

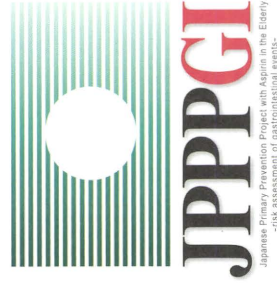
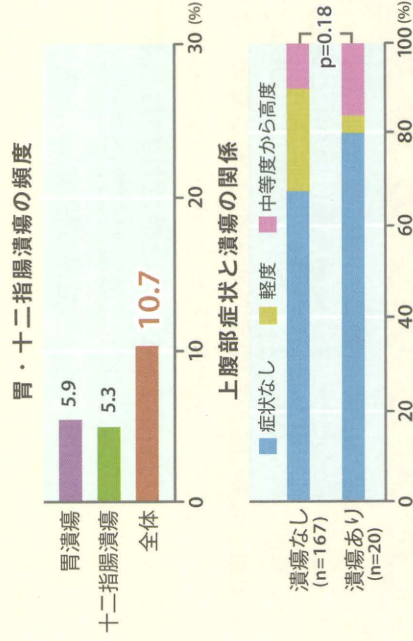
図書カード 1,000円



アスピリンの副作用

最近、アスピリンは低用量であっても、上部消化管の粘膜を傷害する副作用があり、長期に内服すると、消化性潰瘍（胃潰瘍と十二指腸潰瘍）を起こすことが明らかになってきました。アスピリンには抗血小板作用がありますので、難癒から出血しやすい、いったん出血すると止血するのに難渋します。では、低用量のアスピリンを長期に内服すると、どのくらいの頻度で消化性潰瘍が発生するのでしょうか。2005年に発表された欧米の報告では、心筋梗塞の予防の目的で、低用量アスピリンを内服している患者さん187名に内視鏡検査を行うと、20名(10.7%)に消化性潰瘍が見つかっています(図2)。しかし、消化性潰瘍の発見された20名のうち、腹痛、食欲不振などの症状のあった方は4名(20%)だけであり、残りの16名(80%)は無症状でした。このように、アスピリンを内服している患者さんでは、潰瘍があっても症状が出ないことが多い、症状がなくても潰瘍がないという保証はない、潰瘍ができると出血しやすいといった特徴が示されています。また、最近の我が国の学会でも、低用量アスピリンを内服している患者さんの潰瘍の発生頻度は6%から12%程度であると報告されています。

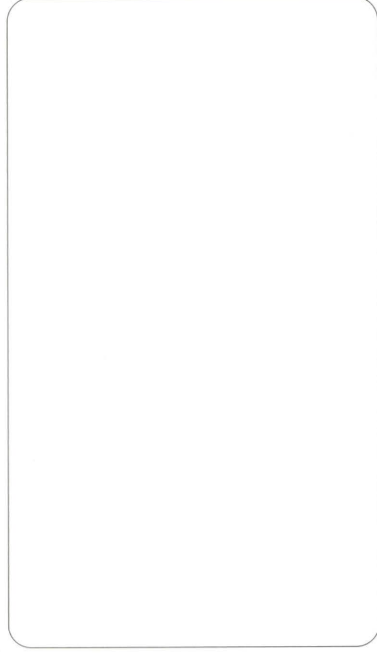
図2 低用量アスピリン服用による潰瘍の発生と上腹部症状との関係



～安心・安全への新しい一歩～

このリーフレットは、脳卒中・心筋梗塞の予防法の確立を目的とした消化管障害の調査(JPPPGI)にご協力いただいた患者様にお渡ししています。

▼ お問い合わせはこちら ▼



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Yeomans, ND : Alliment Pharmacol Ther 22:765-801, 2005

低用量アスピリンによる 消化管粘膜傷害

獨協医科大学 消化器内科

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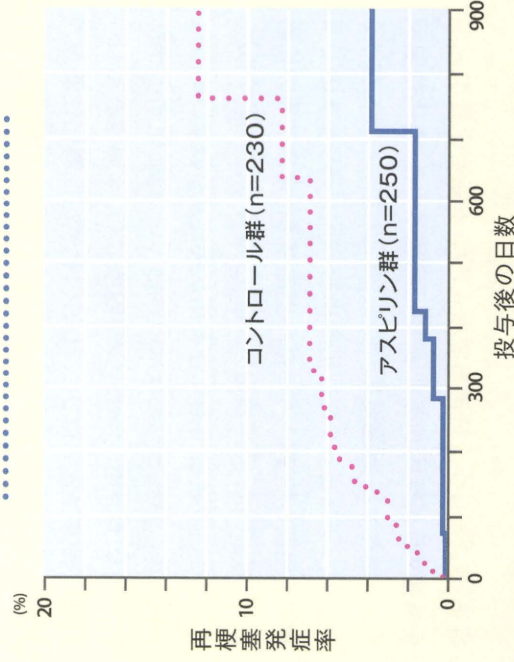
上村 直実

