ワークシート　治療の「閾値」を考えよう

あなたは、ある心臓病になりました。

その病気で亡くなる確率は、3年後に5%です。この病気には、有効性が確かめられている薬剤があります。1錠1日1回内服していただきます。

この効果がどれくらいだったら、内服しますか。治療効果は、リスク比で考えてください

リスク比とは、元の死亡率が何倍になるかを示す指標です。たとえば、リスク比が0.5とは、死亡率が半分になります。もしあなたが、5%が4%に減る効果があるのなら内服しようと思うのなら、あなたのリスク比は0.8となります。1%にならないと内服しないのなら、あなたのリスク比は1/5=0.2 となります。少しでも下がれば内服するのなら「1」と書いてください。どんな治療効果があっても内服しないのなら、「しない」と書いてください。

1）あなたが内服をしようと思うリスク比

2）治療効果以外に、内服するかどうか決めるのに知りたいこと、気になることはありませんか。それを列挙しておきましょう

3）では、食餌療法（カロリー制限と緑黄野菜を主とした食事内容への変更）を勧められたとして、どの程度のリスク比であったら受けますか

4）では、腸を切除して短くしコレステロール値などを下げる手術が勧められたら、あなたはどれくらいのリスク比であったら受けますか

5）最後に、よく調べるとあなたの病状は重く、3年後に死亡率は50%と見積もられました。そこで、内服薬を内服するリスク比はどうしますか

症例

６９才男性　糖尿病の気があると言われ非薬物療法を行っていた。退職を期に田舎暮らしをしたいということで越後湯沢に引っ越し今後当院通院希望とのことで来院。以前通っていた医院では脳梗塞にならないようにとアスピリンを出され飲んでいた。

既往歴　4年前から糖尿病の気があると言われているようだ
高血圧（－）　高脂血症（－）

手術歴　内痔核に対して硬化療法を行っている（手術をせずに最新の治療で治した事を誇りに思っている）

内服歴　バイアスピリン（１００）１T1X　最近は飲んだり飲まなかったり
体調が悪いときはケロリンを飲むとたちまち治る

生活歴　飲酒（－）　喫煙　20本／日X48年　最近減らしここ2ヶ月は10本／日

家族歴　家族内に若年心血管、脳血管イベントあるものなし　突然死なし

体格　１７０ｃｍ　５５ｋｇ

背景　元々　大手商社に勤め、鎌倉から横浜まで毎日通勤していた。これまでも湯沢にリゾートマンションを持っていて時々遊びに来ていたが、昨年退職を機に田舎暮らしを決め妻と二人湯沢に引っ越してきた。子供は4人いずれも関東で家庭を持っている。食事や運動にも気をつけていて、健康雑誌も読み漁り（愛読誌は「わかさ」）健康には自信があると自負している。反面、これから老いていく自分に対しての不安もある。先日、週刊誌でアスピリンは脳出血を増やして怖い薬だ！！という記事を読んだ。

血圧 134/68 脈拍 68
神経障害：なし
眼科：網膜症なし

空腹時血糖 132 HbA1C 6.0 LDL 70 HDL 60 TG 120
尿中微量アルブミン (-)
心電図異常なし

※あなたは都会からやってきた、自称インテリの患者です。
この薬はどうなんですか？私的にはこう思うのですが‥。
と医師を質問攻めにしてあげてください

Background Question

他の血管疾患リスクファクターは
なんだろう？
アスピリンの副作用は？
非薬物療法はどのようか？
非薬物療法はどのようか？

Foreground Question

糖尿病一次予防にアスピリンは有用？

都会暮らしよりも田舎暮らしの方が
血管イベントすくない？？

Background Question

- その疾患、その症候の基礎知識を満たすための質問
  - この病気の標準的治療は？
  - この症候のアプローチは？

いわゆる“教科書”を検索するのがお薦め

Background　　Foreground

Foreground Question

- 個々の患者、問題に対しての質問
  - この薬とこの薬どっちが良いの？
  - 本当に効果あるの？

PECOで定式化して二次文献を検索するのがお薦め

Background　　Foreground

Low-Dose Aspirin for Primary Prevention of Atherosclerotic Events in Patients With Type 2 Diabetes: A Randomized Controlled Trial

Hisao Ogawa; Masafumi Nakayama; Takeshi Morimoto; et al.

JAMA. 2008;300(18):2134-2141 (doi:10.1001/jama.2008.623)

http://jama.ama-assn.org/cgi/content/full/300/18/2134

Low-Dose Aspirin for Primary Prevention of Atherosclerotic Events in Patients With Type 2 Diabetes

A Randomized Controlled Trial

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for the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators

Context Previous trials have investigated the effects of low-dose aspirin on primary prevention of cardiovascular events, but not in patients with type 2 diabetes.

Objective To examine the efficacy of low-dose aspirin for the primary prevention of atherosclerotic events in patients with type 2 diabetes.

Design, Setting, and Participants Multicenter, prospective, randomized, open-label, blinded, end-point trial conducted from December 2002 through April 2008 at 163 institutions throughout Japan, which enrolled 2539 patients with type 2 diabetes without a history of atherosclerotic disease and had a median follow-up of 4.37 years.

Interventions Patients were assigned to the low-dose aspirin group (81 or 100 mg per day) or the nonaspirin group.

Main Outcome Measures Primary end points were atherosclerotic events, including fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease. Secondary end points included each primary end point and combinations of primary end points as well as death from any cause.

Results A total of 154 atherosclerotic events occurred: 68 in the aspirin group (13.6 per 1000 person-years) and 86 in the nonaspirin group (17.0 per 1000 person-years) (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.58-1.10; log-rank test, $P=.16$). The combined end point of fatal coronary events and fatal cerebrovascular events occurred in 1 patient (stroke) in the aspirin group and 10 patients (5 fatal myocardial infarctions and 5 fatal strokes) in the nonaspirin group (HR, 0.10; 95% CI, 0.01-0.79; $P=.0037$). A total of 34 patients in the aspirin group and 38 patients in the nonaspirin group died from any cause (HR, 0.90; 95% CI, 0.57-1.14; log-rank test, $P=.67$). The composite of hemorrhagic stroke and significant gastrointestinal bleeding was not significantly different between the aspirin and nonaspirin groups.

