Early Detection of Damaged Organ

Regional Cardiovascular Center,
Chungbuk National University

Kyung-Kuk Hwang
Contents

• NICE guideline 2011
  - Confirm the diagnosis of HT
    ambulatory blood pressure monitoring (ABPM)
    home blood pressure monitoring (HBPM)
  - Role on the early detection of organ damage

• Early detection of end organ damage
  - Pulse wave velocity (PWV)
  - Carotid intima-media thickness (CIMT)
  - Coronary artery calcification (CAC)
Cardiovascular (Cardiorenal) continuum

Cumulative burden of hypertension

[Ruilope LM, Nat. Rev. Cardiol. 2011]
Office vs 24h BP measurements in high-risk patients

BP Control: 24-h BP measurements < 130/80 mmHg

N=4,729

<table>
<thead>
<tr>
<th>Office BP (mmHg)</th>
<th>% of patients with whose 24-h BP is actually controlled*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with established CHD‡</td>
</tr>
<tr>
<td>&lt;120/80</td>
<td>88.4 (114 of 129)</td>
</tr>
<tr>
<td>120–129/80–84</td>
<td>75.6 (98 of 130)</td>
</tr>
<tr>
<td>130–139/85–89</td>
<td>65.1 (146 of 224)</td>
</tr>
<tr>
<td>140–159/90–99</td>
<td>45.2 (181 of 401)</td>
</tr>
<tr>
<td>≥160/100</td>
<td>25.3 (52 of 205)</td>
</tr>
<tr>
<td>Total</td>
<td>46.1 (502 of 1,089)</td>
</tr>
</tbody>
</table>

Key priorities for implementation

The following recommendations have been identified as priorities for implementation.

Diagnosing hypertension
- If the clinic blood pressure is 140/90 mmHg or higher, offer ambulatory blood pressure monitoring (ABPM) to confirm the diagnosis of hypertension. [new 2011]
- When using ABPM to confirm a diagnosis of hypertension, ensure that at least two measurements per hour are taken during the person’s usual waking hours (for example, between 08:00 and 22:00). Use the average value of at least 14 measurements taken during the person’s usual waking hours to confirm a diagnosis of hypertension. [new 2011]
- When using home blood pressure monitoring (HBPM) to confirm a diagnosis of hypertension, ensure that:
  - for each blood pressure recording, two consecutive measurements are taken, at least 1 minute apart and with the person seated and
  - blood pressure is recorded twice daily, ideally in the morning and evening and
  - blood pressure recording continues for at least 4 days, ideally for 7 days. Discard the measurements taken on the first day and use the average value of all the remaining measurements to confirm a diagnosis of hypertension. [new 2011]
Updated recommendation in NICE guideline 2011

Diagnosing hypertension

- If Clinic BP $\geq 140/90$ mmHg $\rightarrow$ offer ABPM to confirm the diagnosis of HT [new 2011]

- When using ABPM to confirm a diagnosis of HT
  - at least 2 measurements/hr during the person’s usual waking hrs (ie: 08:00 - 22:00)
  - use the average value of at least 14 measurements taken during the person’s usual waking hours [new 2011]

- When using home blood pressure monitoring to confirm a diagnosis of HT, ensure that:
  - for each BP recording, two consecutive measurements are taken, at least 1 minute apart and with the person seated and
  - BP is recorded twice daily, ideally in the morning and evening and
  - BP recording continues for at least 4 days, ideally for 7 days

Discard the measurements taken on the first day and use the average value of all the remaining measurements to confirm a diagnosis of HT [new 2011]
Out-of-office monitoring in NICE guideline 2011

Does the use of HBPM or ABPM improve response to treatment?

- Increasing use of HBPM and for the diagnosis of HT
- Few data of utility of HBPM or ABPM
  - monitoring BP control or indicators of clinical outcome in treated HT compared with clinic BP monitoring

NICE guideline 2011
CV death and ABPM vs HBPM vs Clinic BP

In the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study

N= 2051, follow-up of 148 months

[CV DEATHS]

[Mancia G et al, Hypertension. 2006]
Role of ABPM or HBPM on early detection of damaged organ

