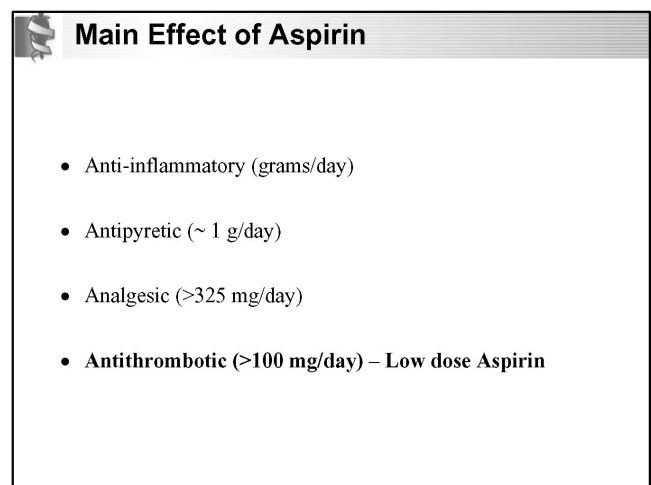
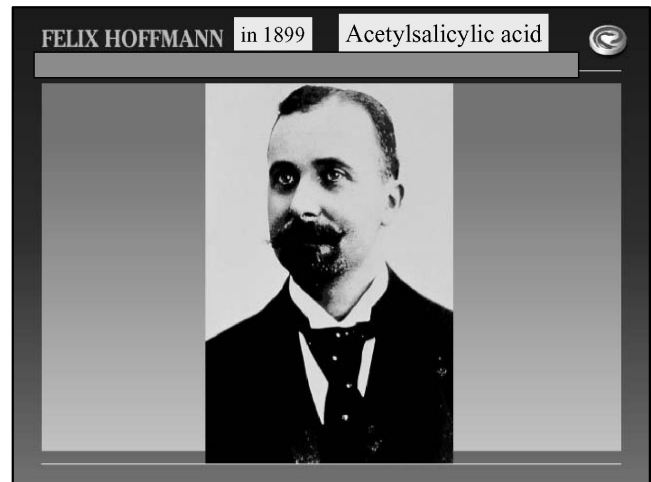
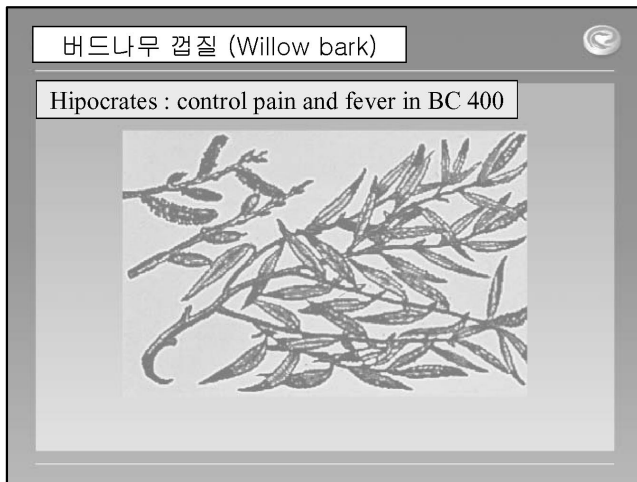


[연수강좌]

## 근거중심의 아스피린 처방 - 심혈관질환1차 예방약으로서의 Low-dose Aspirin -

최 기 준

울산의대 서울아산병원



- “고혈압 환자에게 아스피린을 다 처방해야 하나?”
- “당뇨 환자에게는?”

