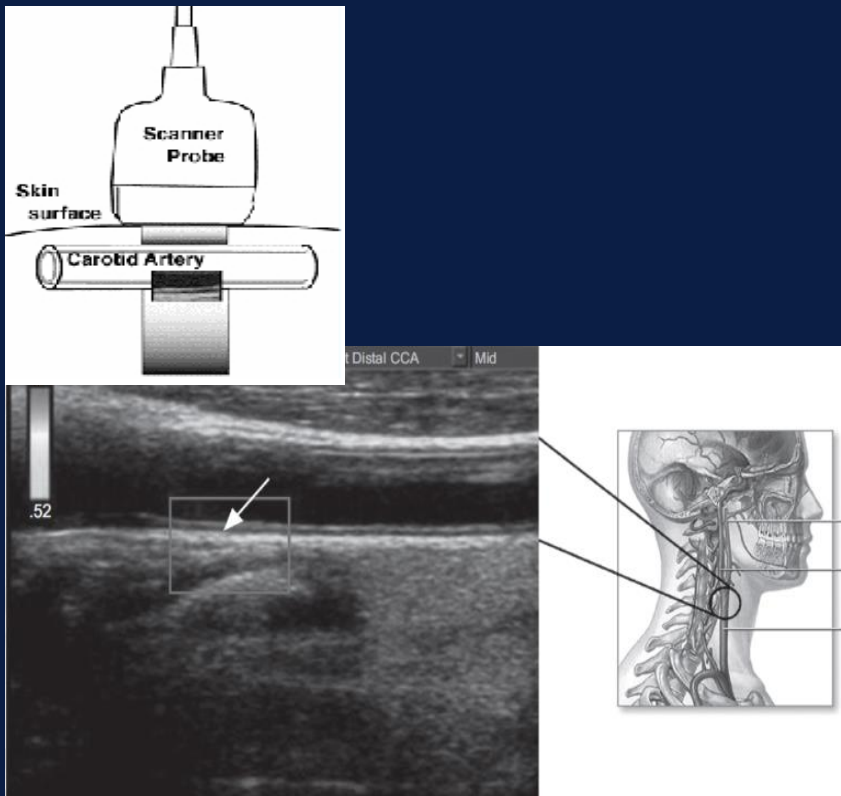
Relatively high levels of radiation

- Organ doses corresponding to a common CT study (two or three scans, resulting in a dose in the range of 30 to 90 mSv) result in an increased risk of cancer.
- It has been estimated that about 0.4% of all cancers in the United States may be attributable to the radiation from CT studies. By adjusting this estimate for current CT use, this estimate might now be in the range of 1.5 to 2.0%. (*N Engl J Med 2007*)
- A multicenter study reported an average effective radiation dose equivalent of 12 mSv associated with cardiac CT and demonstrated large variations (5–30 mSv) among participating centers.

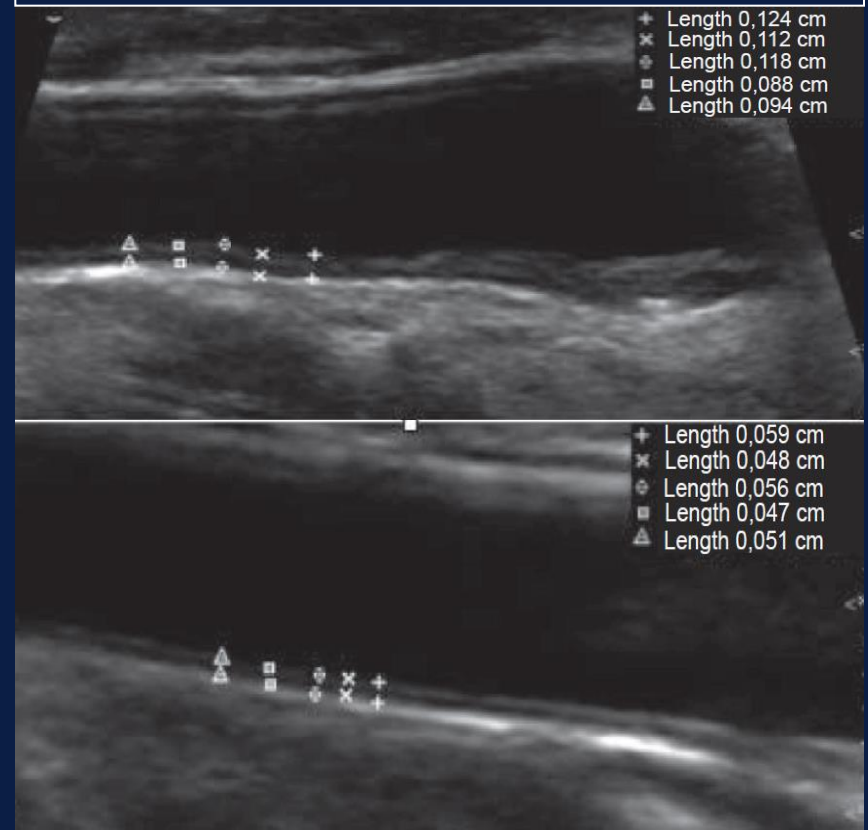


Carotid intima-media thickness (CIMT)

B-mode US image of CCA



US image of thickened, irregular and normal CIMT



● ● ● | CIMT

- Carotid ultrasonography is a very safe, available, and reliable method for evaluation of carotid arteries.
- CIMT may help us detect CAD in the early stages of disease and predict the risk of a future stroke or cardiovascular event.
- CIMT is correlated with most of the major cardiovascular risk factors.
- The presence of carotid plaque is a more powerful index than CIMT for risk stratification.



