

# 뇌졸중 아형, 위험인자, 역학



정근화

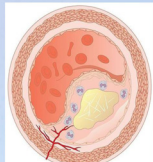
서울대학교병원 신경과

## Flame-up process

### Endothelial Injury

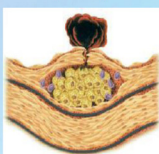


### Inflammation



- Macrophage/mast cell/T cell activation
- Lipid accumulation/Foam cell formation
- Cytokine/GF release
- Smooth muscle cell proliferation
- Neovascularization

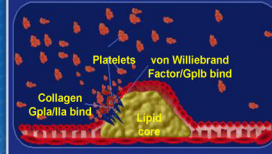
### Plaque rupture



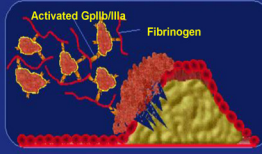
- Smooth muscle cell apoptosis in the atherosclerotic plaque cap
- Secretion of metalloproteinase and other connective tissue enzyme
- Break down the collagen
- Exposure core to arterial blood
- Induce thrombosis

## Formation of the Platelet Plug

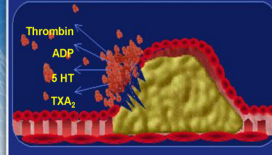
### Adhesion



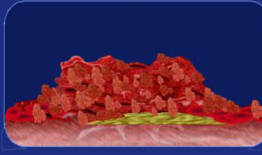
### Aggregation



### Activation

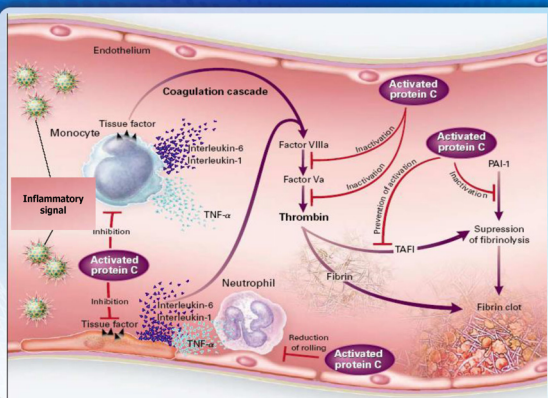


### Platelet Plug

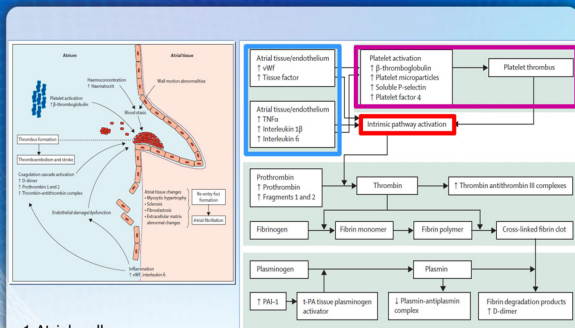


Kumar A et al. Exp Opin Invest Drugs. 1997. SNUH

## Formation of the Fibrin Plug



## Thrombosis in Afib



1. Atrial wall
2. Flow (stasis)
3. Blood constituents (Hb, plt, inflammation, coagulation cascade)

Lancet 2009;373:155-166 SNUH

## Recurrence by ischemic stroke subtype

|                                     | 30-day | 1-yr | 5-yr |
|-------------------------------------|--------|------|------|
| <b>All stroke</b>                   | 2%     | 8%   | 16%  |
| <b>Extracranial atherosclerotic</b> | 9%     | 11%  | 23%  |
| <b>Intracranial atherosclerotic</b> | 8%     | 12%  | 16%  |
| <b>Cardioembolic</b>                | 4%     | 7%   | 21%  |
| <b>Lacunar</b>                      | 1.4%   | 10%  | 14%  |
| <b>Cryptogenic</b>                  | 0.4%   | 6%   | 15%  |

Dhamoon et al., Neurology, 2006

## Oxfordshire Community Stroke Project

- Bamford et al. 1991
- Use of clinical localization of the infarct topography
- Provides information more relevant to the prognosis than to the underlying vascular pathology
- TACI, PACI, LACI, POCI

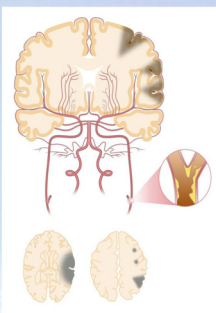
## TOAST classification

- Trial of ORG 10172 in Acute Stroke Treatment (TOAST)
- Adams, 1993
- LAA
- CE
- SVO
- SOE
- SUE

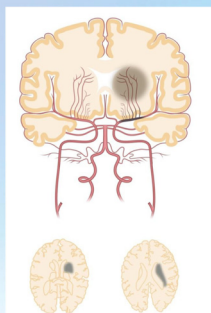
## Modified TOAST classification

- LAA
  - Artery to artery embolism
  - In situ thrombosis
  - Low flow

## Large artery atherosclerosis

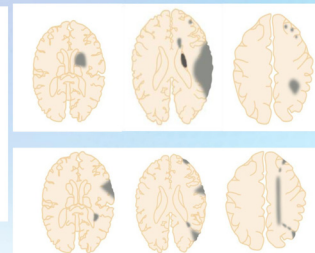
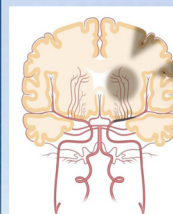


