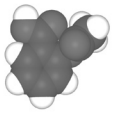
[연수강좌]

심혈관질환 예방 저용량 아스피린 요법

이 상 철

성균관의대 삼성서울병원 내과교실



溫故而知新

- Prevention of Cardiovascular Diseases with Aspirin -

Aspirin

Salicylate

Hippocrates: powder from willow bark as an analgesic / antipyretic (B.C. 400)

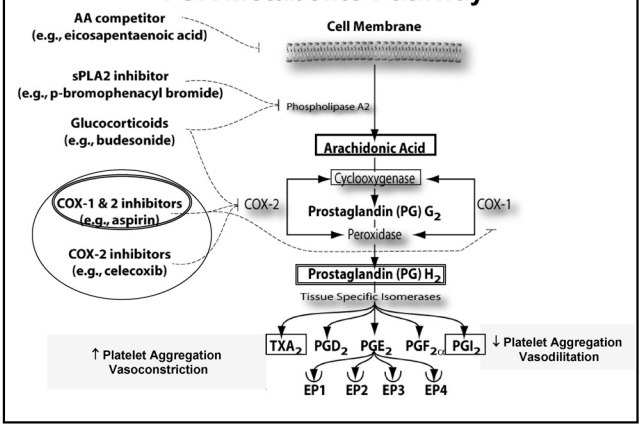
Antipyretic effects have been recognized ≥ 200 years

Acetylsalicylic acid (Aspirin)

Derived in 1897 as antipyretic and anti-inflammatory agent by Felix Hoffman in Lab of Friedrich Bayer & Co.- patented 1899

Antiplatelet activity was not recognized until 1960s

COX Metabolite Pathway



Mechanism of Action

Enhance NO production in endothelial cell

Protect LDL from oxidative modification

Improve endothelial dysfunction

Inhibit cytokine-dependent induction of NOS-II gene expression

Directly scavenge hydroxyl radicals

British Male Doctors' Trial

A randomized but not placebo-controlled, not blind study

Aspirin 500mg/day(or 300mg enteric coated) or not (2: 1 random)

Endpoints

- Incidence of and mortality from stroke, MI or other vascular conditions

Total 5139 participants, F/U for 6 years

- Stop taking aspirin : 24.8%
- Start aspirin in control group : 9.2%

BMJ 1988;296:313-316

British Male Doctors' Trial

Aspirin could not decrease stroke or vascular death

Physicians' Health Study

A randomized, double-blind, placebo-controlled trial

Low dose aspirin (325mg qod, n=11,037) vs placebo (n=11,034) for CV mortality

Beta carotene vs placebo for incidence of cancer

Total 22,071 male physicians

Average F/U of 60.2 months

The aspirin component was prematurely terminated

NEJM 1989;321:129-135

Physicians' Health Study

Apparent reduction in the risk of MI but inconclusive in the risk of stroke and total CV mortality

Thrombosis Prevention Trial

Low intensity oral anticoagulation with wafarin and low-dose aspirin in the primary prevention of ischemic heart disease

Four factorial design of wafarin and as

Aspirin: In HT

In Hypertension

Often considered as a contraindication to aspirin because of the concern of cerebral bleeding

Subgroup analysis of aspirin effect in TPT

	SBP <130mmHg	SBP 130-145	SBP >145mm Hg
Coronary events*	RR 0.55	RR 0.75	RR 0.94
Stroke**	RR 0.41	RR 0.21	RR 1.42
All major CV events*	RR 0.59	RR 0.68	RR 1.08

* p<0.001, **p<0.05

Aspirin: In HT

In Hypertension

PHS, NEJM 1989;321:129-135

	ASPIRIN GROUP	PLACEBO GROUP	RELATIVE RISK	P VALUE OF TREAND IN RELATIVE RISK
	No. of myocardial infarctions/total no. (%)			
Diastolic blood pressure (mm Hg)				
≤ 69	2/583 (0.3)	9/562 (1.6)	0.21	
70 – 79	24/2999 (0.8)	40/3076 (1.3)	0.61	0.88
80 – 89	71/5061 (1.4)	128/5083 (2.5)	0.55	
≥ 90	26/1037 (2.5)	43/970 (4.4)	0.56	
Systolic blood pressure (mm Hg)				
< 109	1/330 (0.3)	4/296 (1.4)	0.22	
110 – 129	40/5072 (0.8)	75/5129 (1.5)	0.52	0.48
130 – 149	63/3829 (1.7)	115/3861 (3.0)	0.55	
≥ 150	19/454 (4.2)	26/412 (6.3)	0.65	

