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JPPPGI

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

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患者を対象に、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

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- 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ことが期待できる。

本調査へのご協力をお願い申し上げます。

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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.

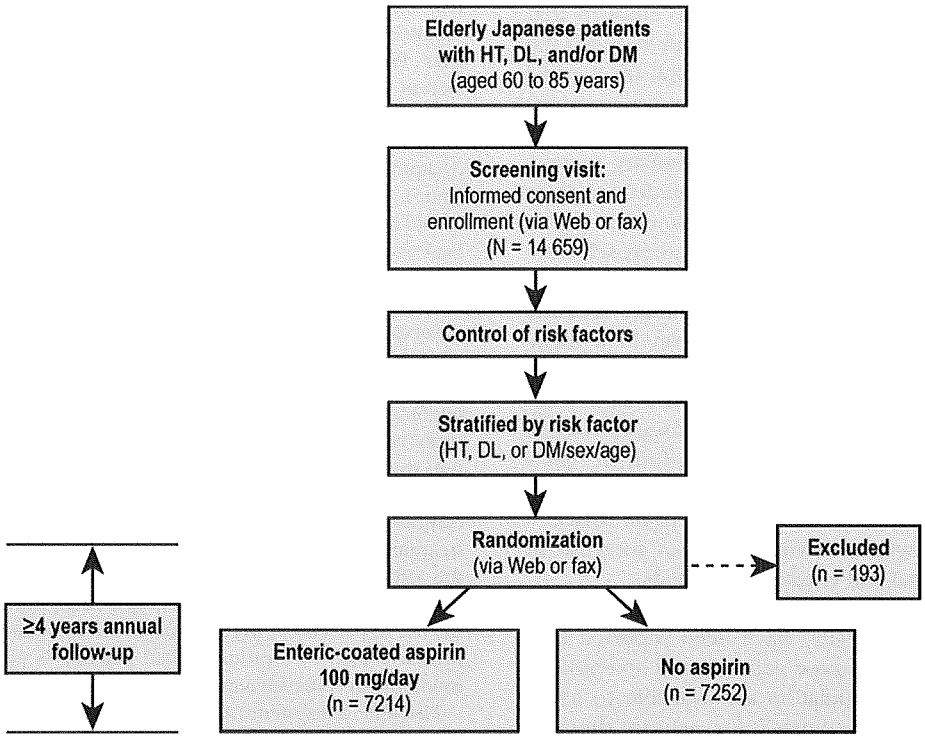
The JPPP is registered at www.clinicaltrials.gov with the trial identification number NCT00225849. The human rights and welfare of individual patients were duly respected and the scientific quality and reliability of the study were ensured as the study was conducted in accordance with the ethical principles 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 ≥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 I. 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/m^2 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.

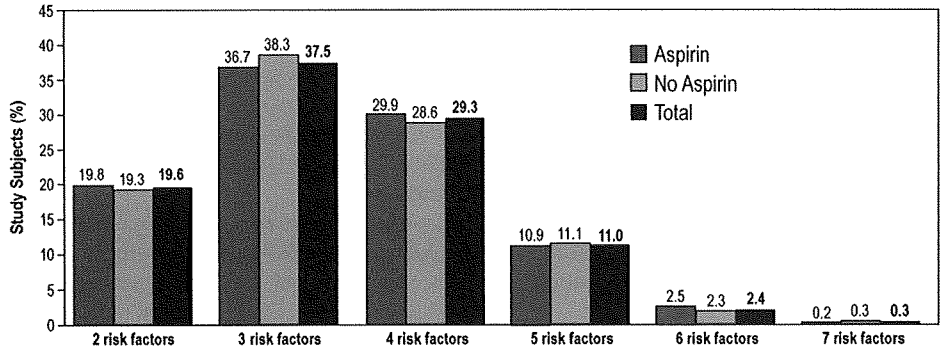
The most commonly used concomitant medications at randomization are shown in Table III. More than 90% of patients with hypertension were taking antihypertensive medication. About 60% of patients with dyslipidemia received lipid-modifying therapy, and 70% of patients with diabetes were being treated with 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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References