Artery to artery embolism



In situ thrombosis

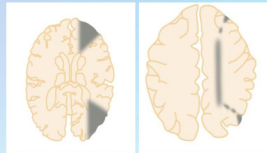
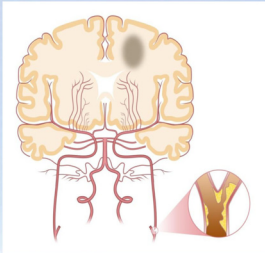
## Large artery atherosclerosis



Artery to artery embolism + in situ thrombosis



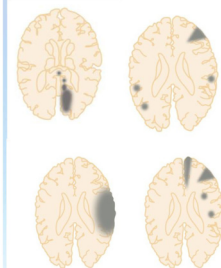
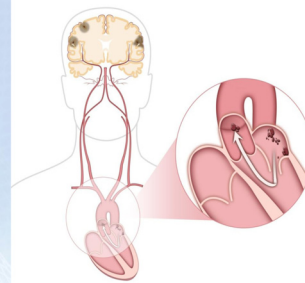
## Large artery atherosclerosis



Low flow or hemodynamic

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## Cardioembolism



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## Cardioembolism

### 2/3: nonvalvular atrial fibrillation

| Definite risk                  | Possible/Probable risk                            |
|--------------------------------|---------------------------------------------------|
| Atrial fibrillation            | Patent foramen ovale                              |
| Sustained atrial flutter       | Atrial septal aneurysm                            |
| Sick sinus syndrome            | Atrial or ventricular septal defects              |
| Atrial myxoma                  | Spontaneous echocontrast in left atrial appendage |
| Left atrial appendage thrombus | Subaortic hypertrophic cardiomyopathy             |
| Recent myocardial infarction   | Mitral valve prolapsed                            |
| Left ventricular akinesia      | Calcified aortic stenosis                         |
| Left ventricular thrombus      | Valve strands                                     |
| Dilated cardiomyopathy         | Fibroelastoma                                     |
| Prosthetic heart valve         | Left ventricular hypokinesia                      |
| Rheumatic mitral stenosis      |                                                   |
| Infective endocarditis         |                                                   |

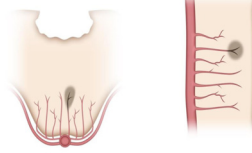
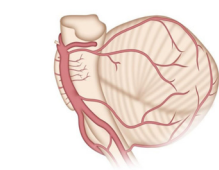
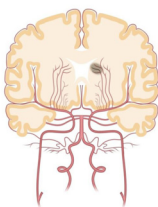
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## Difficulty in subtyping CE

- Many cardiac problems may coexist with cerebral atherosclerosis, and atrial fibrillation may occur just after an ischemic stroke.
- Clinical and radiological findings
  - Hemorrhagic transformation
  - Multiple territory
  - A smaller number of old T2 high signal lesions

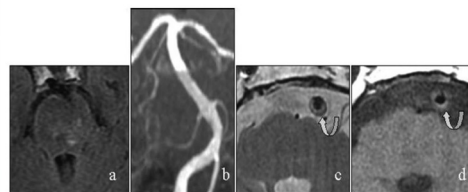
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## Small vessel occlusion



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## Small vessel occlusion ?



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## Stroke of Other Determined Causes

| Nonatherosclerotic vasculopathies | Inherited and miscellaneous disorders | Hypercoagulable disorders           |
|-----------------------------------|---------------------------------------|-------------------------------------|
| Arterial dissection               | Moyamoya disease                      | Antithrombin III deficiency         |
| Radiation-induced vasculopathy    | MELAS                                 | Protein C, S deficiency             |
| Migrainous infarction             | CADASIL                               | Factor V Leiden mutation            |
| Cerebral vasculitis               | Fibromuscular dysplasia               | Antiphospholipid antibody syndrome  |
| Infectious vasculitis             | Homocystinuria                        | Malignancy                          |
| Necrotizing vasculitis            | Fabry's disease                       | Pregnancy                           |
| Polyarteritis nodosa              | Marfan's syndrome                     | Oral contraceptives                 |
| Wegener's granulomatosis          | Ehlers-Danlos syndrome                | Polycythemia vera                   |
| Churg-Strauss syndrome            |                                       | Essential thrombocythemia           |
| Collagen vascular disease         |                                       | Thrombotic thrombocytopenic purpura |
| Systemic lupus erythematosus      |                                       | Chemotherapeutic agents             |
| Rheumatoid arthritis              |                                       |                                     |
| Scleroderma                       |                                       |                                     |
| Spargen's syndrome                |                                       |                                     |
| Giant cell arteritis              |                                       |                                     |
| Takayasu's arteritis              |                                       |                                     |
| Temporal arteritis                |                                       |                                     |
| Hypersensitivity vasculitis       |                                       |                                     |
| Henoch-Schönlein purpura          |                                       |                                     |
| Drug induced vasculitis           |                                       |                                     |
| Sarcoidosis                       |                                       |                                     |
| Behcet's disease                  |                                       |                                     |
| Ulcerative colitis                |                                       |                                     |

## 뇌졸중의 위험인자

### 고칠 수 없는 위험 요인

1. 나이 : 고령
2. 성별 : 남자
3. 가족력

### 고칠 수 있는 위험 요인

1. 고혈압
2. 흡연
3. 당뇨병
4. 고지혈증(콜레스테롤)
5. 심방세동
6. 심장병



## Relative risk, Prevalence

- Hypertension (4-5, 25-40%)
- Dyslipidemia (2, 6-50%)
- Smoking (1.5-3, 20-30%)
- Low activity (2.7, 20-30%)
- Obesity (2, 20%)
- Diabetes mellitus (1.5-3, 4-8%)
- Alcohol (1-4, 5-30%)
- Heart disease (2-4, 10-20%)
- Atrial fibrillation (5.6-17.6, 1%)