Advantages and Disadvantages of CIMT

CHD Risk Assessment Tool

Major Advantages

Major Disadvantages

CAC scoring
(CT scan)

Widely available and often used;
Images calcified plaque;

Significant radiation exposure;
Unsuitable for serial examinations;

CIMT testing

Simple to perform;
Cost-effective;
Can be frequently performed
without any adverse effects;
Images actual site of
atherosclerosis;
Suitable for serial examinations;

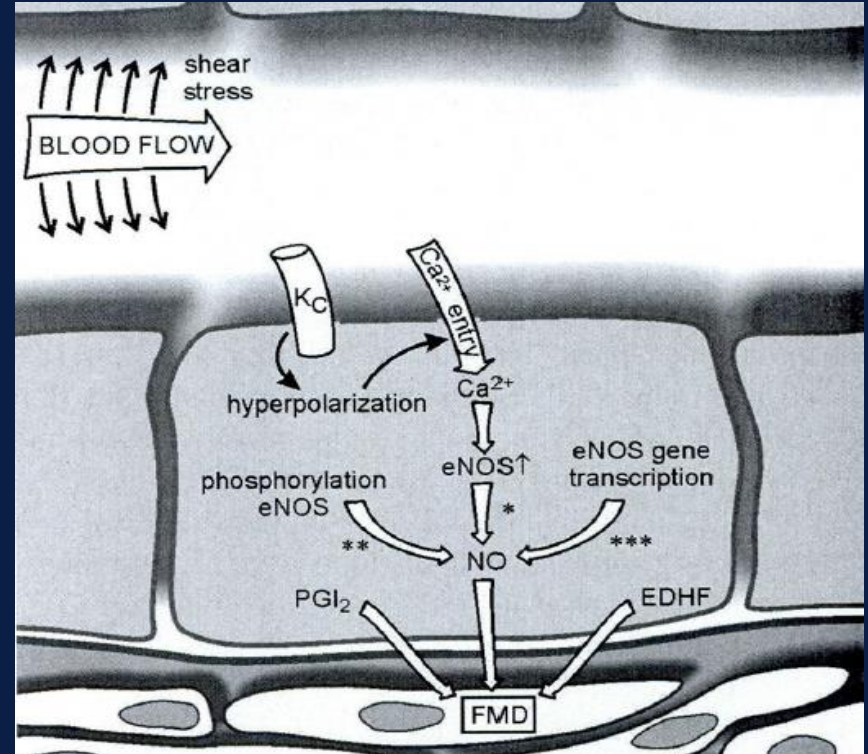
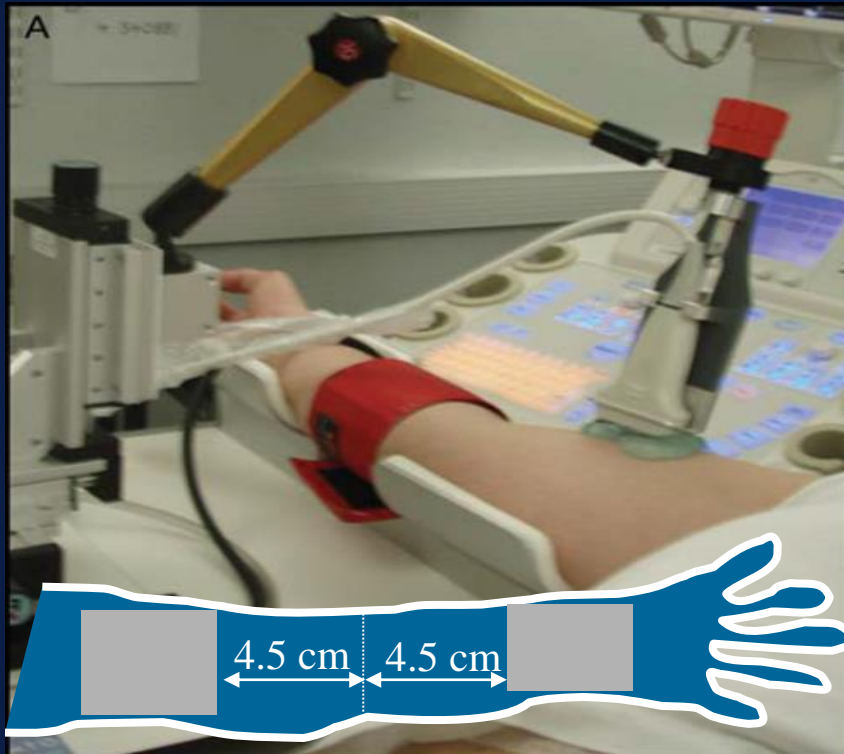
Limited to carotid arteries;
Identifies changes not only due to
atherosclerosis (eg, age and
inflammation);
Clear standardized protocol
lacking;

Intima-medial thickness demand highly trained observers



Flow mediated dilatation (FMD)

Shear stress-induced NO release and subsequent vasodilatation



Baseline

250 mmHg
for 4.5-5 min

60 sec after
cuff release

Reactive Hyperemia



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● ● ● | Flow mediated dilatation (FMD)

- FMD reflects endothelium-dependent vasodilator function.
- FMD is diminished in patients with atherosclerosis and with coronary risk factors
- FMD improves with risk-reduction therapy
- **FMD is useful**
 - to predict short-term postoperative cardiovascular events in a high-risk population
 - to assess long-term cardiovascular risk in a lower risk population
 - to detect changes in endothelial function after new therapeutic interventions.

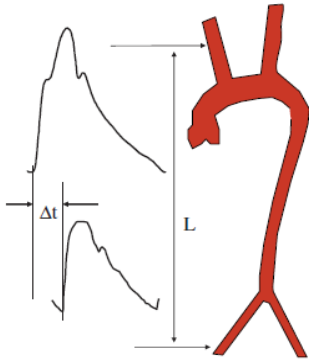


● ● ● | **Clinical limitations**

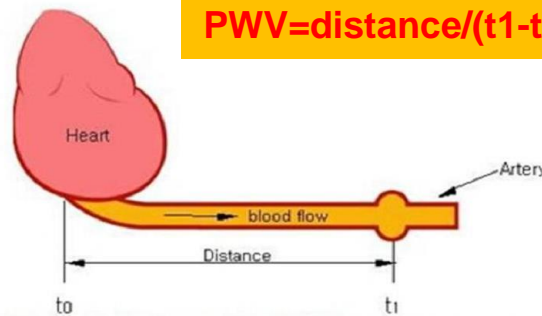
- It is difficult to perform, requiring a skilled sonographer and an appropriate training period.
- There is no consensus about upper vs lower cuff placement. In addition, arteries < 2.5 mm in diameter are difficult to measure, and vasodilatation is generally less difficult to perceive in vessels > 5.0 mm in diameter.
- FMD value is influenced by change in baseline diameter.

