

Efficacy and Safety of ASA/DP ER



Kwang-Yeol Park

Dep. of Neurology, Chung-Ang University, Seoul South Korea

① Stroke in Korea

② Antiplatelet agents in stroke prevention

- Aspirin
- Clopidogrel
- ASA/Dipyridamole ER

③ Summary

Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble



Vasilis Kontis*, James E Bennett*, Colin D Mathers, Guangxuan Li, Kyle Foreman, Majid Ezzati

Summary

Background Projections of future mortality and life expectancy are needed to plan for health and social services and

Lancet 2017; 389: 1323–35

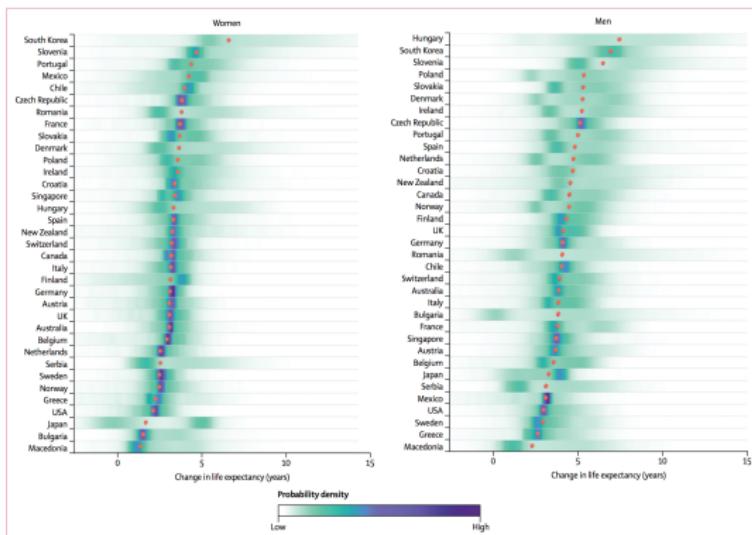
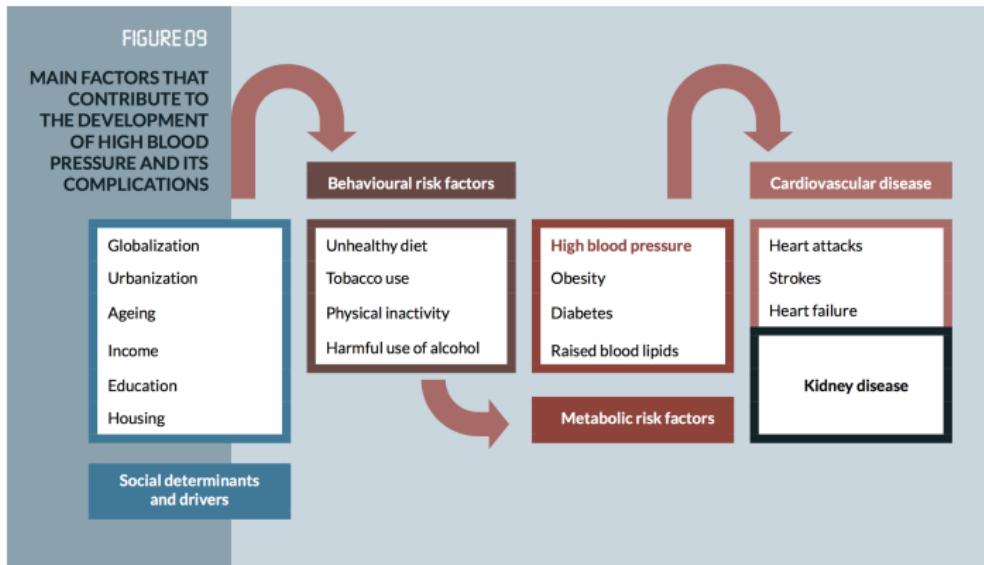


Figure 1: Posterior distribution of projected change in life expectancy at birth from 2010 to 2030
Red dots show the posterior medians. Countries are ordered vertically by median projected increase from largest (at the top) to smallest (at the bottom).

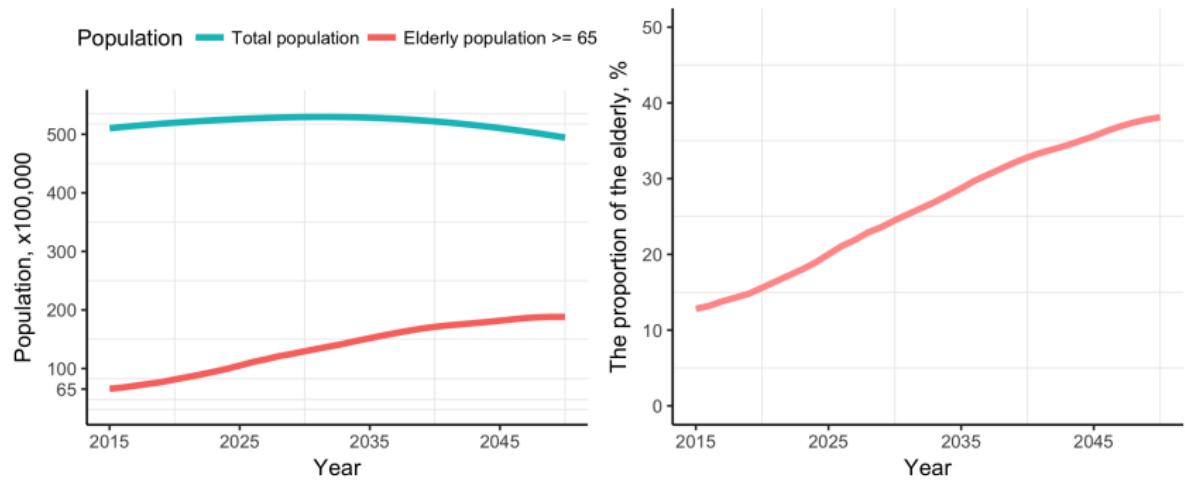
There is a 90% probability that life expectancy at birth among South Korean women in 2030 will be higher than 86·7 years, and a **57% probability that it will be higher than 90 years.**

There is a greater than 95% probability that life expectancy at birth among men in South Korea, Australia, and Switzerland will surpass 80 years in 2030, and a greater than 27% probability that it will surpass 85 years.