## 한국인에서 허혈성 뇌졸중에 대한 주요 위험인자들의 인구기여위험도

TABLE 2. Population-attributable risk for major risk factors of ischemic stroke

| Factors                | Sex   | Prevalence (%) | PAR (%)   | RR                                     |
|------------------------|-------|----------------|-----------|----------------------------------------|
| Hypertension           | Men   | 24.9*          | 19.9-30.5 | 212-2.76 <sup>13</sup>                 |
|                        | Women | 20.6*          | 17.1-26.6 | 212-2.76 <sup>13</sup>                 |
| Diabetes               | Men   | 7.2*           | 2.8- 7.2  | 1.414-2.08 <sup>14</sup>               |
|                        | Women | 5.9*           | 4.1- 7.2  | 1.7214-2.32 <sup>14</sup>              |
| Hyperlipidemia         | Men   | 6.2*           | 2.8- 4.0  | 1.46-1.67 <sup>15</sup>                |
|                        | Women | 7.4*           | 3.3- 4.7  | 1.46-1.67 <sup>15</sup>                |
| Smoking                | Men   | 62.2*          | 26.5      | 1.58 <sup>17</sup>                     |
|                        | Women | 5.5*           | 3.2       | 1.6 <sup>18</sup>                      |
| Atrial fibrillation    | Men   | 1.1*           | 3.5       | 4.27 <sup>21</sup>                     |
|                        | Women | 0.5*           | 2.8       | 6.85 <sup>21</sup>                     |
| Obesity                | Men   | 35.3*          | 6.6-23.5  | 1.29 <sup>19</sup> -1.87 <sup>24</sup> |
|                        | Women | 28.4*          | 5.4       | 1.2 <sup>25</sup>                      |
| Ischemic heart disease | Men   | 1.1*           | 0.8       | 1.73 <sup>26</sup>                     |
|                        | Women | 1.2*           | 0.7       | 1.55 <sup>26</sup>                     |
| History of stroke      | Men   | 1.6*           | 3.3       | 3.1 <sup>27</sup>                      |
|                        | Women | 1.2*           | 2.5       | 3.1 <sup>27</sup>                      |

Park et al, J KNA, 2009

## Risk factor assessment

| Step 1: Age |        | Step 4: Systolic Blood Pressure |                     |                   |                         | Step 6: Adding Up the Points |  |
|-------------|--------|---------------------------------|---------------------|-------------------|-------------------------|------------------------------|--|
| Years       | Points | Systolic BP (mm Hg)             | Points if Untreated | Points if Treated | Age                     |                              |  |
| 20-34       | -9     | <120                            | 0                   | 0                 | Total cholesterol       | —                            |  |
| 35-39       | -4     | 120-129                         | 0                   | 1                 | HDL-cholesterol         | —                            |  |
| 40-44       | 0      | 130-139                         | 1                   | 2                 | Systolic blood pressure | —                            |  |
| 45-49       | 3      | 140-159                         | 1                   | 2                 | Smoking status          | —                            |  |
| 50-54       | 6      | ≥160                            | 2                   | 3                 | Point total             | —                            |  |
| 55-59       | 8      |                                 |                     |                   |                         |                              |  |
| 60-64       | 10     |                                 |                     |                   |                         |                              |  |
| 65-69       | 11     |                                 |                     |                   |                         |                              |  |
| 70-74       | 12     |                                 |                     |                   |                         |                              |  |
| 75-79       | 13     |                                 |                     |                   |                         |                              |  |

| Step 2: Total Cholesterol |                     |                     |                     |                     |                     |
|---------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| TC (mg/dL)                | Points at Age 20-39 | Points at Age 40-49 | Points at Age 50-59 | Points at Age 60-69 | Points at Age 70-79 |
| <160                      | 0                   | 0                   | 0                   | 0                   | 0                   |
| 160-199                   | 4                   | 3                   | 2                   | 1                   | 0                   |
| 200-239                   | 7                   | 5                   | 3                   | 1                   | 0                   |
| 240-279                   | 9                   | 6                   | 4                   | 2                   | 1                   |
| ≥280                      | 11                  | 8                   | 5                   | 3                   | 1                   |

| Step 3: HDL-Cholesterol |        |  |  |  |  |
|-------------------------|--------|--|--|--|--|
| HDL-C (mg/dL)           | Points |  |  |  |  |
| ≥60                     | -1     |  |  |  |  |
| 50-59                   | 0      |  |  |  |  |
| 40-49                   | 1      |  |  |  |  |
| <40                     | 2      |  |  |  |  |

| Step 5: Smoking Status |                     |                     |                     |                     |                     |
|------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
|                        | Points at Age 20-39 | Points at Age 40-49 | Points at Age 50-59 | Points at Age 60-69 | Points at Age 70-79 |
| Nonsmoker              | 0                   | 0                   | 0                   | 0                   | 0                   |
| Smoker                 | 8                   | 5                   | 3                   | 1                   | 1                   |

| Step 7: CHD Risk |              |             |              |
|------------------|--------------|-------------|--------------|
| Point Total      | 10-Year Risk | Point Total | 10-Year Risk |
| <0               | <1%          | 11          | 8%           |
| 0                | 1%           | 12          | 10%          |
| 1                | 1%           | 13          | 12%          |
| 2                | 1%           | 14          | 16%          |
| 3                | 1%           | 15          | 20%          |
| 4                | 1%           | 16          | 25%          |
| 5                | 2%           | 17          | 30%          |
| 6                | 2%           | 18          | 35%          |
| 7                | 3%           | 19          | 40%          |
| 8                | 4%           | 20          | 45%          |
| 9                | 5%           | 21          | 50%          |
| 10               | 6%           | 22          | 55%          |

## 나이

55세 이후로 10세 증가 마다  
뇌졸중 발생률이 약 2배씩 증가

즉, 60세에 비해 70세는 약 2배,  
80세는 4배 정도로  
뇌졸중 발생률이  
높아진다.





