# Low-dose aspirin for primary prevention of cardiovascular events in elderly Japanese patients with atherosclerotic risk factors: a randomized clinical trial

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ClinicalTrials.gov Identifier: NCT00225849

# Introduction and objective

- Prevention of cardiovascular (CV) diseases is an important public health priority both worldwide and in Japan
- The role of aspirin in the primary prevention of CV disease has been hotly debated for several years
  - Meta-analyses indicate benefits as well as risks[1]
  - Recently, the US Food and Drug Administration cautioned against the general use of aspirin for the primary prevention of heart attacks and strokes[2]

**Japanese Primary Prevention Project (JPPP)**
**Study objective**
*To determine whether daily, low-dose aspirin reduces the incidence of CV events compared with no aspirin in elderly Japanese patients with atherosclerotic risk factors*

1. Raju NC *et al. Curr Opin Cardiol* 2012;27:499–507
2. FDA. 2014. Available from: http://www.fda.gov/drugs/resourcesforyou/consumers/ucm390574.htm

# Study design: Prospective Randomized Open Blinded Endpoint (PROBE)

Patients aged 60–85 years
- Hypertension
- Dyslipidemia
- Diabetes mellitus
  (one or more condition)

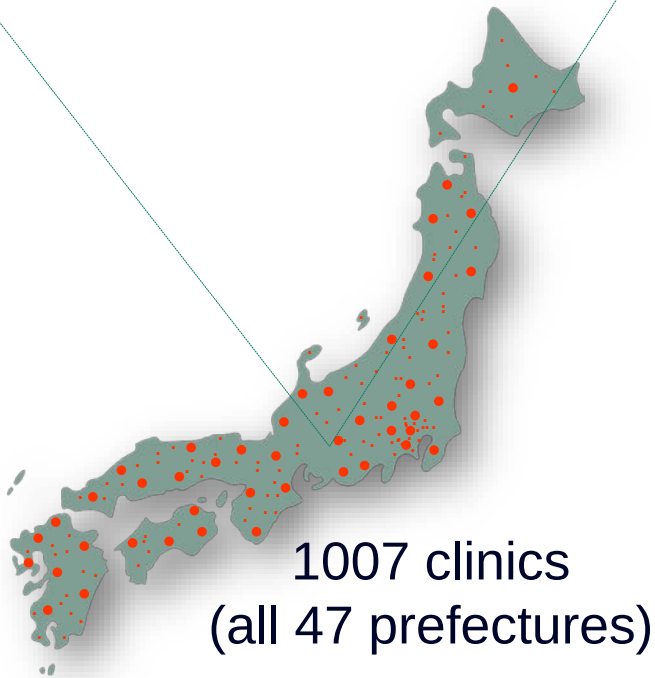
Eligible ✓

1:1 randomization

Enteric-coated aspirin 100 mg/day

No aspirin

Ongoing medications to control underlying disease(s)



1007 clinics
(all 47 prefectures)