Conclusion In this study of patients with type 2 diabetes, low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events.

Trial Registration clinicaltrials.gov Identifier: NCT00110448

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DIABETES MELLITUS IS A POWERful risk factor for cardiovascular events. The Framingham Heart Study reported that diabetes was associated with odds ratios for coronary heart disease of 1.5 and 1.8 for men and women, respectively, and relative risks for stroke of 1.4 and 1.7 for men and women, respectively.[1-5] Individuals with diabetes have a 2- to 4-fold increased risk of developing cardiovascular events than those without diabetes.[6]

Several earlier investigations have shown that aspirin therapy is established as a secondary prevention strategy for cardiovascular events.[7-9] Clinical guidelines have recommended that individuals with risk factors for coronary heart disease should take aspirin for primary prevention and for secondary prevention; in particular, those with diabetes were considered good candidates for aspirin except for those with contraindications.[10-13] The American Diabetes Association recommends use of aspirin as a primary prevention strategy in patients with diabetes who are at increased cardiovascular risk, including those who are older than 40 years or who have additional risk factors, such as family history of coronary heart disease, hypertension, smoking, dyslipidemia, or albuminuria.[14] Nonetheless, the clinical trial data for aspirin in primary preven-

For editorial comment see p 2180.

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tion are limited. Several large trials of aspirin for primary prevention have examined its effects in subgroups with diabetes; these subgroup analyses did not demonstrate a significant effect on reducing vascular events because they were underpowered.[17-21] Thus, a primary prevention trial of aspirin for diabetic patients is needed.

The Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial was undertaken to examine the efficacy of low-dose aspirin therapy for the primary prevention of atherosclerotic events in patients with type 2 diabetes.

METHODS

The JPAD trial was a prospective, randomized, open-label, controlled trial with blinded end-point assessment. Patient enrollment started in December 2002 and was completed in May 2005; patients were followed up until April 2008. Patients were enrolled and followed up at 163 institutions throughout Japan. The institutional review board at each participating hospital approved this trial, and written informed consent was obtained from each patient.

Trial Population

The inclusion criteria were diagnosis of type 2 diabetes mellitus, age between 30 and 85 years, and ability to provide informed consent. The exclusion criteria were electrocardiographic changes consisting of ischemic ST-segment depression, ST-segment elevation, or pathologic Q waves; a history of coronary heart disease confirmed by coronary angiography; a history of cerebrovascular disease consisting of cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and transient ischemic attack; a history of arteriosclerotic disease necessitating medical treatment; atrial fibrillation; pregnancy; use of antiplatelet or antithrombotic therapy, defined as aspirin, ticlopidine, cilostazol, dipyridamole, trapidil, warfarin, and argatroban; a history of severe gastric or duodenal ulcer; severe liver dysfunction; severe renal dysfunction, and allergy to aspirin.

Trial Protocol

Enrolled patients were randomly assigned to the aspirin group or the nonaspirin group. The randomization was performed as nonstratified randomization from a random number table. The study center prepared the sealed envelopes with random assignments and distributed them by mail to the physicians in charge at the study sites. Patients in the aspirin group were assigned to take 81 mg or 100 mg of aspirin once daily. Patients were followed up at each hospital visit or by telephone if necessary. Follow-up visits were scheduled every 2 weeks for patients seen in a clinic setting and every 4 weeks for patients seen in a hospital setting. Data for patients who were lost to follow-up were included at the day of last follow-up. Patients were allowed to use any concurrent treatment. Patients in the nonaspirin group were also allowed to use antiplatelet/thrombotic therapy, including aspirin, if needed and vice versa.

End Points

The primary end point was any atherosclerotic event, which was a composite of sudden death; death from coronary, cerebrovascular, and aortic causes; nonfatal acute myocardial infarction; unstable angina; newly developed exertional angina; nonfatal ischemic and hemorrhagic stroke; transient ischemic attack; or nonfatal aortic and peripheral vascular disease (arteriosclerosis obliterans, aortic dissection, mesenteric arterial thrombosis) during the follow-up period. Key secondary end points were each primary end point and combinations of primary end points and death from any cause. Adverse events analyzed included gastrointestinal (GI) events and any hemorrhagic events other than hemorrhagic stroke. All potential primary end points, secondary end points, and adverse events were adjudicated by an independent committee on validation of data and events that was unaware of the group assignments.

Sample Size Calculation

For sample size calculation, we first estimated the incidences of cardiovascular and cerebrovascular events among Japanese diabetic patients. The incidence of cardiovascular death, myocardial infarction, and cerebrovascular events were 7.5, 7.5, and 8.0 events per 1000 Japanese diabetic patients per year, respectively, according to the Hisayama-cho study[22] and Funagata study.[23] The total incidence of the atherosclerotic events, including peripheral arterial disease, was suggested to be 3 times the aforementioned number by the Hypertension Optimal Treatment (HOT) study.[24] Because the recent incidence of atherosclerotic events among Japanese individuals seemed relatively lower than that previously reported in Japan, we discounted 25% of the estimated 69 events that were expected to occur and estimated that 52 events per 1000 Japanese diabetic patients would occur annually.