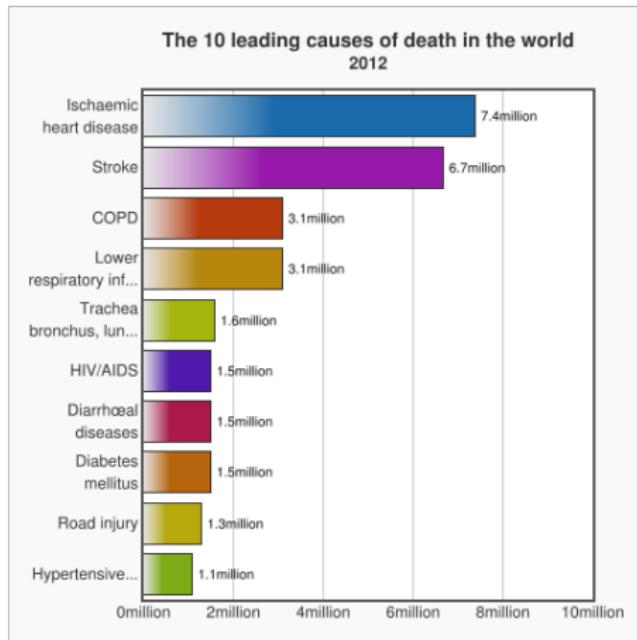
http://www.who.int/cardiovascular_diseases/publications/global_brief_hypertension/en/ accessed on May 07, 2017

Rapid increase of Korean elderly population



<http://kosis.kr/visual/populationKorea/>

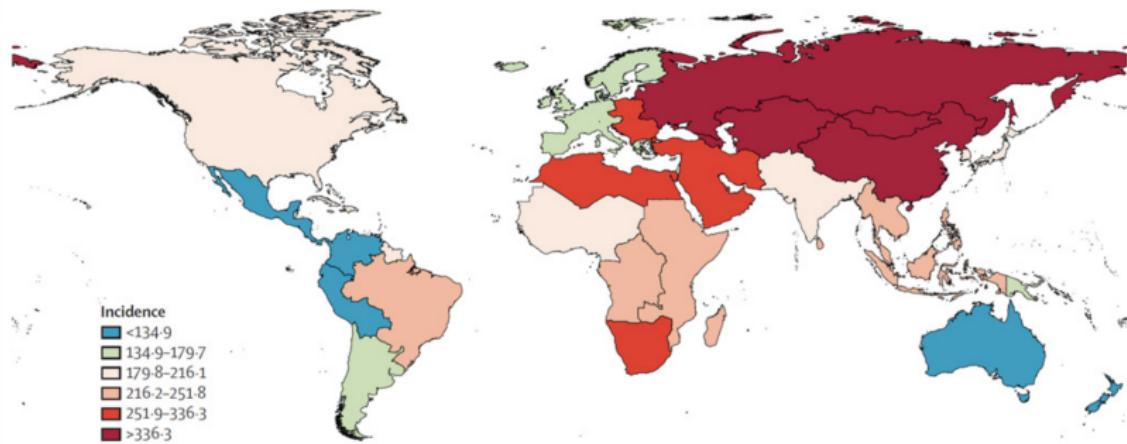
Global burden of stroke



<http://www.who.int/mediacentre/factsheets/fs310/en/> accessed on Jan 16, 2016

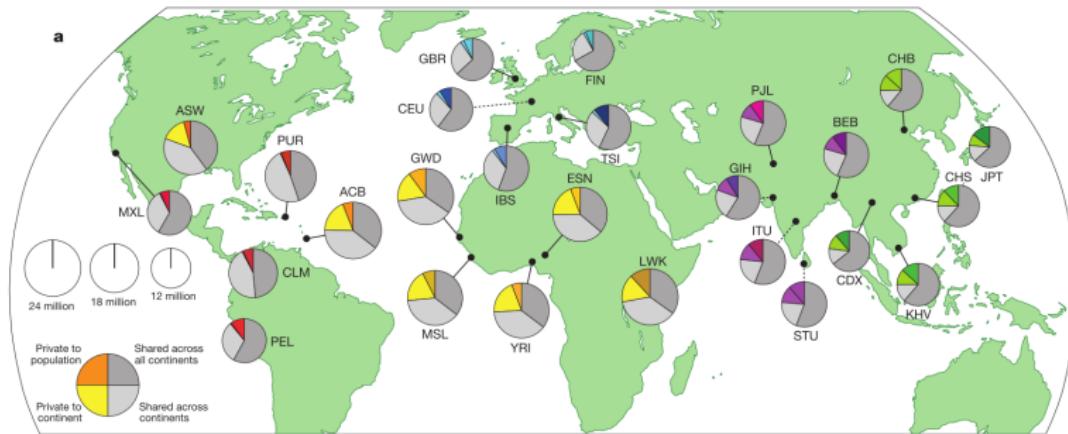
Age-standardised stroke incidence

per 100 000 person-years for 2010



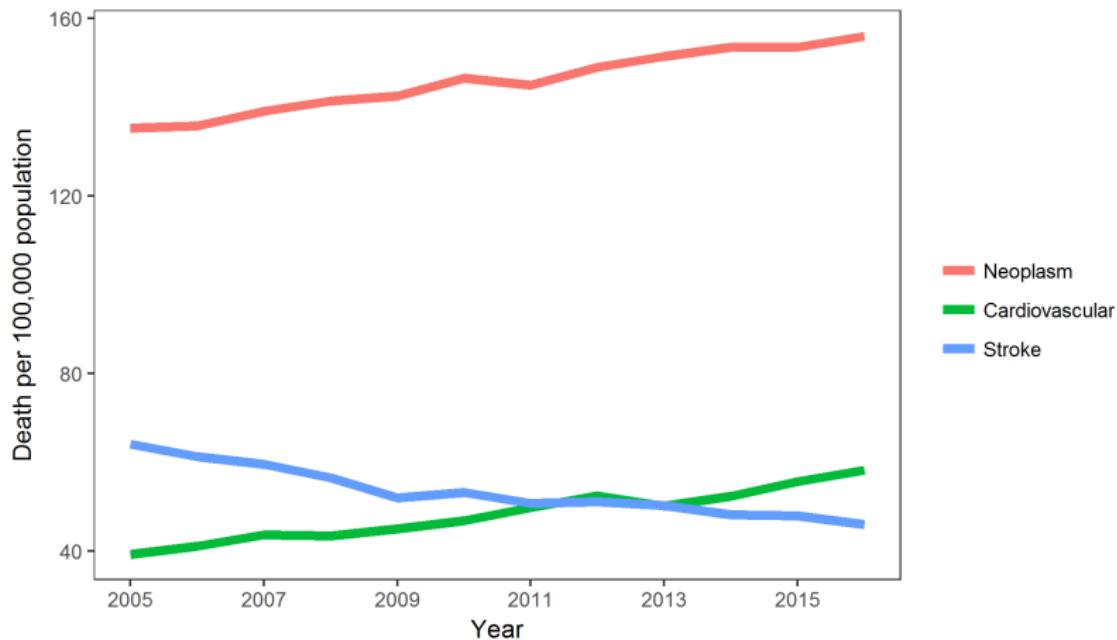
Lancet Neurol. 2014 383(9913): 245–254.