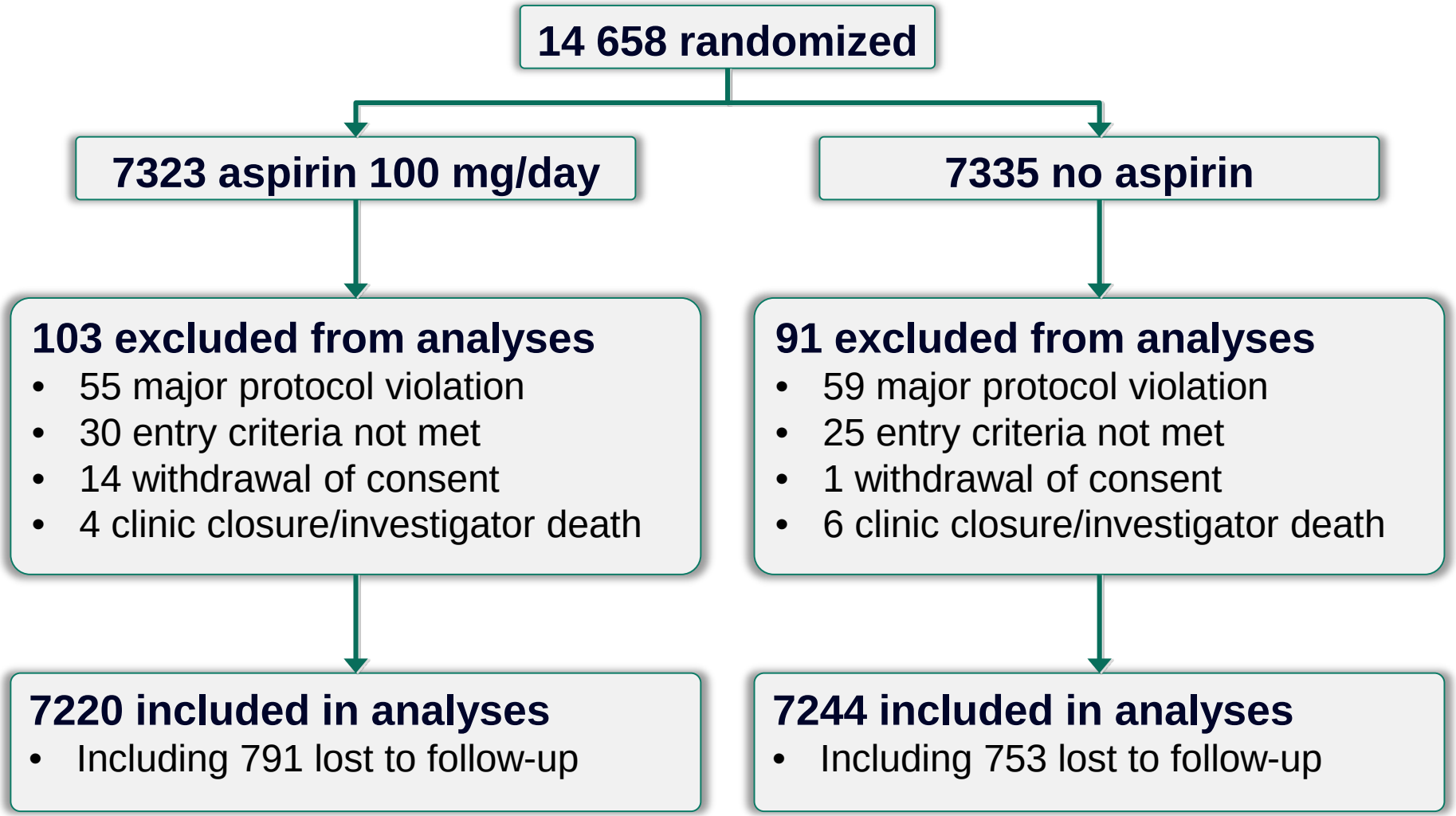
# Primary and secondary endpoints

| Outcome measure | Composite primary endpoint | Composite secondary endpoint | Individual secondary endpoints |
|---|---|---|---|
| Death from CV causes: myocardial infarction (MI), stroke and other CV causes | ✓ | ✓ | ✓ |
| Non-fatal stroke (ischemic or hemorrhagic) | ✓ | ✓ | ✓ |
| Non-fatal MI | ✓ | ✓ | ✓ |
| Transient ischemic attack (TIA) | | ✓ | ✓ |
| Angina pectoris | | ✓ | ✓ |
| Arteriosclerotic disease requiring surgery or intervention | | ✓ | ✓ |
| Death from causes other than CV disease | | | ✓ |
| Any cause of death | | | ✓ |
| Serious extracranial hemorrhage requiring transfusion or hospitalization | | | ✓ |

# Timing of final analyses

- Sample size determination for final analyses
  - Target: 15 000 patients for 624 primary endpoint events to occur
  - 80% power to detect a 20% reduction in annual frequency of events, from 0.874% without aspirin to 0.698% with aspirin (two-sided $\alpha = 0.05$)
- Independent Data Monitoring Committee (DMC) recommended to discontinue the study prematurely owing to futility
- The DMC believed that statistical power would not be reached, and that continuing the study might put patients at unnecessary risk of adverse events
- Median duration of patient follow-up at final analysis was 5.02 years (interquartile range: 4.55–5.33)