1. The Ministry of Health, Labour and Welfare, Japan. Ministry of Health, Labour and Welfare Report: 2007. [Japanese]. Available at: http://www.mhlw.go.jp/wp/hakusyo/kousei/07/dl/0102-a.pdf. Published 2007. Last accessed July 30, 2009.
2. Antithrombotic Trialists', Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324:71-86.
3. Ryan TJ, Antman EM, Brooks NH, et al. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). J Am Coll Cardiol 1999;34:890-911.
4. Smith Jr SC, Blair SN, Bonow RO, et al. AHA/ACC Scientific Statement: AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update: a statement for health care professionals from the American Heart Association and the American College of Cardiology. Circulation 2001;104:1577-9.
5. Albers GW, Hart RG, Lutsep HL, et al. AHA Scientific Statement. Supplement to the guidelines for the management of transient ischemic attacks: a statement from the Ad Hoc Committee on Guidelines for the Management of Transient Ischemic Attacks, Stroke Council, American Heart Association. Stroke 1999;30: 2502-11.
6. Second Joint Task Force of European and other Societies on Coronary Prevention. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention. Eur Heart J 1998;19: 1434-503.
7. Royal College of Physicians. National clinical guidelines for stroke. 2nd ed. London: RCP; 2004. Prepared by the Intercollegiate Stroke Working Party.
8. The Joint Study Group 1998-1999. Guidelines for secondary prevention of myocardial infarction. Jpn Circ J 2000;64(Suppl IV): 1081-127 [Japanese].
9. The Joint Study Group 2000-2001. Guidelines for management of acute coronary syndrome without persistent ST-segment elevation (JCS 2002). Circ J 2002;66(Suppl VI):1123-63 [Japanese].
10. Joint Committee on Guidelines for the Management of Stroke. Japanese guidelines for the management of stroke (2004). Tokyo: Kyowa Kikaku, Inc.; 2004 [Japanese].
11. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989;321:129-35.
12. Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. BMJ 1988;296:313-6.
13. The Medical Research Council's General Practice Research Framework. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. Lancet 1998;351:233-41.
14. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351:1755-62.
15. Collaborative Group of the Primary Prevention Project (PPP). Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Lancet 2001;357:89-95.
16. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352:1293-304.
17. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849-60.
18. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 2008;300: 2134-41.
19. Yamazaki T, Goto S, Shigematsu H, et al. Prevalence, awareness and treatment of cardiovascular risk factors in patients at high risk of atherothrombosis in Japan: results from domestic baseline data of the REduction of Atherothrombosis for Continued Health (REACH) Registry. Circ J 2007;71:995-1003.
20. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA 2006;295:180-9.
21. World Health Organization. Mortality Database, 2007. Available at: http://www.who.int/healthinfo/statistics/bodgbddeathdalyestimates.xls. Last accessed July 30, 2009.