#### Should this patient be advised to take aspirin to reduce the risk of CHD?

- 53-year-old man
- No DM
- Cholesterol level 225mg
- A high-density lipoprotein(HDL) cholesterol level - 35mg
- A low-density lipoprotein(LDL) cholesterol level - 160mg
- Systolic blood pressure - 145/90 mmHg
- Never taken any medications for hypertension
- Smoker

#### Benefit of aspirin to prevent CHD

- Secondary prevention (with known heart disease)
  - Angina, Myocardial infarct patients --
    - Ischemic stroke / TIA
- Primary prevention
  - Prevention of thromboembolism in patients with Atrial fibrillation
  - Hypertensive patients
  - Diabetes patients

#### Recommendation for anticoagulation in chronic AF

(Harrison 2005, from ACC/AHA/ESC)

	< 65	65 - 75	> 75
- risk	A	A / W	W
+ risk	W	W	W

A : Aspirin  
W : Warfarin

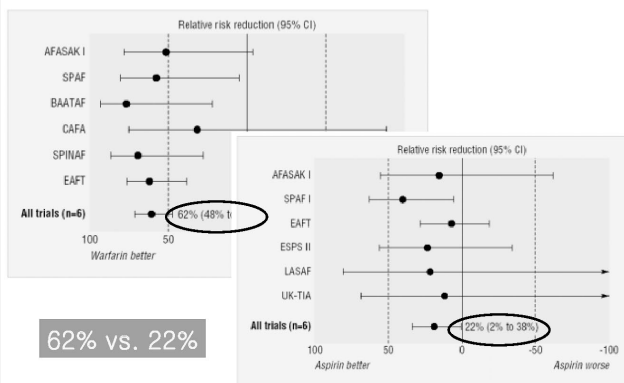
Aspirin :  
75-325mg/d

#### Risk Factors

Prior TIA, systemic embolus or stroke  
HT, poor LV function, CHF,  
rheumatic MVD, prosthetic valves,

#### Warfarin vs. Aspirin in AF

- meta analysis, *BMJ* 2002, *Lip et al.* -



#### Low-dose Aspirin in the Primary prevention of cardiovascular disease

#### How to balance the benefits

#### and the risks ?

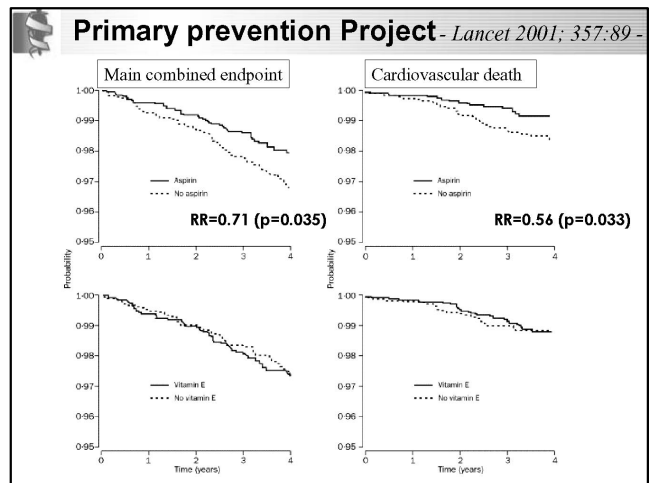
- Risk : Hemorrhagic stroke / major GI bleeding
- Benefit ← assessment of risk for CHD



### Primary Prevention Project (PPP)

- Lancet 2001; 357:89 -

- The efficacy in prevention of CV events
  - low-dose Aspirin (100mg/day)
  - vitamin E (300mg/day)
- Prospective randomized controlled trial
- N=4495 people with  $\geq 1$  major CV risk factors
  - Hypertension
  - Diabetes
  - Obesity
  - Hypercholesterolemia
  - Familial Hx of premature MI (< 55 years)
  - Old age ( $\geq 65$  years)
- Mean F/U of 3.6 years, study was prematurely stopped
- Primary endpoint : Combined endpoint (CV death, non-fatal MI, non-fatal stroke)



### Primary prevention Project

- Lancet 2001; 357:89 -

**Result :**

In patients  $\geq 50$  years old with 1 or more cardiovascular risk factors

Hypertension, Diabetes, Obesity, Hypercholesterolemia, Familial Hx of premature MI (< 55 years), elderly ( $\geq 65$  years)