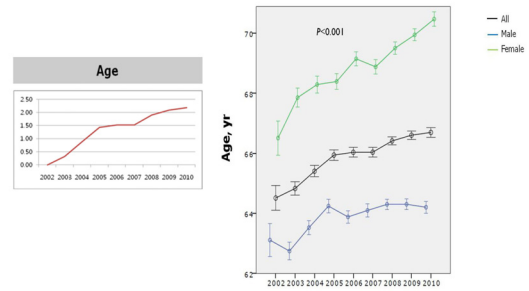
## 수명 연장

|    | 1970 | 1980 | 1985 | 1990 | 1999 | 2008 | 2009 | 2009-1999 | 2009-2008 |
|----|------|------|------|------|------|------|------|-----------|-----------|
| 전체 | 61.9 | 65.7 | 68.4 | 71.4 | 75.6 | 80.1 | 80.5 | 4.9       | 0.4       |
| 남자 | 58.7 | 61.8 | 64.4 | 67.3 | 71.7 | 76.5 | 77.0 | 5.3       | 0.5       |
| 여자 | 65.6 | 70.0 | 72.8 | 75.5 | 79.2 | 83.3 | 83.8 | 4.6       | 0.5       |
| 차이 | 6.9  | 8.2  | 8.4  | 8.2  | 7.5  | 6.8  | 6.8  | -0.7      | 0.0       |

2009 Life Tables for Korea, KOSIS

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## 뇌졸중의 발생연령



Jung et al., Circ Cardiovasc Qual Outcomes, 2012

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## 고혈압

| 분류      | 수축기혈압   |     | 이완기혈압 |
|---------|---------|-----|-------|
| 정상      | <120    | and | <80   |
| 전고혈압    | 120-139 | or  | 80-89 |
| 1단계 고혈압 | 140-159 | or  | 90-99 |
| 2단계 고혈압 | ≥160    | or  | ≥100  |

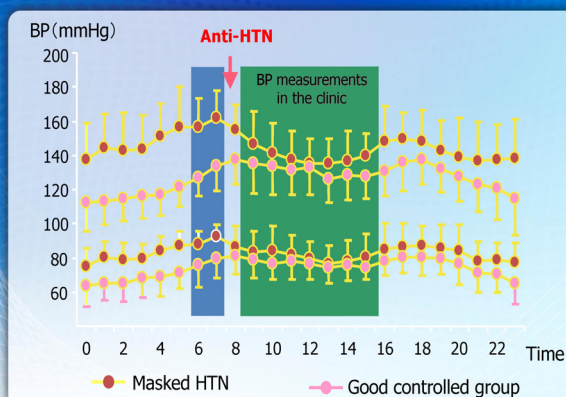
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## Home BP versus Hospital BP

|                              |                            |                               |
|------------------------------|----------------------------|-------------------------------|
| Home BP<br>(135/85 mmHg)     | Masked Hypertension (MHT)  | Sustained Hypertension (SHT)  |
|                              | Sustained Normal BP (SNBP) | White Coat Hypertension (WCH) |
| Hospital BP<br>(140/90 mmHg) |                            |                               |

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## Masked hypertension



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## 혈압을 낮추면

TABLE 3. Effect of Lowering Blood Pressure on Stroke, Myocardial Infarction, All Vascular Events, and Death

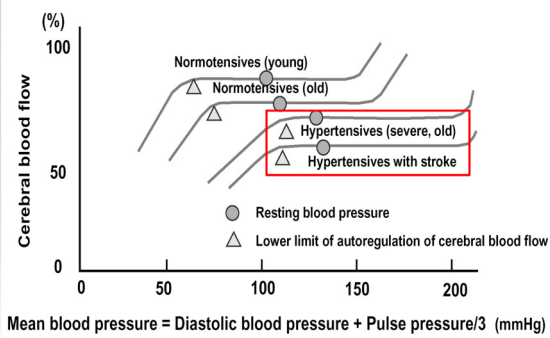
| Outcome                    | Trials | Events | Subjects | Rate in Control Group, % | OR   | 95% CI    | P     | Heterogeneity, P |
|----------------------------|--------|--------|----------|--------------------------|------|-----------|-------|------------------|
| Stroke, all                | 7      | 1577   | 15 527   | 11.5                     | 0.76 | 0.63-0.92 | 0.005 | 0.01             |
| Stroke, fatal              | 7      | 329    | 15 527   | 2.4                      | 0.76 | 0.56-1.03 | 0.08  | 0.16             |
| Stroke, nonfatal           | 7      | 1268   | 15 527   | 9.2                      | 0.79 | 0.65-0.95 | 0.01  | 0.042            |
| Myocardial infarction, all | 6      | 555    | 15 428   | 4.0                      | 0.79 | 0.63-0.98 | 0.03  | 0.19             |
| Vascular events, all       | 6      | 2225   | 15 428   | 16.0                     | 0.79 | 0.66-0.95 | 0.01  | 0.002            |
| Death, vascular            | 7      | 852    | 15 527   | 5.9                      | 0.86 | 0.70-1.06 | 0.16  | 0.066            |
| Death, all                 | 7      | 1427   | 15 527   | 9.6                      | 0.91 | 0.79-1.05 | 0.18  | 0.17             |

Odds ratio (OR) and 95% confidence intervals (CI) determined using a random effects model.