Evaluation of arterial stiffness

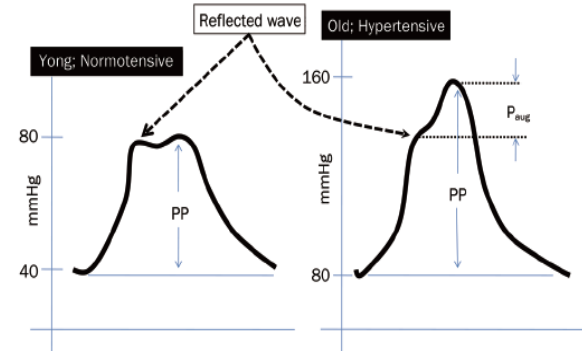
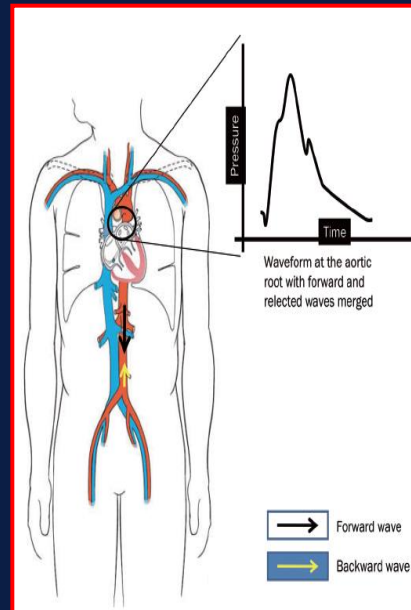
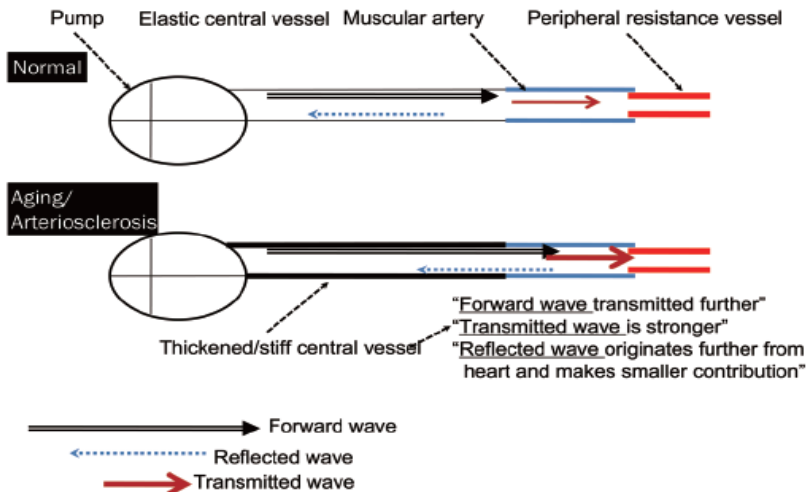
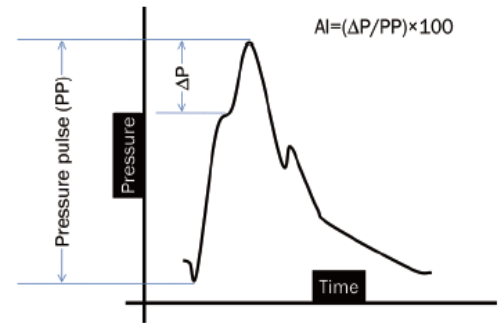
$$PWV = \frac{\Delta L}{\Delta t} = \sqrt{\frac{dP}{\rho} \cdot \frac{V}{dV}}$$



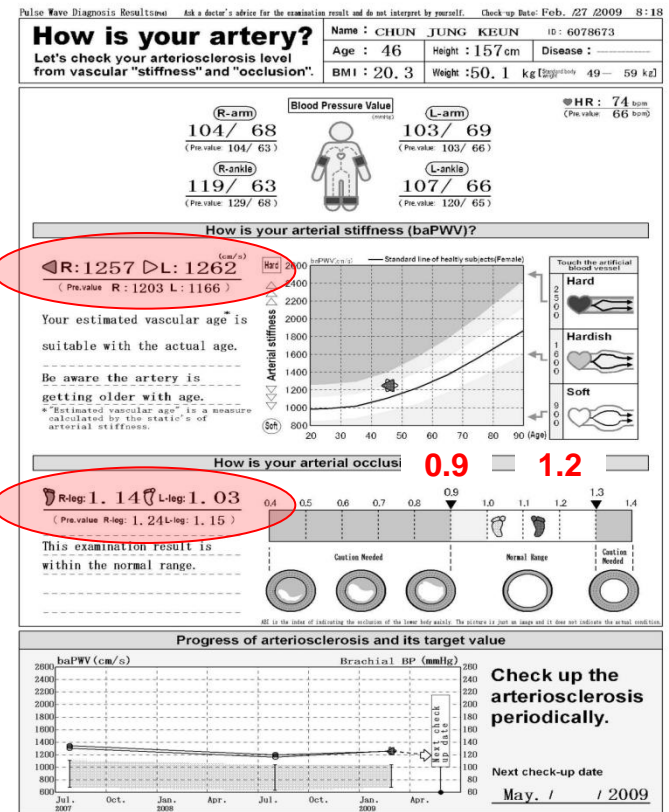
$$PWV = \text{distance} / (t_1 - t_0)$$



$$AI = (\Delta P / PP) \times 100$$



Pulse wave velocity (PWV) and Ankle-Brachial Index (ABI)



Adjusted odds ratios of metabolic syndrome components for coronary atherosclerosis

293 non-diabetic, postmenopausal women aged over 40 years who visited the health promotion center for a routine health checkup were included