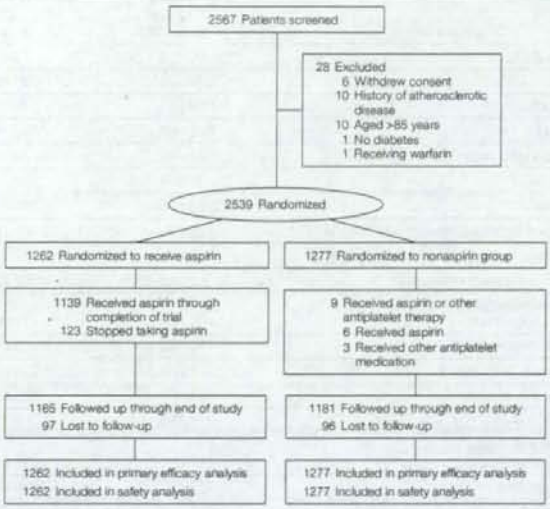
Based on a 2-sided α level of .05, a power of 0.95, an enrollment period of 2 years, and a follow-up period of 3 years after the last enrollment, we estimated that 2450 patients would need to be enrolled to detect a 30% relative risk reduction for an occurrence of atherosclerotic disease by aspirin.[19]

Statistical Analyses

Efficacy comparisons were performed on the basis of time to the first event, according to the intention-to-treat principle, including all patients in the group to which they were randomized with patients lost to follow-up censored at the day of the last visit. Safety analyses were performed on data from all enrolled patients. Following the descriptive statistics, cumulative incidences of primary and secondary end points were estimated by the Kaplan-Meier method and differences between groups were assessed with the log-rank test. We used the Cox proportional hazards model to estimate hazard ratios (HRs) of aspirin use along with 95% confidence intervals (CIs). We used the χ^2 test or Fisher exact test to evaluate adverse events.

We also conducted subgroup analyses for predetermined subgroups: sex (men, women); age (younger than 65 years, 65 years or older); hypertensive

Figure 1. Participation in Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial



status (hypertensive, normotensive); smoking status (current or past smoker, nonsmoker); and lipid status (hyperlipidemia, normolipidemia). Using the Cox proportional hazard model, proportional hazard assumptions were assessed on the plots of log (time) vs log [–log(survival)] stratified by index variables. Patients with missing values for any selected variable were excluded from the analyses that used the variable.

All statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina) and S-Plus version 7.0 (Insightful Corp, Seattle, Washington). *P* values of less than .05 were considered statistically significant. An independent safety monitoring board monitored the safety and efficacy of the study after 2 years of follow-up for an interim assessment and at the end of the study.

RESULTS

Study Population

The study screened 2567 patients with type 2 diabetes mellitus without a history of atherosclerotic disease, including cardiovascular disease, stroke, and peripheral vascular disease, from December 2002 to May 2005 in 163 institutions (FIGURE 1). Six patients who withdrew their informed consent were excluded. Twenty-two patients met exclusion criteria. We randomly assigned 2539 patients as follows: 1262 patients in the aspirin group and 1277 patients in the nonaspirin group. Patients were followed up until April 2008. The median follow-up period was 4.37 years (95% CI, 4.35-4.39). A total of 193 patients were lost to follow-up, and data for those patients were censored at the day of last follow-up.

Baseline Clinical Characteristics

Baseline clinical characteristics, including treatments for diabetes, hypertension, and dyslipidemia and diabetic microvascular complications, were similar between the 2 groups (TABLE 1). Overall mean (SD) age was 65 (10) years; 55% of patients were men. Median duration of diabetes was 7.3 years in the aspirin group and 6.7 years in the nonaspirin group. Diabetes was well controlled in both groups: mean (SD) levels of glycated hemoglobin were 7.1% (1.4%) in the aspirin group and 7.0% (1.2%) in the nonaspirin group. The prevalence of hypertension and dyslipidemia was 58% and 53%, respectively. Blood pressure was well controlled in both groups: mean (SD) systolic pressure, 136 (15) mm Hg; mean (SD) diastolic pressure, 77 (9) mm Hg in the aspirin group and mean (SD) systolic pressure, 134 (15) mm Hg; mean (SD) diastolic pressure, 76 (9) mm Hg in the nonaspirin group.

By the end of the study, 123 patients (10%) in the aspirin group had stopped taking the study medication. Since aspirin therapy was allowed in the nonaspirin group, 6 patients (0.5%) had taken aspirin and 3 patients (0.2%) had taken other antiplatelet medication.

Efficacy Analysis

A total of 154 atherosclerotic events occurred (TABLE 2). The incidence of the primary end point of any atherosclerotic event, a composite of sudden death, death from cardiovascular or aortic causes, nonfatal acute myocardial infarction, unstable angina, exertional angina, nonfatal ischemic and hemorrhagic stroke, transient ischemic attack, and nonfatal aortic and peripheral vascular disease (arteriosclerosis obliterans, aortic dissection, mesenteric arterial thrombosis), was not significantly different in the aspirin group (68 events, 5.4%) than in the nonaspirin group (86 events, 6.7%) (HR, 0.80; 95% CI, 0.58-1.10; log-rank test, $P=.16$) (Table 2 and FIGURE 2).

The combined end point of fatal coronary events and fatal cerebrovascular events occurred in 1 patient (stroke) in the aspirin group and 10 patients (5 fatal myocardial infarctions and 5 fatal strokes) in the nonaspirin group (HR, 0.10; 95% CI, 0.01-0.79; $P=.0037$). Other secondary coronary, cerebrovascular, and peripheral vascular disease end points are shown in Table 2; there were no significant differences between the aspirin group and the nonaspirin group in these end points. There were 2 deaths due to aortic dissection, both in the low-dose aspirin group, and 1 nonfatal aortic dissection in the nonaspirin group. A total of 13 hemorrhagic strokes occurred; the incidences in each group were similar (6 in the aspirin group and 7 in the

nonaspirin group). There was 1 fatal hemorrhagic stroke in the aspirin group and 4 in the nonaspirin group.

Death from causes other than cardiovascular events were as follows for the aspirin group and nonaspirin group, respectively: there were 15 and 19 deaths due to malignancy, 2 and 5 due to infection, 3 and 0 due to suicide, 2 and 0 due to traffic crashes, and 1 and 1 due to liver cirrhosis. Therefore, 23 patients in the aspirin group and 25 patients in the nonaspirin group died from causes other than cardiovascular events. Eight patients in the aspirin group and 3 patients in the nonaspirin group died from unknown causes. A total of 34 patients in the aspirin group and 38 patients in the nonaspirin group died from any cause (HR, 0.90; 95% CI, 0.57-1.14; log-rank test, $P = .67$).