Aspirin: In HT

In Hypertension

In HOT trial, in addition to benefit of BP control, Aspirin reduced

- Fatal and nonfatal acute MI by 36% (p=0.002)
- Major CV events by 15% (p=0.03)

Aspirin increased

- Bleeding complications by 1.8 times but not fatal bleeding

Aspirin: In HT

Conclusion

Aspirin therapy for primary prevention in

In Primary Prevention Trials

% of diabetics : 2% ~ 17% (PPP)

Dose of aspirin : 75mg/day ~ 500mg/day (BMD)

PHS (Physicians' Heath Study)
- Aspirin 325 mg qod
- Fewer MI in diabetics taking aspirin : RR 0.39

HOT (Hypertension Optimal Treatment)
- Diabetics in 8%, aspirin 75mg/day
- Greater benefit form aspirin in diabetics

DM Subgroup Analysis 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

EDITORIAL (SEE JACCO ET AL., P. 3264)

Aspirin for Primary Prevention of Cardiovascular Events in Diabetes

Diabetes Care, Volume 26, Supplement 1, Janurary 2003

POSITION STATEMENT

Aspirin Therapy in Diabetes

AMERICAN DIABETES ASSOCIATION

People with diabetes have a two- to fourfold increase in the risk of dying from the complications of cardiovascular disease. Both men and women are at increased risk. Atherosclerosis and vascular thrombosis are major contributors, and it is generally accepted that platelets are contributory. Platelets from men and women with diabetes are often

were about one-quarter in each of these categories, and diabetic subjects had risk reductions that were comparable to nondiabetic individuals. There was a trend toward increased risk reductions with doses of aspirin of 325 mg/day or less. It was estimated that 38 ± 12 vascular events per 1,000 diabetic patients would be prevented if they were treated with aspirin as

Primary prevention trials

The U.S. Physicians' Health Study was a primary prevention trial in which a low-dose aspirin regimen (325 mg every other day) was compared with placebo in male physicians. There was a 44% risk reduction in the treated group, and subgroup analyses in the diabetic physicians revealed a reduction in myocardial infarc-

In Low Risk for CV Disease

BMD
- History of MI in 6%, HT in 10%, smoking in 75%
- 500mg/day of aspirin
- No significant difference of MI or total mortality

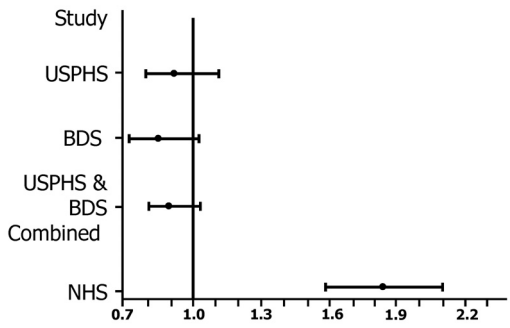
PHS (Physicians' Health Study)
- HT in 9%, smoking in 50%
- 325mg of aspirin every other day
- Lower rate of MI : RR 0.58 but no difference of total mortality

NHS (Nurses' Health Study)
- HT in 15%, smoking in 29%
- No separate analysis of low-risk subjects
- More endpoints in aspirin group

Boltri JM et al. J Family Practice 2002;51:700-704

Mortality in Healthy Patients on Aspirin

Low Risk



Conclusion

Low Risk

To date, none of studies demonstrated a statistically significant decrease in all-cause mortality. The use of aspirin caused more side effects.