監修

アスピリンの効果

アスピリンは、もともとは鎮痛解熱薬(NSAIDと総称)として開発されたお薬です。一日の内服量が1,000mg以上では、解熱、腫れを抑えるなどの作用を発揮しますが、75-325mgの低用量では血小板が凝集するのを抑える働きがあり、抗血小板作用と呼ばれます。日本ではアスピリン81mgと100mgの製剤が用いられていますが、この抗血小板作用から血液が固まって心臓や脳の血管が血栓で詰まるのを防ぎます。図1は、過去1ヶ月以内に急性心筋梗塞を発症しアスピリン81mgの内服を開始した患者さん(アスピリン群)と内服しなかった患者さん(コントロール群)を長期に経過観察した成績で、横軸に内服開始からの日数、縦軸に心筋梗塞の累積の再発率を示しますが、アスピリンにより心筋梗塞の再発のリスクが73%減少しています。このように、アスピリンを内服すると心筋梗塞や脳梗塞などのアテローム性血栓症の再発を確実に減らすことができます。

図1 アスピリンによる心筋梗塞の再発予防効果



リスク因子

潰瘍を発生しやすいのはどのような方でしょうか。これまでの多くの研究から、以前潰瘍に罹った方、高齢者、アスピリンとNSAIDの併用、他の抗血小板薬や抗凝固薬などとの併用、ピロリ菌陽性などがリスク因子になります。

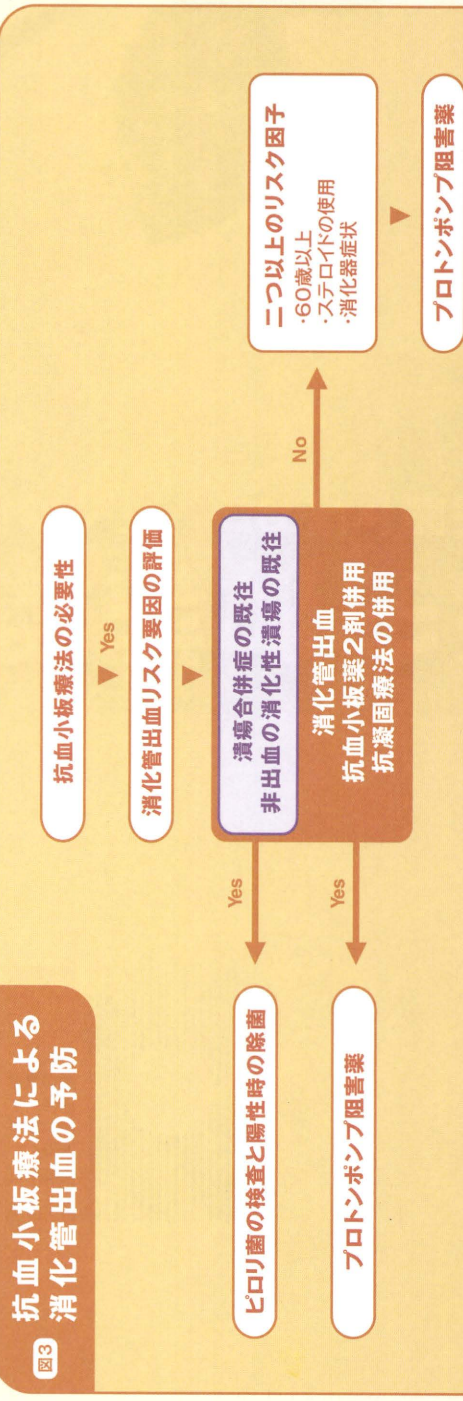
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アスピリンによる潰瘍と合併症のリスク因子
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予防対策

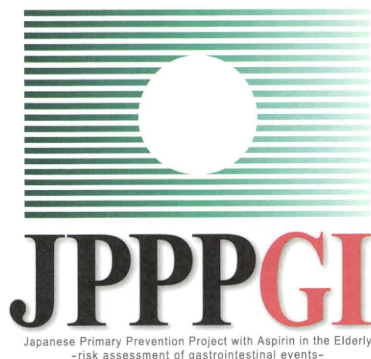
アメリカの学会では、図3に示すようなアスピリンを用いた抗血小板療法による出血、潰瘍の予防を提案しています。リスク因子を評価して、ピロリ菌が陽性であれば除菌、それに加えて胃酸の分泌を抑制するお薬を内服することが推奨されています。日本での現状(2010年3月)は、アスピリンによる潰瘍を予防するために抗潰瘍薬を予防投与することは保険診療では認められていませんが、アスピリンによる潰瘍の実態調査、予防薬などの研究が進んでいます。

図3 抗血小板療法による消化管出血の予防



安心・安全への新しい一歩

JPPPGI 調査が始まります



厚生労働科学研究医療技術実用化総合研究事業

高齢者におけるアスピリンの一次予防効果に関する研究 消化管障害に注目したリスク&ベネフィットの検討

Japanese Primary Prevention Project with Aspirin in the Elderly
- risk assessment of gastrointestinal events - (JPPPGI)

目的

脳血管、冠動脈を含めたアテローム血栓症を診断されていない高血圧症、高脂血症または糖尿病を有する高齢者を対象に、アスピリンによる一次予防効果を検証する大規模臨床研究(JPPP)を実施されているが、2008年10月にACCF/ACG/AHAにより出された非ステロイド系消炎鎮痛剤の消化管障害に関する提言を受けて、JPPP試験において日本人の低用量アスピリンによる消化管障害の詳細な実態調査を行う。

研究計画

試験方法 : 中央登録法による多施設共同ランダム化比較試験
アスピリン腸溶錠(100mg/日)投与群vs非投与群

対象 : 脳血管、冠動脈を含めた動脈硬化性疾患を診断されていない
高血圧症、高脂血症または糖尿病を有する高齢患者(60歳~85歳)

症例数 : 14,500例(追跡4年以上)