A global reference for human genetic variation



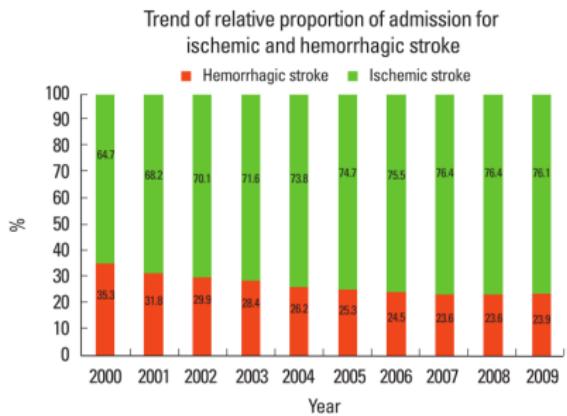
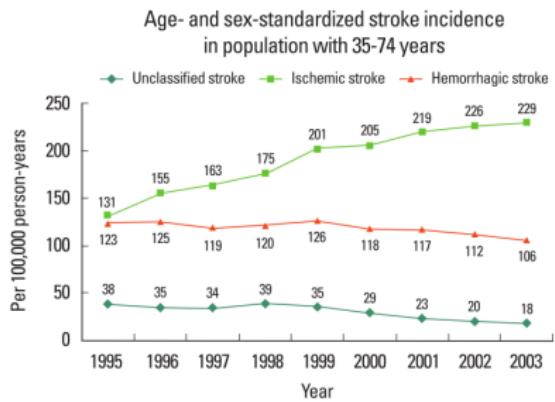
The 1000 Genomes Project. Nature 2015

Secular trend of mortality in Korea



http://www.index.go.kr/potal/main/EachDtlPageDetail.do?idx_cd=1012 accessed on June 6, 2018

Incidence of stroke is increasing



Etiologies of stroke

Ischemic Stroke

- Atherosclerosis
- Small artery occlusion
- Cardiac disease causing embolism
- Other causes such as moyamoya disease

Hemorrhagic Stroke

- Hypertensive hemorrhage
- Cerebral amyloid angiopathy
- Arteriovenous malformations
- Subarachnoid hemorrhage

Q. How effective is aspirin on the prevention of stroke ?

Aspirin in vascular prevention

| | Number of events (aspirin vs control) | | Rate ratio (95% CI) (aspirin vs control) | | | Yearly absolute difference (% per year) | |
|----------------------------|--|---|--|----------------------|---------------------------|---|----------------------|
| | Primary prevention (660 000 person-years) | Secondary prevention (43 000 person-years) | Primary prevention | Secondary prevention | p value for heterogeneity | Primary prevention | Secondary prevention |
| Major coronary event | 934 vs 1115 | 995 vs 1214 | 0.82 (0.75-0.90) | 0.80 (0.73-0.88) | 0.7 | -0.06 | -1.00* |
| Non-fatal MI | 596 vs 756 | 357 vs 505 | 0.77 (0.69-0.86) | 0.69 (0.60-0.80) | 0.5 | -0.05 | -0.66 |
| CHD mortality | 372 vs 393 | 614 vs 696 | 0.95 (0.82-1.10) | 0.87 (0.78-0.98) | 0.4 | -0.01 | -0.34 |
| Stroke | 655 vs 682 | 480 vs 580 | 0.95 (0.85-1.06) | 0.81 (0.71-0.92) | 0.1 | -0.01 | -0.46* |
| Haemorrhagic | 116 vs 89 | 36 vs 19 | 1.32 (1.00-1.75) | 1.67 (0.97-2.90) | 0.4 | 0.01 | ..† |
| Ischaemic | 317 vs 367 | 140 vs 176 | 0.86 (0.74-1.00) | 0.78 (0.61-0.99) | 0.5 | -0.02 | ..† |
| Unknown cause | 222 vs 226 | 304 vs 385 | 0.97 (0.80-1.18) | 0.77 (0.66-0.91) | 0.1 | -0.001 | ..† |
| Vascular death | 619 vs 637 | 825 vs 896 | 0.97 (0.87-1.09) | 0.91 (0.82-1.00) | 0.4 | -0.01 | -0.29 |
| Any serious vascular event | 1671 vs 1883 (0.51% vs 0.57% per year) | 1505 vs 1801 (6.69% vs 8.19% per year) | 0.88 (0.82-0.94) | 0.81 (0.75-0.87) | 0.1 | -0.07 | -1.49* |
| Major extracranial bleed | 335 vs 219 | 23 vs 6 | 1.54 (1.30-1.82) | 2.69 (1.25-5.76) | 0.2 | 0.03 | ..† |

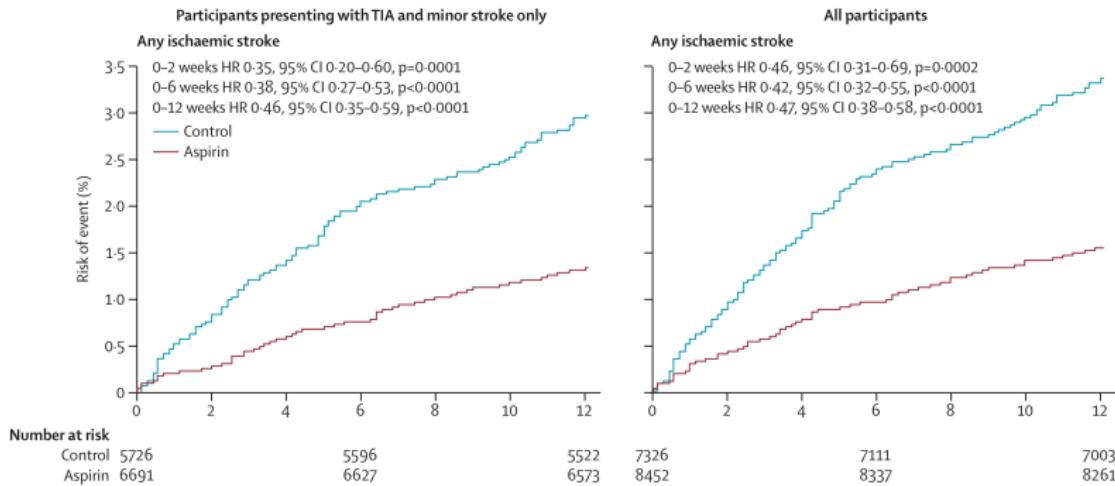
ML=myocardial infarction. CHD=coronary heart disease. Non-fatal MI definitions vary; see methods. *Major coronary event rates (percent per year, aspirin vs control) 6.0 vs 7.4 in post-MI trials and 2.4 vs 3.0 in post-cerebral vascular disease trials; corresponding rates of stroke (mainly of unknown cause) 0.6 vs 0.8 in post-MI trials and 3.9 vs 4.7 in post-cerebral vascular disease trials (webappendix pp 14-18). †Stroke causes, and extracranial bleeds, very incompletely reported.

Table 2: Comparison of proportional and absolute effects of aspirin in primary and secondary prevention trials

meta-analyses of serious vascular events (myocardial infarction, stroke, or vascular death) and major bleeds in six primary prevention trials (95000 individuals at low average risk, 660000 person-years, 3554 serious vascular events) and 16 secondary prevention trials (17000 individuals at high average risk, 43000 person-years, 3306 serious vascular events) that compared long-term aspirin versus control

ATT collaboration. Lancet 2009;373:1849-60

The effect of aspirin after TIA/ischemic stroke



Rothwell PM et al. Lancet 2016;388:365-75

The effect of aspirin after TIA/ischemic stroke

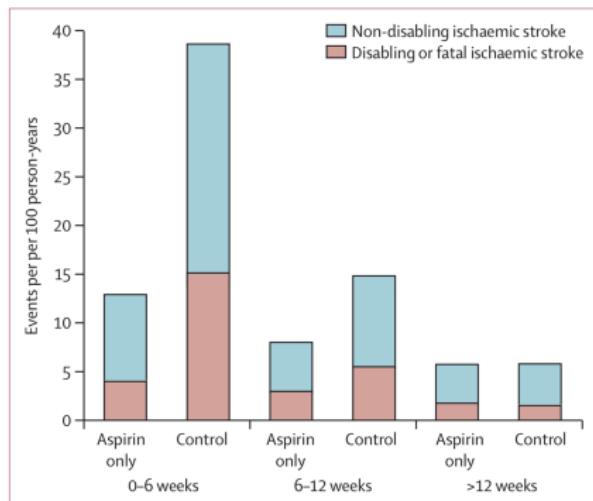


Figure 2: Pooled analysis of the effect of aspirin only versus control in secondary prevention after transient ischaemic attack and ischaemic stroke on the absolute risk of recurrent ischaemic stroke

Time course of treatment effect interaction: $p_{\text{interaction}} < 0.0001$ for both outcomes.