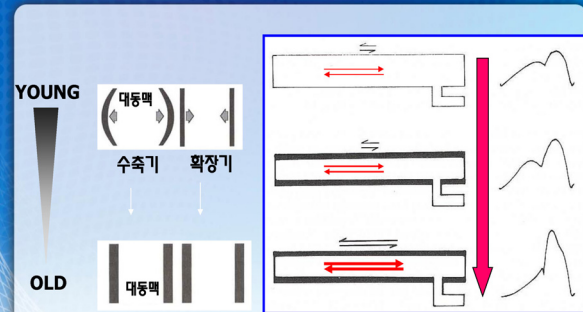
Rashid et al. Stroke 2003

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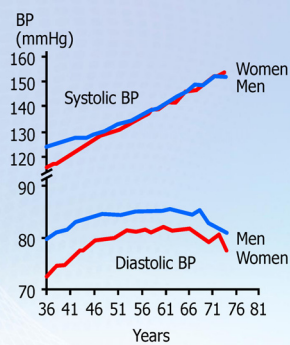
## Impaired autoregulation



## 혈관 탄성 변화 → 맥압 변화

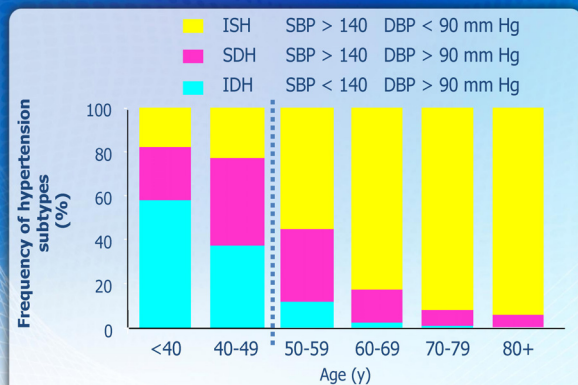


## Change of blood pressure parameter

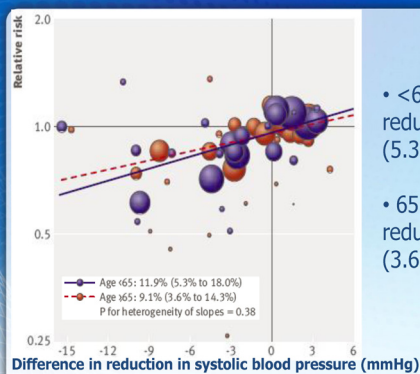


- 50세 이전: 확장기혈압
- 50-60세: 수축기혈압
- 60대 이후: 맥압

## Prevalence of ISH

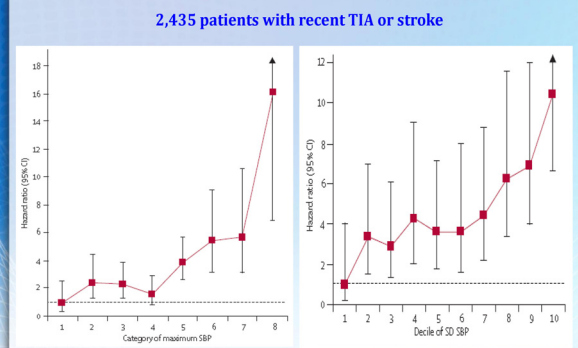


## Comparison of SBP lowering effect



- <65 : 11.9% risk reduction (5.3% vs 18.0%)
- 65+ : 9.1% risk reduction (3.6% vs 14.3%)

## BP variability



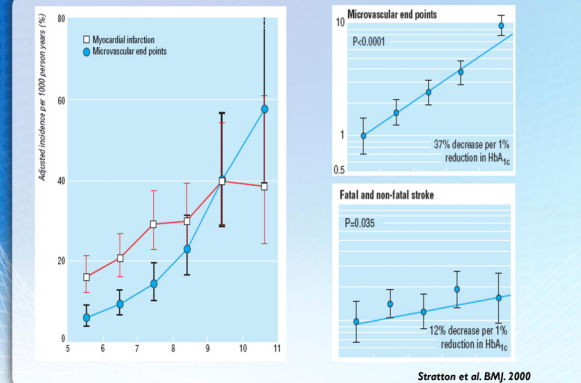


## Therapeutic target

- SBP as a more informative CV risk factor in patients older than 50 years
- Arterial Stiffness
  - Carotid-femoral PWV
  - PP is an independent marker of CV risk
- In subjects > 50 years of age, arterial stiffness becomes the main determinant of increased SBP and PP

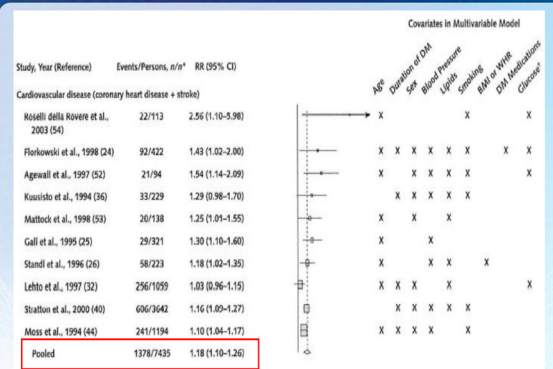
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## 당뇨