👩‍⚕️ Ohsama study: ABPM vs HBPM vs clinic BP

👩‍⚕️ HBPM: maximum home SBP

👩‍⚕️ Masked HT
Ambulatory Versus Home Versus Clinic Blood Pressure

The Association With Subclinical Cerebrovascular Diseases:
The Ohasama Study

Azusa Hara, Kazushi Tanaka, Takayoshi Ohkubo, Takeo Kondo, Masahiro Kikuya, Hirohito Metoki, Takanao Hashimoto, Michihiro Satoh, Ryusuke Inoue, Kei Asayama, Taku Obara, Takuo Hirose, Shin-Ichi Izumi, Hiroshi Satoh, Yutaka Imai

See Editorial Commentary, pp XX–XX

Abstract—The usefulness of ambulatory, home, and casual/clinic blood pressure measurements to predict subclinical cerebrovascular diseases (silent cerebrovascular lesions and carotid atherosclerosis) was compared in a general population. Data on ambulatory, home, and casual/clinic blood pressures and brain MRI to detect silent cerebrovascular lesions were obtained in 1007 subjects aged ≥55 years in a general population of Ohasama, Japan. Of the 1007 subjects, 583 underwent evaluation of the extent of carotid atherosclerosis. Twenty-four-hour, daytime, and nighttime ambulatory and home blood pressure levels were closely associated with the risk of silent cerebrovascular lesions and carotid atherosclerosis (all $P<0.05$). When home and one of the ambulatory blood pressure values were simultaneously included in the same regression model, each of the ambulatory blood pressure values remained a significant predictor of silent cerebrovascular lesions, whereas home blood pressure lost its predictive value. Of the ambulatory blood pressure values, nighttime blood pressure was the strongest predictor of silent cerebrovascular lesions. The home blood pressure value was more closely associated with the risk of carotid atherosclerosis than any of the ambulatory blood pressure values when home and one of the ambulatory blood pressure values were simultaneously included in the same regression model. The casual/clinic blood pressure value had no significant association with the risk of subclinical cerebrovascular diseases. Although the clinical indications for ambulatory blood pressure monitoring and home blood pressure measurements may overlap, the clinical significance of each method for predicting target organ damage may differ for different target organs. (Hypertension. 2012;59:00-00.) ● Online Data Supplement
Ambulatory vs home vs clinic blood pressure

Usefulness of ABPM, HBPM, clinic BP (CBP) to predict subclinical cerebrovascular dis.  
- silent cerebrovascular lesions (SCLs), carotid atherosclerosis (CAS)

ABP, HBP, CBP and brain MRI to detect SCLs  
- N= 1007 (aged ≥ 55 year-old) in a general population of Ohasama, Japan.

Evaluation of CAS extent : mean IMT > 0.9 mm or focal carotid plaque (+)  
- N= 583 of 1007

**ABPM**  
: daytime and nighttime - according to the diary  
  BP measurement- every 30 min

**HBP** - HEM701C (Omron Healthcare Co. Ltd, Japan)  
: measured BP every morning within 1 h of waking in the sitting position  
  after an interval of rest of more than 2 min  
  record the results over a 4-week period

Results

- 24 hr, daytime, nighttime ABP and HBP: closely associated with risk of SCLs and CAS (all $P<0.05$)

- Each of the ABP values: significant predictor of SCLs
  - Nighttime BP: strongest predictor of SCLs

- HBP value: more closely associated with the risk of CAS

- CBP: no significant association with the risk of subclinical cerebrovascular disease

Clinical significance of each method for predicting TOD
- may differ for different target organs

[Har A et al, *Hypertension*. 2012]
Risk of SCLs per 1-SD increase in SBP

Adjusted for age, sex, BMI, smoking, drinking status, anti-HT medication, and history of cardiovascular dis., hypercholesterolemia, or diabetes mellitus.

[Hara A et al, Hypertension. 2012]
Risk of carotid atherosclerosis per 1-SD increase in SBP

Adjusted for age, sex, BMI, smoking, drinking status, anti-HT medication, and history of cardiovascular dis., hypercholesterolemia, or diabetes mellitus.