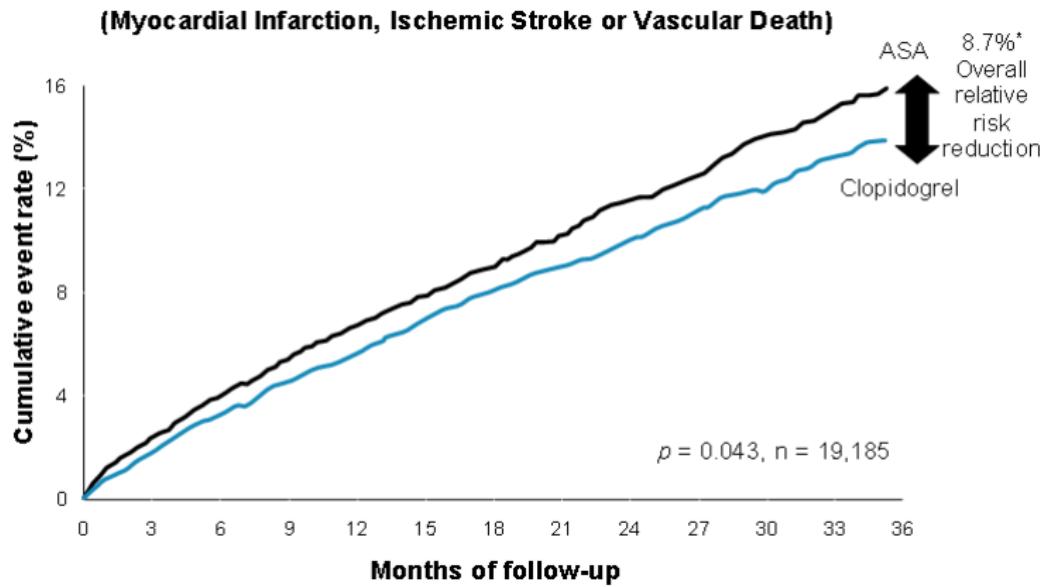
- Q. How effective is aspirin on the prevention of stroke ?
- Q. What is the role of clopidogrel ?

Aspirin vs. Clopidogrel in CAPRIE study

- Objective: To compare the efficacy and safety of clopidogrel 75 mg/day with active control – ASA 325 mg/day
- Methodology: Double-blind, randomized, prospective trial, multi-center (384 centers in 16 countries)
- Population: Follow-up of 19,185 patients for one to three years with: Ischemic stroke, Myocardial infarction (MI), or, Peripheral arterial disease
- Combined primary endpoint: Cluster of ischemic stroke, MI and vascular death

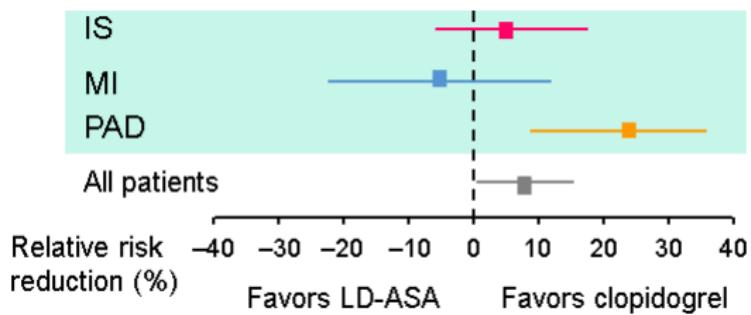
CAPRIE Steering Committee. *Lancet* 1996; 348:1329–39.

Aspirin vs. Clopidogrel in CAPRIE study

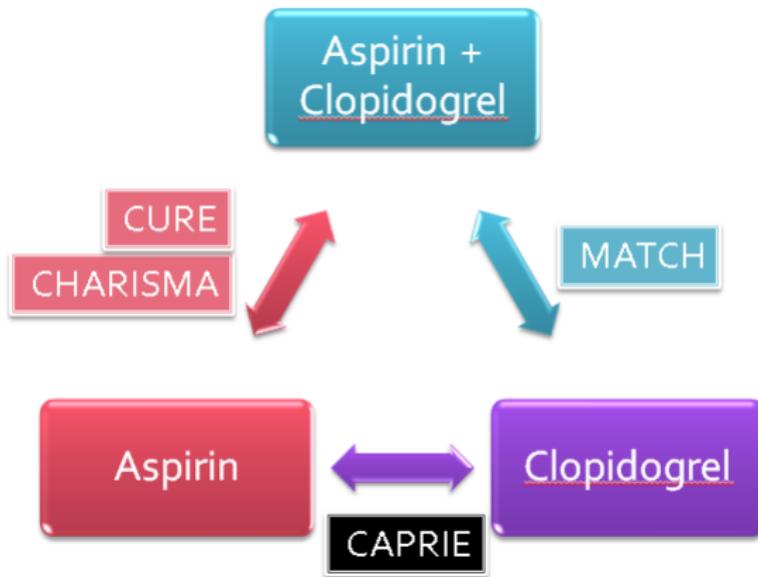


CAPRIE Steering Committee. Lancet 1996; 348:1329–39.

Aspirin vs. Clopidogrel in CAPRIE study



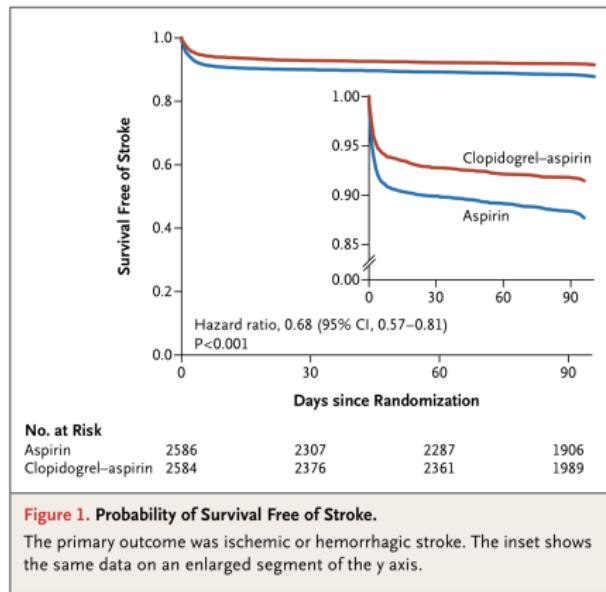
CAPRIE Steering Committee. Lancet 1996; 348:1329–39.