# Study flow

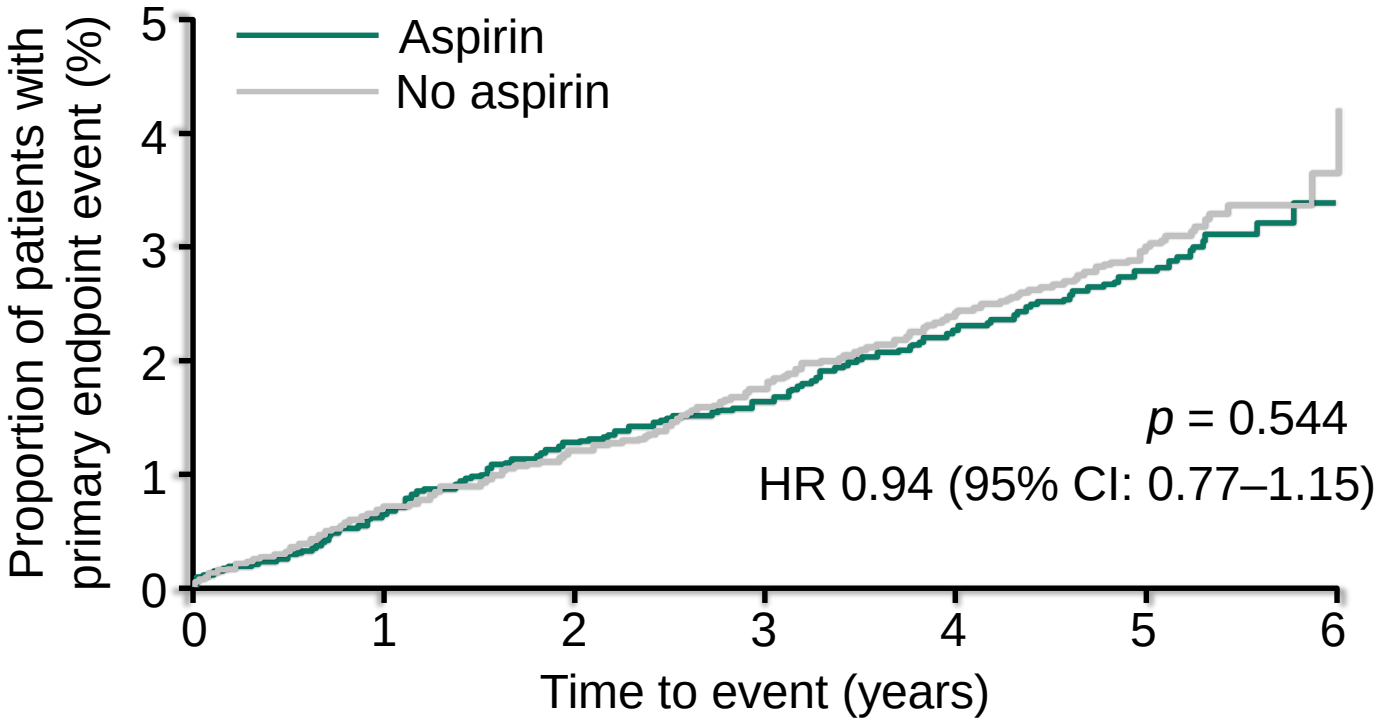

14 658 randomized
7323 aspirin 100 mg/day
7335 no aspirin
103 excluded from analyses
• 55 major protocol violation
• 30 entry criteria not met
• 14 withdrawal of consent
• 4 clinic closure/investigator death
91 excluded from analyses
• 59 major protocol violation
• 25 entry criteria not met
• 1 withdrawal of consent
• 6 clinic closure/investigator death
7220 included in analyses
• Including 791 lost to follow-up
7244 included in analyses
• Including 753 lost to follow-up

# Baseline demographics

| | Aspirin (n = 7220) | No aspirin (n = 7244) |
|---|---|---|
| **Age, mean ± SD, years** | 70.6 ± 6.2 | 70.5 ± 6.2 |
| ≥ 70 | 3986 (55.2) | 3985 (55.0) |
| **Men** | 3055 (42.3) | 3068 (42.4) |
| **Body mass index, mean ± SD, kg/m$^2$** | 24.2 ± 3.5 | 24.2 ± 3.4 |
| ≥ 25 | 2644 (36.6) | 2604 (35.9) |
| **Currently smoking** | 959 (13.3) | 934 (12.9) |