Subgroup Analyses

In the 1363 patients aged 65 years or older (719 in the aspirin group and 644 in the nonaspirin group), the incidence of atherosclerotic events was significantly lower in the aspirin group (45 events, 6.3%) than in the nonaspirin group (59 events, 9.2%) (HR, 0.68; 95% CI, 0.46-0.99; $P = .047$). In the 1176 patients younger than age 65 years, there were 23 events in the aspirin group (4.2%) and 27 events in the nonaspirin group (4.3%), a difference that was not significant (HR, 1.0; 95% CI, 0.57-1.70; $P = .98$). A formal test of interaction with age did not show a significant result ($P = .27$). There were no significant differences between the aspirin group and nonaspirin group in other subgroup analyses, including men, women, hypertensive, normotensive, current or past smokers, nonsmokers, dyslipidemia, and normolipidemia (FIGURE 3).

Safety

The prespecified analysis of adverse events is shown in TABLE 3. The hemorrhagic events consisted of GI bleeding in 12 patients in the aspirin group and 4 in the nonaspirin group and retinal hemorrhage in 8 patients in the aspirin group and 4 in the nonaspirin group. In the aspirin group, 4 patients had serious adverse events that needed a transfusion; no patients in the non-

Table 1. Baseline Clinical Characteristics

Characteristic	No. (%) Aspirin Group (n = 1262)	No. (%) Nonaspirin Group (n = 1277)
Age, mean (SD), y	65 (10)	64 (10)
Male	706 (56)	681 (53)
Current smoker	289 (23)	248 (19)
Past smoker	545 (43)	482 (38)
Body mass index, mean (SD)[a]	24 (4)	24 (4)
Hypertension	742 (59)	731 (57)
Dyslipidemia	680 (54)	665 (52)
Systolic blood pressure, mean (SD), mm Hg	136 (15)	134 (15)
Diastolic blood pressure, mean (SD), mm Hg	77 (9)	76 (9)
Duration of diabetes, median (IQR), y	7.3 (2.8-12.3)	6.7 (3.0-12.5)
Diabetic microvascular complication		
Diabetic retinopathy	187 (15)	178 (14)
Diabetic nephropathy	169 (13)	153 (12)
Proteinuria, ≥15 mg/dL	222 (18)	224 (18)
Diabetic neuropathy	163 (13)	137 (11)
Dermal ulcer	6 (0.5)	6 (0.5)
Treatment for diabetes		
Sulfonylureas	737 (58)	710 (56)
α-Glucosidase inhibitors	422 (33)	414 (32)
Biguanides	168 (13)	186 (15)
Insulin	166 (13)	160 (13)
Thiazolidines	63 (5)	65 (5)
Treatment for hypertension and dyslipidemia		
Calcium channel blockers	436 (35)	440 (34)
Angiotensin-II receptor antagonists	269 (21)	266 (21)
Angiotensin-converting enzyme inhibitors	178 (14)	195 (15)
β-Blockers	75 (6)	87 (7)
α-Blockers	53 (4)	38 (3)
Statins	322 (26)	328 (26)
Family history		
Type 2 diabetes mellitus	526 (42)	513 (40)
Ischemic heart disease	147 (12)	143 (11)
Stroke	275 (22)	251 (20)
Patient medical history		
Peptic ulcer	83 (7)	96 (8)
Clinical laboratory measurements, mean (SD)		
Hemoglobin A_{1c} level, %	7.1 (1.4)	7.0 (1.2)
Fasting plasma glucose level, mg/dL	148 (50)	146 (48)
Total cholesterol level, mg/dL	202 (34)	200 (34)
Fasting triglyceride level, mg/dL	135 (88)	134 (89)
HDL cholesterol level, mg/dL	55 (15)	55 (15)
Blood urea nitrogen level, mg/dL	16 (5)	16 (5)
Serum creatinine level, mg/dL	0.8 (0.3)	0.8 (0.2)
Red blood cells, ×10^6/mL	45.2 (4.7)	45.0 (4.8)
White blood cells, ×10^3/mL	6.2 (1.6)	6.1 (1.7)
Hemoglobin level, g/dL	14.0 (1.5)	14.0 (1.5)

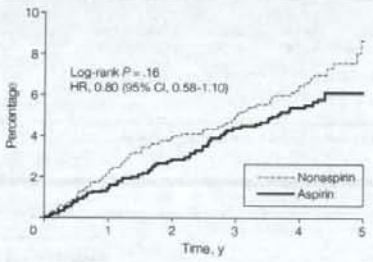
Abbreviations: HDL, high-density lipoprotein; IQR, interquartile range.
SI conversion factors: To convert glucose to mmol/L, multiply by 0.0555; to convert total and HDL cholesterol to mmol/L, multiply by 0.0259; to convert triglyceride to mmol/L, multiply by 0.0113; to convert urea nitrogen to mmol/L, multiply by 0.357; to convert creatinine to μmol/L, multiply by 88.4.
[a] Calculated as weight in kilograms divided by height in meters squared.