CHANCE trial

- Objective: To compare the efficacy and safety of clopidogrel + ASA vs. ASA in pts with minor stroke or TIA
- Methodology: Double-blind, randomized, prospective trial
ASA 75mg(21d) + clopidogrel (300 → 75mg)(90d) vs ASA (75 mg, 90d)
- Population: Acute minor stroke with NIHSS <=3 or high risk TIA, start drug within 24h onset
- Primary endpoint: New stroke (ischemic or hemorrhagic at 90d)

CHANCE trial



Stroke occurred in 8.2% of patients in the clopidogrel-aspirin group, as compared with 11.7% of those in the aspirin group (HR, 0.68; 95% CI, 0.57 to 0.81; $P < 0.001$)

Wang Y et al. NEJM 2013

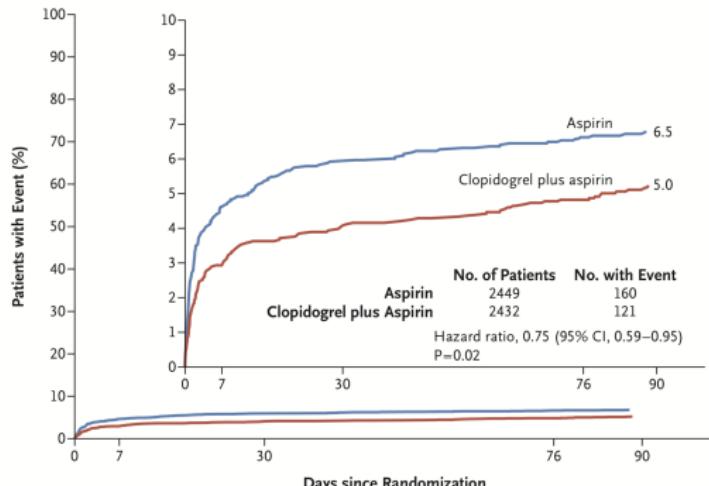
POINT trial

- Objective: To compare the efficacy and safety of clopidogrel + ASA vs. ASA in pts with minor stroke or TIA
- Methodology: Double-blind, randomized, prospective trial
ASA 50 - 325mg + clopidogrel (600 → 75mg) vs ASA (50 - 325 mg)
- Population: Acute minor stroke with NIHSS <=3 or high risk TIA, randomized within 12h onset
- Primary endpoint: ischemic stroke, MI, death due to ischemic event

POINT trial

A

Primary Efficacy Outcome



No. at Risk

| | | |
|--------------------------|------|------|
| Aspirin | 2449 | 2269 |
| Clopidogrel plus aspirin | 2432 | 2279 |

2153

2178

2105

2113

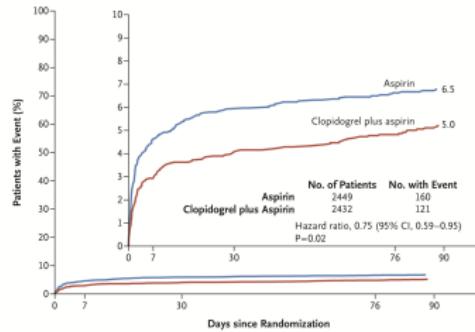
1365

1445

HR, 0.75; 95% CI, 0.59 to 0.95; P=0.02

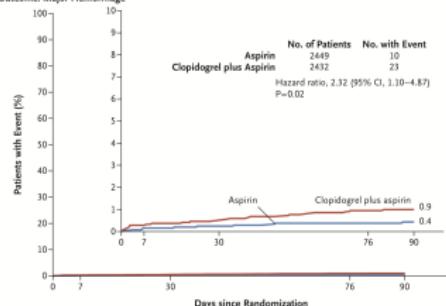
Johnston SC et al. NEJM 2018

POINT trial - 30 days

A Primary Efficacy Outcome

No. at Risk
Aspirin
Clopidogrel plus aspirin

2449 2369
2153 2178
2105 2113
1365 1445

B Primary Safety Outcome: Major Hemorrhage

No. at Risk
Aspirin
Clopidogrel plus aspirin

2449 2372
2432 2356
2271
2230 1448
1505

Ischemic event: HR, 0.75; 95% CI, 0.59 to 0.95; P=0.02

Major hemorrhage: HR, 2.32; 95% CI, 1.10 to 4.87; P=0.02

CHANCE vs. POINT

| | CHANCE | POINT |
|---------------------------|--------------------------|-------------------------|
| Ischemic stroke | 7.9 vs. 11.4% | 4.6 vs. 6.4% |
| Hemorrhagic stroke | 0.3 vs. 0.3% (ns) | 0.2 vs. 0.1% (ns) |
| Recurrent stroke | 8.2 vs. 11.7% RR 0.68 | 4.8 vs. 6.4% RR 0.74 |
| CI/MI/ischemic vas. death | 8.4 vs. 11.9% RR 0.69 | 5.0 vs. 6.5% RR 0.75 |
| ≥ mod. bleeding | 0.3 vs. 0.3% (ns) | |
| Major hemorrhage | | 0.9 vs. 0.4% |
| Any bleeding | 2.3 vs. 1.6% (ns) | 2.5 vs. 0.9% |

POINT: larger clopidogrel loading dose, longer duration of combined treatment, CYP2C19 in Asian

Wang Y et al. NEJM 2013; Johnston SC et al. NEJM 2018

- Q. How effective is aspirin on the prevention of stroke ?
- Q. What is the role of clopidogrel ?
- Q. What is the role of ASA/DP ER ?

ESPS-2 (1996)

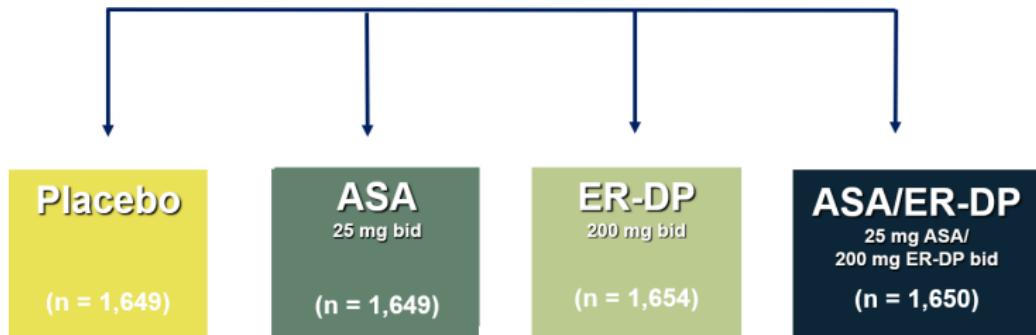
ESPS-2: European Stroke Prevention Study

- ▲ Multicentre, randomized, double-blind, placebo-controlled trial
- ▲ 6,602 patients randomized within 3 months of qualifying event (TIA or stroke)
- ▲ Treatment and follow-up time: 2 years
 - Visits at 1 month and 3 months, then at 3-month intervals

Diener HC et al. J Neurol Sci. 1996 Nov;143(1-2):1-13.