Values are n (%) unless otherwise stated

# Primary endpoint: Kaplan−Meier estimate

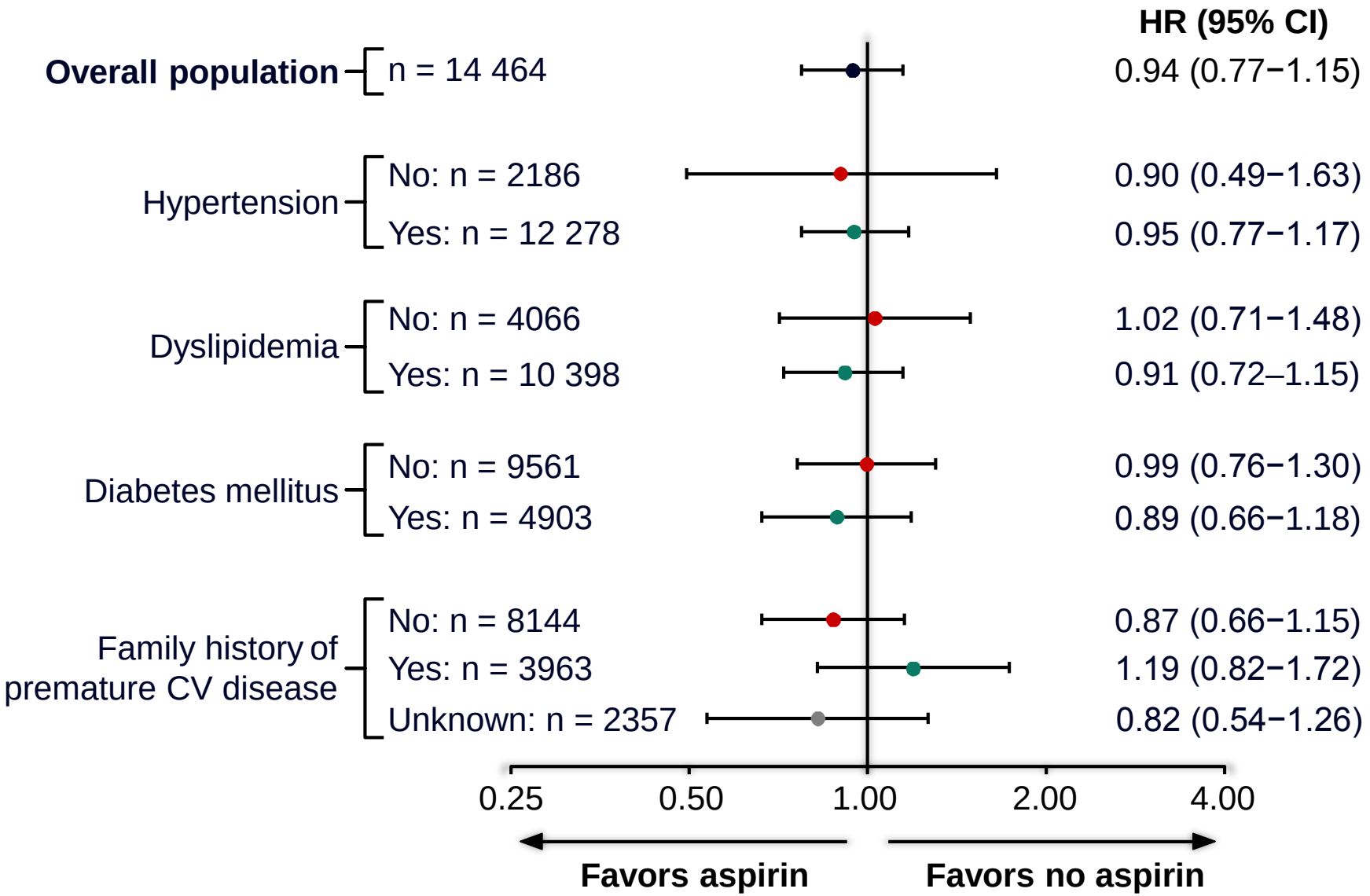



| Number at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Aspirin | 7220 | 7021 | 6771 | 6583 | 6322 | 3639 | 169 |
| No aspirin | 7244 | 7073 | 6861 | 6645 | 6359 | 3711 | 182 |