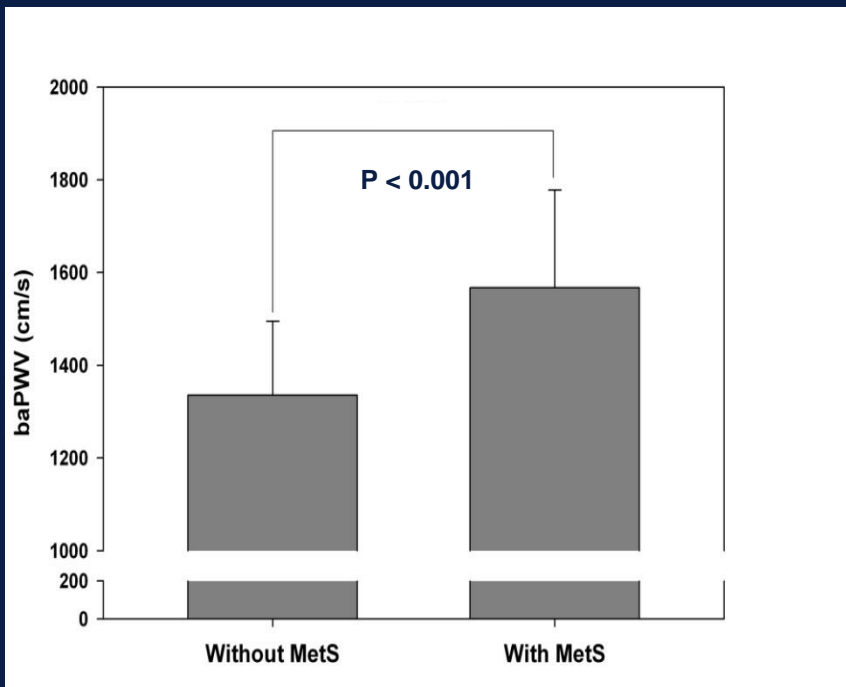
| | Unadjusted OR (95% CI); P value | Adjusted OR (95% CI); P value |
|--------------------------------------|------------------------------------|----------------------------------|
| Age 1-y increment | 1.17 (1.09 – 1.26); < 0.001 | 1.16 (1.08 - 1.24); < 0.001 |
| Metabolic syndrome present/absent | 3.72 (1.67 – 8.29); 0.001 | 2.38 (1.01 – 5.60); 0.046 |

Age (continuous), smoking (categorical), exercise (categorical), and HT use (categorical) were used for confounding factors

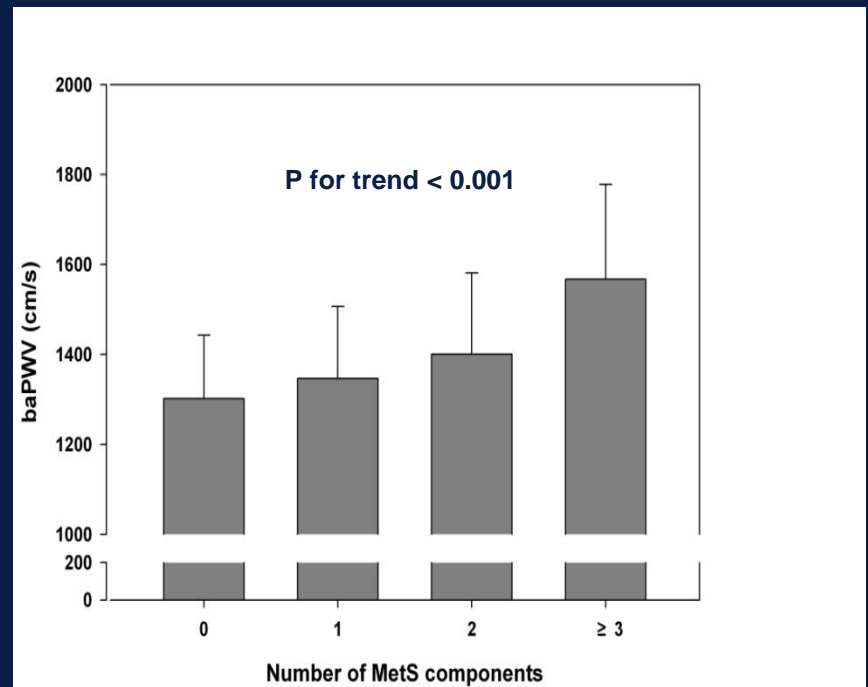


The influence of MetS and its components on baPWV.

MetS and arterial stiffness



MetS components cluster and arterial stiffness

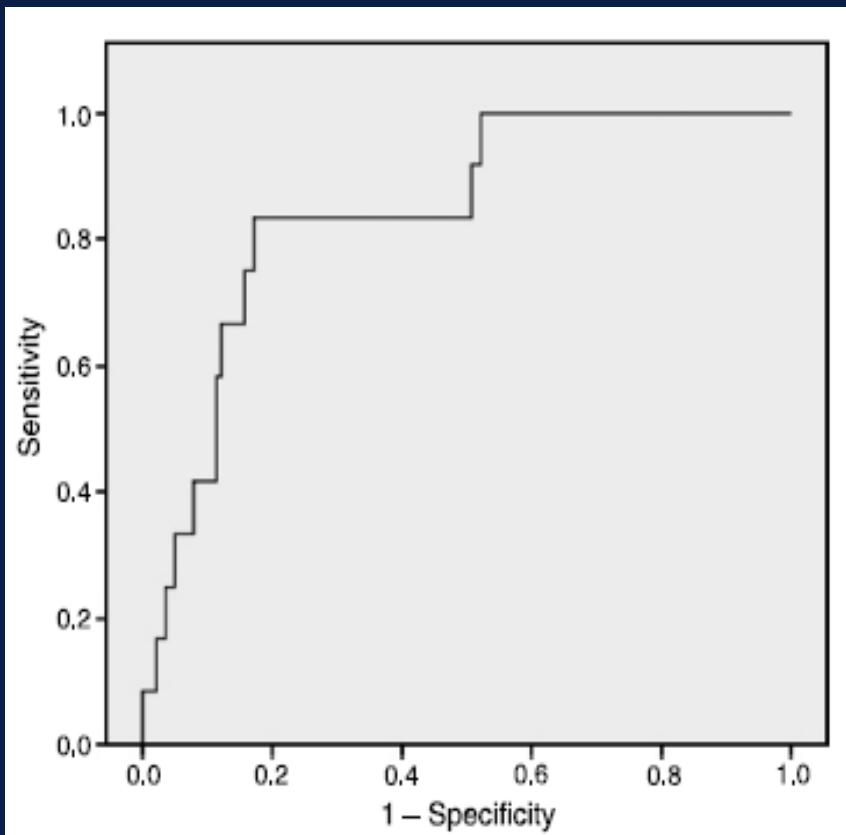


These comparisons were adjusted for age (continuous), smoking (categorical), exercise (categorical), and HT use (categorical).