Currently no evidence to recommend for or against the use of aspirin in low risk individuals to decrease mortality

Meta-analysis of Total CHD Events

Hayden, M. et. al. Ann Intern Med 2002;136:161-172

Study (Reference)	Aspirin, *n/n*	Control, *n/n*	OR (95% CI Random)	Weight, %	OR (95% CI Random)
BMD (5)	169 / 3429	88 / 1710		22.0	0.96 (0.73–1.24)
PHS (4)	163 / 11 037	266 / 11 034		27.8	0.61 (0.50–0.74)
TPT (7)	83 / 1268	107 / 1272		19.6	0.76 (0.57–1.03)
HOT (8)	82 / 9399	127 / 9391		20.9	0.64 (0.49–0.85)
PPP (9)	26 / 2226	35 / 2269		9.7	0.75 (0.45–1.26)
Total (95% CI)	523 / 27 359	623 / 25 676		100.0	0.72 (0.60–0.87)

0.20 0.50 1.0 2.0 5.0
Favors Aspirin Favors Control

P=0.089

Meta-analysis of CHD Mortality

Hayden, M. et. al. Ann Intern Med 2002;136:161-172

Study (Reference)	Aspirin, *n/n*	Control, *n/n*	OR (95% CI Random)	Weight, %	OR (95% CI Random)
BMD (5)	89 / 3429	47 / 1710		37.2	0.94 (0.66–1.35)
PHS (4)	34 / 11 037	53 / 11 034		25.6	0.64 (0.42–0.99)
TPT (7)	36 / 1268	34 / 1272		21.1	1.06 (0.66–1.71)
HOT (8)	14 / 9399	14 / 9391		8.7	1.00 (0.48–2.10)
PPP (9)	11 / 2226	13 / 2269		7.4	0.86 (0.39–1.93)
Total (95% CI)	184 / 27 359	161 / 25 676		100.0	0.87 (0.70–1.09)

0.20 0.50 1.0 2.0 5.0
Favors Aspirin Favors Control

P=NS

Meta-analysis of Stroke Events

Hayden, M. et. al. Ann Intern Med 2002;136:161-172

Study (Reference)	Aspirin, *n/n*	Control, *n/n*	OR (95% CI Random)	Weight, %	OR (95% CI Random)
BMD (5)	91 / 3429	39 / 1710		18.4	1.17 (0.80–1.71)
PHS (4)	119 / 11 037	98 / 11 034		29.8	1.22 (0.93–1.59)
TPT (7)	18 / 1268	26 / 1272		8.4	0.69 (0.38–1.27)
HOT (8)	146 / 9399	148 / 9391		35.6	0.99 (0.78–1.24)
PPP (9)	16 / 2226	24 / 2269		7.7	0.68 (0.36–1.28)
Total (95% CI)	390 / 27 359	335 / 25 676		100.0	1.02 (0.85–1.23)

0.20 0.50 1.0 2.0 5.0
Favors Aspirin Favors Control

P=NS

Meta-analysis of All-cause Mortality

Hayden, M. et. al. Ann Intern Med 2002;136:161-172

Study (Reference)	Aspirin, *n/n*	Control, *n/n*	OR (95% CI Random)	Weight, %	OR (95% CI Random)
BMD (5)	270 / 3429	151 / 1710		20.9	0.88 (0.72–1.09)
PHS (4)	217 / 11 037	227 / 11 034		25.6	0.95 (0.79–1.15)
TPT (7)	113 / 1268	110 / 1272		12.0	1.03 (0.79–1.36)
HOT (8)	284 / 9399	305 / 9391		33.6	0.93 (0.79–1.09)
PPP (9)	62 / 2226	78 / 2269		7.9	0.80 (0.57–1.13)
Total (95% CI)	946 / 27 359	871 / 25 676		100.0	0.93 (0.84–1.02)

0.20 0.50 1.0 2.0 5.0
Favors Aspirin Favors Control

P=NS

Summary Estimates of the Effect of Aspirin

Hayden, M. et. al. Ann Intern Med 2002;136:161-172

Recent Recommendations

U.S. Preventive Services Task Force (Ann Intern Med. 2002;136:157)
: in patients at high risk for CHD, 5 year risk ≥ 3%

AHA guideline (Circulation 2002;106:388)
: in higher risk patients, especially 10 year risk of CHD ≥ 10%

Uncontrolled HT may attenuate benefits of aspirin
Dose : 75mg/d – 160mg/d (or 325mg every other day)