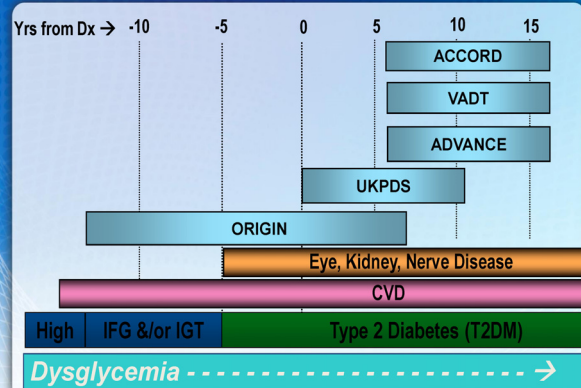
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## Meta-Analysis: HbA1c & CV Risk



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## Glucose Lowering to Prevent CVD



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## Glucose Lowering & Complications

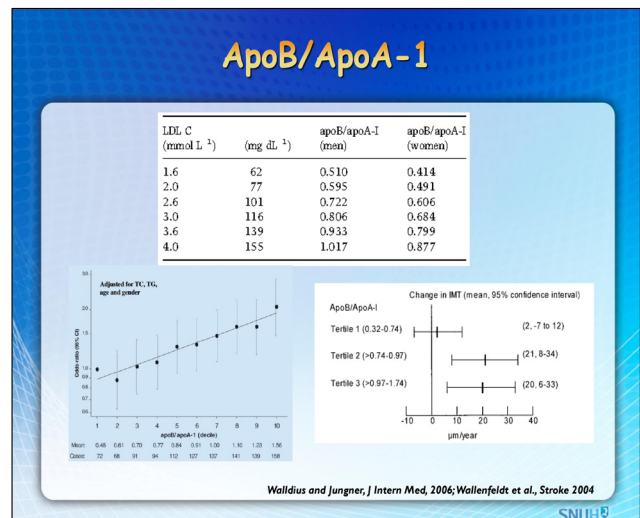
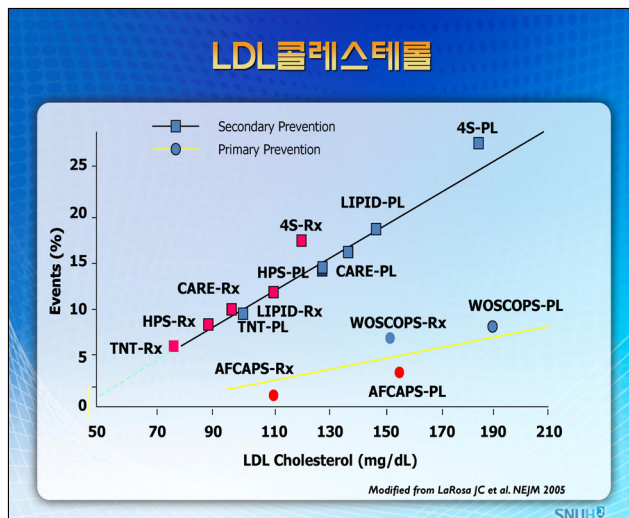
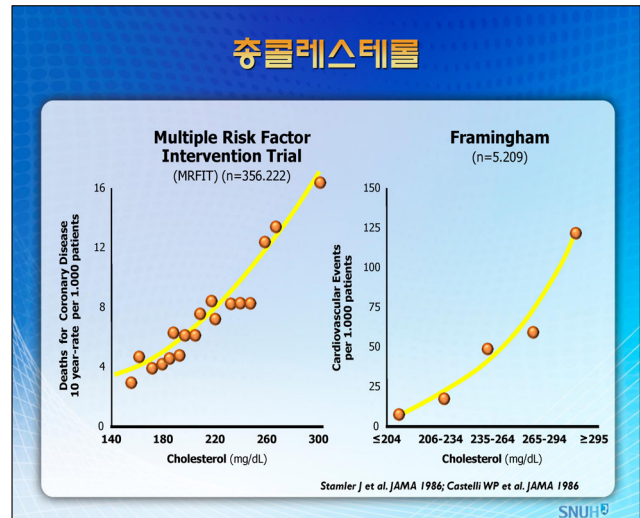
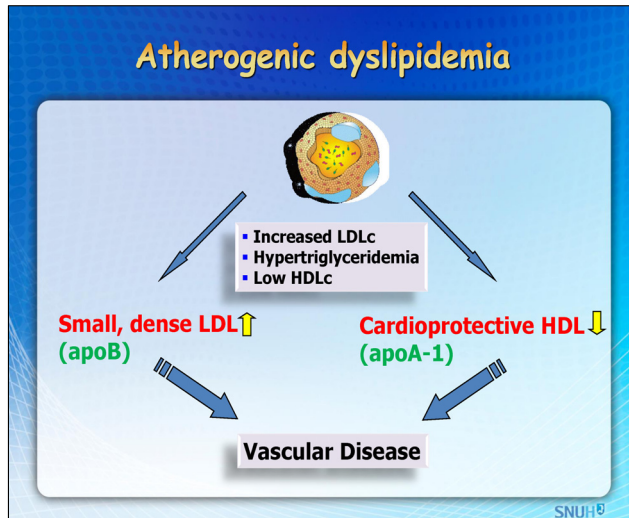
|             | Macrovascular                | Microvascular |
|-------------|------------------------------|---------------|
| Early DM    | Benefit                      | Benefit       |
| Advanced DM | No Benefit;<br>Possible Harm | Benefit       |