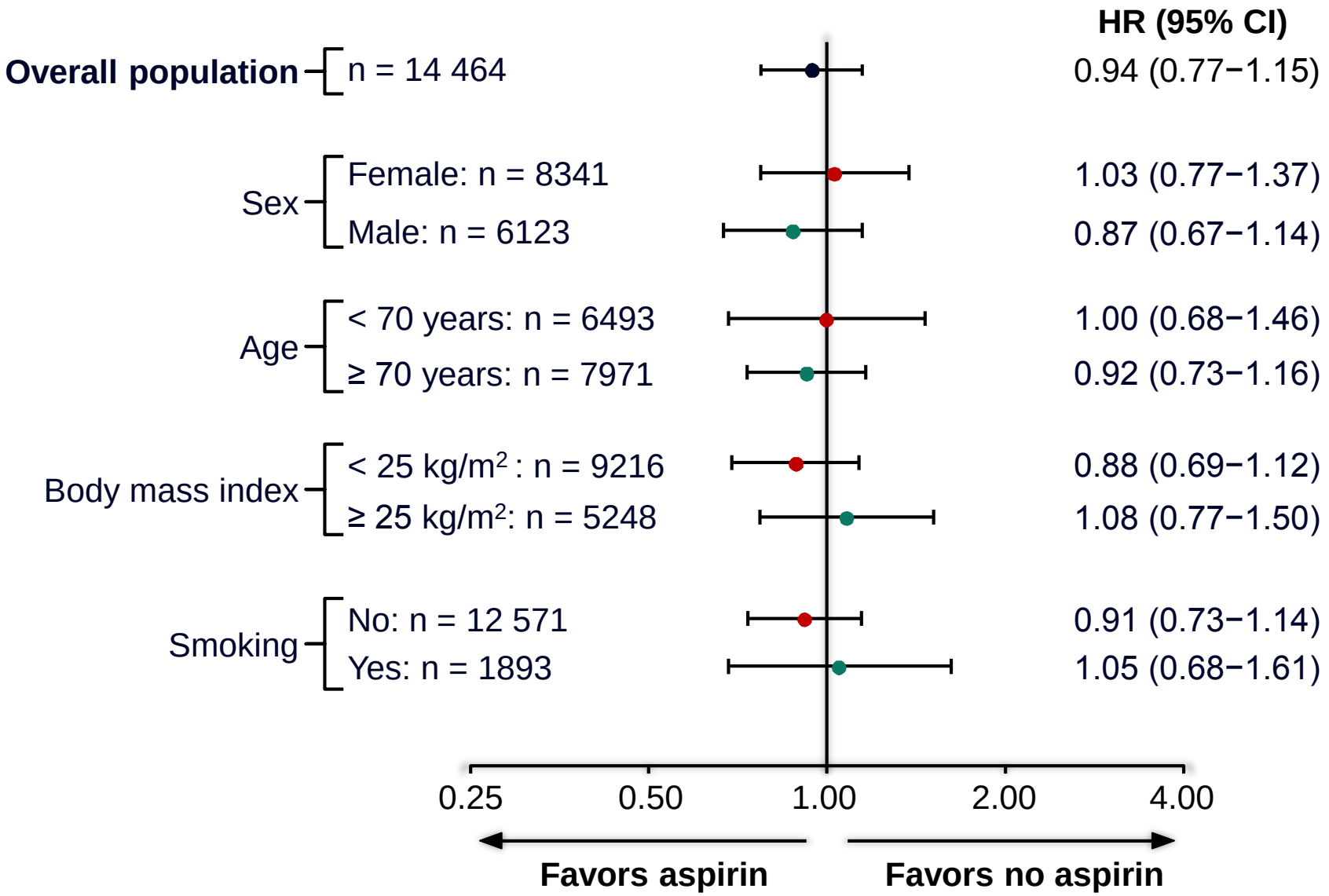
# Primary endpoint: observed events

| | Aspirin (n = 7220) | No aspirin (n = 7244) |
|---|---|---|
| **Total events** | **193** | **207** |
| **Fatal events** | **56** | **56** |
| Cerebral infarction | 2 | 7 |
| Intracranial hemorrhage | 5 | 5 |
| Subarachnoid hemorrhage | 2 | 4 |
| MI | 7 | 9 |
| Other fatal CV events | 40 | 31 |
| **Non-fatal events** | **137** | **151** |
| Cerebral infarction | 83 | 94 |
| Intracranial hemorrhage | 23 | 10 |
| Subarachnoid hemorrhage | 8 | 4 |
| MI | 20 | 38 |
| Undefined cerebrovascular events | 3 | 5 |

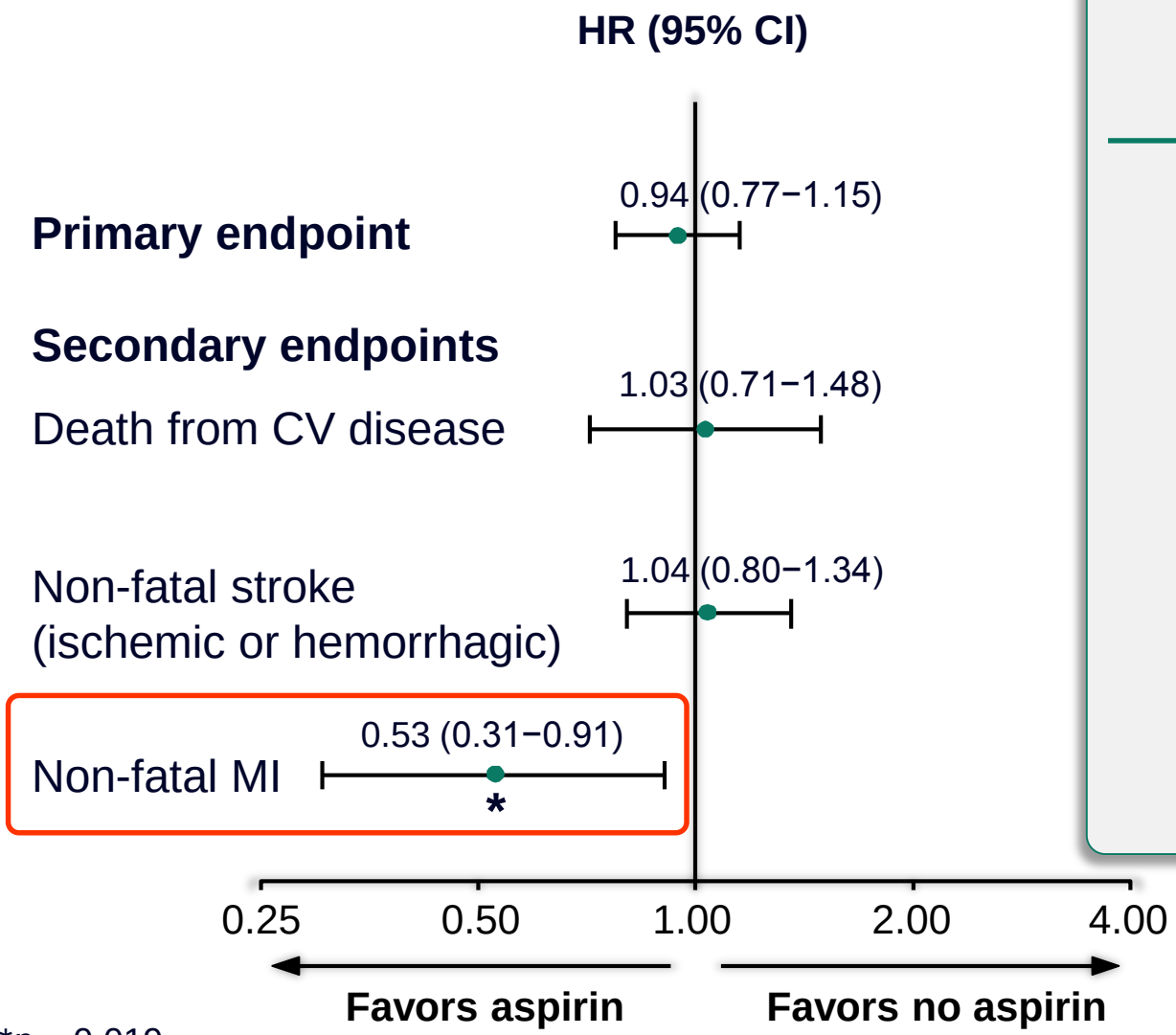
# Primary endpoint: disease risk factor subgroups