[Hara A et al, Hypertension. 2012]
Strength of this Ohasama study

✦ First study
  compare ABP, HBP, CBP values for their associations with the risk of subclinical cerebrovascular dis. in a large general population

✦ Advantage of ABP and HBP over CBP measurements
  - absence of the white-coat effect
  - lack of digit preference & observer bias when automated devices are used
  - better correlation to target organ damage and prognosis

Maximum value of home blood pressure

 Novel indicator of target organ damage in hypertension
 - n=356 (never treated hypertensives), age: 66.6± 11.0 year-old, M:F= 47:53

Maximum home SBP and TOD

Multivariate regression analyses between maximum home SBP and TOD

Transcript:

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Total Population (n=356)</th>
<th>Mean Home BP &lt;135/85 mm Hg (n=135)</th>
<th>Mean Home BP ≥135/85 mm Hg (n=221)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI*, g/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum home SBP, mm Hg</td>
<td>0.598 (0.094) &lt;0.001</td>
<td>0.512 (0.188) 0.007</td>
<td>0.655 (0.145) &lt;0.001</td>
</tr>
<tr>
<td>Model R² = 0.32</td>
<td></td>
<td>Model R² = 0.21</td>
<td>Model R² = 0.24</td>
</tr>
<tr>
<td>Carotid IMT†, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum home SBP, mm Hg</td>
<td>0.003 (&lt;0.001) &lt;0.001</td>
<td>0.003 (0.001) 0.006</td>
<td>0.003 (0.001) &lt;0.001</td>
</tr>
<tr>
<td>Model R² = 0.27</td>
<td></td>
<td>Model R² = 0.26</td>
<td>Model R² = 0.24</td>
</tr>
<tr>
<td>Log UACR‡, mg/gCr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum home SBP, mm Hg</td>
<td>0.004 (0.002) 0.02</td>
<td>0.001 (0.003) 0.68</td>
<td>0.003 (0.002) 0.18</td>
</tr>
<tr>
<td>Model R² = 0.20</td>
<td></td>
<td>Model R² = 0.15</td>
<td>Model R² = 0.17</td>
</tr>
</tbody>
</table>

Transient high BP readings at home - not noise, should be taken seriously as meaningful indicators for hypertensive TOD

[Matsui Y et al, 2011]
Masked hypertension

- Inverse of white-coat hypertension: masked hypertension
  : clinic BP <140/90 mmHg, and 24-h or home BP value above normal values

- First described by Pickering approximately 20 years ago

- Available data are consistent with regard to the prevalence, association with other risk factors, organ damage, and prognostic significance of masked HT

Masked HT: prevalence and patients at risk

- Prevalence of masked HT: about 9% in the whole population
  Sega, R. Circulation 2001, Mancia, G. Hypertension 2006

- Approximate 1/7 pt with normal clinic BP: to have elevated ABP or HBP

- Characterized by clinic BP are higher than those of normotensives
  Mancia, G. Hypertension 2006

- Demographic and clinical profile of pts who are prone to develop masked HT
  - young individuals (age <50 years)
  - pts with transiently elevated BP (particularly in stressful conditions)
  - Pts with high-normal clinic BP

Masked HT: pathogenesis

- Sustained activation of the sympathetic nervous system
  - impairment of baroreflex-mediated cardiovascular control
    - that affects, in a fairly selective fashion, control of heart rate
      Grassi, G. Hypertension, 2007

- An increased reactivity to stressful stimuli

- Smoking and excessive alcohol intake
  - via adrenergic activation, endothelial dysfunction, or both
    Schnall PI, Hypertension, 1992, Mann S J, JAMA 1991

- Mechanisms for normal BP in the clinic in combination with elevated BP load during 24-h or home BP measurement
  - still remain unknown
**Masked HT: clinical importance**

- Masked HT
  - clearly associated with a higher prevalence of organ damage (such as LVH, ↑ in carotid IMT)
  - increased cardiovascular risk and all-cause mortality
    - RR- 1.5 (PAMELA study, Ohasama study)
    - masked HT= sustained HT (SHEAF study)
  - associated with increased prevalence and severity of metabolic risk factors and greater risks of developing sustained hypertension and diabetes

Survival: normotensives, masked HT, sustained HT

Clinic BP and 24h ABP

Clinic BP and Home BP

Masked HT: clinical importance

- Detection: not easy in clinical practice
  - requires the collection of HBP or ABPM in all pts,
    even if normotensives in the clinical setting.