SNUH

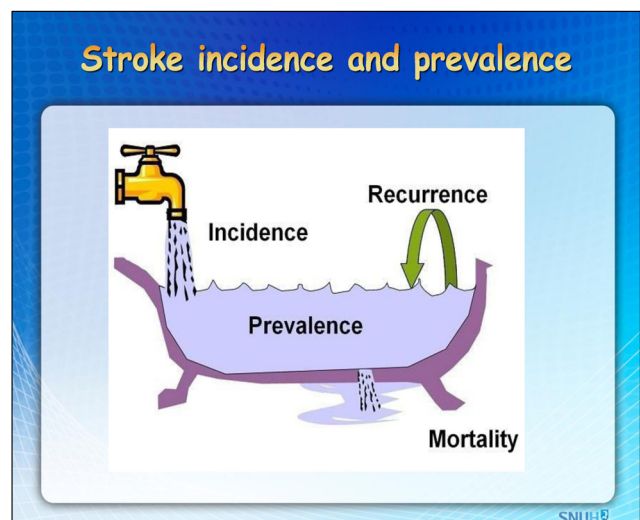
## 혈당과 뇌졸중

- Diabetes & non-diabetic dysglycemia may be independent risk factors for CVD.
- Tight glucose control in diabetic patients usually benefits the microvascular complications, not the macrovascular complications.
- Controlling combined RFs (HTN, HL) is more effective than tight glucose control for preventing stroke.

SNUH



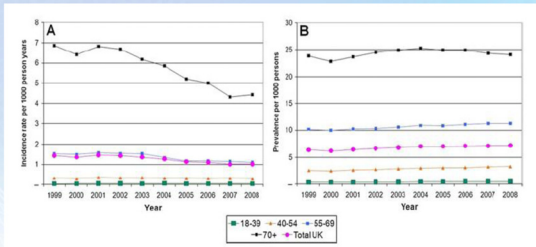
- ### Other risk factors
- Smoking
  - Alcohol
  - Inactivity
  - Metabolic syndrome
  - Sleep apnea
  - Nutrition, vitamin
  - Air pollution
  - Intestinal microorganism





## Incidence and prevalence in UK

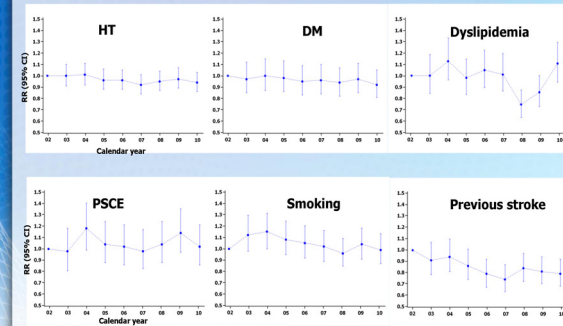
- Incidence fall by 30% (1.38/1000py→1.04)
- Prevalence increase by 12.5% (6.4 to 7.2)



Lee S, BMJ Open, 2011

SNUH

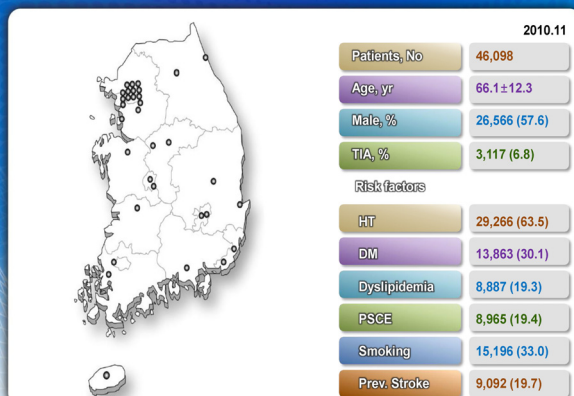
## Risk factors



Jung et al., Cir Cardiovasc Qual Outcomes, 2012

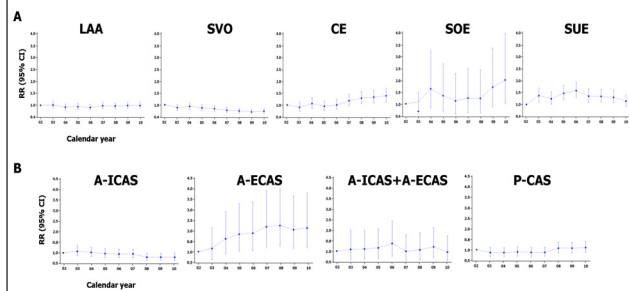
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## Korean Stroke Registry



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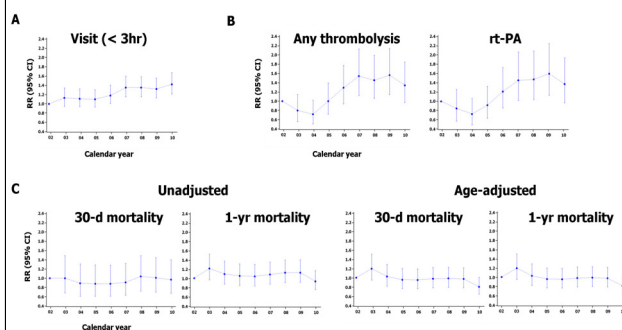
## Stroke subtypes