Table 2. Atherosclerotic Events

	Aspirin Group		Nonaspirin Group			
	No. (%)	No. per 1000 Person-Years	No. (%)	No. per 1000 Person-Years	Hazard Ratio (95% CI)	*P* Value
Primary end point: all atherosclerotic events	68 (5.4)	13.6	86 (6.7)	17.0	0.80 (0.58-1.10)	.16
Coronary and cerebrovascular mortality	1 (0.08)	0.2	10 (0.8)	2.0	0.10 (0.01-0.79)	.0037
CHD events (fatal + nonfatal)	28 (2.2)	5.6	35 (2.7)	6.9	0.81 (0.49-1.33)	.40
Fatal MI	0	0	5 (0.4)	1.0		
Nonfatal MI	12 (1.0)	2.4	9 (0.7)	1.8	1.34 (0.57-3.19)	.50
Unstable angina	4 (0.3)	0.8	10 (0.8)	2.0	0.40 (0.13-1.29)	.13
Stable angina	12 (1.0)	2.4	11 (0.9)	2.2	1.10 (0.49-2.50)	.82
Cerebrovascular disease (fatal + nonfatal)	28 (2.2)	5.6	32 (2.5)	6.3	0.84 (0.53-1.32)	.44
Fatal stroke	1 (0.08)	0.2	5 (0.4)	1.0	0.20 (0.024-1.74)	.15
Nonfatal stroke						
Ischemic	22 (1.7)	4.4	24 (1.9)	4.6	0.93 (0.52-1.66)	.80
Hemorrhagic	5 (0.4)	1.0	3 (0.2)	0.6	1.68 (0.40-7.04)	.48
Transient ischemic attack	5 (0.4)	1.0	8 (0.6)	1.6	0.63 (0.21-1.93)	.42
Peripheral artery disease[a]	7 (0.6)	1.4	11 (0.9)	2.2	0.64 (0.25-1.65)	.35

Abbreviations: CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction.
[a] Arteriosclerosis obliterans (5 in aspirin group and 8 in nonaspirin group); aortic dissection (2 fatal in the aspirin group and 1 nonfatal in the nonaspirin group); mesenteric artery thrombosis (1 in the nonaspirin group), and retinal artery thrombosis (1 in the nonaspirin group).

Figure 2. Total Percentage of Atherosclerotic Events According to Treatment Group



CI indicates confidence interval; HR, hazard ratio.

aspirin group required transfusion. Another 13 patients in the aspirin group had minor bleeding. There was no significant difference in the composite of hemorrhagic stroke and severe GI bleeding, which occurred in 10 patients in the aspirin group and in 7 patients in the nonaspirin group.

COMMENT

Myocardial infarction and ischemic stroke are leading causes of mortality and morbidity in patients with type 2 diabetes.[25] Given the rapid increase in the number of patients with type 2 diabetes worldwide and especially in Asia, establishing effective means of primary prevention of coronary and cerebrovascular events is an important public health priority.[26] In the JPAD primary prevention trial of 2539 type 2 diabetic patients without documented cardiovascular disease, the incidence of the primary end point of total atherosclerotic events, consisting of coronary, cerebrovascular, and peripheral vascular events, was not significantly different in the group that received prophylactic aspirin (81 or 100 mg once daily) than in the nonaspirin group. With the exception of fatal coronary and cerebrovascular events, none of the prespecified secondary end points were reduced significantly in the low-dose aspirin group. The incidence of fatal coronary and cerebrovascular events, a prespecified secondary end point, was significantly reduced in the low-dose aspirin group ($P = .0037$). A benefit of low-dose aspirin on the primary end point also was suggested in the subgroup of patients aged 65 years or older, which had a significant 32% relative reduction in total atherosclerotic events ($P = .047$). The cardiovascular mortality benefit was achieved with a small increase in cases of serious GI bleeding (4 patients in the aspirin group had bleeding that required transfusion), but no excess of fatal GI or cerebral hemorrhages.

The JPAD trial enrolled 2539 diabetic patients without documented coronary or cerebrovascular complications; the sample size was the largest among the previous primary prevention studies in respect to the number of diabetic patients enrolled. However, no difference was found in the effect of aspirin on the primary end point or most secondary end points.

The interpretation of these results is challenging because the overall event rates were low: 17 in 1000 Japanese diabetic patients. This is one-third of the event rate anticipated in our sample-size calculations, which were based on the Hisayama-cho[22] and Funagata[23] epidemiologic studies conducted in Japan in the 1990s. Current treatment of cardiovascular risk factors in patients with type 2 diabetes has improved since the 1990s and may have ac-

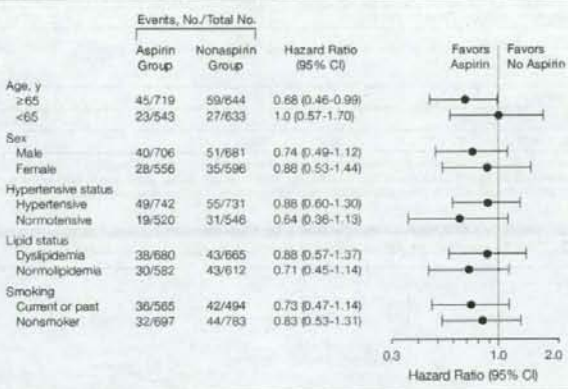
counted for the lower event rates: there is better control of glucose, blood pressure, and lipid levels in clinical practice. The baseline characteristics of patients in the JPAD trial were similar to those in previous studies except that body mass index was relatively lower in the JPAD trial than that in the previous studies, although similar to that in other studies of Japanese diabetics.[4,6,10,21,27,28]

A meta-analysis of primary prevention trials that included the British Doctors' Trial, the Physicians' Health Study, the Thrombosis Prevention Trial, the Hypertension Optimal Treatment (HOT) study, the Primary Prevention Project (PPP) trial, and the Women's Health Study showed that aspirin therapy significantly reduced the risk of total coronary heart disease, nonfatal myocardial infarction, and total cardiovascular events with a nonsignificant trend for decreased risk of stroke, cardiovascular mortality, and all-cause mortality.[29] However, the evidence for aspirin in prevention of cardiovascular events in diabetic patients has been surprisingly scant. Previous studies investigating the effects of low-dose aspirin on primary prevention of cardiovascular events did not enroll solely diabetic patients but enrolled patients with hypertension in the HOT study; patients with 1 or more cardiovascular risk factors in the Thrombosis Prevention Trial and the PPP trial; and a healthy population in the British Doctors' Trial, the Physicians' Health Study, and the Women's Health Study.