- One practical suggestion: to suspect the presence of masked HT
  - despite normal clinic BP values, pts with the presence of end-organ damage

- In these patients, performance of home or 24-h ambulatory blood-pressure monitoring is highly recommended.
Summary-I

Potential role of ABPM or HBPM on early detection of TOD

Recent data suggests

- HBPM or ABPM might be useful for early detection of TOD in HT compared with clinic BP monitoring
### End organ damage in arterial hypertension

<table>
<thead>
<tr>
<th>Vasculopathy</th>
<th>Cerebrovascular damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial dysfunction</td>
<td>Acute hypertensive encephalopathy</td>
</tr>
<tr>
<td>Remodeling</td>
<td>Stroke</td>
</tr>
<tr>
<td>Generalized atherosclerosis</td>
<td>Intracerebral hemorrhage</td>
</tr>
<tr>
<td>Atheroscleortic stenosis</td>
<td>Lacunar infarction</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>Vascular dementia</td>
</tr>
<tr>
<td></td>
<td>Retinopathy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Heart disease</th>
<th>Nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular hypertrophy</td>
<td>Albunimuria</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Proteinuria</td>
</tr>
<tr>
<td>Coronary microangiopathy</td>
<td>Chronic renal insufficiency</td>
</tr>
<tr>
<td>Coronary heart disease, Myocardial infarction</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
</tr>
</tbody>
</table>

[Schmieder RE, 2010]
Generalized vasculopathy

[Schmieder RE, 2010]
Hypertensive heart disease

Hemodynamic load
- Blood pressure magnitude (afterload)
- Hypervolemia (preload)
- Elevated PWV

- Age
- Sex
- Ethnic factors
- Genes (positive family history)

LVH

- Reduced coronary reserve (microangiopathy)
- Impaired contractility
- Reduced LV filling

- Salt consumption
  - Obesity
  - Sympathetic nervous system
  - Cathecolamines
  - Angiotensin II
  - Aldosteron

- Myocardial infarction (macroangiopathy)
- Systolic
- Diastolic
- Heart failure

- Atrial fibrillation
- Ventricular arrhythmias
  - Sudden death
  - Cardiac emboli

[Schmieder RE, 2010]
Diagnosis of early hypertensive end organ damage

Definitions of subclinical organ damage associated with HT: 2007 ESC guideline

<table>
<thead>
<tr>
<th>Electrocardiographic left ventricular hypertrophy</th>
<th>Sokolow-Lyon ≥ 38 mm, Cornell &gt; 2440 mm×msec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiographic left ventricular hypertrophy</td>
<td>LVMI ≥ 125 g/m² for men and ≥ 110 g/m² for women</td>
</tr>
<tr>
<td>Carotid intima-media thickness (Carotid IMT) &gt; 0.9 mm or plaque</td>
<td></td>
</tr>
<tr>
<td>Carotid-femoral pulse wave velocity &gt; 12 m/sec</td>
<td></td>
</tr>
<tr>
<td>Ankle-Brachial BP Index &lt; 0.9</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine elevated</td>
<td>Men: 1.3–1.5mg/dl (115–33 μmol/l), Women:1.2–1.4mg/dl (107–24 μmol/l)</td>
</tr>
<tr>
<td>Elevated albumin excretion</td>
<td>Microalbuminuria: 30–300 mg/24 hours, Albumin-creatinine ratio: men ≥ 22, women ≥ 31 mg/g creatinine</td>
</tr>
<tr>
<td>Low estimated glomerular filtration rate (&lt; 60 ml/min/1.73 m²)</td>
<td>or creatinine clearance &lt; 60 ml/min</td>
</tr>
</tbody>
</table>

[Mancia G et al, 2009]
Increased arterial stiffness: independent predictor of adverse CV outcomes including mortality, MI, stroke, Af, cognitive decline, renal dysfunction

GENOA study cohort
N= 812, mean age: 58 years, F:58%, hypertensives: 71%

Burden of subclinical disease

higher PWV (1 m/s increase) was significantly associated

- with higher log (CAC+1) ($\beta\pm SE = 0.14\pm0.04$; $p=0.003$),
- lower ABI ($\beta\pm SE= -0.005 \pm0.002;p=0.02$),
- greater log (WMH) ($\beta\pm SE=0.03\pm0.009; p=0.002$),
- but not with log (UACR+1) ($p= 0.66$)

[Coutinho T et al, 2011]
Subclinical atherosclerosis and arteriosclerosis

Higher aPWV was independently associated with greater burden of subclinical disease in coronary, lower extremity, and cerebral arterial beds.