Arterial stiffness and coronary atherosclerosis in healthy postmenopausal women

156 healthy postmenopausal women aged over 40 years who visited the health promotion center for a routine health checkup were included



Optimum predictive value of brachial-ankle pulse wave velocity (baPWV) for detecting women with coronary atherosclerosis

- Highest detecting baPWV at baPWV = **1,506 cm/second**
 - Sensitivity: **83.3%**
 - Specificity: **82.9%**
- The area under the receiver operating characteristic curve: **0.842 (95% CI, 0.740-0.945; $P < 0.01$)**

Independent influence of baPWV $\geq 1,500$ cm/s on detection of postmenopausal women with coronary atherosclerosis

| | OR | 95% CI | P |
|--------------------------------|--------|--------------|-------|
| Age, y | 1.289 | 1.100-1.511 | 0.002 |
| BMI, kg/m ² | 0.852 | 0.628-1.156 | 0.305 |
| SBP, mmHg | 0.907 | 0.815-1.010 | 0.075 |
| DBP, mmHg | 1.052 | 0.895-1.236 | 0.539 |
| HDL-cholesterol, mg/dL | 0.965 | 0.888-1.048 | 0.401 |
| Glucose, mg/dL | 1.061 | 0.969-1.161 | 0.200 |
| WBC count, 10 ³ /mL | 1.087 | 0.621-1.903 | 0.770 |
| baPWV $> 1,500$, cm/s | 11.768 | 1.391-99.532 | 0.024 |





IDENTIFYING APPROPRIATE CANDIDATES FOR MHT



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Chart for identifying appropriate candidates for MHT

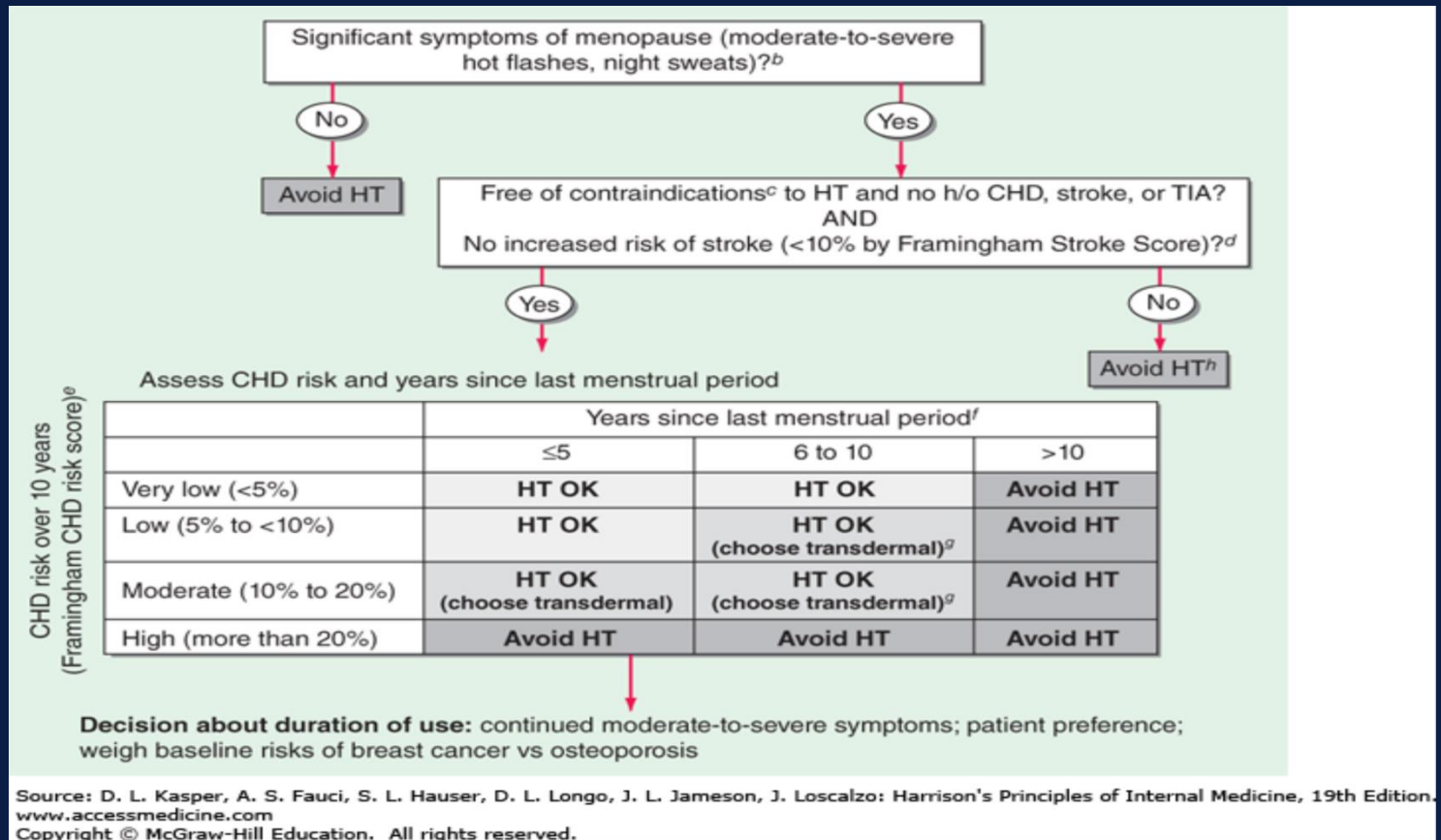




Chart for identifying appropriate candidates for MHT

- Traditional contraindications
 - Unexplained vaginal bleeding
 - Active liver disease
 - History of VT (임신, OC, unknown etiology)
 - Blood-clotting disorder
 - History of breast or endometrial cancer
 - Diabetes
- Oral HT should be avoided but transdermal HT may be an option for other contraindications
 - High triglyceride levels (>400 mg/dL)
 - Active gallbladder disease
 - History of VT (past immobility, surgery, bone fracture)