Several large primary prevention trials have included subgroup analyses of patients with diabetes. The Physicians' Health Study of 22 071 healthy men randomized to receive 325 mg of aspirin every other day or placebo showed a significant reduction in myocardial infarction for the entire population, but there was no significant difference for the small number of individuals with diabetes in the 2 treatment groups (11/275 in the aspirin group and 26/258 in the placebo group).[18] The Antithrombotic Trialists' Collaboration meta-analysis of 287 randomized trials reported effects of antiplatelet therapy (mainly aspirin) vs control in 135 000 patients and showed a nonsignificant 7% reduction in the odds for serious vascular events for the subgroup of 5126 patients with diabetes.[19]

Sacco et al[30] described the effects of aspirin on atherosclerotic disease in patients with diabetes as a subgroup of the PPP trial, which investigated the effects of aspirin and vitamin E in a 2-by-2 factorial trial of 4495 patients with at least 1 known major cardiovascular risk factor.[21] The original study was stopped on ethical grounds after a mean follow-up of 3.6 years because aspirin was associated with a lower risk of atherosclerotic disease in the overall group. The results of a subgroup analysis of 1031 diabetic patients did not

Figure 3. Subgroup Analysis of Incidence of Atherosclerotic Events



CI indicates confidence interval (shown as error bars in the plot).

Table 3. Adverse Effects

	No.	
	Aspirin Group	Nonaspirin Group
Bleeding, gastrointestinal[a]		
Hemorrhagic gastric ulcer	5	3
Bleeding from esophageal varices	1	0
Bleeding from colon diverticula	2	0
Gastrointestinal bleeding due to cancer	2	0
Hemorrhoid bleeding	1	0
Gastrointestinal bleeding (cause unknown)	1	1
Bleeding, other		
Retinal bleeding	8	4
Bleeding after tooth extraction	1	0
Subcutaneous hemorrhage	3	0
Hematuria	2	1
Nose bleeding	6	1
Chronic subdural hematoma	2	0
Nonbleeding gastrointestinal event		
Nonhemorrhagic gastritis	3	0
Nonhemorrhagic gastric ulcer	17	3
Nonhemorrhagic duodenal ulcer	1	1
Only gastrointestinal symptom	26	0
Other		
Anemia	4	0
Asthma	1	0

[a] In the aspirin group, 4 cases of severe gastrointestinal bleeding required transfusion.

reach statistical significance, possibly because of the early stopping of the trial and the subgroup size.[20] In addition, medication adherence was poor in the PPP trial: 28.2% of subjects assigned to aspirin had stopped this therapy by the conclusion of the trial. In the JPAD study, only 10% of patients in the aspirin group stopped this therapy by the end of the mean 4.37 years of follow-up.

Because of the low event rate in JPAD, our study was underpowered for demonstrating that aspirin had a significant effect on reducing total atherosclerotic events. However, the observation in the JPAD trial of an effect of aspirin on the secondary outcome of fatal cardiovascular events was also seen in the PPP trial. Aspirin did not reduce cardiovascular mortality in the HOT study, and it did not reduce fatal stroke in the Women's Health Study. The reason for the discrepancy in the preventive effect of aspirin on fatal cardiovascular events is not clear at present. The total number of fatal events was small (ranging from 13 to 49) in the JPAD trial as well as the PPP trial and in the subgroup population with diabetes in the HOT study. A larger trial is needed to determine the efficacy of low-dose aspirin on mortality.

The JPAD trial composite primary end point also included hemorrhagic stroke. The finding that aspirin did not increase the risk of hemorrhagic stroke was consistent with findings from prior reports,[21,24,30,31] although the population studied was patients with diabetes. The finding of no increase in hemorrhagic stroke in the JPAD trial is of particular clinical importance because hemorrhagic stroke is more common in Japanese populations than in the West.[32,33] Moreover, there was no fatality due to hemorrhagic events except for hemorrhagic stroke; however, the hemorrhagic events that required surgical interventions or transfusion were observed in 4 patients in aspirin group.

The study design may be considered a limitation of the JPAD trial (prospective, randomized, open-label, controlled trial with blinded end-point assessment), as it did not have the advantages of a double-blind, randomized trial. The Japanese Pharmaceutical Affairs Law limits the use of placebo in physician-initiated studies because it is an unapproved medicine. However, the end-point classification was conducted by a blinded, independent committee on validation of data and events that was unaware of the group assignments.

Previous clinical studies indicate that a cardiovascular risk reduction is difficult to achieve by aggressively controlling plasma glucose levels in diabetic patients.[34-37] These studies suggested that the contribution of lowering glucose levels to the reduction of macrovascular events appears to be minimal, at least in the first few years of treatment. Although improved glucose control can protect against the development of microvascular complications, the absence of a reduction in macrovascular events implicates an additive effect of nonglycemic risk factors that often accompany diabetes, such as hypertension, hyperlipidemia, and hypercoagulability. Additional medications such as angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, statins, and antiplatelet agents may be needed in patients with type 2 diabetes mellitus. The JPAD trial indicates that among these medications, aspirin is well tolerated for primary prevention and may provide an additional low-cost option.

In summary, in the JPAD trial, the first prospectively designed trial to evaluate low-dose aspirin in patients with type 2 diabetes without previous cardiovascular disease, low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events. Despite a large sample size, the event rate in the study was lower than anticipated. Aspirin was well tolerated in these patients, as there was no increase in hemorrhagic strokes and a small increase in serious GI hemorrhagic events (4 patients required transfusion). These findings should be interpreted in context with the low incidence of atherosclerotic disease in Japan and the current management practice for cardiovascular risk factors and suggest the need to conduct additional studies of aspirin for primary prevention of cardiovascular disease in diabetic patients.