22. Hansson L, Hedner T, Dahlof B. Prospective randomized blinded endpoint (PROBE) Study: a novel design for intervention trials. Blood Press 1992;1:113-9.
23. Committee on Guidelines for the Management of Hypertension in the Japanese Society of Hypertension. Guidelines for the management of hypertension (JSH 2004). The Japanese Society of Hypertension; 2004 [Japanese].
24. Japan Atherosclerosis Society. Japan Atherosclerosis Society (JAS) guidelines for diagnosis and treatment of atherosclerotic cardiovascular diseases 2002. Japan Atherosclerosis Society; 2002 [Japanese].
25. Japan Diabetes Society. Evidence-based practice guideline for the treatment of diabetes in Japan. Tokyo: Nankodo Co Ltd; 2004 [Japanese].
26. Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a Statement From the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. Circulation 2003;108:2543-9.
27. Arai H, Yamamoto A, Matsuzawa Y, et al. Prevalence of metabolic syndrome in the general Japanese population in 2000. J Atheroscler Thromb 2006;13:202-8.
28. Morimoto T, Fukui T, Lee TH, Matsui K. Application of U.S. Guidelines in other countries: aspirin for the primary prevention of cardiovascular events in Japan. Am J Med 2004;117:459-68.
29. Ohkubo T, Obara T, Funahashi J, et al, and the J-HOME Study Group. Control of blood pressure as measured at home and office, and comparison with physicians' assessment of control among treated hypertensive patients in Japan: first report of the Japan Home versus Office Blood Pressure Measurement Evaluation (J-HOME) Study. Hypertens Res 2004;27:755-63.
30. Teramoto T, Kashiwagi A, Mabuchi H, for the J-LAP Investigators. Status of lipid-lowering therapy prescribed based on recommendations in the 2002 report of the Japan Atherosclerosis Society Guideline for Diagnosis and Treatment of Hyperlipidemia in Japanese Adults; a study of the Japan Lipid Assessment Program (J-LAP). Curr Ther Res Clin Exp 2005;66:80-95.
31. Sone H, Kawai K, Takagi H, et al. Outcome of one-year of specialist care of patients with type 2 diabetes: a multi-center prospective survey (JDDM 2). Intern Med 2006;45:589-97.
32. Yamamoto T, Sanaka M, Nagasawa K, et al. Gastroduodenal mucosal injury in patients on antiplatelet therapy. Thromb Res 2007; 120:465-9 [Epub 2007 Jan 24].
33. Derry S, Loke YK. Risk of gastrointestinal hemorrhage with long-term use of aspirin: meta-analysis. BMJ 2000;321:1183-7.

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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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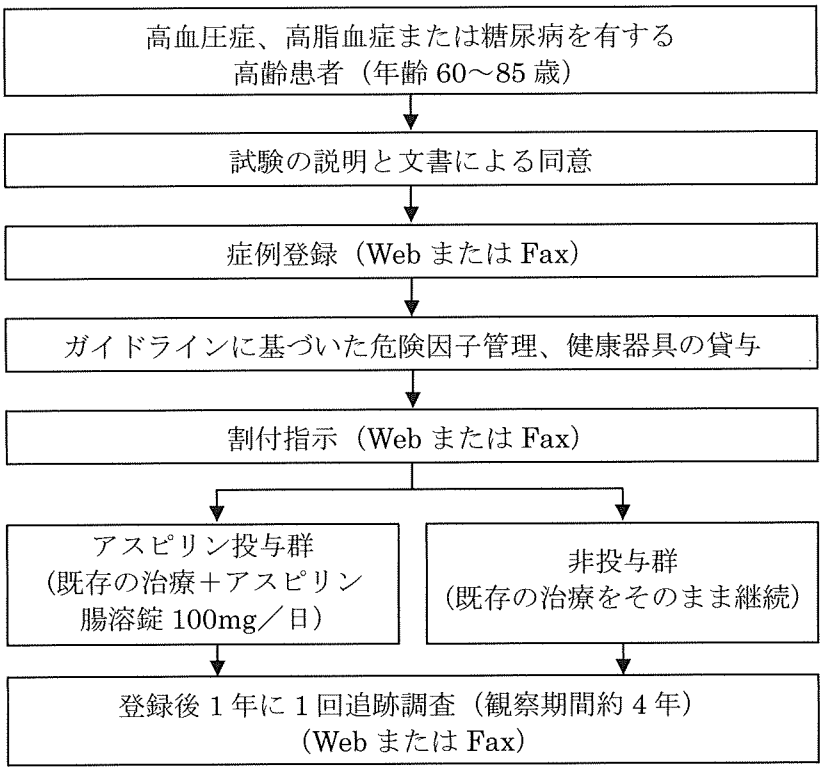
0. 概要

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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別添

・バイアスピリン®錠 100mg の添付文書
・参考資料
・同意文書
・症例登録票、追跡調査票

1. 研究課題名

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）

2. 研究の背景と目的

2.1. 背景

平成 14 年度厚生労働省人口動態によると、脳血管障害や心疾患などの動脈硬化性疾患は我が国の全死亡原因の約 30%を占める [1]。動脈硬化性疾患は、一度発症すると後遺症が残ることも多い上再発のリスクが高く、患者やその家族の QOL を大きく低下させる。さらには、介護が長期にわたることから高額な医療費を要し、我が国全体で毎年脳血管障害に約 1 兆 7 千億円、虚血性心疾患に約 7 千億円が治療や予後改善に使用されると推計されている [2]。したがって、これらの疾患においては、一度発症した後の治療から、発症をさせない予防策（一次予防策）の確立へと、対策の重要性が移行している。