Low-dose Aspirin was effective in reducing cardiovascular events

❖ Acceptable safety profile (Severe bleeding 1.1% vs. 0.3%)

### Who should be taken the Low-dose Aspirin for primary prevention of Cardiovascular disease?

- Hypertension
- Diabetes

### Hypertension Optimal Treatment (HOT)

- Lancet 1998;351:1755 -

- Prospective randomized study
- Patients with HT, DBP 100-115 mmHg
- 1. To assess the optimum target diastolic BP
  - :  $\leq 90$ mmHg in 6264 patients,  $\leq 85$ mmHg in 6264 patients
  - $\leq 80$ mmHg in 6262 patients
- 2. To assess the potential benefit of a low dose of aspirin in Hypertension
  - : 9399 patients in 75mg/day of aspirin
  - 9391 patients in Placebo
- Average F/U of 3.8 years
- Endpoint : Major CV event

### Hypertension Optimal Treatment (HOT)

- Lancet 1998;351:1755 -

- Low dose Aspirin Group
  - ✓ Reduce major CV event by 15% (p=0.03)
  - ✓ Reduce all MI by 36% (p=0.002)
  - ✓ No effect on Stroke
  - ✓ Same fatal bleeding
  - ✓ More non-fatal bleeding episodes in aspirin group (129/9399 vs 70/9391, p<0.001)

## In Hypertension

Intensive lowering of BP in patients with Hypertension was associated with a low-rate of CV events

Low-dose Aspirin significantly reduced the risk of Major CV events, but no effect on stroke



**Who should be taken the Low-dose Aspirin for primary prevention of Cardiovascular disease?**

- Hypertension
- Diabetes



## In Diabetics

- ✓ A 2-to 4-fold increased risk of CV death
- ✓ Enhanced production of thromboxane and hypersensitive to platelet aggregation in diabetics

## Results of DM subgroup in Randomized primary prevention studies

- % of diabetics : 2% ~ 17%
- Dose of aspirin : 75mg/day ~ 500mg/day
- PHS (Physicians' Health Study) - *NEJM 1989;321:129* -
  - Aspirin 325 mg qod
  - Fewer MI in diabetics taking aspirin : RR 0.39 (4.0% vs 10.1%)
- HOT (Hypertension Optimal Treatment) - *Lancet 1998;351:1755* -
  - Diabetics in 8%, aspirin 75mg/day
  - Greater benefit from aspirin in diabetics

## Results of DM subgroup in Randomized primary prevention studies

- ETDRS (Early Treatment of Diabetic Retinopathy Study) - *JAMA 1992* -
  - All type I or II diabetic patients, aspirin 650mg/day
  - Mixed primary and secondary prevention trial
  - All-cause mortality : RR 0.91, P=NS
  - Fatal and nonfatal MI : RR 0.83, p=0.04
  - No additional risk of retinal bleeding in aspirin group
- PPP (Primary Prevention Project) - *Diabetes Care 2003;26:3264* -
  - Diabetics in 17%, aspirin 100 mg/day
  - Lower effect of primary prevention of CV disease with low-dose aspirin in diabetics, as opposed to other CV risk factors

## Recommendation of American Diabetes Association

### Aspirin Therapy in Diabetes

AMERICAN DIABETES ASSOCIATION

- Diabetes Care 2003 -

1. Use aspirin as a secondary prevention in DM with evidence of CV disease
2. Consider aspirin therapy as a primary prevention in high risk men and women with type 1 or type 2 diabetes
  - Family Hx of CHD
  - Smoking
  - Hypertension
  - Obesity
  - Albuminuria
  - Age > 30 yrs
  - Lipid : cholesterol > 200mg/dl, LDL > 100mg/dl
3. Use enteric-coated Aspirin

## Contraindications to Aspirin Therapy

1. Aspirin therapy should not be recommended for patients under the age of 21 years (: Reye's synd.)
2. Aspirin allergy
  - Bleeding tendency
  - Anticoagulation therapy
  - Recent GI bleeding
  - Clinically active hepatic disease