Jung et al., Cir Cardiovasc Qual Outcomes, 2012

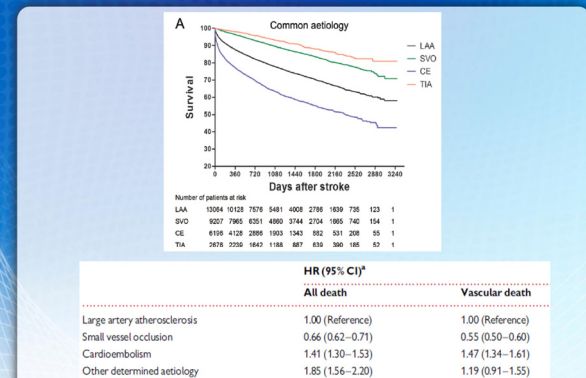
SNUH

## Practice and mortality



SNUH

## Mortality per mechanism



Kim et al., Eur Heart J, 2013

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### Ethnic distribution of RFs

|                               | Total<br>CVD<br>population<br>n<br>(n=18,992) | North<br>America<br>(n=5,967) | Latin<br>America<br>(n=423) | Western<br>Europe<br>(n=4,801) | Eastern<br>Europe<br>(n=2,194) | Middle<br>East<br>(n=221) | Asia incl.<br>Japan<br>(n=4,587) | Asia<br>without<br>Japan<br>(n=2,552) | Japan<br>(n=2,033) | Australia<br>(n=44) |
|-------------------------------|-----------------------------------------------|-------------------------------|-----------------------------|--------------------------------|--------------------------------|---------------------------|----------------------------------|---------------------------------------|--------------------|---------------------|
| Mean age $\pm$ SD, years      | 69.3 $\pm$ 10.1                               | 71.9 $\pm$ 10.3               | 69.1 $\pm$ 10.1             | 70.0 $\pm$ 9.5                 | 64.6 $\pm$ 9.3                 | 68.0 $\pm$ 10.1           | 67.9 $\pm$ 9.7                   | 65.5 $\pm$ 9.7                        | 70.9 $\pm$ 8.8     | 73.8 $\pm$ 8.8      |
| Male                          | 99.5                                          | 91.2                          | 86.3                        | 84.2                           | 99.7                           | 73.3                      | 66.1                             | 61.4                                  | 69.6               | 88.5                |
| Hypertension                  | 83.2                                          | 87.5                          | 79.0                        | 82.3                           | 87.6                           | 82.4                      | 78.0                             | 80.9                                  | 74.4               | 79.0                |
| Hypercholesterolemia          | 58.0                                          | 71.8                          | 48.5                        | 61.9                           | 44.2                           | 74.2                      | 42.5                             | 47.7                                  | 35.9               | 61.4                |
| Atrial fibrillation           | 13.4                                          | 16.0                          | 9.0                         | 15.1                           | 15.7                           | 10.0                      | 7.7                              | 7.0                                   | 8.6                | 16.3                |
| Diabetes                      | 37.2                                          | 43.3                          | 37.1                        | 34.7                           | 26.9                           | 49.3                      | 38.2                             | 39.6                                  | 36.5               | 22.9                |
| Treated diabetes              | 33.0                                          | 38.9                          | 35.8                        | 31.5                           | 22.4                           | 46.6                      | 33.5                             | 37.3                                  | 28.6               | 18.5                |
| Diabetic nephropathy          | 8.5                                           | 11.4                          | 6.7                         | 8.6                            | 4.1                            | 16.7                      | 7.7                              | 7.7                                   | 7.7                | 1.5                 |
| Obesity (BMI $\geq$ 30)       | 23.5                                          | 35.3                          | 22.0                        | 25.4                           | 25.9                           | 24.3                      | 5.3                              | 6.9                                   | 3.4                | 25.6                |
| Waist circumference obesity   | 42.5                                          | 53.1                          | 46.7                        | 50.2                           | 50.6                           | 35.1                      | 16.1                             | 20.6                                  | 10.7               | 54.4                |
| Current smokers               | 14.2                                          | 14.3                          | 6.9                         | 15.0                           | 17.8                           | 13.6                      | 13.8                             | 12.0                                  | 16.2               | 6.6                 |
| Former smokers                | 38.6                                          | 41.4                          | 36.5                        | 42.2                           | 27.3                           | 31.9                      | 35.6                             | 27.8                                  | 45.8               | 52.0                |
| Asymptomatic carotid stenosis | 8.8                                           | 9.8                           | 7.9                         | 13.2                           | 6.8                            | 8.6                       | 4.5                              | 4.2                                   | 4.8                | 4.2                 |
| Carotid plaque                | 32.0                                          | 28.4                          | 33.9                        | 45.1                           | 42.8                           | 34.4                      | 20.5                             | 21.8                                  | 18.7               | 11.5                |
| ABI $\leq$ 0.9                | 7.0                                           | 6.0                           | 6.6                         | 10.6                           | 10.5                           | 5.9                       | 3.6                              | 2.5                                   | 5.1                | 2.1                 |
| Mean ABI measured $\pm$ SD    | 0.91 $\pm$ 0.22                               | 0.92 $\pm$ 0.23               | 0.85 $\pm$ 0.22             | 0.97 $\pm$ 0.22                | 0.96 $\pm$ 0.22                | 0.91 $\pm$ 0.21           | 0.96 $\pm$ 0.20                  | 0.95 $\pm$ 0.19                       | 0.97 $\pm$ 0.20    | 1.00 $\pm$ 0.18     |
| Intermittent claudication     | 5.1                                           | 5.9                           | 4.8                         | 8.0                            | 2.8                            | 2.3                       | 2.4                              | 1.7                                   | 3.4                | 4.5                 |

REACH Registry Investigators, Cerebrovasc. Dis. 2008

### 최근의 뇌졸중 환자의 경향

- 뇌졸중 환자의 연령이 증가한다.
- 고지혈증의 빈도가 증가한다.
- 심장 색전증에 의한 뇌졸중의 빈도가 증가한다.
- 경동맥질환에 의한 뇌졸중의 빈도가 증가한다.
- 조급성기 치료율이 증가한다.
- 뇌졸중에 의한 사망률이 감소한다.