# Primary endpoint: demographic risk factor subgroups



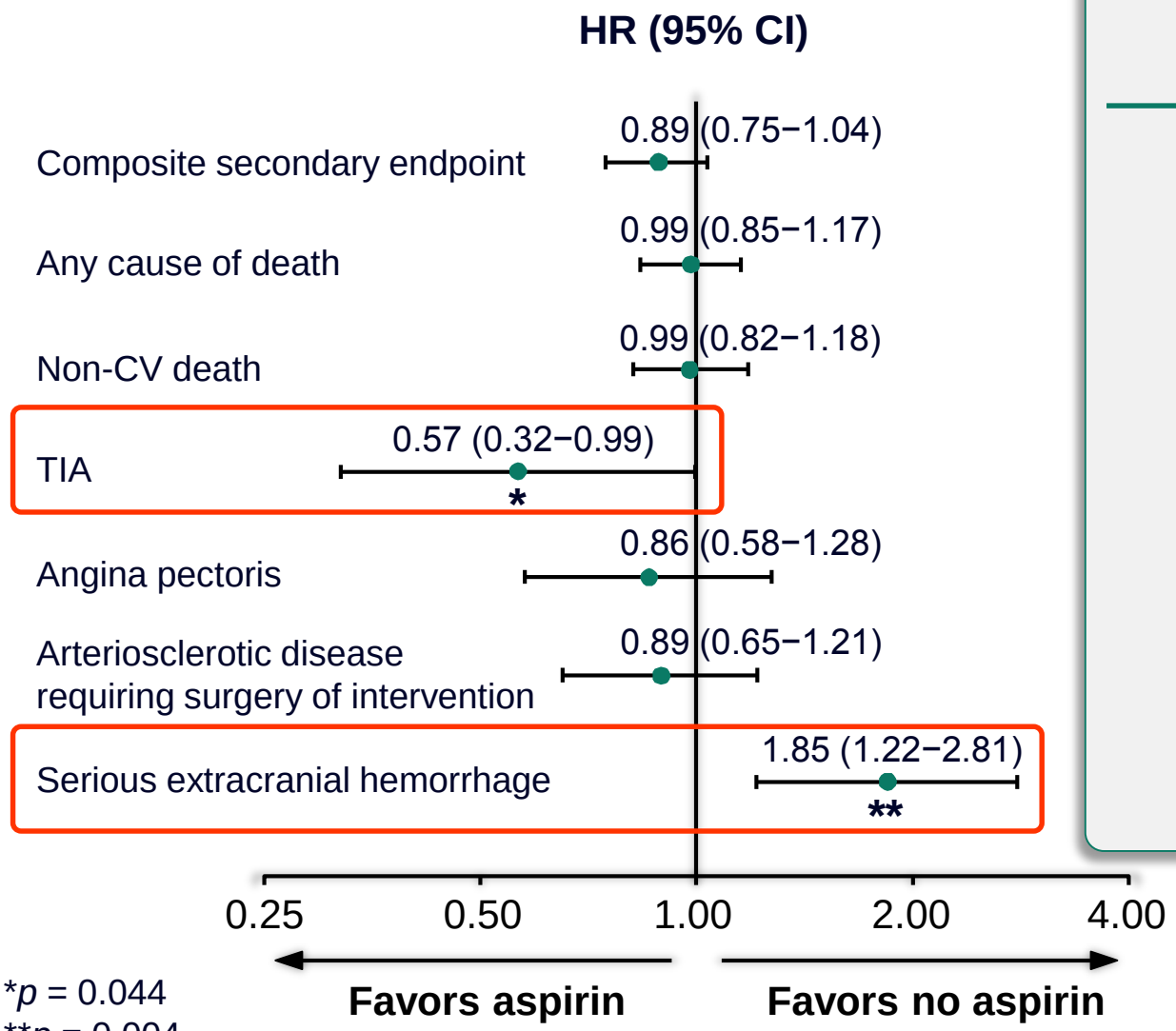
# Secondary efficacy endpoints: primary endpoint components




| 5-yr event rate [number of events] | |
|---|---|
| **Aspirin (n = 7220)** | **No aspirin (n = 7244)** |
| 2.77% [n = 193] | 2.96% [n = 207] |
| 0.86% [n = 58] | 0.78% [n = 57] |
| 1.65% [n = 117] | 1.64% [n = 114] |
| 0.30% [n = 20] | 0.58% [n = 38] |