試験期間 :
2005年3月~2007年6月 JPPP試験としてすでに登録済み
2006年より追跡調査を実施、追跡率98%以上
2009年~2011年 追跡調査、患者啓発活動、中間解析(年1回)
2012年 最終解析、データ公表

研究組織

試験総括医師 : 池田 康夫
(早稲田大学理工学術院生命医科学科教授)

ステアリングコミッティ(各分野専門家)

データセンター

モニタリング委員会

イベント判定委員会

試験事務局

研究の意義と期待される効果

- ◇ 本研究によりアスピリンの一次予防効果が確認されれば、毎年5~10万人の脳梗塞・心筋梗塞という死亡原因・要介護原因の上位を占める重篤な疾患が回避され、高齢化社会を迎えた我が国の医療費・介護費の削減に大きく貢献することができる。一方その為には消化管出血などを含む出血性合併症の正確な把握が必要である。
- ◇ そして健康余命の延長により患者にとっても豊かな老後を健康に過ごすことができ、患者や家族の生活の質の向上にも繋がる事が期待できる。

本調査へのご協力をお願い申し上げます。

お問合せ先

JPPPGI 試験事務局(コールセンター)



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Rationale, design, and baseline data of the Japanese Primary Prevention Project (JPPP)—A randomized, open-label, controlled trial of aspirin versus no aspirin in patients with multiple risk factors for vascular events

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Background Prevention of atherosclerotic disease has become an important public health priority in Japan due to the aging of the population and changes in diet and lifestyle factors.

Methods The Japanese Primary Prevention Project (JPPP) is a multicenter, open-label, randomized, parallel-group trial that is evaluating primary prevention with low-dose aspirin in Japanese patients aged 60 to 85 years with hypertension, dyslipidemia, or diabetes mellitus. The study cohort will be followed for a mean of 4 years. The primary end point is a composite of death from cardiovascular causes (including fatal myocardial infarction [MI], fatal stroke, and other cardiovascular death), nonfatal stroke (ischemic or hemorrhagic), and nonfatal MI. Key secondary end points include a composite of cardiovascular death, nonfatal stroke, nonfatal MI, transient ischemic attack, angina pectoris, or arteriosclerotic disease requiring surgery or intervention; each component of the primary end point; noncerebrovascular and noncardiovascular death; and extracranial hemorrhage requiring transfusion or hospitalization. End point assessment is done by a central adjudication committee that is blinded to treatment assignments.

Results Enrollment began in March 2005 and was completed in June 2007. A total of 14,466 patients were randomly allocated to receive enteric-coated aspirin, 100 mg/d, or no aspirin. At randomization, the study cohort had a mean (SD) age of 70.6 (6.2) years; 57.8% were women, 85.0% had hypertension, 71.7% had dyslipidemia, and 33.9% had diabetes. In the study cohort, 80.4% of patients had ≥ 3 risk factors.

Conclusion The JPPP is the largest primary prevention trial of aspirin in a Japanese population that is investigating whether the benefit of aspirin in reducing risk of vascular events outweighs any bleeding risk in elderly patients with multiple risk factors. (*Am Heart J* 2010;159:361-369.e4.)

By the year 2030, an estimated 1 of every 4 persons in Japan will be aged ≥ 60 years.¹ Together with the aging of the population, adoption of Western diets and lifestyles has contributed to the rising prevalence of lifestyle-related diseases, including hypertension, dyslipidemia,

and diabetes mellitus. As a result, the prevention of atherosclerotic disease has become one of the most important public health issues in Japan.

It is well recognized that aspirin reduces the incidence of serious vascular events in high-risk patients with acute

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or established atherosclerotic disease. The meta-analysis conducted by the Antithrombotic Trialists' Collaboration involving >30 countries (including Japan) showed that aspirin at daily doses of ≥ 75 mg significantly reduced the risk of serious vascular events (ie, nonfatal myocardial infarction [MI] or stroke, or death due to a vascular cause) by 23% overall (19% to 32% when stratified by dose) compared with no aspirin use in the secondary prevention setting.² Recognizing this benefit, guidelines from Japan, as well as other countries, recommend the use of aspirin for secondary prevention of atherosclerotic disease.³⁻¹⁰

The Antithrombotic Trialists' Collaboration recently evaluated primary prevention with aspirin in a meta-analysis of the 6 large clinical studies in Europe and North America.¹¹⁻¹⁶ Aspirin was associated with a significant 12% proportional reduction in serious vascular events, due mainly to a reduction of about one fifth in major coronary events. There was a trend toward a reduction in ischemic stroke but an increase in hemorrhagic stroke.¹⁷ Aspirin allocation was associated with an increase in major gastrointestinal and extracranial bleeds.

To date, no trials with aspirin for primary prevention of ischemic heart disease (IHD) have been reported in a general population of Japanese patients, and no epidemiological data for this population are available to allow selection of suitable candidates for aspirin therapy. Although a primary prevention trial of low-dose aspirin in Japanese patients with diabetes was recently reported, it lacked statistical power to demonstrate a significant reduction in atherosclerotic events.¹⁸ In Japan, the use of aspirin for primary prevention of IHD has not been widespread in clinical practice. In the Reduction of Atherothrombosis for Continued Health (REACH) Registry, 14.4% of Japanese patients with ≥ 3 risk factors received aspirin, compared with 49.8% for the total population.^{19,20}

Whereas the IHD mortality rate is higher than stroke mortality in the United States, Europe, and the Middle East, the situation is reversed in East Asia including Japan where the stroke mortality rate exceeds that of IHD.²¹ Accordingly, the Japanese Primary Prevention Project (JPPP) was designed to test the clinical hypothesis that the benefit of primary prevention with low-dose, enteric-coated aspirin in reducing total atherosclerotic events (IHD and stroke) will outweigh risks of gastrointestinal or cerebrovascular bleeding in elderly Japanese patients with hypertension, hyperlipidemia, or diabetes.