Treatment arms

N=6,602

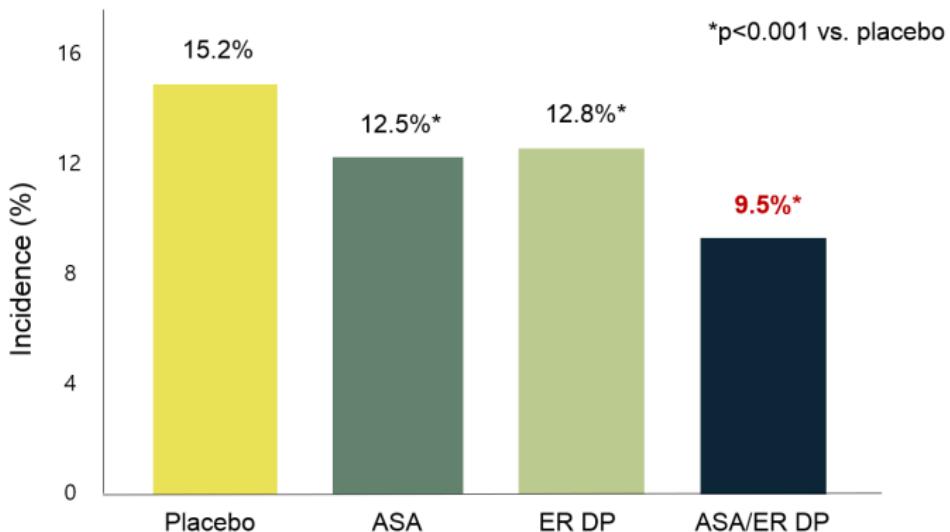


Study design. 무작위, 이중맹검, 위약대조, 다기관 연구로 3개월 이내 허혈성 뇌출증 또는 일과성허혈발작이 나타난 환자 6,602명을 대상으로 Placebo군, Aspirin 25mg 투여군, Dipyridamole ER 100mg 투여군, Aspirin 25mg + Dipyridamole ER 100mg 병용투여군으로 무작위 배정하여 일차종료점으로 2년 후 뇌출증 발생률 평가

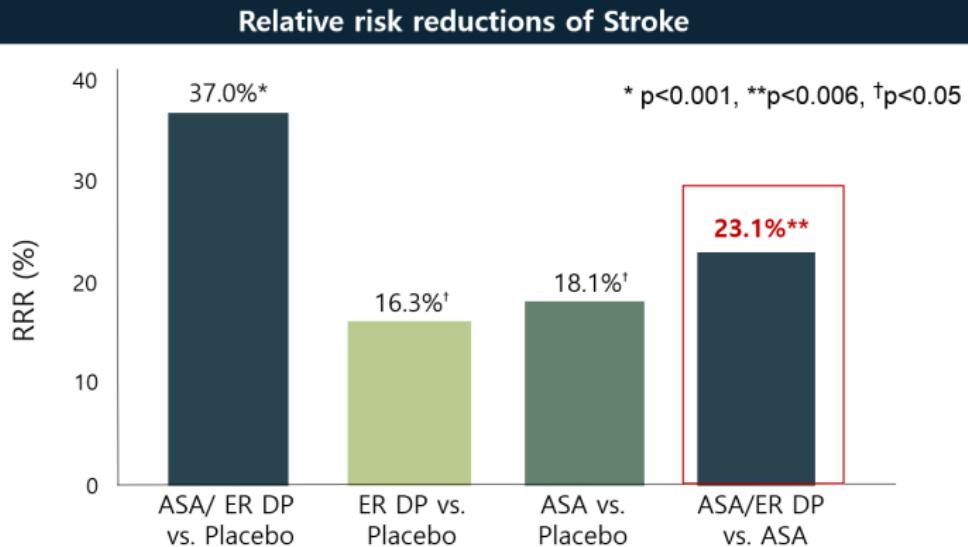
Diener HC et al. J Neurol Sci. 1996 Nov;143(1-2):1-13.

Primary outcome

Stroke Rates at 24 Months



Relative risk reductions of Stroke



* RRR = Relative Risk Reduction



Diener HC et al. J Neurol Sci. 1996 Nov;143(1-2):1-13.

Number Needed to Treat (NNT)

| Intervention | To prevent one stroke in | NNT |
|---|-----------------------------|-----|
| Antiplatelet therapy | | |
| a. ESPS-2 (ER DP + ASA vs. ASA) | 2 years | 34 |
| b. CAPRIE (Clopidogrel vs. ASA) (patients with inclusion criterion stroke) | 1.91 years | 143 |
| Antihypertensive therapy | | |
| vs. placebo in the elderly (MRC) | 5 years | 70 |
| Lipid-lowering therapy | | |
| Simvastatin vs. placebo (4S) | 5 years | 101 |

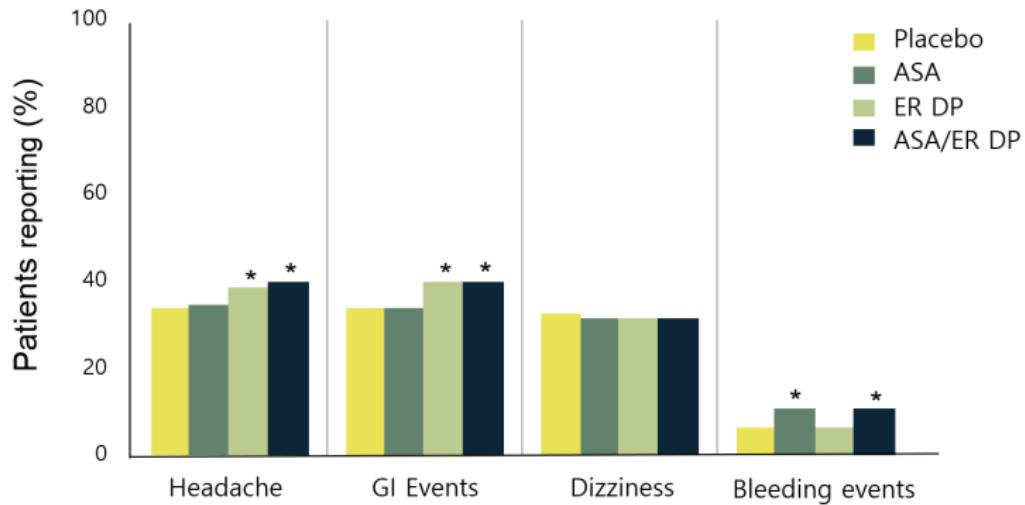
ER DP = Extended release dipyridamole

ASA = Acetylsalicylic acid



Safety

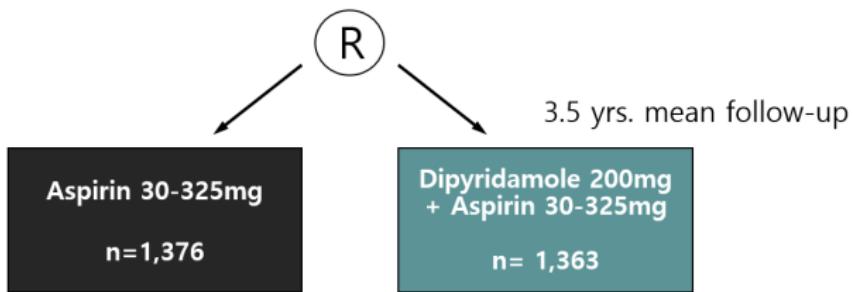
Adverse Events



ESPRIT (2006)