## Meta-analysis of pooled data of aspirin

- Physicians' Health Study (1989)
- Aspirin in British Male Doctors (1988)
- Thrombosis Prevention Trial (1998)
- HOT study (1998)
- Primary Prevention Project (2001)

- Aspirin Tx reduced CHD risk 28%
- No significant effects on total mortality and stroke
- Major GI bleeding : 2-4 / 1000 middle aged persons (4-12 / 1000 older persons) given aspirin for 5 years
- Hemorrhagic stroke : 0-2 / 1000 persons for 5 years

- Ann Intern Med. 2002;136:157 -

## Estimates of Benefits and Harms of Aspirin Given for 5 years to 1000 Persons with Various Levels of Baseline Risk for Coronary Heart Disease

	Baseline risk for CHD over 5 year		
	1%	3%	5%
Total mortality	no effect	no effect	no effect
CHD events, n	1-4 avoided	4-12 avoided	6-20 avoided
Hemorrhagic strokes, n	0-2 caused	0-2 caused	0-2 caused
Major GI bleeding events, n#	2-4 caused	2-4 caused	2-4 caused

# Rates may be two to three times higher in persons older than 70 years of age

- Ann Intern Med. 2002;136:161 -

## Recent Recommendation

- U.S. Preventive Services Task Force (*Ann Intern Med.* 2002;136:157)  
: in patients at high risk for CHD, 5 year risk  $\geq$  3%
- AHA guideline (*Circulation* 2002;106:388)  
: in higher risk patients, especially 10 year risk of CHD  $\geq$  10%
- Uncontrolled HT may attenuate benefits of aspirin
- Dose : 75mg/d - 160mg/d (or 325mg every other day)

## How can estimate Coronary Heart Disease Risk?

### The Framingham Risk Score

[www.med-decisions.com](http://www.med-decisions.com) → heart to heart  
[www.intmed.mcw.edu/clincalc/heartrisk.html](http://www.intmed.mcw.edu/clincalc/heartrisk.html)



- Circulation 1999;100:1482 -

## Should this patient be advised to take aspirin to reduce the risk of CHD?

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- Cholesterol level 225mg
- A high-density lipoprotein(HDL) cholesterol level - 35mg
- A low-density lipoprotein(LDL) cholesterol level - 160mg
- Systolic blood pressure - 145/90 mmHg
- Never taken any medications for hypertension
- Smoker

Estimate of 10-Year Risk (Framingham Point Scores) Example		
<b>Step 1</b>		
Age		
Years	Points	
30-34	-1	
35-39	0	
40-44	1	
45-49	2	
50-54	3	
55-59	4	
60-64	5	
65-69	6	
70-74	7	
<b>Step 2</b>		
Total Cholesterol		
(mg/dl)	(mmol/L)	Points
<160	≤4.14	-3
160-199	4.15-5.17	0
200-239	5.18-6.21	1
240-279	6.22-7.24	2
≥280	≥7.25	3
<b>Key</b>		
Color		Risk
green		Very low
white		Low
yellow		Moderate
rose		High
red		Very high

Estimate of 10-Year Risk (Framingham Point Scores) Example		
<b>Step 3</b>		
HDL - Cholesterol		
(mg/dl)	(mmol/L)	Points
<35	≤0.90	2
35-44	0.91-1.16	1
45-49	1.17-1.29	0
50-59	1.30-1.55	0
≥60	≥1.56	-2

Estimate of 10-Year Risk (Framingham Point Scores) Example		
<b>Step 4</b>		
Blood Pressure		
Systolic (mmHg)	Diastolic (mmHg)	
	<80	80-84 85-89 90-99 ≥100
<120	0	
120-129		0 pts
130-139		1
140-159		2
>160		3 pts

Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Estimate of 10-Year Risk (Framingham Point Scores) Example		
<b>Step 5</b>		
Diabetes		Points
No		0
Yes		2
<b>Step 6</b>		
Smoker		Points
No		0
Yes		2