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診断セミナー　資料

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注意：セミナーを楽しむために　この資料はセミナーの進行に合わせて使います。先には「読み進めない」でください。事前にこのページに目を通すだけにしてください。

今日のお題

救急外来での診断演習　感度・特異度・そして尤度比の活用方法を知る

目的

鑑別診断手順を整理する

目標

感度、特異度の意味をおさらいする

尤度比の使い方を確認する

所見の観察者間の一致率を評価する指標を知る

このセミナーを終えるとあなたは

- 感度の高い検査、特異度の高い検査が、確定診断や除外診断にどう役立つのか説明できるようになる
- 尤度比の求め方を説明できる
- 尤度比を使うノモグラムが使えるようになる

セクション１：あなたの救急外来を振り返る

まず質問１

あなたの病院の救急外来を受診する患者を思い返してみましょう。

どんな疾患が多いでしょうか。

以下の主訴の患者が占める割合をちょっと考えてみましょう。

発熱	（　%）	腹痛・腹部症状	（　%）
胸痛・胸部症状	（　%）	頭痛・頭部症状	（　%）
けが・外傷	（　%）	意識障害	（　%）

他に頻度の多い主訴は何がありますか ＿＿＿＿＿＿＿＿＿＿＿＿

質問２

あなたの救急外来に、「胸部症状」「胸痛」を訴えて来院する患者の最終診断はどんなものがありますか。以下に列挙してみましょう。少なくとも３つ以上。目標５つ以上。できれば、１０個以上。

EBOnCallの記述 http://www.eboncall.org

Chest pain

Causes

Common causes of chest pain include [c]

1) myocardial infarction
2) angina
3) pulmonary embolism
4) chest infection
5) musculoskeletal pain
6) pericarditis

Rarer causes include [d]

1) aortic dissection
2) oesophageal spasm

Note:

One in six patients with anterior or left-sided chest pain have a myocardial infarction (14% to 20%) [a]

The risk is higher in elderly patients (20%: 95% CI: 19% to 22%) [a] and patients with a typical history [a]

One in four patients anterior or left-sided chest pain have unstable angina (24%: 95% CI: 21% to 27%) [a] - the risk is higher in elderly patients (44%: 95% CI: 42% to 45%) [a]

Myocardial infarction, angina and pulmonary embolism are common causes of chest pain

Chest pain in emergency departments [a] [c]	% (95% CI)
myocardial infarction	17% (14% to 20%)
unstable angina	24% (21% to 27%)
stable angina	9.0% (5.6% to 12%)
pulmonary embolism	5.8% (3.0% to 8.5%)
other pulmonary disease	5.8% (3.0% to 8.5%)
chest wall pain	5.4% (2.7% to 8.1%)
pericarditis	5.0% (2.5% to 7.6%)
psychogenic	2.9% (0.9% to 4.8%)
other heart disease	1.1% (0.0% to 2.3%)
other disease	1.1% (0.0% to 2.3%)
unknown	11% (7.5% to 15%)

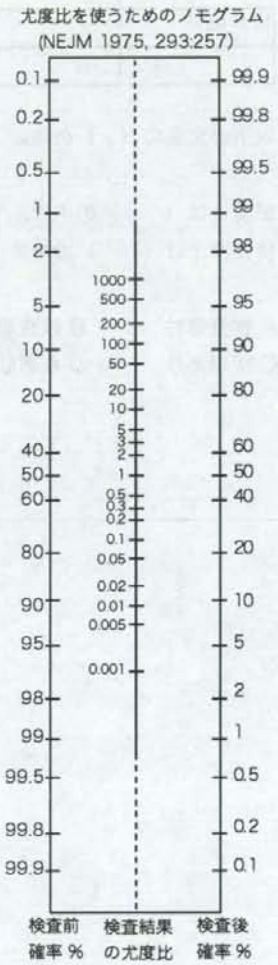
Only 40% of cases or aortic dissection are diagnosed following history, physical, ECG and CXR. (14% mistaken for ischaemic heart disease, 14% for other aortic disease, 7% heart failure) [c]

できれば、鑑別診断のリストアップの時に、その疾患の確率まで予測できると次のステップに進みやすい。もちろん、おおざっぱでよい。

力試しあなたの救急外来に受診した「2時間続く胸痛・胸部症状」を主訴とした患者が急性心筋梗塞あるいは不安定狭心症である確率をおおざっぱに見積もろう

あなたの予測する確率：＿＿＿％

以下に示す要因があった場合に、その確率はどうなるだろうか。予測してみよう。もちろん、おおざっぱに。



要因１：年齢

	あなたの予測する確率	あなたの尤度比
その患者の年齢が２７才だったら		
その患者の年齢が４５才だったら		
その患者の年齢が６５才だったら		
その患者の年齢が８５才だったら		

要因２：性別

	あなたの予測する確率	あなたの尤度比
その患者が男性だったら		
その患者が女性だったら		

要因３：症状

	あなたの予測する確率	あなたの尤度比
「胸が圧迫される」「押される」		
「左を下にすると痛む」		
「息をすると痛む」		
痛みを訴える場所に圧痛がある		
左肩から腕も痛む		
右肩から腕も痛む		

要因４：検査結果

	あなたの予測する確率	あなたの尤度比
連続する２誘導でST上昇がある		
心電図は正常である		
白血球数が12000/mm3である		
血清トロポニン値が上昇していない		

確認作業：あなたの所見の重み付けを見積もる

配布したハンドカード、あるいは上記のノモグラムを用いて、それぞれの所見のあなたの重み付けを求めてみよう。

重み付けは、「尤度比（ゆうどひ）：Likelihood Ratio」という値で求められる。

求め方：まずあなたが最初に見積もった確率を左端のライン上にマークする。次に、その所見によって変わった確率を右端のラインのマークし、その二つの点を結んだ線と中央の線との交点が、その所見の尤度比である。

たとえば、あなたが最初の確率を１０％だと見積もっていて、患者が２７才だったらその確率が２％になると考えた場合、右端の１０という点から、右端の２という点まで結んで線を書くと中央の線と０．２あたりで交わる。これが、あなたの見積もった尤度比である。

感度と特異度もおさらいしておこう

	疾患あり	疾患なし	
検査陽性			
検査陰性			

以下の文章の（ ）の中に、選択肢A-Dのうちからもっとも適切なものを一つずつ選んで記入せよ

感度とは（ ）の中で、（ ）の占める割合である
特異度とは（ ）の中で、（ ）の占める割合である

A 検査陽性　　B 検査陰性
C 疾患あり　　D 疾患なし

診断の指標の使い方：感度、特異度、そして尤度比（ゆうどひ）

感度と特異度

	疾患あり	疾患なし
検査陽性	a	b
検査陰性	c	d

感度 a/(a+c)、 **特異度** d/(b+d)