Methods

Study design

The JPPP is a multicenter, open-label, parallel-group, centrally randomized controlled trial. Patients were recruited by General Practitioners at 1,000 centers (clinics) in 47 prefectures in Japan. Patients underwent a screening examination, and if eligibility

criteria were met, they were asked to participate. Those who consented to participate received treatments to control their risk factors at the screening examination and returned for baseline evaluation and randomization approximately 1 month later. Patients were randomized using a central computerized system to receive aspirin or no treatment (Figure 1). To ensure that both groups were well balanced, randomization was stratified by the patients' underlying diseases (hypertension, dyslipidemia, diabetes, or various combinations of each for 7 strata). It was assumed that sex and age (<70 vs ≥ 70 years) would be balanced by the minimization method in each stratum. Patients allocated to the aspirin group were treated with one 100-mg tablet of enteric-coated aspirin (Bayaspirin, 100-mg tablet, Bayer Yakuhin, Ltd., Osaka, Japan) per day. The observation period was defined as the day of randomization until the day of the patient's final visit for their final general examination. Patients in both groups continued to receive their ongoing medications throughout the study. The schedule of study visits and assessments is shown in Figure 2. The JPPP trial uses the Prospective Randomized Open Label Blinded End point (PROBE) design, whereby the adjudication of end points is done centrally by an event adjudication committee that is blinded to treatment assignments.²² This is a limitation of the study because the PROBE design does not control for lack of ascertainment; however, the Japanese Pharmaceutical Affairs Law strictly limits the use of placebo in large physician-driven studies of approved products such as aspirin. Blinded placebo is permitted to be used only in some small preregistration studies in Japan.

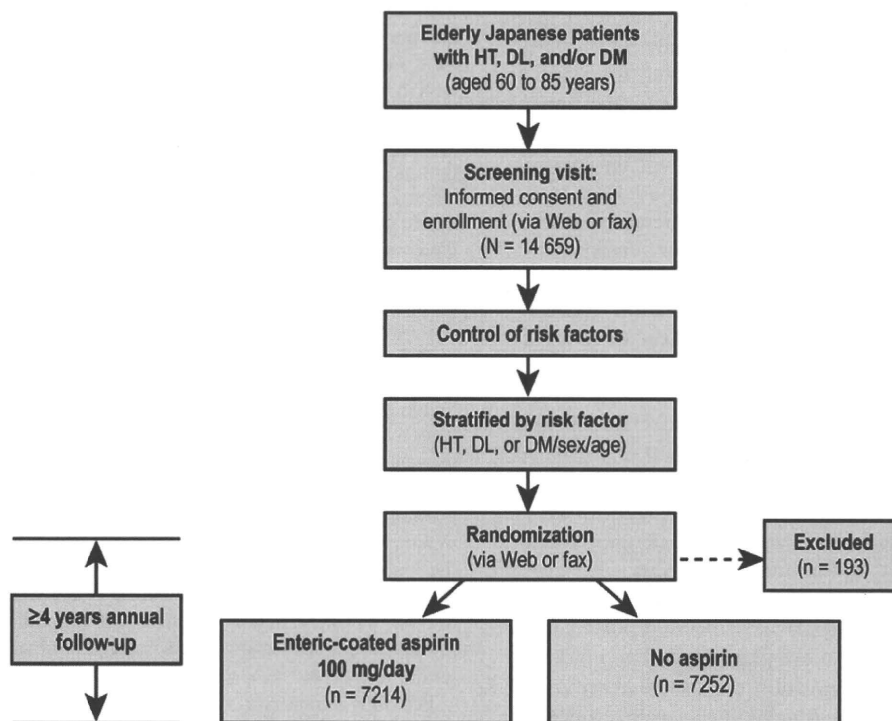
The JPPP is registered at www.clinicaltrials.gov with the trial identification number NCT00225849. The human rights and welfare of individual patients were duly respected and the scientific quality and reliability of the study were ensured as the study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies. Before enrollment of any patient, the protocol and consent form were approved by the institutional review board of each participating center. All patients provided written informed consent.

The JPPP study is funded by the Japanese Ministry of Health, Labour and Welfare (Tokyo, Japan) and the Waksman Foundation of Japan Inc (Tokyo, Japan). Enteric-coated aspirin, 100 mg, tablets are provided at no charge by Bayer Yakuhin Ltd (Osaka, Japan).