アスピリンによる動脈硬化性疾患の急性期治療および二次予防については、日本を含め世界 30 カ国以上が参加した国際共同研究 Antithrombotic Trialists' Collaboration（ATT）によるメタアナリシスにおいて脳梗塞、心筋梗塞等の脳・心血管系イベント発生率の有意な低下（リスク低下率 19～32%）が認められている [3]。アスピリンの有用性は ATT を始め、国内外の調査研究により証明され、国内外の各種動脈硬化性疾患ガイドラインでは、アスピリンを全例に使用することが推奨されている [4-11]。

一方、一次予防効果に関する調査研究としては、米国で約 2 万人の男性医師を対象として行われ、アスピリンにより心筋梗塞が 44%減少することが示された Physicians' Health Study[12]など、1988 年から 2001 年にかけて海外で 5 件の臨床試験が発表されている [12-16]。2002 年にこれらを統合したメタアナリシス（合計約 5.5 万症例、平均 4.5 年追跡）が発表され、アスピリンにより心筋梗塞と血管死が 28%抑制されることが確認された。また、冠動脈疾患発症リスクが 5 年間で 5%の患者では、ベネフィットとして心筋梗塞および血管死発生率が 5 年あたり 1000 人中 14 人減少、リスクとして脳出血 1 人、消化管出血が 3 人増加し、これらの患者においてアスピリンによる血管イベント予防のベネフィットはリスクを上回ることが示された [17]。同年発表された米国心臓協会（American Heart Association）の循環器疾患・脳卒中一次予防ガイドラインでは、今後 10 年間で 10%以上の冠動脈疾患発症リスクを有する対象においてアスピリン投与を考慮するよう推奨している [18]。

本邦では日本人データの調査研究はないものの、既存の海外データに基づき、合同研究班による虚血性心疾患の一次予防ガイドラインでは、危険因子[注)]を多数有する患者または危険因子を合わせ持つ糖尿病患者においてアスピリンの投与を考慮するよう推奨している [19]。ただし、本ガイドラインは上述の海外における臨床試験及び疫学データ [20]が根拠となっており、日本人において、アスピリンの有益性を検証

注）加齢、冠動脈疾患の家族歴、喫煙習慣、高血圧、肥満、耐糖能異常（境界型および糖尿病型）、高コレステロール血症、高中性脂肪血症、低 HDL コレステロール血症、精神的・肉体的ストレス

した介入試験、アスピリンが有益な対象を選定しうる疫学データは存在しない。このため、合同研究班のガイドラインにおけるアスピリン投与も「考慮」にとどまっている。また、実際の医療現場においてアスピリンの一次予防投与は十分浸透しているとは言えないのが現状である。

2.2. 意義

本研究により日本人においても海外と同様のアスピリン一次予防投与の有益性が確認されれば、患者の予後に重大な影響を与える重篤な動脈硬化性疾患の予防法の確立につながる。これにより毎年約 5～10 万人の動脈硬化性疾患の回避が期待され、患者やその家族の QOL は大幅に向上する。また、アスピリンは 1 錠約 6 円と安価であり、年間約 2 兆 4 千億円と推計される多額の医療費の削減にも貢献すると考えられる。

2.3. 主要目的

海外におけるデータと比較して精度が劣るものの、国内の疫学調査[21]および介入試験成績[22-29]より、日本人においても高血圧、高脂血症または糖尿病を有する高齢患者では動脈硬化性疾患の発症率が 10 年間で 10%以上になると推定される。これらの対象では海外と同様に、アスピリン一次予防投与のベネフィットはリスクを上回るものと推察される。そこで、本研究ではこの臨床仮説を検証することを主目的として実施する。