*$p$ = 0.019

# Secondary efficacy endpoints: other




| 5-yr event rate [number of events] | |
|---|---|
| Aspirin (n = 7220) | No aspirin (n = 7244) |
| 4.00% [n = 280] | 4.59% [n = 319] |
| 4.29% [n = 297] | 4.11% [n = 303] |
| 3.46% [n = 239] | 3.36% [n = 246] |
| 0.26% [n = 19] | 0.49% [n = 34] |
| 0.66% [n = 46] | 0.81% [n = 54] |
| 1.08% [n = 75] | 1.24% [n = 85] |
| 0.86% [n = 62] | 0.51% [n = 34] |

*$p$ = 0.044
**$p$ = 0.004

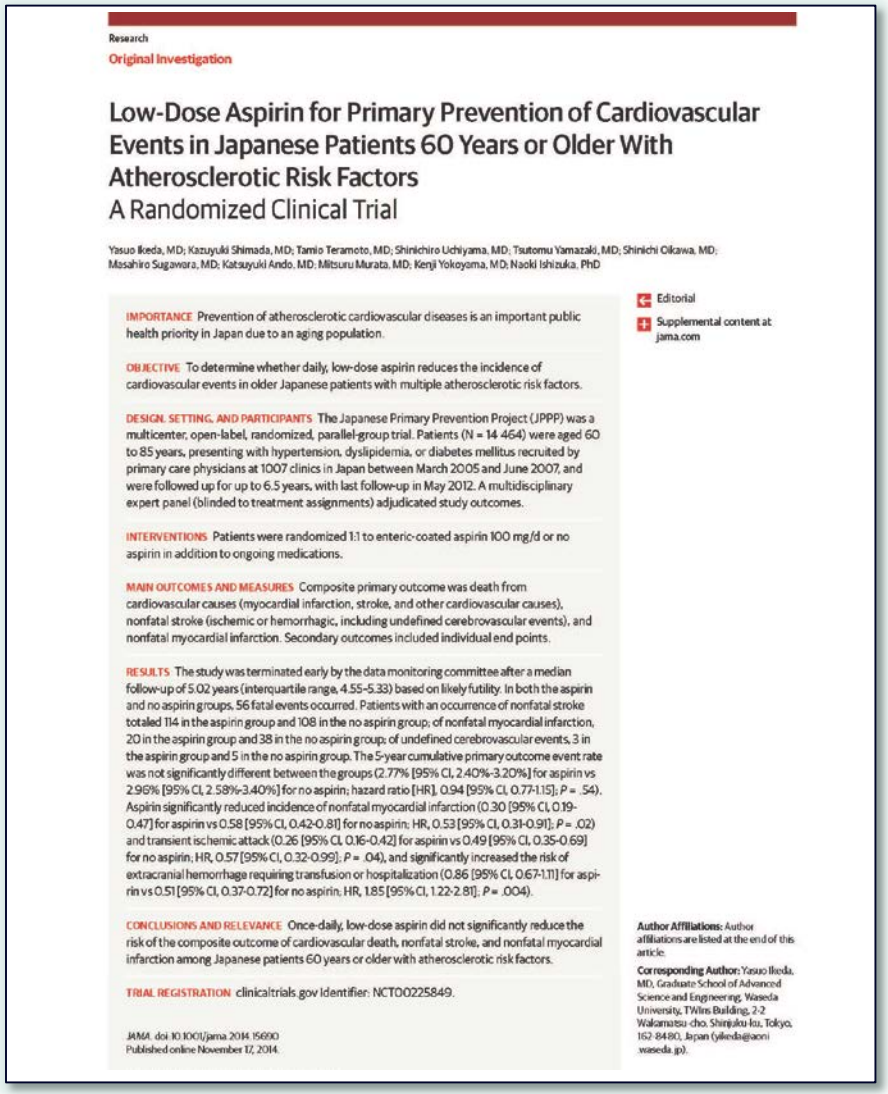
# Incidence of pre-specified gastrointestinal events of interest

| Event | Aspirin (n = 7323) | No aspirin (n = 7335) | *p* value |
|---|---|---|---|
| Stomach/abdominal discomfort | 335 (4.57) [4.11–5.08] | 175 (2.39) [2.05–2.76] | < 0.001 |
| Heartburn | 202 (2.76) [2.40–3.16] | 137 (1.87) [1.57–2.20] | < 0.001 |
| Gastroduodenal ulcer | 191 (2.61) [2.26–3.00] | 91 (1.24) [1.00–1.52] | < 0.001 |
| Stomach/abdominal pain | 168 (2.29) [1.96–2.66] | 81 (1.10) [0.88–1.37] | < 0.001 |
| Reflux esophagitis | 160 (2.18) [1.86–2.55] | 125 (1.70) [1.42–2.03] | 0.036 |
| Gastrointestinal hemorrhage | 103 (1.41) [1.15–1.70] | 31 (0.42) [0.29–0.60] | < 0.001 |
| Erosive gastritis | 89 (1.22) [0.98–1.49] | 40 (0.55) [0.39–0.74] | < 0.001 |
| Nausea | 79 (1.08) [0.85–1.34] | 50 (0.68) [0.51–0.90] | 0.010 |
| Stomach/abdominal pressure | 31 (0.42) [0.29–0.60] | 21 (0.29) [0.18–0.44] | 0.168 |