Study population

Patients aged 60 to 85 years who had not been previously diagnosed with any atherosclerotic disease were eligible if at the initial screening examination, they met the criteria for hypertension, dyslipidemia, or diabetes, or were receiving medication for one or more of these diseases. Hypertension was defined by a systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg; dyslipidemia was defined by any of the following: total cholesterol ≥ 220 mg/dL, low-density-lipoprotein cholesterol ≥ 140 mg/dL, high-density-lipoprotein cholesterol <40 mg/dL, or triglycerides ≥ 150 mg/dL; and diabetes by any of the following: fasting morning blood glucose ≥ 126 mg/dL, any blood glucose ≥ 200 mg/dL, 2-hour blood glucose ≥ 200 mg/dL in the 75-g glucose tolerance test, or glycated hemoglobin $\geq 6.5\%$ in accordance with Japanese

Figure 1



Study design. DL, Dyslipidemia; DM, diabetes mellitus; HT, hypertension.

guidelines.²³⁻²⁵ In principle, hypertension, dyslipidemia, and diabetes were to be controlled after the screening examination to respective target values in accordance with therapeutic guidelines proposed by academic societies in Japan.²³⁻²⁵ We did not include patients aged >85 years in the study because in Japan, the clinical significance of aggressive treatment of patients aged >85 years for their cardiovascular (CV) risk factors is uncertain in accordance with the current CV prevention guidelines.

Patients were excluded if they had a history of coronary artery disease or cerebrovascular disease (including transient ischemic attack), atherosclerotic disease requiring surgery or intervention, atrial fibrillation, peptic ulcers, von Willebrand disease or other conditions associated with a tendency for bleeding, clotting factor deficiencies and other serious blood abnormalities, or aspirin-sensitive asthma. Patients receiving treatment with aspirin or other antiplatelet agents (eg, clopidogrel, ticlopidine, cilostazol, dipyridamole, and trapidil) or anticoagulants (warfarin) or long-term treatment with nonsteroidal antiinflammatory drugs were also excluded, as were those with a history of hypersensitivity to aspirin or salicylic acid.

End point definitions

The primary end point is a composite of death from CV causes (including fatal MI, fatal stroke, and other CV death), nonfatal stroke (ischemic or hemorrhagic), and nonfatal MI. The most important secondary end points are: (1) a composite of death

from CV causes, nonfatal stroke (ischemic or hemorrhagic), nonfatal MI, transient ischemic attack, angina pectoris, and arteriosclerotic disease requiring surgery or intervention; (2) death from CV disease; (3) death from causes other than CV; (4) each end point event individually; and (5) serious extracranial hemorrhage requiring transfusion or hospitalization. Myocardial infarction was diagnosed according to the European Society of Cardiology/American College of Cardiology guidelines.²⁶ Ischemic stroke is defined as acute regional neurologic deficit maintained for 24 hours, with imaging evidence of cerebral infarction or intracerebral hemorrhage. In accordance with the PROBE methods, adjudication of end point events is done centrally twice a year by an independent event adjudication committee that is blinded to treatment assignments.

Sample size determination

The originally expected primary end point event rate in the control group was 1.5% to 2.0% per year. Assuming a mean follow-up of 4 years and a relative risk reduction of 20% with aspirin compared with no treatment, a sample size of 10,000 patients was originally considered to be sufficient to provide 80% power at a 2-sided $\alpha = .05$ level of significance. However, the first general examination, after the enrollment of 6,745 patients in July 2006 revealed 14 primary end point events (including unsettled ones) indicating that the incidence of events was lower than that estimated before the start of

Figure 2

Check items	Initial	Follow-up period					
		2006	2007	2008	2009	2010	2011 or end of follow-up
Background	xx						
Vascular events		xx	xx	xx	xx	xx	xx
Adverse events		xx	xx	xx	xx	xx	xx
Compliance with the treatment		x	x	x	x	x	x
Risk factors							
Blood pressure, serum lipids, blood glucose	xx	x*	x*	x*	x*	x*	x*
Body weight	xx	xx	xx	xx	xx	xx	xx
Smoking	xx	xx	xx	xx	xx	xx	xx

Schedule of examinations. xx, essential; x, to be reported wherever possible. Asterisk indicates examination results related to the disease under treatment are essential.

the study. Assuming that the maximum frequency of events in the aspirin and control groups was 0.786%, the number of required patients was recalculated without change in the relative rate of event reduction, which remained at 20%. The revised estimation indicated that approximately 14,960 patients for an expected number of events of 624 cases would be required to demonstrate a 20% reduction in the annual frequency of events from 0.874% to 0.698% by aspirin administration at a 2-sided $\alpha = .05$ and 80% statistical power during the enrollment period from the end of September 2006 until the end of June 2007. On the basis of this calculation, the enrollment target was reset at an estimated 14,960 patients to achieve 624 primary end point events, which is expected by the end of September 2011.

Statistical analysis

The primary goal of this study is to test the hypothesis that the time to the composite primary end point is significantly longer in patients treated with aspirin than in patients who were not given aspirin. The null hypothesis is that the time to onset of events does not differ between the 2 groups. The effect of treatment on the primary end point will be tested by the stratified log-rank test on all patients meeting inclusion criteria, with underlying disease (hypertension, dyslipidemia, and/or diabetes) used for stratification. End point analyses are planned for the stratified risk factor subgroups and for subgroups by sex and age. The statistical test will be performed in a 2-sided manner with a significance level set at .05. If aspirin is found to be inferior to no treatment, whether the difference is statistically significant is not of interest. To estimate the efficacy of aspirin therapy, the Cox proportional hazards model