大まかな憶え方：

感度が高い検査→偽陰性がほとんどない。従って陰性だったらその疾患の除外診断に役立つ。

特異度の高い検査→偽陽性がほとんどない。従って陽性だったらその疾患の確定診断に役立つ。

尤度比（ゆうどひ）の求め方

まず、感度と特異度を用いて2×2表を埋める。横方向に疾患あり/疾患なしを求めると尤度比が得られる。

	疾患あり	疾患なし	尤度比
検査陽性	感度	1−特異度	感度/（1−特異度）
検査陰性	1−感度	特異度	（1−感度）/特異度

例：感度95% 特異度90%の検査であれば以下のようになる。

	疾患あり	疾患なし	尤度比
検査陽性	95	10	95/10=9.5
検査陰性	5	90	5/90=0.056

検査陽性の尤度比9.5、検査陰性の尤度比0.056

感度90% 特異度10%の検査（疾患があろうがなかろうが90%の確率で陽性になる、無意味な検査）であれば以下のようになる。

	疾患あり	疾患なし	尤度比
検査陽性	90	90	90/90=1
検査陰性	10	10	10/10=1

いずれの尤度比も1．つまり、どちらの検査結果であっても確率に影響を与えないことを示している。

尤度比の目安	
LRが＞10あるいは＜0.1	効果大
LRが5-10あるいは0.1-0.2	効果中
LRが2-5あるは0.2-0.5	効果小
LRが＜2あるいは＞0.5	効果僅か
LRが1	効果なし

迷ったときは、オッズ1の状況で考える。オッズ1とは病気かそうでないか50%ずつの確率であることを示す。この患者で陽性であったテストの尤度比が10であればオッズは10となり、確率はほぼ90%になる。逆に陰性であって、その尤度比が0.1であればオッズは0.1となり確率はほぼ10%となる。しかし、尤度比が2であれば陽性であってもオッズは2となり確率は67%程度、陰性の検査の尤度比が0.5であれば、オッズは0.5となり確率はせいぜい33%になる。

検査が陽性であった場合のオッズ=検査前のオッズ×sens/(1−spec)←検査陽性の尤度比
検査が陰性であった場合のオッズ=検査前のオッズ×spec/(1−sens)←検査陰性の尤度比

確率（p）からオッズ（Odds）へ：Odds=p/(1-p)

オッズから確率へ：p=Odds/(1+Odds)

50%の確率のオッズは1．確率は0から1までの値をとり、オッズは0から無限大までの値をとる

鑑別診断を進めるときの原則

「１つの選択肢の確率は０から１まで（0%から100%まで）の値である」
「すべての選択肢の確率の合計は１（100%）である」

従って　鑑別診断名が１つしか思い浮かばなければ、それは「確定診断」になってしまう。

救急外来で鑑別を効率よく行う手順の一例
1）とりあえず、５つ、できれば１０くらいの診断名（なるべく病態ではなく、診断名を考慮すること）をリストアップする。
2）次に、その中で頻度、重要度、緊急度を考慮して３つくらいの疾患に絞る。
3）その疾患に関して、確定診断に役立つ検査結果や除外診断に役立つ検査結果を求めて問診や身体所見を取り、検査計画を立て検査結果を読む。
4）もし、その３つのうち除外されるものがでたら、一番最初のリストから最も重要と思われるものを加えて、また３つのリストにする。
5）3）−4）の手順を繰り返す。確定診断が得られたらそこで終了。重要な疾患が除外され、緊急性が高くないと判断されれば、救急外来から返す。重要な疾患が除外されず緊急を要する可能性が残ると判断されれば、a)一旦入院、b)しばらく救急外来で様子を見る、c)重要な疾患の可能性が残ること、状態が変わればすぐ来院することを指示して帰宅させる　といったオプションを考慮する。

非常に感度の高い検査結果が陰性であれば、まず診断は否定されるし（SnNout）、非常に特異度の高い検査結果が陽性であれば診断は確実なものになる（SpPin）。
語呂合わせ：　Sensitivityの高い検査がNegativeだったらRule-Out
　　Specificityの高い検査がPositiveだったらRule-In
従って、その検査結果も陽性だったら意味があるか、陰性だったら意味かを、ちゃんと憶えておくことが重要になる。
注意点：感度と特異度はペアで知っておいて意味がある。例えば、「感度９０％で特異度１０％の検査」は診断する力はまったくない。よく考えてみれば、この検査は病気があろうがなかろうが、どっちにしても９０％の確率で陽性になる検査である。感度が特異度の一方が良くても、もう一方がわるければその診断力を大きく損なってしまう。

尤度比（ゆうどひ：likelihood ratio）は感度と特異度から求められ、検査結果からより客観的に疾患の可能性を予測するのに有用な概念である。

診断の問いかけの具体例と課題
実際の診療の現場での診断検査治療の過程は、仮説（hypothesis）と問いかけ（questions）をもとに進められる。

仮説１：この患者は労作性狭心症だ。
問いかけ１：診断を確かめるために運動負荷心電図は行なうべきだろうか？
仮説２：この患者は急性硬膜下血腫ではない。
問いかけ２：この除外診断のために、頭部ＣＴをとるべきだろうか？

最初に疑わしいと考えた診断にとらわれて、臨床所見や検査所見をその診断に都合の良いように判断し、考えた診断に対してさほど重要でない検査を繰り返すと、真の診断にたどり着けない危険は高くなる。

身体所見の感度・特異度・尤度比はどこにあるか

1）身体所見を活用するための情報源：もちろんこの他にもたくさんある。

マクギーの身体診断学　エルゼビアジャパン

特に第12部の尤度比の表は、それぞれの所見の強さを見極める上で助けになる。注意：必ず、表の尤度比だけですまさず、適宜本文を参照すること。どんな対象患者で検討したかが重要なので。

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