具体的には、対象は、医療機関を受診している高血圧症、高脂血症（高コレステロール血症、高中性脂肪血症、低 HDL コレステロール血症）または糖尿病を有する高齢患者とし、一次エンドポイント（脳・心血管系要因による死亡・非致死性脳血管障害・非致死性心筋梗塞からなる複合エンドポイント）の発生が、非投与群よりアスピリン投与群で少ないことを検証する。その際、重篤な有害事象（輸血または入院を要する重篤な頭蓋外の出血）の発生と比較し、ベネフィット（イベント抑制）がリスク（重篤な有害事象発生）を上回っているか否かのリスク／ベネフィット比を検証する。

2.4. 副次的目的

高齢者において、(1)患者の危険因子（高血圧症、高脂血症、糖尿病）の種類と合併数によってアスピリンによるイベント抑制効果（イベント減少率）に差があるか否か (2)イベント発生の危険度が相対的に高いと想定される対象（糖尿病合併例、危険因子の合併数の多い症例、危険因子管理状態の不良例）において、イベント発生危険度の低い対象と比べて、アスピリン投与によるリスク／ベネフィット比が改善されているか否か (3)二次エンドポイント（7.2.項参照）においてアスピリン投与が有効か否かについて、探索的検討を行う。

2.5. 特色・独創的な点

本研究は、国際共同研究 ATT メタアナリシスが解析対象とする研究（中央管理によるランダム割付、客観的評価が可能なハードエンドポイントによる評価）である。また、日本で行われるアスピリン一次予防試験として最大級のランダム化比較試験

（RCT）である。

現在海外で4件、国内では平成14年度厚生労働科学研究補助金に基づき、2型糖尿病を対象とした動脈硬化性疾患一次予防試験JPAD（Japanese primary Prevention of Atherosclerosis with aspirin for Diabetes）が進行しているものの、JPADは2型糖尿病患者のみを対象としたものであり、複数の危険因子保有者（高齢かつ、高血圧症、高脂血症または糖尿病を有する患者）を対象としたRCTはない。本研究では、基礎疾患、性別、年齢を割付調整因子としていることから（5.7.項）、副次的目的（2.4.項）のとおり、高齢患者における種々の探索的検討（危険因子の種類や合併数によるアスピリンのリスク／ベネフィット比の比較等）が可能である。

3. 薬物情報

試験薬：アスピリン腸溶錠（バイアスピリン®錠100mg）
作用機序：血小板凝集抑制作用
適応症：・下記疾患における血栓・塞栓形成の抑制
狭心症（慢性安定狭心症、不安定狭心症）
心筋梗塞
虚血性脳血管障害（一過性脳虚血発作（TIA）、脳梗塞）
・冠動脈バイパス術（CABG）あるいは経皮経管冠動脈形成術（PTCA）施行後における血栓・塞栓形成の抑制
用法・用量：通常、成人にはアスピリンとして100mgを1日1回経口投与する。
なお、症状により1回300mgまで増量できる。
使用上の注意：別添「バイアスピリン®錠100mgの添付文書」参照

4. 対象患者

4.1. 選択基準：以下を満たす患者

（1）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、以下のいずれかの基準[30-32]を満たす高齢患者。または過去にいずれかの基準を満たし薬物治療中の患者

1. 高血圧症　収縮期血圧≧140mmHgまたは拡張期血圧≧90mmHg
2. 高脂血症（高コレステロール血症[注1)]、高中性脂肪血症[注2)]または低HDLコレステロール血症[注3)]）
   [注1)] 総コレステロール≧220mg/dLまたは
   LDLコレステロール≧140mg/dL
   [注2)] 中性脂肪≧150mg/dL
   [注3)] HDLコレステロール＜40mg/dL
3. 糖尿病　早朝空腹時血糖≧126mg/dLまたは随時血糖≧200mg/dLまたは75g糖負荷試験で2時間値≧200mg/dLまたはHbA1c≧6.5%

（2）年齢：60歳以上85歳以下
（3）文書による同意が得られた対象

4.2. 除外基準

（1）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のある症例
（2）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のある症例