ESTIMATE OF 10-YEAR RISK FOR STROKE FRAMINGHAM POINT SCORES



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| Point Total | 10-year Risk | |
|-------------|--------------|---------------|
| 1 | <1% | Very low risk |
| 2 | 1% | |
| 3 | 2% | |
| 4 | 2% | |
| 5 | 2% | |
| 6 | 3% | |
| 7 | 4% | |
| 8 | 4% | |
| 9 | 5% | |
| 10 | 6% | Low risk |
| 11 | 8% | |
| 12 | 9% | |
| 13 | 11% | Moderate risk |
| 14 | 13% | |
| 15 | 16% | |
| 16 | 19% | High risk |
| 17 | 23% | |
| 18 | 27% | |
| 19 or more | 32% < | |

***10-Year Risk by
Total Framingham Point Scores***



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Framingham Point Scores by Age Group

| Age | Points |
|-------|--------|
| <56 | 0 |
| 57-59 | 1 |
| 60-62 | 2 |
| 63-64 | 3 |
| 65-67 | 4 |
| 68-70 | 5 |
| 71-73 | 6 |
| 74-76 | 7 |
| 77-78 | 8 |
| 79-81 | 9 |
| 82-84 | 10 |

Framingham Point Scores by smoking status

| Smoking status | Points |
|----------------|--------|
| Non-smoker | 0 |
| Smoker | 3 |

Framingham Point Scores by DM status

| DM status | Points |
|-----------|--------|
| Non-DM | 0 |
| DM | 3 |

Framingham Point Scores by BMI

| BMI | Points |
|-------------------|--------|
| <25 (<23) | 0 |
| 25-29.9 (23-24.9) | 2 |
| 30< (25<) | 4 |

Framingham Point Scores by Systolic Blood Pressure and Treatment Status

If untreated

| Systolic BP (mmHg) | Points |
|-----------------------|--------|
| 95-106 | 1 |
| 107-118 | 2 |
| 119-130 | 3 |
| 131-143 | 4 |
| 144-155 | 5 |
| 156-167 | 6 |
| 168-180 | 7 |
| 181-192 | 8 |
| 193-204 | 9 |
| 205< | 10 |

If treated

| Systolic BP (mmHg) | Points |
|-----------------------|--------|
| 95-106 | 1 |
| 107-113 | 2 |
| 114-119 | 3 |
| 120-125 | 4 |
| 125-131 | 5 |
| 132-139 | 6 |
| 140-148 | 7 |
| 149-160 | 8 |
| 161-204 | 9 |
| 205< | 10 |

Framingham Point Scores by Hx. of A-fib

| A-fib Hx. | Points |
|-----------|--------|
| No | 0 |
| Yes | 6 |

Framingham Point Scores by LV hypertrophy

| LV hypertrophy | Points |
|----------------|--------|
| No | 0 |
| Yes | 4 |

Framingham Point Scores by other heart disease

| Other heart disease | Points |
|---------------------|--------|
| No | 0 |
| Yes | 2 |

Framingham Point Scores by physical activity

1. Do you walk at least 30 minutes every day or exercise above moderate intensity every day? Or do you exercise above moderate intensity more than three hours a week?

Do you do vigorous physical activities such as jogging, at least 20 minutes more than three times a weeks? Or do you do vigorous exercise more than an hour a week?
- 2.

| | |
|---------------------------------------|----|
| If one of the two questions has "yes" | -2 |
| If both questions are "no" | 0 |

Framingham Point Scores by family history of heart attack and stroke

1. Does your father or your brother have a history of a heart attack or stroke before the age of 55?
2. Does your mother or your sister have a history of a heart attack or stroke before the age of 65?

| | |
|---------------------------------------|---|
| If one of the two questions has "yes" | 2 |
| If both questions are "no" | 0 |



ESTIMATE OF 10-YEAR RISK FOR CHD FRAMINGHAM POINT SCORES



Framingham Point Scores by Age Group

| Age | Points |
|-------|--------|
| 20-34 | -7 |
| 35-39 | -3 |
| 40-44 | 0 |
| 45-49 | 3 |
| 50-54 | 6 |
| 55-59 | 8 |
| 60-64 | 10 |
| 65-69 | 12 |
| 70-74 | 14 |
| 75-79 | 16 |

Framingham Point Scores by Age Group and Total Cholesterol

| Total Cholesterol | Age | | | | |
|-------------------|-------|-------|-------|-------|-------|
| | 20-39 | 40-49 | 50-59 | 60-69 | 70-79 |
| <160 | 0 | 0 | 0 | 0 | 0 |
| 160-199 | 4 | 3 | 2 | 1 | 1 |
| 200-239 | 8 | 6 | 4 | 2 | 1 |
| 240-279 | 11 | 8 | 5 | 3 | 2 |
| 280< | 13 | 10 | 7 | 4 | 2 |

Framingham Point Scores by Age and Smoking Status

| Smoking status | Age | | | | |
|----------------|-------|-------|-------|-------|-------|
| | 20-39 | 40-49 | 50-59 | 60-69 | 70-79 |
| Non-smoker | 0 | 0 | 0 | 0 | 0 |
| Smoker | 9 | 7 | 4 | 2 | 1 |

Framingham Point Scores by HDL Level

| HDL | Points |
|-------|--------|
| 60+ | -1 |
| 50-59 | 0 |
| 40-49 | 1 |
| <40 | 2 |