ESPRIT study (Aspirin plus Dipyridamole vs. Aspirin alone)

- Randomized, controlled trial in 2763 patients, mean age 63 years, within 6 months of TIA or minor stroke of presumed arterial origin



- Primary outcome event: Composite of death from all vascular causes, nonfatal stroke, nonfatal MI or major bleed
- ITT analysis

Patients

- **Inclusion Criteria**

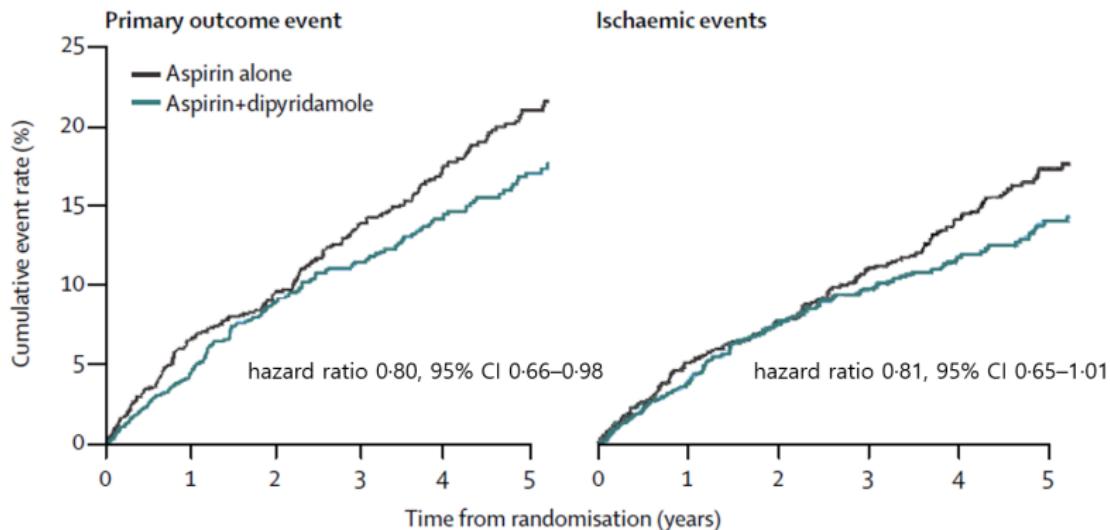
- All patients who were referred to one of the participating hospitals within 6 months of a transient ischemic attack (including transient monocular blindness) or minor ischemic stroke (grade ≤ 3 on the modified Rankin scale^{17,18}) of presumed arterial origin

- **Exclusion Criteria**

- Possible cardiac source of embolism (atrial fibrillation on ECG)
- Valvular heart disease, or recent myocardial infarction)
- Cerebral ischemia associated with high-grade carotid stenosis for which carotid endarterectomy or endovascular treatment was planned
- Any blood coagulation disorder
- Any contraindication for aspirin or dipyridamole, and a limited life expectancy.

Primary outcome

Time-to-event curves for primary outcome event and all ischemic events



ESPRIT outcomes

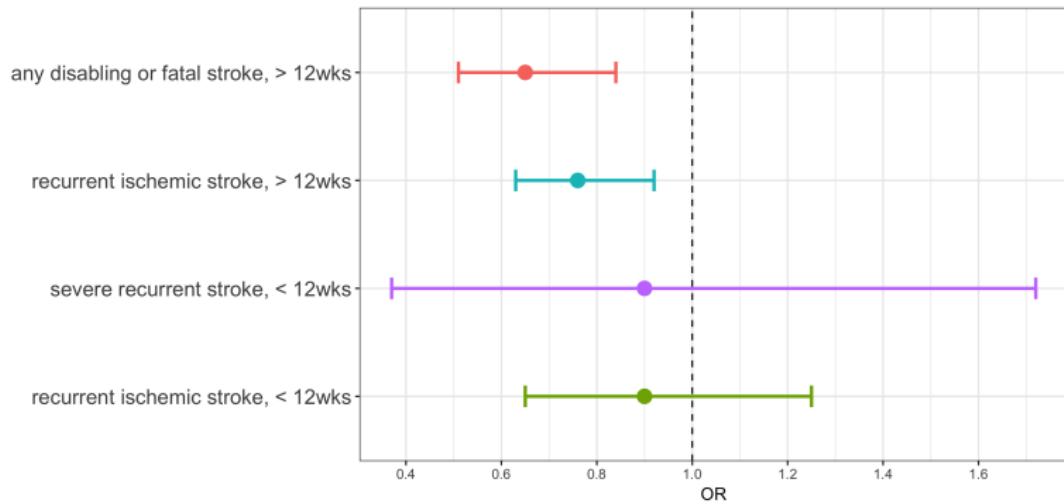
Occurrence of first outcome events, according to treatment

| | ASA+DP (N=1,363) | ASA (N=1,376) | HR | 95% CI |
|--|---------------------|------------------|------|-----------|
| Primary endpoint | 173 | 216 | 0.80 | 0.66-0.98 |
| Death from all causes | 93 | 107 | 0.88 | 0.67-1.17 |
| Death from all vascular causes | 44 | 60 | 0.75 | 0.51-1.10 |
| Death from all vascular causes, nonfatal stroke | 132 | 171 | 0.78 | 0.62-0.92 |
| Major bleeding complications | 35 | 53 | 0.67 | 0.44-1.03 |
| Death from all vascular causes, nonfatal stroke, nonfatal MI | 149 | 192 | 0.78 | 0.63-0.97 |
| First ischemic stroke | 36 | 116 | 0.84 | 0.64-1.10 |
| First cardiac event | 43 | 60 | 0.73 | 0.49-1.08 |

* Death from all vascular causes, nonfatal stroke, nonfatal MI, nonfatal major bleeding complications



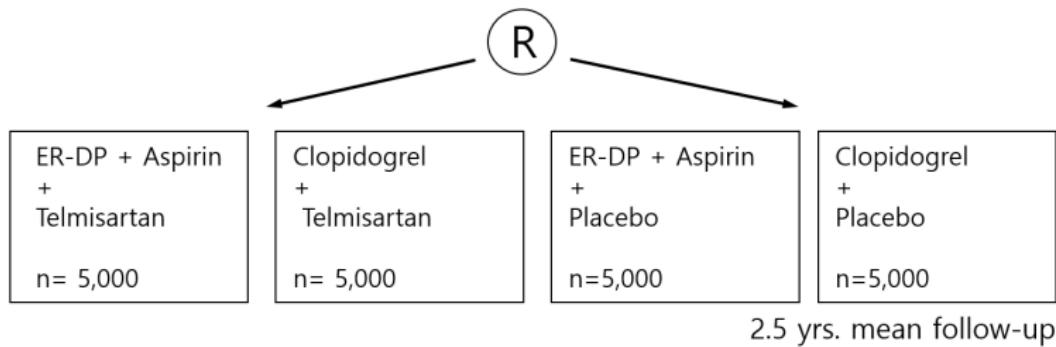
Dipyridamole added to aspirin vs. aspirin after TIA/ischemic stroke