[Coutinho T et al, 2011]
Further prospective studies are needed
- temporality of association b/t arterial stiffness and TOD

Randomized clinical trials
- improvement of arterial stiffness could prevent or slow the progression of TOD in HT patients

[Coutinho T et al, 2011]
CIMT and presence or absence of plaque improves prediction of CHD Risk

Baseline characteristics: Atherosclerosis Risk In Communities (ARIC) study, 1987-99
n= 13,415. mean age: 54.0 year-old, mean FU duration: 15.1 years

Traditional CV risk (TRF) vs add CIMT and pretense of plaque → improved CHD prediction ?

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 5,682)</th>
<th>Women (n = 7,463)</th>
<th>Entire Sample (n = 13,145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>54.42 (5.8)</td>
<td>53.75 (5.7)</td>
<td>54.0 (5.8)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.23 (4.0)</td>
<td>27.46 (5.8)</td>
<td>27.36 (5.1)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>122.1 (17.7)</td>
<td>119.7 (19.1)</td>
<td>120.72 (18.6)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>75.5 (11.2)</td>
<td>71.9 (10.9)</td>
<td>73.46 (11.2)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>210.2 (39.4)</td>
<td>217.0 (42.1)</td>
<td>214.0 (41.1)</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>130.4 (67.0)</td>
<td>117.1 (60.5)</td>
<td>122.9 (63.7)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>45.3 (13.9)</td>
<td>58.2 (17.2)</td>
<td>52.6 (17.1)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>138.8 (37.2)</td>
<td>135.4 (40.2)</td>
<td>136.8 (39.0)</td>
</tr>
<tr>
<td>CIMT 25th percentile (unadjusted), mm</td>
<td>0.65</td>
<td>0.58</td>
<td>0.61</td>
</tr>
<tr>
<td>CIMT 75th percentile (unadjusted), mm</td>
<td>0.84</td>
<td>0.74</td>
<td>0.78</td>
</tr>
<tr>
<td>Fasting glucose, mg/dl</td>
<td>106.3 (28.0)</td>
<td>104.1 (32.6)</td>
<td>105.0 (30.7)</td>
</tr>
<tr>
<td>Whites</td>
<td>77.7%</td>
<td>72.6%</td>
<td>74.8%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10.3%</td>
<td>10.0%</td>
<td>10.1%</td>
</tr>
<tr>
<td>Current tobacco use</td>
<td>27.6%</td>
<td>25.0%</td>
<td>26.1%</td>
</tr>
<tr>
<td>Former tobacco use</td>
<td>43.2%</td>
<td>22.48%</td>
<td>31.5%</td>
</tr>
<tr>
<td>Cholesterol-lowering medication use</td>
<td>2.3%</td>
<td>2.6%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Aspirin use (%)</td>
<td>41.1%</td>
<td>49.4%</td>
<td>45.8%</td>
</tr>
<tr>
<td>Statin use (%)</td>
<td>0.3%</td>
<td>0.6%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

[Nambi V et al, 2010]
Adjusted area under curve (AUC) for different model: Compared with with TRF-Only

<table>
<thead>
<tr>
<th>Model</th>
<th>Overall</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRF only</td>
<td>0.742</td>
<td>0.674</td>
<td>0.759</td>
</tr>
<tr>
<td>TRF+CIMT</td>
<td>0.750 (0.005 to 0.012)</td>
<td>0.690 (0.009 to 0.022)</td>
<td>0.762 (−0.002 to 0.006)</td>
</tr>
<tr>
<td>TRF+plaque</td>
<td>0.751 (0.006 to 0.013)</td>
<td>0.686 (0.005 to 0.017)</td>
<td>0.770 (0.005 to 0.016)</td>
</tr>
<tr>
<td>TRF+CIMT+plaque</td>
<td>0.755 (0.008 to 0.017)</td>
<td>0.694 (0.011 to 0.027)</td>
<td>0.770 (0.005 to 0.017)</td>
</tr>
<tr>
<td>TRF+CIMT+plaque vs. TRF+IMT</td>
<td>(0.001 to 0.006)</td>
<td>(−0.001 to 0.006)</td>
<td>(0.003 to 0.012)</td>
</tr>
<tr>
<td>TRF+IMT+plaque vs. TRF+plaque</td>
<td>(0.001 to 0.005)</td>
<td>(0.002 to 0.011)</td>
<td>(−0.002 to 0.002)</td>
</tr>
</tbody>
</table>

AUC = area under the curve; CI = confidence interval; CIMT = carotid intima-media thickness; TRF = traditional risk factors.

