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

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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.

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Editorial

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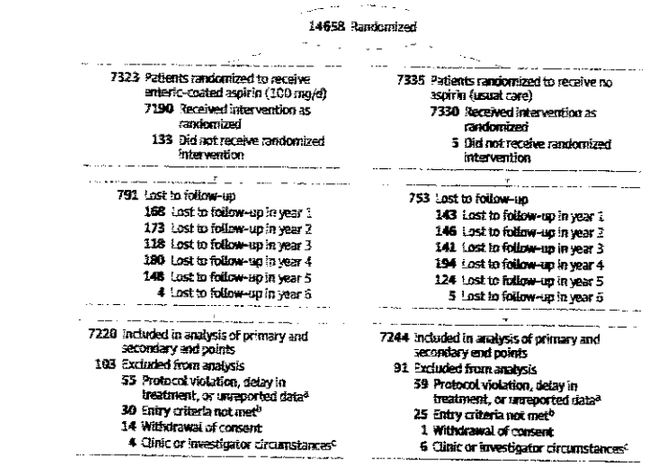
Figure 1. Flow of Patients Through the Japanese Primary Prevention Project (JPPP)



Data on patients assessed for eligibility are not available.

[a] Protocol violations (aspirin, n=19; no aspirin, n=22); delay in start of treatment (aspirin, n=10; no aspirin, n=15); unreported data by investigators in the clinics (aspirin, n=26; no aspirin, n=22).

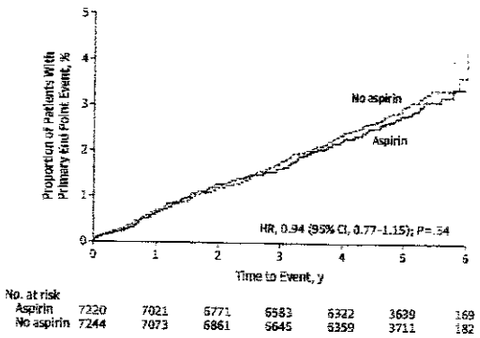
[b] Reasons for not meeting inclusion criteria were serious blood abnormalities (aspirin, n = 2), history of prohibited drugs (aspirin, n = 12; no aspirin, n = 18), cerebrovascular disease (aspirin, n = 6; no aspirin, n = 7), atrial fibrillation (aspirin, n = 3), hypersensitivity to aspirin (aspirin, n = 3), peptic ulcer (aspirin, n = 2), atherosclerotic disease (aspirin, n = 1), or long-term use of nonsteroidal anti-inflammatory drugs (aspirin, n = 1).

[c] Clinic or investigator circumstances were closure of clinic and investigator death.

Table 2. Fatal and Nonfatal Events Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors Receiving Aspirin or No Aspirin (Modified Intention-to-Treat Population)

	Aspirin (n = 7220)	No Aspirin (n = 7244)
Fatal events	56	56
Cerebral infarction	2	7
Intracranial hemorrhage	5	5
Subarachnoid hemorrhage	2	4
Myocardial infarction	7	9
Other fatal cardiovascular events	40	31
Nonfatal events	137	151
Cerebral infarction	83	94
Intracranial hemorrhage	23	10
Subarachnoid hemorrhage	8	4
Myocardial infarction	20	38
Undefined cerebrovascular events	3	5

Figure 2. Time to Primary End Point Composite Event[a] Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors Receiving Aspirin vs No Aspirin (Modified Intention-to-Treat Population)



HR indicates hazard ratio. The *P* value was determined using the log-rank test stratified for underlying disease (hypertension, dyslipidemia, or diabetes). The HRs were calculated using the Cox proportional hazards model.

[a] Death from cardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), and nonfatal myocardial infarction.