Table 1. Patient characteristics and underlying risk factors at baseline

Factor, n (%)	Aspirin (n = 7214)	No aspirin (n = 7252)	Total (N = 14 466)
Male	3046 (42.2%)	3061 (42.2%)	6107 (42.2%)
HT	6134 (85.0%)	6156 (84.9%)	12,290 (85.0%)
DL	5179 (71.8%)	5196 (71.6%)	10,375 (71.7%)
Diabetes	2442 (33.9%)	2461 (33.9%)	4903 (33.9%)
HT and DL	2821 (39.1%)	2824 (38.9%)	5645 (39.0%)
DL and DM	344 (4.8%)	354 (4.9%)	698 (4.8%)
HT and DM	492 (6.8%)	499 (6.9%)	991 (6.9%)
HT, DL, and DM	1442 (20.0%)	1442 (19.9%)	2884 (19.9%)
Obesity (BMI ≥ 25 kg/m ²)	2644 (36.7%)	2617 (36.1%)	5261 (36.4%)
Smoking	950 (13.2%)	936 (12.9%)	1886 (13.0%)
Family history	1967 (27.3%)	1986 (27.4%)	3953 (27.3%)
Low HDL-cholesterol (<40 mg/dL)	672 (9.3%)	663 (9.1%)	1335 (9.2%)

HT, Hypertension; DL, dyslipidemia; DM, diabetes mellitus; BMI, body mass index; HDL, high-density lipoprotein.

will be used to determine the intergroup hazard ratios for each end point and their corresponding 95% CIs. Corrections will also be incorporated for other factors used in the allocation of patients and for biased background variables as needed. The length of time until the onset of events will be estimated by the Kaplan-Meier method.

Interim analysis and data monitoring

The JPPP Steering Committee is overseeing the conduct of this study (see Appendix, available online). Case report form pages are entered into the study Web site or faxed to a central data center in Tokyo for input into the study database. An independent Data Monitoring Committee, composed of 4 academic members and an independent statistician, regularly monitors the results of the trial. Interim analyses have been planned at 1-year intervals beginning 6 months after the end of patient enrollment and continuing until final study analysis. After each interim analysis, the Data Monitoring Committee will advise whether the study should be continued and if the study protocol should be amended based on several factors including occurrence of unforeseen or serious adverse reactions, occurrence of adverse reactions at a higher incidence than expected, publication of new results from a similarly designed study, ethical issues generated by changes in the social environment, or if the interim analysis shows the clear superiority of aspirin over no treatment or no possibility of obtaining beneficial effects with aspirin relative to no treatment. To keep the α error for the study at 2.5% (1-sided), adjustment for multiple testing will be done using the Lan-Demets α consumption function; the α consumption function of the O'Brien-Fleming type will also be used.

Results

A total of 14,659 patients were enrolled at 1,000 study sites in 47 prefectures in Japan from March 28, 2005, to June 30, 2007, at which time patient recruitment was completed. Of these, baseline data were available for

Table II. Demographic and clinical characteristics at baseline

Parameter, mean (SD)	Aspirin (n = 7214)	No aspirin (n = 7252)	Total (N = 14 466)
Age (y)	70.6 (6.2)	70.5 (6.2)	70.6 (6.2)
Systolic blood pressure (mm Hg)	137.2 (15.8)	137.2 (15.8)	137.2 (15.7)
Diastolic blood pressure (mm Hg)	77.7 (10.4)	77.6 (10.3)	77.6 (10.3)
Total cholesterol (mg/dL)	202.8 (33.2)	203.6 (32.7)	203.2 (32.9)
Low-density-lipoprotein cholesterol (mg/dL)	118.7 (30.8)	119.3 (30.5)	119.0 (30.6)
High-density-lipoprotein cholesterol (mg/dL)	57.8 (16.0)	58.4 (16.0)	58.1 (16.0)
Triglycerides (mg/dL)*	115.5 (84-160)	114 (82-158)	115 (83-158)
Fasting blood glucose (mg/dL)†	107.8 (31.5)	107.8 (32.4)	107.8 (32.0)
Glycated hemoglobin (%)	5.7 (1.0)	5.7 (0.9)	5.7 (1.0)
Body mass index (kg/m ²)	24.2 (3.6)	24.2 (3.4)	24.2 (3.5)
Waist circumference (cm)‡	85.1 (9.9)	84.7 (10.3)	84.9 (10.1)

* Median [interquartile range].

† Values for diabetes mellitus (DM) and non-DM subjects; DM subjects had fasting blood glucose (mean [SD]) as follows: 132.9 (42), aspirin group; 133 (43.7), nonaspirin group; 132.9 (42.8), all; non-DM subjects had fasting blood glucose (mean [SD]) as follows: 95.0 (10.8), aspirin group; 94.8 (10.8), nonaspirin group; 94.9 (10.8), all.

‡ Waist circumference data were available for 3950 patients, including 1967 patients in the aspirin group and 1983 patients in the no-aspirin group.

14,466 patients (98.7%). With regard to the other patients, 88 (0.6%) did not meet eligibility criteria, 11 (0.1%) withdrew consent, 52 (0.4%) stopped attending study visits, and 42 (0.3%) were withdrawn by their enrolling physicians.