[Folak JF et al, 2011]
Number and percent re-classified in CHD risk category and observed CHD risk
- CIMT and plaque information added to TRF (traditional risk) prediction models

### Table: Net reclassification index (NRI) in intermediate group

<table>
<thead>
<tr>
<th>Model</th>
<th>Overall</th>
<th>Clinical NRI</th>
<th>Men</th>
<th>Clinical NRI</th>
<th>Women</th>
<th>Clinical NRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRF vs. TRF + CIMT</td>
<td>NRI: 7.1 (2.2 to 10.6)</td>
<td>Clinical NRI: 16.7 (9.3 to 22.4)</td>
<td>NRI: 8.9 (3.4 to 15.1)</td>
<td>Clinical NRI: 15.8 (8.6 to 24.6)</td>
<td>NRI: 6.1 (-2.3 to 9.4)</td>
<td>Clinical NRI: 15.9 (1 to 23.3)</td>
</tr>
<tr>
<td>TRF vs. TRF + plaque</td>
<td>NRI: 7.7 (2.3 to 11.4)</td>
<td>Clinical NRI: 17.7 (10.9 to 24.7)</td>
<td>NRI: 4.2 (0.2 to 12.2)</td>
<td>Clinical NRI: 10.5 (4.5 to 20.5)</td>
<td>NRI: 10.2 (0.7 to 15.4)</td>
<td>Clinical NRI: 25.6 (7.8 to 37.6)</td>
</tr>
<tr>
<td>TRF vs. TRF + CIMT + plaque</td>
<td>NRI: 9.9 (3.8 to 13.5)</td>
<td>Clinical NRI: 21.7 (13.4 to 28.2)</td>
<td>NRI: 8.9 (4.1 to 17.1)</td>
<td>Clinical NRI: 16.4 (9.5 to 27)</td>
<td>NRI: 9.8 (1.1 to 15.4)</td>
<td>Clinical NRI: 25.4 (9 to 37)</td>
</tr>
<tr>
<td>TRF + CIMT vs. TRF + CIMT + plaque</td>
<td>NRI: 2.8 (-1.2 to 6.4)</td>
<td>Clinical NRI: 10.6 (3.8 to 16.5)</td>
<td>NRI: 0.03 (-2.6 to 6.3)</td>
<td>Clinical NRI: 5.1 (0.3 to 13.2)</td>
<td>NRI: 3.6 (-1.7 to 11.6)</td>
<td>Clinical NRI: 12.8 (2.5 to 28.6)</td>
</tr>
<tr>
<td>TRF + plaque vs. TRF + CIMT + plaque</td>
<td>NRI: 2.1 (-1.1 to 5.3)</td>
<td>Clinical NRI: 7.9 (2.6 to 13.3)</td>
<td>NRI: 4.8 (-0 to 10)</td>
<td>Clinical NRI: 10.7 (4.3 to 19)</td>
<td>NRI: -0.3 (-3.7 to 3.6)</td>
<td>Clinical NRI: 2.5 (-3.5 to 10.3)</td>
</tr>
</tbody>
</table>

Values are n (%) and Kaplan-Meier 10-year risk (%). All observed risks have been interpolated to 10-year event rates by Kaplan-Meier risk estimates using the actual observed events over a mean follow-up of 15.7 years.
CIMT and presence or absence of plaque improves prediction of CHD Risk

CHD incidence rate/1,000 person-years

[Nambi V et al, 2010]
CIMT and Cardiovascular Events

Framingham Offspring Study cohort
N= 2965, mean FU: 7.2 years → CVD (+), n=296

- mean IMT of common carotid artery, maximum IMT in internal carotid artery
- Re-classification of CHD risk using 8-year Framingham risk score after adding IMT

![Table](image)

**Characteristics**
- Duration of follow-up (yr)
- Age (yr)
- Female sex (no. %)
- Systolic blood pressure (mm Hg)
- Treatment for high blood pressure (no. %)
- Cholesterol (mg/dl)
- Intima-media thickness

**Values**
- No CVD at Follow-up (N=2669)
- CVD at Follow-up (N=296)

**Intima-media thickness**
- Mean CCA thickness (mm)
- Maximum ICA thickness (mm)
- ICA thickness > 1.5 mm, indicating plaque (no. %)