Estimate of 10-Year Risk (Framingham Point Scores) Example		
<b>Step 7 (sum from steps 1-6)</b>		
Adding up the points		
Age	Points	3
Total Cholesterol	Points	1
HDL Cholesterol	Points	1
Blood Pressure	Points	2
Diabetes	Points	0
Smoker	Points	2
Point Total	Points	9

## Estimate of 10-Year Risk (Framingham Point Scores) Example

Age	30-34 (2%)	35-39 (3%)	40-44 (3%)	45-49 (4%)	50-54 (5%)	55-59 (7%)	60-64 (8%)	65-69 (10%)	70-74 (13%)	Absolute Risk	Absolute Risk:
Points ↑										Total CHD	Hard CHD
0	1.0									2%	2%
1	1.5	1.0	1.0							3%	2%
2	2.0	1.3	1.3	1.0						4%	3%
3	2.5	1.7	1.7	1.3						5%	4%
4	3.5	2.3	2.3	1.8	1.4					7%	5%
5	4.0	2.6	2.6	2.0	1.6	1.1	1.0			8%	6%
6	5.0	3.3	3.3	2.5	2.0	1.4	1.3	1.0		10%	7%
7	6.5	4.3	4.3	3.3	2.6	1.9	1.6	1.3	1.0	13%	9%
8	8.0	5.3	5.3	4.0	3.2	2.3	2.0	1.6	1.2	16%	11%
9	10.0	6.7	6.7	5.0	4.0	2.9	2.5	2.0	1.5	20%	16%
10	12.5	8.3	8.3	6.3	5.0	3.6	3.1	2.5	1.9	25%	20%
11	15.5	10.3	10.3	7.8	6.1	4.4	3.9	3.1	2.3	31%	25%
12	18.5	12.3	12.3	9.3	7.4	5.2	4.6	3.7	2.8	37%	30%
13	22.5	15.0	15.0	11.3	9.0	6.4	5.6	4.5	3.5	45%	35%
≥14	26.5	≥17.7	≥17.7	≥13.3	≥10.6	≥7.6	≥6.6	≥5.3	≥4.1	≥53%	≥45%

### Color Key for Relative Risk

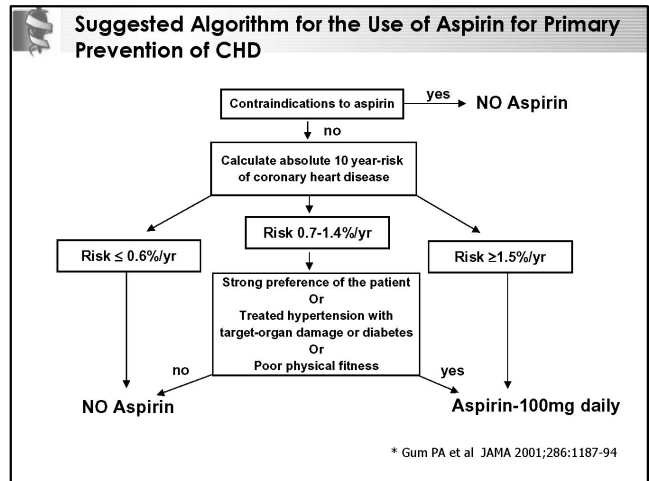
Green	Violet	Yellow	Red
Below Average risk	Average risk	Moderately above average risk	High risk

**Estimate of 10-Year Risk (Framingham Point Scores) Example**

**Absolute Risk (Total CHD) is over 16% / 10 years**  
*\* total CHD – all forms of clinical CHD*

**Absolute Risk (Hard CHD) is over 13% / 10 years**  
*\* hard CHD – clinical evidence of MI and coronary death*

→ **Low-dose aspirin should be recommended for primary prevention**



### Conclusion - Hypertension, Diabetes

Aspirin therapy for primary prevention can be recommended in patients with Hypertension and Diabetes with high CHD risk, provided that blood pressure is well controlled and the risk of GI and nasal bleedings is carefully assessed.