Framingham Point Scores by Systolic Blood Pressure and Treatment Status

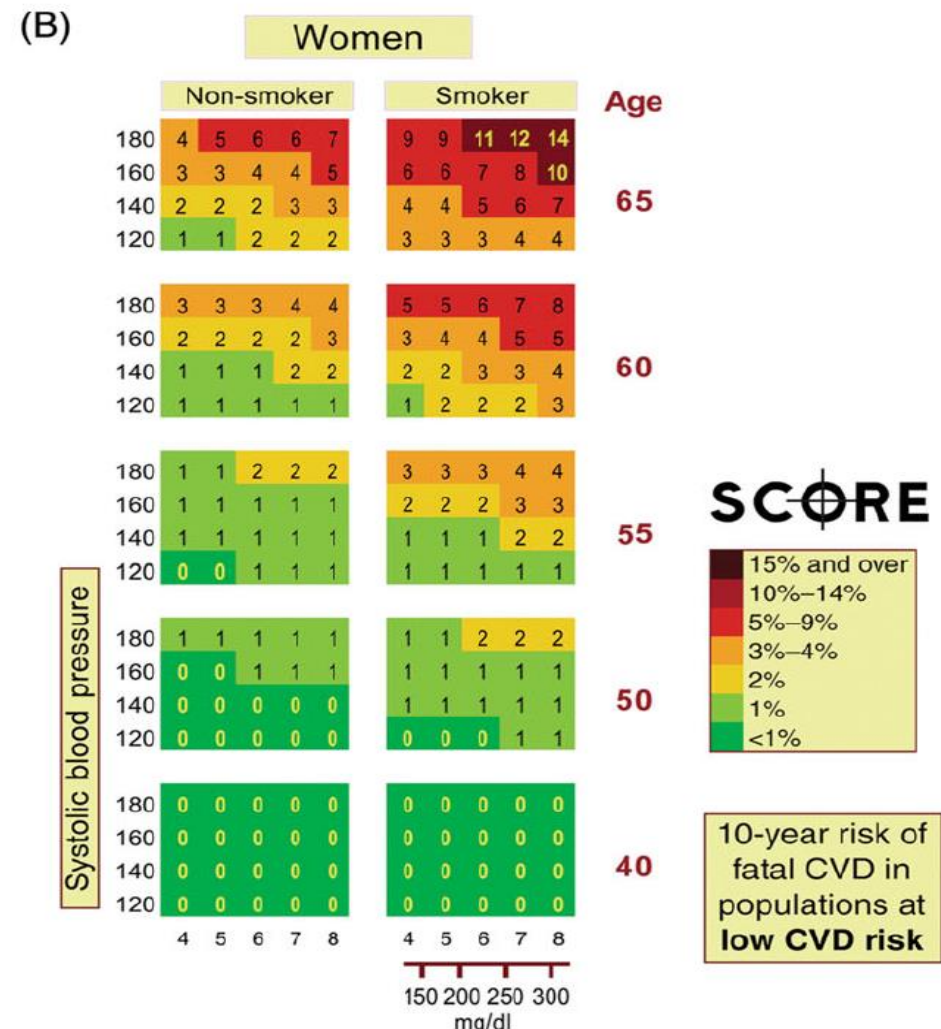
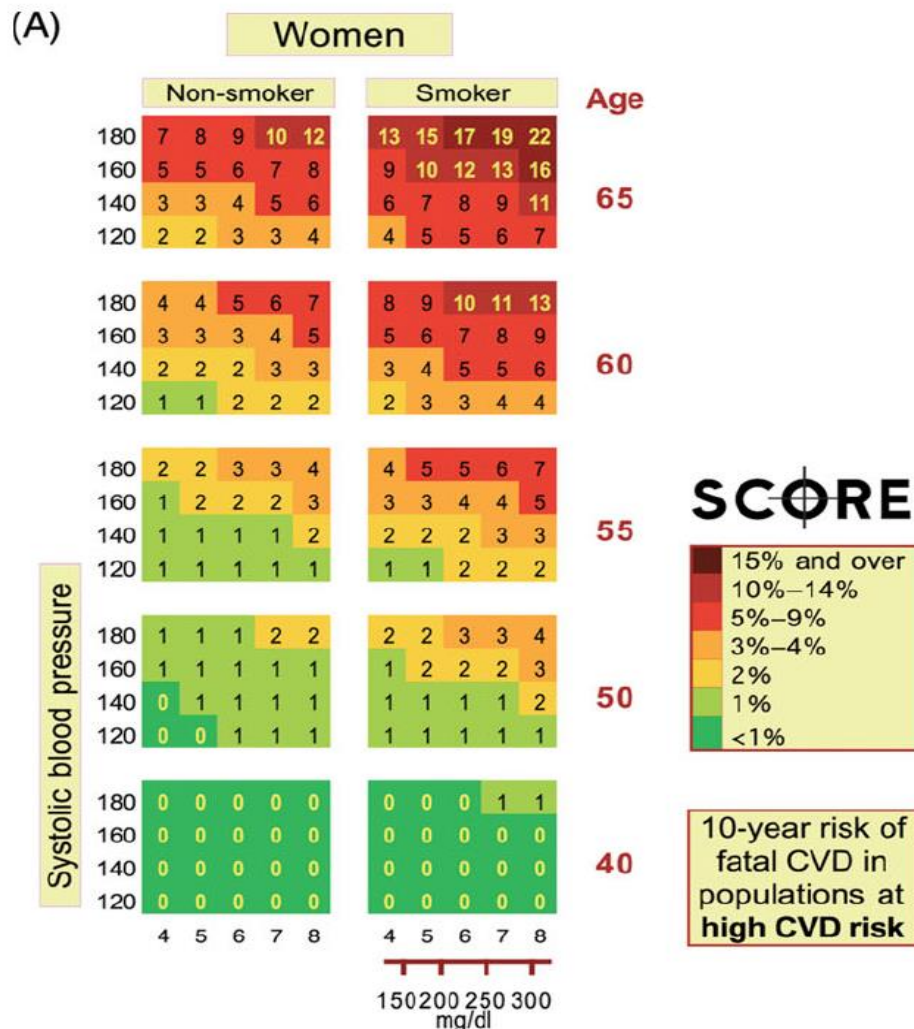
| Systolic BP | If untreated | If treated |
|-------------|--------------|------------|
| <120 | 0 | 0 |
| 120-129 | 1 | 3 |
| 130-139 | 2 | 4 |
| 140-159 | 3 | 5 |
| 160< | 4 | 6 |

10-Year Risk by Total Framingham Point Scores

| Point Total | 10-year Risk |
|-------------|--------------|
| <9 | <1% |
| 9 | 1% |
| 10 | 1% |
| 11 | 1% |
| 12 | 1% |
| 13 | 2% |
| 14 | 2% |
| 15 | 3% |
| 16 | 4% |
| 17 | 5% |
| 18 | 6% |
| 19 | 8% |
| 20 | 11% |
| 21 | 14% |
| 22 | 17% |
| 23 | 22% |
| 24 | 27% |
| 25 or more | >30% |

European Society of Cardiology SCORE charts for women in (A) high-risk and (B) low-risk countries

European Heart Journal 2007;28,:2028-2040.