[Folak JF et al, 2011]
Hazard Ratio for Cardiovascular disease

with and without Internal Carotid Artery (ICA) Intima–Media Thicknesses

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Model with Risk Factors Only</th>
<th>Model with Risk Factors and ICA Intima–Media Thickness</th>
<th>Model with Risk Factors and ICA Intima–Media Thickness &gt;1.5 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio or C Statistic (95% CI)</td>
<td>P Value</td>
<td>Hazard Ratio or C Statistic (95% CI)</td>
</tr>
<tr>
<td>Sex, female vs. male</td>
<td>0.74 (0.57–0.95)</td>
<td>0.02</td>
<td>0.78 (0.61–1.01)</td>
</tr>
<tr>
<td>Age, per increase of 1 yr</td>
<td>1.05 (1.04–1.07)</td>
<td>&lt;0.001</td>
<td>1.05 (1.03–1.06)</td>
</tr>
<tr>
<td>Systolic pressure, per increase of 1 mm Hg</td>
<td>1.01 (1.01–1.02)</td>
<td>&lt;0.001</td>
<td>1.01 (1.01–1.02)</td>
</tr>
<tr>
<td>Treatment for high blood pressure, yes vs. no</td>
<td>1.55 (1.21–2.00)</td>
<td>&lt;0.001</td>
<td>1.51 (1.18–1.95)</td>
</tr>
<tr>
<td>Cholesterol, per increase of 1 mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.00 (1.00–1.01)</td>
<td>0.02</td>
<td>1.00 (1.00–1.01)</td>
</tr>
<tr>
<td>HDL</td>
<td>0.98 (0.97–0.99)</td>
<td>&lt;0.001</td>
<td>0.98 (0.97–0.99)</td>
</tr>
<tr>
<td>Diabetes, yes vs. no</td>
<td>1.44 (1.06–1.97)</td>
<td>0.02</td>
<td>1.41 (1.03–1.92)</td>
</tr>
<tr>
<td>Cigarette smoking, yes vs. no</td>
<td>2.23 (1.67–2.98)</td>
<td>&lt;0.001</td>
<td>2.10 (1.57–2.81)</td>
</tr>
</tbody>
</table>

[ICA intima–media thickness]

- Per increase of 1 mm: 1.26 (1.16–1.36) <0.001
- Per increase of 1 SD: 1.21 (1.13–1.29) <0.001
- Thickness ≥1.5 mm, representing plaque: 1.92 (1.49–2.47) <0.001

C statistic: 0.748 (0.719–0.776) 0.758 (0.730–0.785) 0.762 (0.734–0.789)

[Folak JF et al, 2011]
Net Reclassification Index

Reclassification of Framingham risk score categories after addition of IMT of ICA

<table>
<thead>
<tr>
<th>Original Risk Category</th>
<th>Reclassification</th>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants without cardiovascular events</td>
<td>NRI : 1.8 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>&lt; 6%</td>
<td>1125</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>6-20 %</td>
<td>85</td>
<td>1126</td>
<td>45</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt; 20%</td>
<td>0</td>
<td>40</td>
<td>234</td>
</tr>
<tr>
<td>Participants with cardiovascular events</td>
<td>NRI : 5.8 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>&lt; 6%</td>
<td>27</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>6-20 %</td>
<td>1</td>
<td>112</td>
<td>13</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt; 20%</td>
<td>0</td>
<td>5</td>
<td>94</td>
</tr>
</tbody>
</table>

NRI: Overall 7.6 %, p<0.001

[Folak JF et al, 2011]
Plaque vs New onset CVD

Overall, n=2964

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>No Plaque</th>
<th>Plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CVD Risk</td>
<td>134/1191</td>
<td>11.3%</td>
</tr>
<tr>
<td>Low CVD Risk (0 to &lt;6%)</td>
<td>513/1382</td>
<td>37.1%</td>
</tr>
<tr>
<td>Intermediate CVD Risk (6 to 20%)</td>
<td>257/373</td>
<td>68.9%</td>
</tr>
</tbody>
</table>

[Oake JF et al, 2011]
Subclinical coronary atherosclerosis vs cardiovascular risk in different stages of HT

Population-based Heinz Nixdorf Recall Study cohort. N= 4181, median FU: 7.18 years, Cross sectional longitudinal outcome study