Rothwell PM et al. Lancet 2016;388:365-75

PRoFESS[®] Trial: Study design

- 20,332 patients \geq 50 years with at least ischemic stroke* (see inclusion criteria)
- Double-blind. Placebo-controlled. Simultaneous randomization.
- Doses: (200 mg ER-DP + 25 mg Aspirin) 2x/day, 80 mg Telmisartan, 75 mg Clopidogrel 1x/day

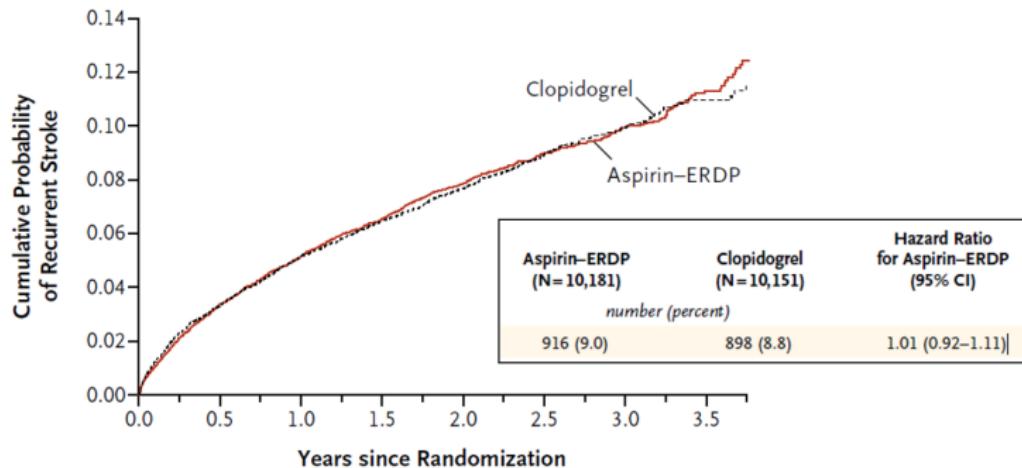


- Primary Endpoint: rate of first recurrent stroke
- Secondary Endpoints: stroke, MI, vascular death, rate of new diabetes mellitus
- Tertiary Endpoints: major hemorrhagic event, all deaths, new or worsening congestive heart failure

Sacco RL et al. N Engl J Med. 2008 Sep 18;359(12):1238-51

Primary outcome

Primary outcome: recurrent stroke



Study design. 무작위, 이중맹검, 위약대조, 다기관 연구로 3개월 이내에 허혈성 뇌졸중을 겪은 환자 20,332명을 대상으로 Aspirin/Dipyridamole 군과 Clopidogrel 군 Clopidogrel/Telmisartan 군으로 무작위 배정하여 Primary endpoint로 any type 뇌졸중 재발률 평가.



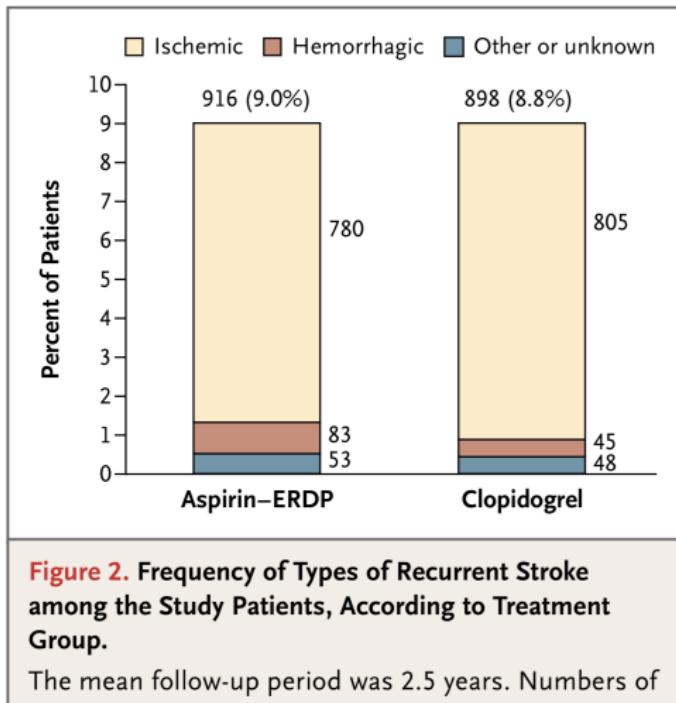
Sacco RL et al. N Engl J Med. 2008 Sep 18;359(12):1238-51

Safety

Safety data

| Safety outcome | | | |
|---|-----------|-----------|------------------|
| Major hemorrhagic event§ | 419 (4.1) | 365 (3.6) | 1.15 (1.00–1.32) |
| Life-threatening | 128 (1.3) | 116 (1.1) | |
| Non-life-threatening | 291 (2.9) | 249 (2.5) | |
| Hemorrhagic event (minor or major)¶ | 535 (5.3) | 494 (4.9) | 1.08 (0.96–1.22) |
| Intracranial hemorrhage | 147 (1.4) | 103 (1.0) | 1.42 (1.11–1.83) |
| Intracerebral hemorrhage (hemorrhagic stroke) | 90 (0.9) | 55 (0.5) | |
| Fatal | 28 (0.3) | 29 (0.3) | |
| Nonfatal | 62 (0.6) | 26 (0.3) | |
| Intraocular hemorrhage | 22 (0.2) | 22 (0.2) | |
| Nonstroke intracranial hemorrhage | 35 (0.3) | 26 (0.3) | |

Sacco RL et al. N Engl J Med. 2008 Sep 18;359(12):1238-51



2014 ASA guideline about antiplatelet agents

- **Aspirin** (50–325 mg/d) monotherapy (Class I; Level of Evidence A) or the **combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily** (Class I; Level of Evidence B) is indicated as **initial therapy** after TIA or ischemic stroke for prevention of future stroke. (Revised recommendation)
- Clopidogrel (75 mg) monotherapy is a reasonable option for secondary prevention of stroke in place of aspirin or combination aspirin/dipyridamole (Class IIa; Level of Evidence B). This recommendation also applies to patients who are allergic to aspirin.

Take-Home Message

- Aspirin is one of the first line drug.
 - The combination of aspirin and clopidogrel is more effective than aspirin alone during acute phase of minor stroke or TIA.
-
- The combination of aspirin and dipyridamole ER is more effective than aspirin according to ESPS-2, ESPRIT study and meta analysis.
 - Aspirin/ER-DP combination therapy is not superior to clopidogrel in reducing stroke recurrence rate according to PRoFESS study.

APIDAMOL ER cap

성분 함량 아스피린 25mg, 디피리다몰 200mg

효능 효과 뇌의 일과성 허혈 또는 혈전에 의한 허혈성 뇌졸중을 경험한 환자의 뇌졸중 재발에 대한 위험성 감소

- 용법 용량
- 1회 1캡슐, 1일 2회
 - 식사와 함께 또는 식사 후에 한번에 통째로 삼켜야 하며, 씹어서 복용하지 않음.
 - 개개의 성분(디피리다몰 및 아스피린)을 함유한 단일제제로 대체 복용 금지

보험코드 645405190

보험약가

304원/캡슐