● ● ● | Key cardiovascular risk factors

| Non-modifiable | Modifiable |
|----------------|---------------------|
| Age | Hypertension |
| Gender | Dyslipidaemia |
| Hereditiy | Obesity |
| | Glucose intolerance |
| | Cigarette smoking |
| | Diabetes mellitus |
| | Sedentarism |

Treatment advice for women with menpausal symptoms

- Hormone therapy should not be prescribed in **women >60 years of age** and in **women at high risk for CHD, such as women with a previous CHD event or stroke.**
- Caution should be taken in women who are **current smokers**, women with **diabetes**, women with the **metabolic syndrome** and women with **≥2 CHD risk factors.**

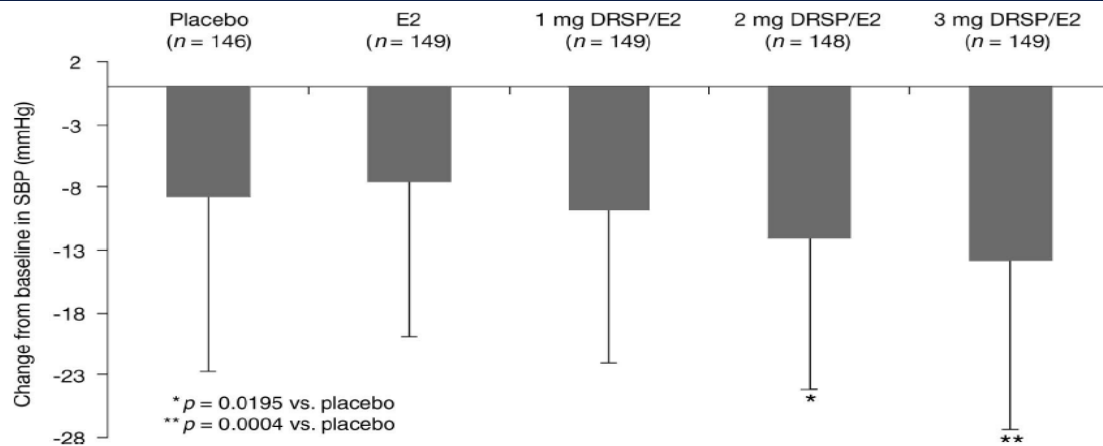
Cardiac risk in menopause and safety of HT

- **High-risk HT**
 - Documented atherosclerosis
 - Previous CHD event, stroke
 - Current smokers
 - Diabetes mellitus
 - Metabolic syndrome
 - Age >60 years
- **Intermediate-risk HT**
 - ≥2 CHD risk factors
- **Low-risk HT**
 - 1 risk factor
 - Age 45-55 years

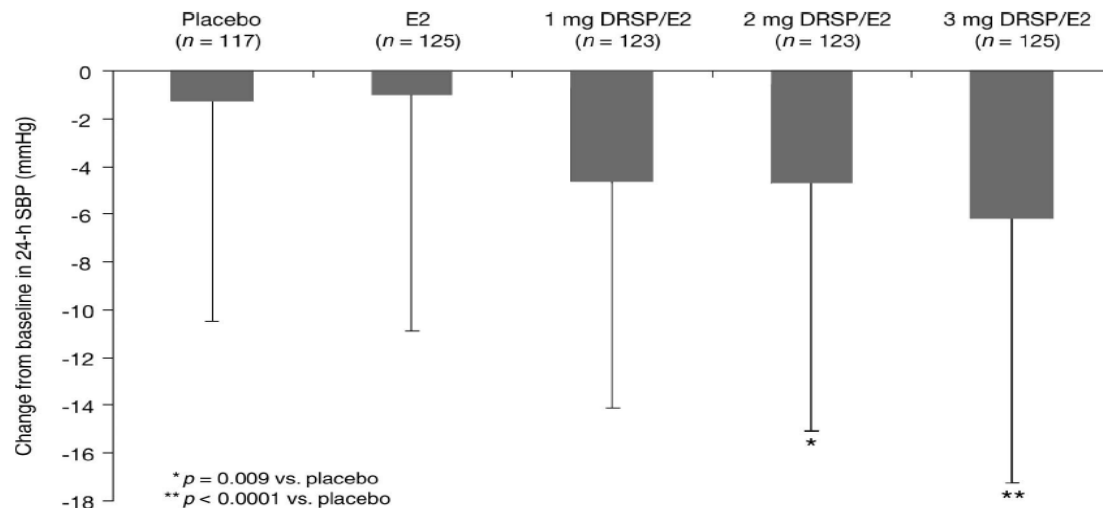


Drospirenone with 17b-estradiol in the PMW with hypertension

Change from baseline to week 8 in office SBP monitoring



Change from baseline to week 8 with ambulatory SBP monitoring



Drospirenone is a novel progestogen with aldosterone receptor antagonism (PARA), and therefore has antihypertensive effects through reduced salt and water retention.



Effect of estradiol/drospirenone combination on the lipid profile

| | 1 mg E2 | 0.5 mg DRSP + E2 | 1.0 mg DRSP + E2 | 2.0 mg DRSP + E2 | 3.0 mg DRSP + E2 |
|-------------------|---------|---------------------|---------------------|---------------------|---------------------|
| Total cholesterol | 1.3 | -16.0 | -17.2 | -13.2 | -18.5 |
| Triglycerides | 6.1 | -9.7 | -5.9 | -1.3 | -10.7 |
| HDL-cholesterol | 7.6 | 3.7 | 3.0 | 3.7 | 0.9 |
| LDL-cholesterol | -5.3 | -14.8 | -15.6 | -12.5 | -15.9 |
| Lipoprotein(a) | -5.7 | -8.4 | -3.1 | -3.1 | -5.6 |

● ● ● | **Key messages**

- **Assessment of the CV risk of the individual woman should be the first step in the evaluation and treatment of menopausal symptoms.**
- **In women with severe menopausal complaints and who are at low risk for CHD the use of HT in the years proximal to menopause may be very helpful.**
- **Age of initiation: ideally therapy begins within 10 years of menopause or by 60 years of age.**
- **Route of administration: transdermal administration has reduced risk of blood clotting compared with oral administration.**



● ● ● | **Key messages**

Diabetes ?



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Thank you for your attention