Baseline characteristics of patients in the aspirin and control groups were similar (Tables I and II). Overall, the mean (SD) age of the study cohort was 70.6 (6.2) years; 6,107 (42.2%) were men and 8,359 (57.8%) were women. Hypertension was the most common underlying disease found in 85.0% of the study cohort, with dyslipidemia and diabetes seen in 71.7% and 33.9%, respectively. Hypertension was comorbid with both dyslipidemia and diabetes in 19.9%, with only dyslipidemia in 39.0% and only diabetes in 6.9%. Among other risk factors, current smoking was reported by 13.0% of the study cohort overall (25.2% of men and 4.1% of women), family history of premature CV disease by 27.3%, and a body mass index ≥ 25 kg/m² by 36.4% of patients. Overall, 80.4% of the study cohort—80.2% in the aspirin group and 80.6% in the no aspirin group—had ≥ 3 risk factors (Figure 3). Waist circumference, measured in 3,950 patients (27.3%

of the study cohort), averaged 84.9 cm. In this subset of patients, 44% of men and 21.7% of women met the criteria for metabolic syndrome established by the Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome (waist circumference ≥ 85 cm in men, or ≥ 90 cm in women, and presence of ≥ 2 abnormalities: triglycerides ≥ 150 mg/dL and/or high-density-lipoprotein cholesterol < 40 mg/dL or under treatment of dyslipidemia, systolic blood pressure ≥ 130 mm Hg and/or diastolic blood pressure ≥ 85 mm Hg or under treatment of hypertension, fasting glucose ≥ 110 mg/dL or under treatment of diabetes).²⁷ The percentages of patients with at least 3 risk determinants for the metabolic syndrome, according to the criteria established by the Adult Treatment Panel III of the National Cholesterol Education Program, were 44.3% of men and 60.5% of women, and 54.1% and 53.8% of patients in the aspirin and no aspirin groups, respectively.

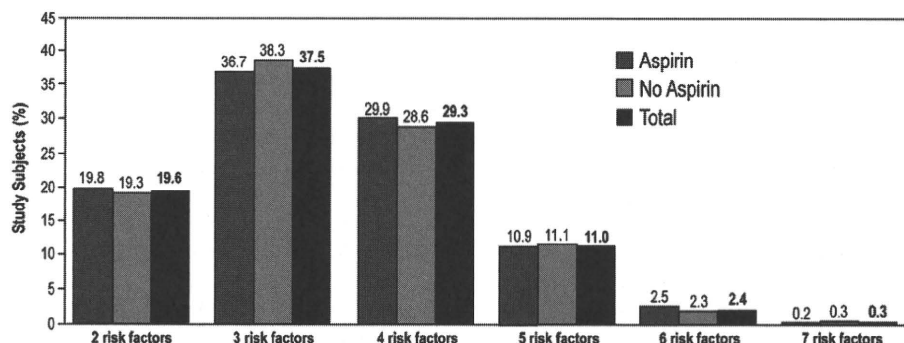
The most commonly used concomitant medications at randomization are shown in Table III. More than 90% of patients with hypertension were taking antihypertensive medication. About 60% of patients with dyslipidemia received lipid-modifying therapy, and 70% of patients with diabetes were being treated with diabetes medication. The mean blood pressure at randomization was 137/78 mm Hg, and the mean total cholesterol was 203 mg/dL (Table II).

Discussion

The JPPP is designed to evaluate the benefit-risk relationship of primary prevention of CV disease with low-dose, enteric-coated aspirin in the Japanese population, which has a lower CV risk compared with Western populations.²⁸ The JPPP was planned to enroll moderate- or higher risk Japanese patients, who had ≥ 2 risk factors, namely elderly patients with underlying hypertension, dyslipidemia, or diabetes. However, the results of the first general data examination showed that the incidence of end point events was lower than that estimated before the start of the study, and patient accrual was increased from the initially planned 10,000 patients to nearly 15,000 patients. The results of this initial data examination showed that CV event risk in the study population was lower than was initially estimated for elderly Japanese patients with ≥ 2 risk factors.

The lower CV event rate found in the JPPP study population might be explained by risk factors that were well controlled. Patients screened for the study were initiated on medication to control their risk factors. The percentage of patients in the JPPP at baseline who were at their control goals specified in guidelines was 38% for blood pressure, 59% for dyslipidemia (total cholesterol), and 40% for diabetes (blood glucose), similar to the control rates in recent surveys of Japanese patients with CV risk factors.²⁹⁻³¹ More than 90% of

Figure 3



Distribution of patients according to number of risk factors at baseline. Risk factors included hypertension, dyslipidemia, diabetes, smoking, family history, high-density-lipoprotein cholesterol <40 mg/dL, and age.

Table III. Medication use according to underlying disease

Disease medication, n (%)	Aspirin	No aspirin	Total
Hypertension	n = 6134	n = 6156	N = 12 290
Calcium blocker	3949 64.4%	4016 65.2%	7965 64.8%
β-Blocker	675 11.0%	688 11.2%	1363 11.1%
α-Blocker	385 6.3%	411 6.7%	796 6.5%
ACE inhibitor	846 13.8%	857 13.9%	1703 13.9%
ARB	2779 45.3%	2780 45.2%	5559 45.2%
Diuretic	506 8.2%	518 8.4%	1024 8.3%
Others	42 0.7%	37 0.6%	79 0.6%
No medication	414 6.7%	407 6.6%	821 6.7%
Dyslipidemia	n = 5179	n = 5196	N = 10 375
Statin	2639 51.0%	2649 51.0%	5288 51.0%
Cholestyramine	29 0.6%	22 0.4%	51 0.5%
Fibrate	363 7.0%	356 6.9%	719 6.9%
Probucol	59 1.1%	50 1.0%	109 1.1%
Others	26 0.5%	22 0.4%	48 0.5%
No treatment	2114 40.8%	2150 41.4%	4264 41.1%
Diabetes	n = 2442	n = 2461	N = 4903
Insulin	179 7.3%	154 6.3%	333 6.8%
Sulfonylurea	976 40.0%	930 37.8%	1906 38.9%
α-Glucosidase inhibitor	657 26.9%	639 26.0%	1296 26.4%
Biguanide	283 11.6%	248 10.1%	531 10.8%
Thiazolidinedione	333 13.6%	370 15.0%	703 14.3%
Nateglinide	207 8.5%	184 7.5%	391 8.0%
Others	0 0.0%	0 0.0%	0 0.0%
No medications	711 29.1%	795 32.3%	1506 30.7%

ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

patients with hypertension were taking antihypertensive medication. Approximately 40% of patients with dyslipidemia and 30% of patients with diabetes were not receiving medication for those conditions, suggesting that among individuals poorly responding to diet therapy or exercise therapy or those receiving routine examinations there seem to be cases where intensification of treatment of dyslipidemia or diabetes is overlooked, possibly due to infrequent blood tests. When the patients

in this study are observed for 4 years, we may be able to obtain data that endorse the importance of early detection and monitoring with medication initiation.

Currently, there is no good clinical evidence that determines whether there is a benefit to aspirin use in Japanese individuals with multiple CV risk factors, especially if their risk factors, as has been observed in this study, are well controlled. Furthermore, the pattern of atherosclerotic events is different in Japanese than

in Western patients; stroke mortality is higher than IHD mortality in Japan, whereas the opposite occurs in Western populations.²¹ The meta-analysis of Western studies showed a benefit on serious vascular events due to reduction in coronary events, a trend benefiting ischemic stroke, but an increase in gastrointestinal and extracranial bleeding.¹⁷ Aspirin has also been reported to be associated with gastrointestinal bleeding in Japanese patients.^{32,33} These differences emphasize the need to develop valid strategies for preventing atherosclerotic events in Japan based on national studies such as this one or on joint studies among multiple Asian countries rather than on Western studies.

In summary, the JPPP is the first and largest trial designed to evaluate whether the benefit of low-dose aspirin in elderly Japanese patients with CV risk factors for the primary prevention of atherosclerotic events outweighs any bleeding risk for a mean follow-up of 4 years. The results should be applicable to the lower risk Japanese populations and may affect guidelines and clinical practice.

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試験計画書

厚生労働科学研究費補助金（循環器疾患等総合研究事業）による臨床研究

動脈硬化性疾患危険因子を有する高齢者に 及ぼすアスピリンの一次予防効果に関する研究

Japanese Primary Prevention Project with Aspirin in the elderly
with one or more risk factors of vascular events: JPPP

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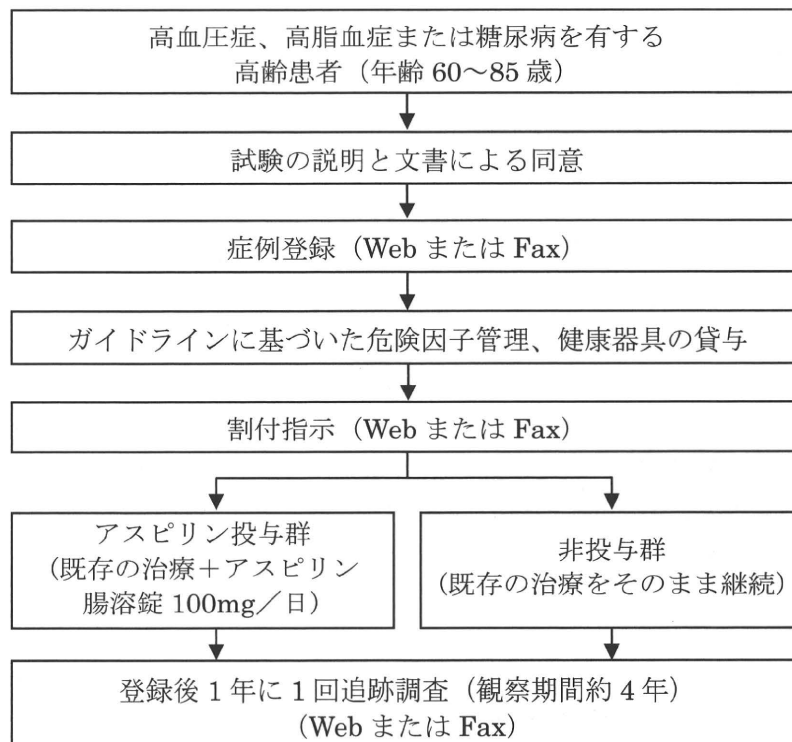
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0. 概要

0.1. シェーマ



0.2. 目的

動脈硬化性疾患危険因子を有する高齢者における、アスピリン一次予防投与のリスク／ベネフィットの評価

0.3. 対象

脳血管、冠動脈を含めた動脈硬化性疾患^{注)}を診断されていない、高血圧症、高脂血症または糖尿病を有する高齢患者（年齢 60 歳以上 85 歳以下）

注) 脳血管障害（一過性脳虚血発作を含む）または冠動脈疾患の既往、もしくは外科手術またはインターベンションを要する動脈硬化性疾患

0.4. 治療

中央登録法によりアスピリン投与群（腸溶錠 100mg/日）または非投与群に割付

0.5. 予定登録症例数と予定試験期間

予定登録症例数：15,000 例

予定登録期間：2005 年 3 月～2007 年 3 月

予定観察期間：2005 年 3 月～2011 年 9 月

0.6. 問い合わせ先

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