Values are n (%) [95% CI]

# Summary and conclusions

- This seminal study indicates that primary prevention with daily low-dose aspirin does not reduce the overall risk of atherosclerotic events in elderly Japanese patients with CV risk factors
- However, the study was discontinued prematurely before the study reached statistical power
- Therefore, lack of power or absence of a beneficial effect of aspirin may account for the non-significant outcome
- Irrespective, the clinical importance of aspirin in the primary prevention of CV events is less than originally anticipated in this patient population
- Aspirin significantly reduced the incidence of non-fatal MI and TIA, while it increased the risk of serious extracranial bleeding
- Further analyses are planned



Research

Original Investigation

# Low-Dose Aspirin for Primary Prevention of Cardiovascular Events in Japanese Patients 60 Years or Older With Atherosclerotic Risk Factors

## A Randomized Clinical Trial

Yasuo Ikeda, MD; Kazuyuki Shimada, MD; Tamio Teramoto, MD; Shinichiro Uchiyama, MD; Tsutomu Yamazaki, MD; Shinichi Oikawa, MD; Masahiro Sugawara, MD; Katsuyuki Ando, MD; Mitsuru Murata, MD; Kenji Yokoyama, MD; Naoki Ishizuka, PhD

**IMPORTANCE** Prevention of atherosclerotic cardiovascular diseases is an important public health priority in Japan due to an aging population.

**OBJECTIVE** To determine whether daily, low-dose aspirin reduces the incidence of cardiovascular events in older Japanese patients with multiple atherosclerotic risk factors.

**DESIGN, SETTING, AND PARTICIPANTS** The Japanese Primary Prevention Project (JPPP) was a multicenter, open-label, randomized, parallel-group trial. Patients (N = 14 464) were aged 60 to 85 years, presenting with hypertension, dyslipidemia, or diabetes mellitus recruited by primary care physicians at 1007 clinics in Japan between March 2005 and June 2007, and were followed up for up to 6.5 years, with last follow-up in May 2012. A multidisciplinary expert panel (blinded to treatment assignments) adjudicated study outcomes.

**INTERVENTIONS** Patients were randomized 1:1 to enteric-coated aspirin 100 mg/d or no aspirin in addition to ongoing medications.

**MAIN OUTCOMES AND MEASURES** Composite primary outcome was death from cardiovascular causes (myocardial infarction, stroke, and other cardiovascular causes), nonfatal stroke (ischemic or hemorrhagic, including undefined cerebrovascular events), and nonfatal myocardial infarction. Secondary outcomes included individual end points.

**RESULTS** The study was terminated early by the data monitoring committee after a median follow-up of 5.02 years (interquartile range, 4.55-5.33) based on likely futility. In both the aspirin and no aspirin groups, 56 fatal events occurred. Patients with an occurrence of nonfatal stroke totaled 114 in the aspirin group and 108 in the no aspirin group; of nonfatal myocardial infarction, 20 in the aspirin group and 38 in the no aspirin group; of undefined cerebrovascular events, 3 in the aspirin group and 5 in the no aspirin group. The 5-year cumulative primary outcome event rate was not significantly different between the groups (2.77% [95% CI, 2.40%-3.20%] for aspirin vs 2.96% [95% CI, 2.58%-3.40%] for no aspirin; hazard ratio [HR], 0.94 [95% CI, 0.77-1.15]; $P = .54$). Aspirin significantly reduced incidence of nonfatal myocardial infarction (0.30 [95% CI, 0.19-0.47] for aspirin vs 0.58 [95% CI, 0.42-0.81] for no aspirin; HR, 0.53 [95% CI, 0.31-0.91]; $P = .02$) and transient ischemic attack (0.26 [95% CI, 0.16-0.42] for aspirin vs 0.49 [95% CI, 0.35-0.69] for no aspirin; HR, 0.57 [95% CI, 0.32-0.99]; $P = .04$), and significantly increased the risk of extracranial hemorrhage requiring transfusion or hospitalization (0.86 [95% CI, 0.67-1.11] for aspirin vs 0.51 [95% CI, 0.37-0.72] for no aspirin; HR, 1.85 [95% CI, 1.22-2.81]; $P = .004$).

**CONCLUSIONS AND RELEVANCE** Once-daily, low-dose aspirin did not significantly reduce the risk of the composite outcome of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction among Japanese patients 60 years or older with atherosclerotic risk factors.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00225849.

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Editorial

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