115 primary end points (2.8%: fatal and nonfatal myocardial infarction)
152 secondary end points (3.6%: stroke and coronary revascularization)

cross-sectional relationship and longitudinal outcome between JNC VII BP categories and coronary artery calcification (CAC)

[Erbel R et al, 2012]
Hazard Ratio of primary and secondary end points

JNC 7 BP categories compared with normotensives

<table>
<thead>
<tr>
<th>JNC 7 Categories</th>
<th>Crude Estimate (95% CI)</th>
<th>Adjusted Estimate (95% CI), Model 1*</th>
<th>Adjusted Estimate (95% CI), Model 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotension</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>1.45 (1.10–2.09)</td>
<td>1.23 (0.87–1.74)</td>
<td>1.22 (0.87–1.72)</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>3.19 (2.17–4.69)</td>
<td>2.09 (1.44–3.02)</td>
<td>1.96 (1.36–2.83)</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>5.33 (3.75–7.59)</td>
<td>2.95 (2.09–4.15)</td>
<td>2.74 (1.94–3.86)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotension</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>1.93 (1.52–2.47)</td>
<td>1.49 (1.18–1.88)</td>
<td>1.42 (1.13–1.79)</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>2.49 (1.87–3.31)</td>
<td>1.65 (1.25–2.18)</td>
<td>1.55 (1.17–2.04)</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>4.88 (3.93–6.05)</td>
<td>2.80 (2.25–3.48)</td>
<td>2.51 (2.02–3.13)</td>
</tr>
</tbody>
</table>

CAC indicates coronary artery calcification; JNC 7, Seventh Joint National Committee for Prevention Detection and Treatment of High Blood Pressure.

*Model 1 was adjusted for age.
†Model 2 was adjusted for age, cholesterol, diabetes mellitus, and ever smoking.

[Erbel R et al, 2012]
CAC score vs JNC VII BP categories

[Erbel R et al, 2012]
fatal and non-fatal MI

stroke and coronary revascularization
[Erbel R et al, 2012]
Combined Endpoint Event Rates in Prehypertension

Risk of myocardial infarction and stroke in HT but also in pre-HT depends on the degree of CAC

[Erbel R et al, 2012]
Summary-2

- **PWV**
  - independently associated with greater burden of subclinical disease in coronary, lower extremity and cerebral arterial beds.

- **CMIT improves CHD risk prediction**
  - adding plaque and CIMT to TRF
  - adding plaque and max. IMT of internal carotid artery

- **CAC**
  - cumulative event rates were determined by BP categories and CAC
  - risk of MI/ stroke in HT but also in pre-HT depends on the degree of CAC
Take home massage

- ABPM or HBPM
  - useful in early detection of TOD compared with clinic BP monitoring

- PWV, CIMT, CAC - useful biomarker of TOD

? Different clinical significance of each method for predicting TOD

- PWV: association with subclinical burden (cross-sectional study only)
- CIMT: useful for primary prevention (7.2 year, 10 year F/U data)
- CAC: useful in management for prehypertensives
<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of the Study Participants (n = 812 Unless Otherwise Specified)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean/No.</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Age, yrs</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
</tr>
<tr>
<td>Statin use</td>
</tr>
<tr>
<td>Antihypertensive use</td>
</tr>
<tr>
<td>ACE inhibitor/ARB use</td>
</tr>
<tr>
<td>Calcium channel blocker use</td>
</tr>
<tr>
<td>Beta-blocker use</td>
</tr>
<tr>
<td>Diuretic use</td>
</tr>
<tr>
<td>Aspirin use</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Smoking (past or current)</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, ml/min/1.73 m²</td>
</tr>
<tr>
<td>Coronary artery calcification score (n = 791)</td>
</tr>
<tr>
<td>Ankle-brachial index (n = 773)</td>
</tr>
<tr>
<td>White matter hyperintensity volume, cm³ (n = 638)</td>
</tr>
<tr>
<td>Urine albumin-creatinine ratio, mg/g (n = 760)</td>
</tr>
<tr>
<td>Aortic pulse wave velocity, m/s</td>
</tr>
<tr>
<td>Coronary artery calcification present</td>
</tr>
<tr>
<td>Ankle-brachial index &lt;0.9</td>
</tr>
<tr>
<td>White matter hyperintensity volume &gt;5.7 cm³</td>
</tr>
<tr>
<td>Urine albumin/creatinine ratio &gt;10, mg/g</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein.