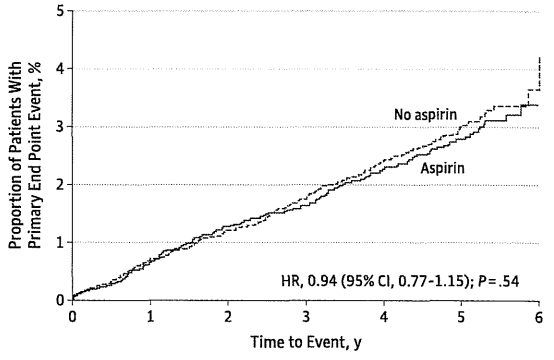
Table 2. Fatal and Nonfatal Events Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors Receiving Aspirin or No Aspirin (Modified Intention-to-Treat Population)

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

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



No. at risk

Aspirin	7220	7021	6771	6583	6322	3639	169
No aspirin	7244	7073	6861	6645	6359	3711	182

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

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

death from cardiovascular causes, nonfatal stroke, and nonfatal myocardial infarction (**Table 2** and **Figure 2**). The estimated HR for aspirin vs no aspirin was 0.94 (95% CI, 0.77-1.15; *P* = .54). At 5 years after randomization, the cumulative primary event rate was similar in participants in the aspirin group (2.77% [95% CI, 2.40%-3.20%]) and those in the no aspirin group (2.96% [95% CI, 2.58%-3.40%]). Overall, few deaths from cardiovascular causes or nonfatal stroke or myocardial infarction were reported with aspirin (n = 193) or no aspirin (n = 207) (Table 2).

Assessment of the primary end point in subgroups of patients defined by the presence or absence of 8 different disease or demographic risk factors (hypertension, dyslipidemia, diabetes mellitus, male sex, aged at least 70 years, body mass index [BMI, calculated as weight in kilograms divided by height in meters squared] of 25 or higher, smoking, or family history of premature cardiovascular disease) did not reveal significant differences between study groups; detailed results from these subgroup analyses are reported in **Figure 3**.

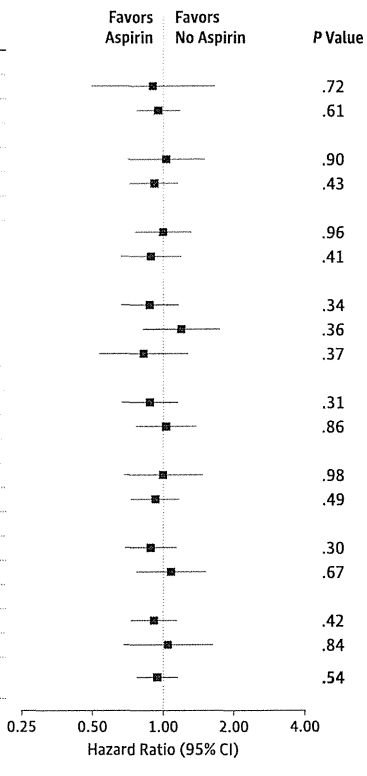
Regression analyses indicated that the risk of a primary end point event was higher in patients 70 years or older vs those younger than 70 years (parameter estimate, 0.92; HR, 2.51 [95% CI, 2.00-3.14]; *P* < .001), in patients with diabetes mellitus vs those without diabetes mellitus (parameter estimate, 0.52; HR, 1.68 [95% CI, 1.38-2.06]; *P* < .001), in patients who were smoking vs nonsmoking (parameter estimate, 0.53; HR, 1.70 [95% CI, 1.31-2.20]; *P* < .001), in men vs women (parameter estimate, 0.34; HR, 1.41 [95% CI, 1.14-1.74]; *P* = .002), and in patients with hypertension vs those without hypertension (parameter estimate, 0.42; HR, 1.52 [95% CI, 1.10-2.09]; *P* = .01). The risk of a primary end point event was not increased in patients with dyslipidemia vs those without dyslipidemia (parameter estimate, 0.13; HR, 1.13 [95% CI, 0.91-1.42]; *P* = .27) or in patients with a BMI of 25 or higher vs those with a BMI lower than 25 (parameter estimate, -0.13; HR, 0.88 [95% CI, 0.72-1.09]; *P* = .24). The risk of a primary end point event was also not significantly lower with aspirin vs no aspirin, irrespective of whether patients had a risk score lower than 4 (1.53% [95% CI, 1.14%-2.05%] for aspirin vs 1.47% [95% CI, 1.08%-1.98%] for no aspirin; HR, 1.09 [95% CI, 0.72-1.63]; *P* = .69) or a risk score of 4 or higher (3.79% [95% CI, 3.21%-4.46%] for aspirin vs 4.19% [95% CI, 3.59%-4.90%] for no aspirin; HR, 0.90 [95% CI, 0.72-1.13]; *P* = .35).

Secondary Outcomes

When TIA, angina pectoris, and arteriosclerotic disease requiring surgery or intervention were added to the composite primary end point, the difference between the aspirin group (event rate, 4.00% [95% CI, 3.55%-4.50%]) and no aspirin group (event rate, 4.59% [95% CI, 4.11%-5.13%]) remained nonsignificant (HR, 0.89 [95% CI, 0.75-1.04]; *P* = .14) (**Figure 4**). There were also no significant differences between the 2 study groups for time to any cause of death (event rate, 4.29% [95% CI, 3.83%-4.82%] for aspirin vs 4.11% [95% CI, 3.66%-4.62%] for no aspirin; HR, 0.99 [95% CI, 0.85-1.17]; *P* = .93), death from cardiovascular disease (event rate, 0.86% [95% CI, 0.66%-1.12%] for aspirin vs 0.78% [95% CI, 0.60%-1.02%] for no aspirin; HR, 1.03 [95% CI, 0.71-1.48]; *P* = .89), death from causes other than cardiovascular disease (event rate, 3.46% [95% CI, 3.04%-3.94%] for aspirin vs 3.36% [95% CI, 2.94%-3.83%] for no aspirin; HR, 0.99 [95% CI, 0.82-1.18]; *P* = .87), nonfatal cerebrovascular disease (ischemic or hemorrhagic) (event rate, 1.65% [95% CI, 1.37%-1.99%] for aspirin vs 1.64% [95% CI, 1.36%-1.98%] for no aspirin; HR, 1.04 [95% CI, 0.80-1.34]; *P* = .78), angina pectoris (event rate, 0.66% [95% CI, 0.49%-0.89%] for aspirin vs 0.81% [95% CI, 0.61%-1.07%] for no aspirin; HR, 0.86 [95% CI, 0.58-1.28]; *P* = .46), and arteriosclerotic diseases requiring surgery or intervention (event rate, 1.08%

Figure 3. Hazard Ratios for Aspirin vs No Aspirin and Event Rates for the Primary Composite Outcome Measure[a] Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors (Modified Intention-to-Treat Population)

	Aspirin			No Aspirin				
Disease Risk Factor	No. of Events	No. of Patients	Event Rate per 5 Years, % (95% CI)	No. of Events	No. of Patients	Event Rate per 5 Years, % (95% CI)	Hazard Ratio (95% CI)	*P* Value
Hypertension								
No	20	1087	1.74 (1.08-2.80)	23	1099	2.12 (1.40-3.20)	0.90 (0.49-1.63)	.72
Yes	173	6133	2.95 (2.54-3.44)	184	6145	3.11 (2.68-3.60)	0.95 (0.77-1.17)	.61
Dyslipidemia								
No	56	2022	2.89 (2.21-3.78)	56	2044	2.93 (2.26-3.81)	1.02 (0.71-1.48)	.90
Yes	137	5198	2.73 (2.30-3.23)	151	5200	2.97 (2.52-3.50)	0.91 (0.72-1.15)	.43
Diabetes mellitus								
No	107	4775	2.30 (1.89-2.79)	109	4786	2.36 (1.95-2.86)	0.99 (0.76-1.30)	.96
Yes	86	2445	3.70 (2.99-4.58)	98	2458	4.14 (3.38-5.06)	0.89 (0.66-1.18)	.41
Family history[b]								
No	94	4058	2.44 (1.98-3.00)	109	4086	2.72 (2.24-3.30)	0.87 (0.66-1.15)	.34
Yes	61	1981	3.13 (2.42-4.03)	52	1982	2.83 (2.16-3.72)	1.19 (0.82-1.72)	.36
Unknown	38	1181	3.33 (2.41-4.59)	46	1176	4.01 (2.98-5.37)	0.82 (0.54-1.26)	.37
Sex								
Men	99	3055	3.42 (2.80-4.18)	114	3068	3.85 (3.19-4.65)	0.87 (0.67-1.14)	.31
Women	94	4165	2.30 (1.87-2.83)	93	4176	2.32 (1.88-2.85)	1.03 (0.77-1.37)	.86
Age, y								
<70	52	3234	1.67 (1.27-2.21)	53	3259	1.73 (1.31-2.28)	1.00 (0.68-1.46)	.98
≥70	141	3986	3.67 (3.10-4.34)	154	3985	3.98 (3.39-4.67)	0.92 (0.73-1.16)	.49
BMI								
<25	122	4576	2.75 (2.29-3.29)	141	4640	3.21 (2.71-3.79)	0.88 (0.69-1.12)	.30
≥25	71	2644	2.82 (2.22-3.57)	66	2604	2.53 (1.97-3.25)	1.08 (0.77-1.50)	.67
Smoker								
No	150	6261	2.48 (2.10-2.92)	167	6310	2.71 (2.32-3.17)	0.91 (0.73-1.14)	.42
Yes	43	959	4.76 (3.51-6.43)	40	934	4.69 (3.43-6.40)	1.05 (0.68-1.61)	.84
Overall	**193**	**7220**	**2.77 (2.40-3.20)**	**207**	**7244**	**2.96 (2.58-3.40)**	**0.94 (0.77-1.15)**	.54



BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared). Data shown for the overall population and for subgroups defined by disease risk factor and by patient characteristics. The *P* values were determined using the log-rank test stratified for underlying disease (hypertension, dyslipidemia, or diabetes). Hazard ratios were calculated using the Cox proportional hazards model.

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

[b] History of premature cardiovascular disease.

[95% CI, 0.86%-1.36%] for aspirin vs 1.24% [95% CI, 0.99%-1.55%] for no aspirin; HR, 0.89 [95% CI, 0.65-1.21]; *P* = .46) (Figure 4). However, compared with no aspirin, aspirin significantly reduced the risk of nonfatal myocardial infarction (event rate, 0.30% [95% CI, 0.19%-0.47%] for aspirin vs 0.58% [95% CI, 0.42%-0.81%] for no aspirin; HR, 0.53 [95% CI, 0.31-0.91]; *P* = .02) and TIA (event rate, 0.26% [95% CI, 0.16%-0.42%] for aspirin vs 0.49% [95% CI, 0.35%-0.69%] for no aspirin; HR, 0.57 [95% CI, 0.32-0.99]; *P* = .04). Conversely, the risk of extracranial hemorrhage requiring transfusion or hospitalization was higher with aspirin than with no aspirin (event rate, 0.86% [95% CI, 0.67%-1.11%] for aspirin vs 0.51% [95% CI, 0.37%-0.72%] for no aspirin; HR, 1.85 [95% CI, 1.22-2.81]; *P* = .004).

Exploratory Analysis

A post hoc exploratory analysis was conducted at the time of study discontinuation (1 year after the second interim analysis) when 400 primary end point events had occurred. It showed that the predictive probability of reaching a significant difference in favor of aspirin over no aspirin was 28% if the study had continued until it was adequately powered (ie, 624 events had occurred).

Safety and Tolerability

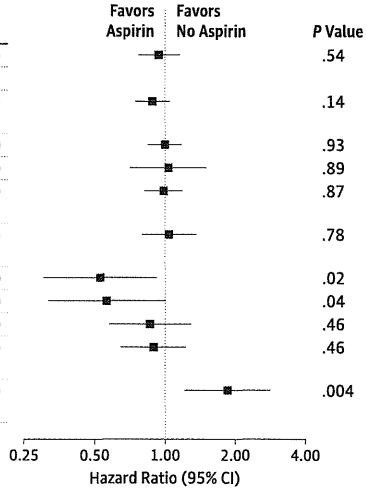
Analysis of gastrointestinal adverse events of interest indicated that these events were reported in a higher proportion of patients receiving daily low-dose aspirin than in those not receiving aspirin (**Table 3**).

Discussion

This study was designed to assess whether primary prevention with once-daily, low-dose aspirin would reduce the combined risk of death from cardiovascular causes, nonfatal stroke, and nonfatal myocardial infarction in Japanese patients (aged ≥60 years) with hypertension, dyslipidemia, or diabetes mellitus. The study was terminated early based on a futility assessment, but an exploratory analysis sug-

Figure 4. Hazard Ratios for Aspirin vs No Aspirin and Event Rates for Secondary End Points Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors (Modified Intention-to-Treat Population)

End Point	Aspirin (n = 7220) No. of Events	Aspirin (n = 7220) Event Rate Over 5 Years, % (95% CI)	No Aspirin (n = 7244) No. of Events	No Aspirin (n = 7244) Event Rate Over 5 Years, % (95% CI)	Hazard Ratio (95% CI)	P Value
Primary end point[a]	193	2.77 (2.40-3.20)	207	2.96 (2.58-3.40)	0.94 (0.77-1.15)	.54
Secondary end point						
Any atherosclerotic or cardiovascular event[b]	280	4.00 (3.55-4.50)	319	4.59 (4.11-5.13)	0.89 (0.75-1.04)	.14
Any cause of death	297	4.29 (3.83-4.82)	303	4.11 (3.66-4.62)	0.99 (0.85-1.17)	.93
Death from cardiovascular disease	58	0.86 (0.66-1.12)	57	0.78 (0.60-1.02)	1.03 (0.71-1.48)	.89
Death from causes other than cardiovascular disease	239	3.46 (3.04-3.94)	246	3.36 (2.94-3.83)	0.99 (0.82-1.18)	.87
Nonfatal cerebrovascular disease (ischemic or hemorrhagic)	117	1.65 (1.37-1.99)	114	1.64 (1.36-1.98)	1.04 (0.80-1.34)	.78
Nonfatal myocardial infarction	20	0.30 (0.19-0.47)	38	0.58 (0.42-0.81)	0.53 (0.31-0.91)	.02
Transient ischemic attack	19	0.26 (0.16-0.42)	34	0.49 (0.35-0.69)	0.57 (0.32-0.99)	.04
Angina pectoris	46	0.66 (0.49-0.89)	54	0.81 (0.61-1.07)	0.86 (0.58-1.28)	.46
Arteriosclerotic diseases requiring surgery or intervention	75	1.08 (0.86-1.36)	85	1.24 (0.99-1.55)	0.89 (0.65-1.21)	.46
Serious extracranial hemorrhage requiring transfusion or hospitalization	62	0.86 (0.67-1.11)	34	0.51 (0.37-0.72)	1.85 (1.22-2.81)	.004



Data shown for the overall population. The *P* values were determined using the log-rank test stratified for underlying disease (hypertension, dyslipidemia, or diabetes). Hazard ratios were calculated using the Cox proportional hazards model.

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

[b] Death from cardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), nonfatal myocardial infarction, transient ischemic attack, angina pectoris, and arteriosclerotic disease requiring surgery or intervention.

Table 3. Incidence of Prespecified Gastrointestinal Adverse Events Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors Receiving Aspirin or No Aspirin (Randomized Population)

	No. (%) [95% CI] Aspirin (n = 7323)	No. (%) [95% CI] No Aspirin (n = 7335)	*P* Value
Stomach/abdominal discomfort	335 (4.57) [4.11-5.08]	175 (2.39) [2.05-2.76]	<.001
Heartburn	202 (2.76) [2.40-3.16]	137 (1.87) [1.57-2.20]	<.001
Gastroduodenal ulcer	191 (2.61) [2.26-3.00]	91 (1.24) [1.00-1.52]	<.001
Stomach/abdominal pain	168 (2.29) [1.96-2.66]	81 (1.10) [0.88-1.37]	<.001
Reflux esophagitis	160 (2.18) [1.86-2.55]	125 (1.70) [1.42-2.03]	.04
Gastrointestinal hemorrhage	103 (1.41) [1.15-1.70]	31 (0.42) [0.29-0.60]	<.001
Erosive gastritis	89 (1.22) [0.98-1.49]	40 (0.55) [0.39-0.74]	<.001
Nausea	79 (1.08) [0.85-1.34]	50 (0.68) [0.51-0.90]	.01
Stomach/abdominal pressure	31 (0.42) [0.29-0.60]	21 (0.29) [0.18-0.44]	.17

gested a 28% probability of finding a significant difference in favor of aspirin had the study been continued through the planned number of events. Therefore, there remains a possibility that the statistically nonsignificant reduction in the risk of death from cardiovascular causes, nonfatal stroke, and nonfatal myocardial infarction was due to the study being inadequately powered, rather than an absence of beneficial effect of aspirin. However, even if the result had become statistically significant through prolongation of the study, the clinical importance of aspirin in the primary prevention of cardiovascular events would have been less than originally assumed. Therefore, it appears that aspirin is unlikely to show a clinically important benefit in the overall population included in this study. We plan to conduct further analyses to establish whether aspirin had beneficial effects in particular subgroups of patients or if there were beneficial effects with respect to cancer prevention.

Study limitations need to be considered. Assessments of between-group differences in any end point in this study were confounded by a decreasing level of adherence with daily low-dose aspirin in the aspirin group (dropping to 76% in year 5) and increasing uptake of daily aspirin in the no aspirin group (reaching 10% in year 5). In addition, the number of patients lost to follow-up could be considered a limitation of large trials conducted in a real-world setting. However, use of Kaplan-Meier time-to-event analyses limits the effect of missing data, and the proportion of patients lost to

follow-up in this study (10.5%) was consistent with that reported for an earlier Japanese study (7.6%) with a similar design, but a shorter follow-up period.[24] This earlier study, the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) study[24] among patients with type 2 diabetes, also had lower than planned power (because of low event rates). It is possible that the low incidence of fatal and nonfatal cardiovascular events is due to the characteristics of Japanese patients. Compared with other relevant studies (eg, JPAD, the Prevention of Progression of Arterial Disease and Diabetes [POPADAD] study,[25] and the Aspirin for Asymptomatic Atherosclerosis Trial [AAAT][26]), baseline characteristics in the JPPP study are broadly similar, except for an apparent lower prevalence of current smoking in JPPP (13.1% in JPPP vs 21%-32% in the other studies) and a lower mean BMI compared with POPADAD (24.2 in JPPP vs 28.7-29.2 in POPADAD), although this is likely to reflect a Japanese population compared with a Western population, because BMI was similar in JPPP and JPAD.[25,26]

The PROBE study design could be considered a limitation, because it does not have all the advantages of a double-blind, randomized, placebo-controlled trial. However, adjudication of end points was performed centrally by an expert committee blinded to treatment assignments. The PROBE design does not control for lack of ascertainment.

Because the study participants were unblinded, it is possible that patients receiving aspirin were more likely to report adverse events believed to be related to aspirin treatment than those not receiving treatment. In addition, it is possible that enrollment in the study led to patients having more physician contact, resulting in better control of risk factors than the general population; if so, this might account for the low observed event rates.

It is likely that some deaths occurred among participants lost to follow-up. However, the potential effect of this underascertainment on the study outcomes is likely to be small. Similarly, although exclusion of nonadherent persons after randomization could have biased the findings away from the null (in either direction), the magnitude of any such bias would be expected to be small.

Hemorrhagic stroke is more common in Japanese populations than in Western populations.[27] In this study, no increase was observed in fatal hemorrhagic strokes (intracerebral and subarachnoid) for aspirin vs no aspirin. However, more patients treated with aspirin had nonfatal intracerebral hemorrhage (23 patients) or subarachnoid hemorrhage (8 patients) than those not receiving aspirin (10 patients for nonfatal intracerebral hemorrhage and 4 patients for subarachnoid hemorrhage).

More recent meta-analyses than the ATTC,[4] not using patient-level data, also included studies completed since 2009 (JPAD, POPADAD, and AAAT)[28-30] and suggested beneficial effects for aspirin in the primary prevention of cardiovascular events. In the meta-analysis performed by Raju and colleagues,[29] primary prevention with aspirin, compared with nonuse of aspirin, was associated with a reduction in all-cause mortality (relative risk [RR], 0.94 [95% CI, 0.88-1.00]), myocardial infarction (composite of fatal and nonfatal; RR, 0.83 [95% CI, 0.69-1.00]), ischemic stroke (RR, 0.86 [95% CI, 0.75-0.98]), and the composite of myocardial infarction, stroke, and cardiovascular death (RR, 0.88 [95% CI, 0.83-0.94]). Bartolucci and colleagues[28] reported in their meta-analysis that aspirin significantly decreased the risk of total cardiovascular events (odds ratio [OR], 0.87 [95% CI, 0.80-0.93]; $P = .001$) and nonfatal myocardial infarction (OR, 0.81 [95% CI, 0.67-0.99]; $P = .042$), compared with no aspirin. In the third meta-analysis, conducted by Seshasai and colleagues,[30] the association of aspirin (compared with no aspirin) with a significant reduction in the risk of cardiovascular events (OR, 0.90 [95% CI, 0.85-0.96]) was primarily accounted for by a large reduction in the risk of nonfatal myocardial infarction (OR, 0.80 [95% CI, 0.67-0.96]). No effect on fatal myocardial infarction was observed, but a modest nonsignificant reduction was apparent for all-cause mortality.

Despite inconsistent evidence for the benefit of aspirin in primary prevention of cardiovascular events, the benefits in secondary prevention are well documented, including in Japanese patients.[31-33] There is also a growing body of evidence to suggest benefits for aspirin in the prevention of colorectal and other cancers,[34,35] and the prevention of cancer recurrence, including in the Japanese population.[36] Reduction in the incidence of colorectal cancer may influence the overall benefit-risk profile of aspirin. Further analyses of the JPPP study data are planned, including analysis of deaths associated with cancers, to allow more precise identification of the patients for whom aspirin treatment may be most beneficial. In addition, other primary prevention studies using aspirin, such as ARRIVE,[37] ASCEND,[38] ASPREE,[39] and ACCEPT-D,[40] are in progress; however, these are being conducted in predominantly Western populations.

Conclusions

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

ARTICLE INFORMATION

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日本医師会生涯教育講座

開催日：平成26年8月21日（木）
会　場：新宿明治安田生命ホール

共催　東京都医師会
大日本住友製薬株式会社

テーマ「循環器疾患の予防最前線：疫学研究のエビデンスから」

座　長：東京都医師会理事　野津原　崇

1. 動脈硬化性疾患の予防のための脂質異常症の管理：最新の疫学知見と日米のガイドラインから

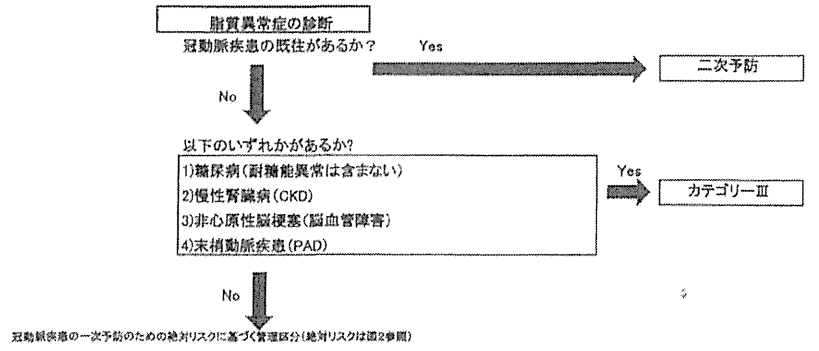
慶應義塾大学医学部衛生学公衆衛生学教室教授　岡村智教

1．臨床ガイドラインと疫学研究

動脈硬化性疾患（脳・心血管疾患）はがんに次いで日本人の主要死因の第二位を占めている。がんの予防は早期発見・早期治療が基本であるが、動脈硬化性疾患の場合、病気そのものを見つけるという早期発見モデルは機能しない。動脈硬化性疾患の予防に有効なのは危険因子に基づくハイリスク者の評価とスクリーニング、そしてその管理ということになる。日本動脈硬化学会のガイドラインが「動脈硬化性疾患予防ガイドライン」という名称であるのも、危険因子として脂質異常症等を考えるという意味が込められている。そしてどのような要因が動脈硬化性疾患の危険因子であるかを明らかにするためには、因果関係を証明するためのコホート研究が必要である。さらに因果関係が証明された危険因子に対しては臨床試験（無作為化比較対照試験）が行われ、治療の有効性が評価されることになる。そしてこのような検証がなされた危険因子が管理目標とすべき対象となる。要するにある集団で適切な予防対策を実施するためには当該集団での疫学研究が必須となる。Evidence－Based Medicine（EBM）普及後は多くの臨床ガイドラインに疫学的な考え方が取り入れられるようになった。

2．動脈硬化性疾患予防ガイドライン2012年版の概要

日本動脈硬化学会の動脈硬化性疾患予防ガイドライン2012年版（以下、ガイドライン2012）では[1]、LDLコレステロール（LDL－C）の管理目標値の設定に、NIPPONDATA80（National Integrated Project for Prospective Observation of Non－communicable Disease and its Trends in the Aged 1980）リスクチャートで評価した絶対リスクが用いられるようになった。NIPPON DATA80は、厚生省（当時）の第三次循環器疾



冠動脈疾患の一次予防のための絶対リスクに基づく管理区分(絶対リスクは図2参照)

NIPPON DATA80による10年間の冠動脈疾患による死亡確率(絶対リスク)	追加リスクの有無	
	追加リスクなし	以下のうちいずれかあり 1) 低HDL-C血症(HDL-C<40 mg/dl) 2) 早発性冠動脈疾患家族歴 (第1度近親者かつ男性55歳未満、女性65歳未満) 3) 耐糖能異常(糖尿病は含まない)
<0.5%	カテゴリーI	カテゴリーII
0.5-1.9%	カテゴリーII	カテゴリーIII
2.0%-	カテゴリーIII	カテゴリーIII

文献1から引用

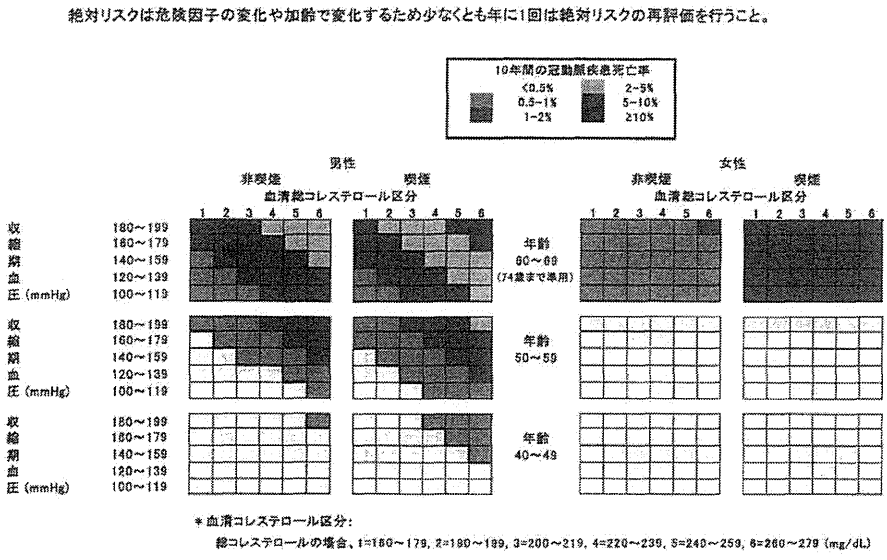
図1　LDLコレステロール管理目標設定のためのフローチャート

患基礎調査（1980年）受検者のコホート研究であり、全国から層化無作為抽出された300地区の住民約1万人を20年以上追跡している。NIPPONDATA80リスクチャートは、性別、年齢、糖尿病（随時血糖値200mg/dl以上）、喫煙、収縮期血圧値、総コレステロール値から10年以内の冠動脈疾患死亡確率を予測する[2]。NIPPONDATA80では、高血圧[3]、高コレステロール血症[4]、糖尿病[5]、喫煙[6]というコントロール可能な危険因子については、それぞれ詳細な評価がなされている。また高血圧、高コレステロール血症、糖尿病については、臨床試験によって薬物治療による予防効果が証明されており、治療すべき危険因子として扱うことに異論はない。また喫煙については有害性を検証する臨床試験は不可能だが、異なる集団、異なる国、異なる時代のほぼすべてのコホート研究で動脈硬化性疾患の危険因子であることが示されており、高血圧等と同列に扱うのが妥当である。

なおガイドライン2012ではリスクチャート使用前に自動的にハイリスクとすべき状態を示している。代表的なのは冠動脈疾患既往者であり、これは危険因子がどのようなレベルでもハイリスクである[7]。すなわちこれは二次予防に該当するため一次予防と分けて考える必要があり、ガイドライン2012では一次予防とは別の厳しい脂質管理目標値が定められている。一方、糖尿病は、随時血糖200mg/dl以上として、オリジナルのNIPPONDATA80リスクチャートに入っているものの、合併症があると非常にハイリスクになるためより厳格な脂質管理が必要と考えられた。欧米のガイドラインでは糖尿病は冠動脈疾患既往と同等として二次予防扱いにしているが、現時点では日本人のエビデンスでは明確なものがない。したがって糖尿病は、リスクチャートを用いず一次予防の中の高リスク病態として評価されることとなった。同様に慢性腎臓病、非心原性脳梗塞、末梢動脈疾患（PAD）もガイドライン2012ではハイリスク病態とされた。

3．ガイドライン2012による脂質管理

ガイドライン2012におけるLDL－C管理目標設定のためのフローチャートを図1に示す。まず対象者の冠動脈疾患の既往を確認する。これに該当すると二次予防となり、LDL－Cの管理目標値は最も厳格なレベルになる。次に前述したよう



文献1から引用

図2　冠動脈疾患絶対リスク評価チャート（一次予防）

に自動的に一次予防のカテゴリーⅢ（高リスク）になるハイリスク病態（糖尿病、CKD、非心原性脳梗塞、PAD）があるかを確認する。これらがない場合は、図2のNIPPONDATA80リスクチャート（オリジナルのリスクチャートから糖尿病と70歳代を除いたもの）に進み、10年以内の冠動脈疾患死亡率のレベルに応じて、カテゴリーⅠ（低リスク）、Ⅱ（中リスク）、Ⅲ（高リスク）に分類される（それぞれ0.5％未満、0.5～2.0％未満、2.0％以上）。なお低HDL－C血症、早発性冠動脈疾患の家族歴、耐糖能異常のいずれか、または複数がある場合は、それぞれ一段階上のカテゴリーに変更される（ただしカテゴリーⅢはそのまま）。そしてガイドライン2012では各区分のLDL－Cの管理目標を、カテゴリーⅠ（低リスク）：160 mg/dl未満、Ⅱ（中リスク）：140 mg/dl未満、Ⅲ（高リスク）：120 mg/dl未満、二次予防：100 mg/dl未満、と定めている。またNon－HDLコレステロールの管理目標値もLDL－Cプラス30mg/dlとされており、これはLDL－Cの管理目標を達成した時の次の目標である。しかし非空腹時採血やトリグリセリドが高い場合は、これを一次目標としても良い。一方、絶対リスクに関わらずTGの管理目標値は150mg/dl未満、HDLコレステロールの管理目標値は40mg/dl以上である。

日本動脈硬化学会では高LDL－C血症の基準値を140mg/dl以上としているが、これはスクリーニング基準であり、薬物療法開始基準ではない。ガイドライン2012では特にカテゴリーⅠ（低リスク）の服薬開始基準がLDL－C 180 mg/dl以上であることが明記されており、安易な薬物治療は慎むべきである。管理目標値の達成のために最も重要なのは生活習慣の改善である。適正な体重（Body Mass Index ＜25kg/m^2）を維持するためにエネルギー摂取量の適正化をはかる。身体活動量や代謝異常の有無にもよるが、〔身長（m）〕^{2}×22×25～30kcalくらいが標準的なエネルギー摂取量である。栄養素のバランスは、エネルギー配分で炭水化物55－60％、蛋白質15－20％、脂質20－25％が標準である。脂質の摂取については、動物の脂肪に多く含まれる飽和脂肪酸の摂取を抑え、逆に魚油や植物油に多く含まれる多価不飽和脂肪酸の摂取を増やすと、体内でのコレステロールの合成の抑制につながる。塩分摂取を控えることは高血圧の管理や予防において

重要である。また野菜や果物を積極的に摂取すると、カリウム摂取量が増えて血圧が低下し、さらに食物繊維の摂取量が増えて食後血糖の急激な上昇を抑える。運動にはエネルギーの摂取量と消費量のバランスを改善させることによる減量効果やインスリン抵抗性の改善効果がある。

4．日本人の冠動脈疾患の絶対リスクはなぜ低いのか

日米の血清コレステロールの平均値の差が小さくなった昨今でも日本人の冠動脈疾患発症率は低い。従来、米国に比して日本人の冠動脈疾患が少ない理由として、両集団のコレステロールレベルの違いが指摘されていた。しかしながら現在の日米の総コレステロール（TC）の平均値に大きな差はない[8]。今から約30年前の1980年近辺では両集団のTCレベルは大きく異なり、40歳以上では30～40mg/dlの差があった。しかしながら米国集団のTCの低下と日本人集団のTCの上昇により、その差は少しずつ小さくなり、2000年頃には10mg/dlくらいまで減少し、特に40歳代や30歳代ではほとんど同じである。

それでも両集団の冠動脈疾患発症率（絶対リスク）に大きな差がある理由としては次の二つが考えられる。一つは、冠動脈疾患の好発年齢である現在60歳代以上の世代の青・壮年期のLDL－Cレベルは高くなく、高LDL－C血症に対する生涯曝露が大きくないという考え方である。もう一つは、何か日本人特有の防御要因があって冠動脈疾患の発症率を低く抑えているという考え方である。なお後者の理由としては生活環境要因と遺伝的要因の両方が考えられるが、それを明らかにするための手段として移民研究や日米比較研究が有用である。NI－HON－SAN研究で日本在住者と米国に移民した日本人の1965年の冠動脈性疾患と脳卒中の有病率を見ると、冠動脈疾患の有病率は、日本在住者、ハワイ日系人、カリフォルニア日系人とより米国化した集団ほど高くなり、脳卒中の有病率はこの逆であった[9]。この研究から遺伝子的にはほとんど変化がないにもかかわらず、居住地によって冠動脈疾患の発症率が大きく変わる可能性が示唆され、両集団の差をもたらしている生活環境要因を同定することが必要と考えられた。

5．ERA－JUMP研究

日米の血清TC値の比較で、特に若い世代では日米差がほとんどないことから、今後、この世代の冠動脈疾患が米国なみに高くなるかどうかが注目された。またこの世代だと高TC血症に対する生涯曝露も両集団で大きな差はないと考えられた。そこで40歳代男性を対象として潜在性動脈硬化所見の日米比較を行った疫学研究がEra Jump（Electron－Beam Tomography and Risk Assessment Among Japanese and US Men in the Post World War II Birth Cohort）研究である（日本側研究代表者：上島弘嗣，滋賀医科大学、米国ピッツバーグ研究代表者：Akira Sekikawa, University of Pittsburgh、米国ハワイ研究代表者：J David Curb, University of Hawaii）[10]。この研究では、当初は、日本人、米国白人各300人の40歳代男性を一般市民から無作為抽出し、冠動脈石灰化（電子ビームCTによる）と頸動脈の内膜中膜複合体（IMT）の厚さを比較した。研究で使用した電子ビームCTや超音波診断装置は日米で同じ機械が用いられ、所見の相互比較が可能なように標準化されている。また血液検査は主に米国側でまとめて測定された。その後、ハワイの日系人や韓国人の集団が加わり、現在は四集団の比較が行われている。

表1にEra－Jumpの冠動脈性疾患の古典的な危険因子の日米比較（滋賀県草津市在住の日本人とピッツバーグ市近郊の白人）の結果を示す。年齢には有意差はなく、予想された通りこの年代の日米のLDLコレステロール値はほぼ同じであった。収縮期血圧値も同レベルだが、日本人のほうがやや空腹時血糖値が高く、喫煙率は日本のほうがはるかに高い。これらの値は服薬者を考慮して

日本人は滋賀県住民、米国白人はペンシルバニア州ピッツバーグ市近郊住民

危険因子	日本人(N=281)	米国白人(N=306)	有意差
年齢(歳)	45	45	NS
LDLコレステロール(mg/dl)	134	135	NS
最大血圧(mmHg)	124	123	NS
空腹時血糖値(mg/dl)	106	101	P<0.05
喫煙率(%)	47	7	P<0.05

文献10から

表1　日米40歳代男性の古典的危険因子の比較

2002年～2006年に調査。日本人は滋賀県住民、米国白人はピッツバーグ近郊住民、日系米国人はハワイ在住の日系人

危険因子	日本人	日系人		米国白人	
	N=281	N=281	有意差 (vs. 日本人)	N=306	有意差 (vs. 日本人)
年齢(歳)	45	46	P<0.05	45	NS
LDLコレステロール(mg/dl)	134	122	P<0.05	135	NS
高脂血症治療中(%)	3	23	P<0.05	12	P<0.05
収縮期血圧(mmHg)	124	127	P<0.05	123	NS
高血圧治療中(%)	4	20	P<0.05	8	NS
空腹時血糖値(mg/dl)	106	112	P<0.05	101	P<0.05
糖尿病治療中(%)	1	6	P<0.05	1	NS
喫煙率(%)	47	13	P<0.05	7	P<0.05

文献10から

表2　40歳代男性の古典的危険因子の比較：ERA-JUMP研究

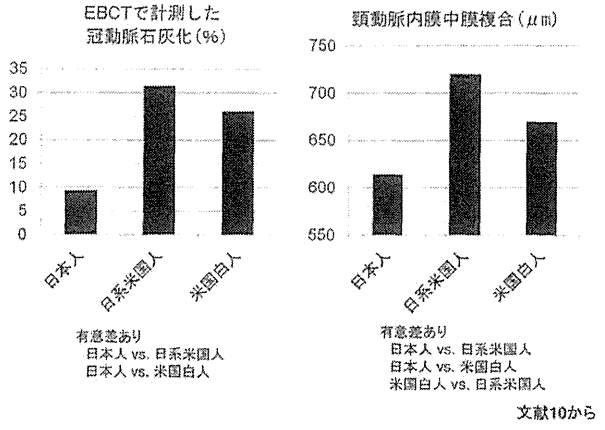
も日米差を認めなかった。要するに古典的な危険因子だけを見ると日本人のリスクプロフィールのほうが米国白人より動脈硬化を進行させやすい状態にあると考えられた。しかし両集団で動脈硬化所見を比較すると、LDL－Cレベルがまったく同じこの年代でも、日本人集団のほうが米国に比して動脈硬化所見が軽度であった。例えば冠動脈石灰化の有病率は日本人9.3％、米国白人26.1％、IMTの厚さは日本人614μm、米国白人670μmであり有意差があった。すなわち将来的に冠動脈性疾患を発症率が米国白人集団より高くなるとは考えにくかった。

表2はハワイの日系人集団も加えて日米の古典的危険因子を比較・再掲した結果である。ハワイ日系人の喫煙率は日本人に比べて米国白人に近いレベルにまで低くなっていたが、空腹時血糖値、収縮期血圧値はハワイの集団で高かった。またLDLコレステロールはハワイ日系人で最も低かったが、高脂血症治療中の割合は最も高く、実質的にこの三集団で大きな差はなかった。表3ではその他の危険因子と肥満度（Body Mass Index, BMI）を比較している。その結果、日本人と米国白人の比較で日本人のほうが“良い”と考えられた危険因子は、High Density Lipoprotein（HDL）コレステロール、BMI、高感度CRP、フィブリノーゲン、N－3系脂肪酸（魚介類由来）であり、日本人のほうがずっと痩身で、炎症反応や血栓形成性が低く、魚介類の摂取が多いと考えられた。一方、ハワイの日系人ではこれらの危険因子はほぼ米国白人と同じレベルであり、“日本人”

危険因子	日本人 (N= 281)	日系人 (N= 281)	有意差 (vs. 日本人)	米国白人 (N= 306)	有意差 (vs. 日本人)
HDLコレステロール (mg/dl)	53.3	47.5	P<0.05	47.5	P<0.05
トリグリセライド(mg/dl)	152	184	P<0.05	151	NS
BMI (kg/m²)	23.6	27.9	P<0.05	27.9	P<0.05
インスリン(μIU/ml)	10.2	15.2	P<0.05	15.3	P<0.05
HOMA-IR	2.67	4.19	P<0.05	3.82	P<0.05
高感度CRP(mg/L)	0.65	1.34	P<0.05	1.64	P<0.05
フィブリノーゲン(mg/dl)	254	318	P<0.05	291	P<0.05
血中脂肪酸濃度(mg/dl)	245	243	NS	237	NS
魚介類N-3系脂肪酸(%)	9.2	4.8	P<0.05	3.9	P<0.05

文献10から

表３　40歳代男性のその他の危険因子の比較：ERA-JUMP 研究



文献10から

図３　40歳代男性の潜在性動脈硬化所見の比較：ERA-JUMP 研究

としての危険因子上の優位性は消失していた。図３に示すように三集団の動脈硬化所見を比較すると、日系米国人の動脈硬化所見の進行度は米国白人と同等以上であり、日本人とは大きな差を認めた。

本研究からは日本と米国の冠動脈疾患の絶対リスクの差の規定要因として、肥満関連指標と魚介類由来のN－3系脂肪酸の摂取が大きく関与している可能性が示唆された。したがって、体型を痩身に保つことと、魚を多く食べる食生活を続けることが日本人の冠動脈疾患の絶対リスクを低く抑えるために重要と考えられた。

6．ACC/AHAガイドラインにおける絶対リスク評価の考え方

日本でガイドライン2012が発表された翌年の2013年に、米国ではACC/AHAの新しいガイドラインが公表された。そして個人の絶対リスクはNew Pooled Cohort ASCVD Risk equations（以下、Pooled Risk equations）で評価されることになった[11]。このガイドラインの治療方針はスタチン治療の適否を軸に構築されている。そしてスタチンの有効性と安全性から、治療が有益と判断される対象として、（1）二次予防、（2）LDL－Cが190mg/dl以上、（3）LDL－Cが70－189mg/dlの糖尿病患者（40－75歳）、（4）LDL－Cが70－189mg/dl、40－75歳で10年間の動脈硬化性疾患の絶対リスクが7.5％以上の者、の４つが定義されている。このうち（1）～（3）は現行の日本のガイドラインから見ても、管理目標値がないことは別として、少なくとも服薬治療の対象とすることに特に異論はないと思われる。ここで

どのような人が治療対象になっているのか最もわかりにくいのは（4）ということになり、「絶対リスク7.5％以上」はこのPooled Risk equationsで算出される。この計算ツールはダウンロード等で容易に入手できるが、これをアジア人に用いると絶対リスクを過剰評価する危険性があることがこのガイドラインにも明記されている。

また今回のPooled Risk equationsでは冠動脈疾患だけでなく脳卒中もエンドポイントに入っている点が日本人への適用をさらにややこしくしている。日本人の脳卒中リスクは欧米よりも高いため、これをエンドポイントに加えると絶対リスクは高くなる。ところが日本人では高コレステロール血症と脳卒中・脳梗塞の関連は弱く、これは主に脳梗塞の病型の違い（日本人ではアテローム血栓性梗塞が少ない）が関与している。そして冠動脈疾患が少ないため、日本人で冠動脈疾患と脳卒中を一つのエンドポイントにすると高コレステロール血症のリスクがほとんど描出されなくなる。一見、脳・心血管疾患を合わせて見るという考え方は合理的であるが、わが国で冠動脈疾患発症率があまり増加していない理由の一つとして、以前から積極的に脂質管理を推進してきたことも関与している。そのため冠動脈疾患発症率が低いという日本人の長所を維持するためには、今後もむしろ冠動脈疾患にターゲットを絞った脂質管理指針のほうが適切かもしれない。いずれにせよ日本人の絶対リスクは日本人集団で評価すべきであり、「借り物」の式を使うのは望ましくない。

7．おわりに

最初に述べたように動脈硬化性疾患の予防の基本は危険因子の適切な管理である。個人が複数の危険因子を併せ持つことは珍しいことではないため、絶対リスクを総合的に判断して治療指針を決めることが重要となる。ガイドライン2012は、現時点の日本人の最良のエビデンスから構築されており、わが国の動脈硬化性疾患の実態に合致している。しかしながらよりきめ細かい予防介入を行うためには、更に大規模なコホート集団に基づいた絶対リスク評価が必要であり、今後も日本人集団における疫学研究、臨床研究によるエビデンスの蓄積が必要とされている。

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Original Article

Risk of Hypercholesterolemia in Patients with Cardiovascular Disease and the Population Attributable Fraction in a 24-year Japanese Cohort Study

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***Aims*: The population-attributable fraction (PAF) is an indicator of the disease burden. In Western countries, the PAF of hypercholesterolemia in cardiovascular disease (CVD) is the highest among that for traditional risk factors; however, data for Asian populations are limited.**

***Methods*: A 24-year cohort study was conducted among 9,209 randomly selected patients who were not taking statins. We estimated the hazard ratio (HR) after adjusting for covariates and PAF associated with the serum total cholesterol (TC) levels in relation to CVD mortality.**

***Results*: The TC level was found to be positively associated with an increased risk of CVD, coronary heart disease (CHD) and cardiac death (CHD plus heart failure), with an HR of 1.08 (95% confidence interval [CI]: 1.00-1.16), 1.33 (95% CI: 1.14-1.55) and 1.21 (95% CI: 1.08-1.35) for a 1-SD increment in the serum TC level, respectively. Similar positive associations between the TC level and both CHD and cardiac death were observed after classifying the patients by age and sex. Furthermore, the highest serum TC level (≥6.72 mmol/L) was positively associated with CVD death, with an HR of 1.76 (95% CI: 1.25-2.47), as well as both CHD death and cardiac death. In contrast, no significant relationships were observed between the serum TC level and stroke. Meanwhile, the PAF for CVD, CHD, and cardiac deaths due to hypercholesterolemia (serum TC level ≥5.69 mmol/L, defined by the Japan Atherosclerosis Society) was 1.7%, 10.6% and 5.6%, respectively.**

***Conclusions*: The estimated PAF of CVD death due to hypercholesterolemia is moderately high, but lower than that for other risk factors, such as hypertension.**

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Key words: Total cholesterol, Cardiovascular disease, Population-attributable fraction, Cohort study, NIPPON DATA80

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Introduction

Cardiovascular diseases (CVDs), such as coronary heart disease (CHD), are common causes of death in developed countries, including Japan[1], and a high serum total cholesterol (TC) level is an established risk factor for CVD. The population attributable fraction (PAF) is the proportional reduction in mortality that would occur if the exposure to a risk factor were to be reduced to an alternative ideal level, a parameter that can be used in the management of CVD patients. In studies from Western countries, the PAF of CVD mortality due to hypercholesterolemia is highest among that for traditional risk factors[2-4]; however, evidence of this relationship in Asian countries, including Japan, in which the CHD incidence is low, is scarce[5]. Specifically, the effects of a high serum TC level on the health of the general Japanese population in the context of disease burden is unknown.

Several Japanese studies have estimated the PAF of CVD death based on established CVD risk factors[6, 7], such as smoking and hypertension. However, to the best of our knowledge, no observational studies with a long-term follow-up period of >20 years estimating the PAF for CVD death due to hypercholesterolemia have been conducted in Japan or other Asian countries. We previously reported the relationship between TC and CVD based on the findings of the National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1980 (NIPPON DATA80), trial, with follow-up examinations conducted at 14 and 19 years after study initiation (until 1994 and 1999, respectively)[8, 9]. However, we did not calculate the PAF of CVD caused by hypercholesterolemia.

Therefore, in the current study, we investigated the relationship between the serum TC level and mortality due to CVD in the NIPPON DATA80 cohort with a longer follow-up period than that used in the former study[8, 9] and estimated the PAF of death due to CVD attributable to a high serum TC level.

Methods

Population

The subjects in this cohort were also participants of the National Survey on Circulation Disorders 1980. A total of 10,546 residents ≥30 years of age from 300 randomly selected areas in Japan participated in the follow-up study, the NIPPON DATA80, for a participation rate of 76.6% (10,546/13,771). The details of the NIPPON DATA80 study have been previously reported[9-15]. The subjects were followed up until 2004.

Of the 10,546 participants, a total of 1,337 were excluded for the following reasons: a history of CHD or stroke (n=280), missing information (n=186) and the absence of a permanent address, which was needed to link the patient to their vital statistical records (n=871). We analyzed the remaining 9,209 participants (4,029 men and 5,180 women). The data collected from these participants were not influenced by the effects of statins, as these drugs were not available at the time of the survey. There were no significant differences in the mean serum TC level between the participants included in this study and those who did not provide their address.

Endpoint Determination

As previously reported[9-15], we confirmed which participants died in each area using computer matching of the area, sex, date of birth and death of the subject with data obtained from the National Vital Statistics database. Information regarding the cause of death, which was coded according to the Ninth International Classification of Death (ICD-9) until the end of 1994 and the Tenth International Classification of Disease (ICD-10) from 1995 onward, was also obtained from the National Vital Statistics database. ICD-coding was carried out by specialists at the Ministry of Health and Welfare who were independent of the NIPPON DATA research group. The details of classification are described elsewhere[9-11]. We defined all deaths due to CVD (ICD-9: 393-459/ICD-10: I00 to I99), CHD (ICD-9: 410-414/ICD-10: I20 to I25), stroke (ICD-9: 430-438/ICD-10: I60 to I69) or cerebral infarction (ICD-9:433, 434 and 437.8a-8b/ICD-10:I63 and I69.3) as the primary endpoint. Furthermore, in the present study, we defined "cardiac death" as death due to CHD or heart failure (HF, ICD-9: 428/ICD-10: I50) and treated HF as a cause of death among CHD survivors because HF is the final outcome of CHD. The use of the National Vital Statistics data was permitted by the Management and Coordination Agency, Japan. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (Nos. 12-18, 2000).

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Table 1. Patient characteristics recorded during the baseline survey in 1980, NIPPON DATA80

	Baseline serum total cholesterol level (mmol/L)							
	<4.14	4.14-4.65	4.66-5.17	5.18-5.68	5.69-6.20	6.21-6.71	6.72-	*p*-values*
Women								
No. of paticipants	951	1183	1142	925	527	275	177	
Age (years, mean ± SD)	44.7 ± 12.9	47.3 ± 13.0	50.6 ± 12.8	53.1 ± 12.9	54.8 ± 12.0	56.3 ± 11.5	57.0 ± 11.7	<0.001
Albumin (g/dL, mean ± SD)	4.3 ± 0.2	4.3 ± 0.2	4.4 ± 0.3	4.4 ± 0.2	4.4 ± 0.2	4.4 ± 0.3	4.4 ± 0.2	<0.001
BMI (kg/m^2, mean ± SD)	22.1 ± 3.1	22.4 ± 3.2	22.8 ± 3.4	23.3 ± 3.5	23.6 ± 3.4	23.8 ± 3.3	24.3 ± 4.0	<0.001
Hypertension (%)	29.0%	35.2%	41.2%	50.7%	59.2%	60.7%	61.6%	<0.001
Diabetes (%)	1.1%	2.0%	1.8%	4.1%	2.8%	6.5%	5.1%	<0.001
Current smoker (%)	7.9%	7.9%	10.1%	9.2%	11.0%	5.5%	9.0%	0.07
Heavy smoker (%) (>20 cigaretts/day)	0.7%	0.3%	0.8%	0.6%	1.5%	0.7%	0.6%	0.29
Daily drinker (%)	3.2%	2.6%	3.0%	2.7%	3.2%	1.8%	2.8%	0.92
Men								
No.of paticipants	848	999	936	648	354	167	77	
Age (years, mean ± SD)	51.0 ± 14.0	50.0 ± 13.4	49.3 ± 13.1	48.8 ± 12.6	48.9 ± 11.8	50.2 ± 12.2	49.5 ± 10.9	0.04
Albumin (g/dL, mean ± SD)	4.3 ± 0.3	4.4 ± 0.3	4.4 ± 0.3	4.5 ± 0.3	4.5 ± 0.3	4.6 ± 0.3	4.6 ± 0.3	<0.001
BMI (kg/m^2, mean ± SD)	21.6 ± 2.7	22.0 ± 2.8	22.6 ± 2.8	23.2 ± 2.9	23.5 ± 2.7	23.9 ± 2.8	24.2 ± 2.5	<0.001
Hypertension (%)	47.2%	47.5%	52.6%	53.1%	58.5%	58.7%	87.0%	<0.001
Diabetes (%)	3.7%	3.8%	5.4%	6.2%	7.6%	7.8%	10.4%	<0.01
Current smoker (%)	66.9%	66.4%	63.9%	56.3%	59.3%	57.5%	54.5%	<0.001
Heavy smoker (%) (>20 cigaretts/day)	21.1%	24.6%	25.0%	23.3%	30.5%	29.3%	28.6%	0.02
Daily drinker (%)	46.5%	49.4%	48.9%	49.4%	48.3%	36.5%	50.6%	0.02

SD: standard deviation
*Analysis of variance for continuous variables, chi-square test for categorical variables

Baseline Examinations

The baseline surveys were conducted at public health centers using criteria from a standardized manual. Non-fasting blood samples were drawn and centrifuged within 60 minutes of collection and stored at −70℃ until the analyses. As previously reported, the serum TC and albumin levels were analyzed at a single central laboratory (present name: Osaka Medical Center for Health Science and Promotion) using an auto-analyzer (SMA12/60; Technicon, Tarrytown, USA). Since April 1975, the precision and accuracy of the cholesterol measurements obtained in this laboratory have been certified by the CDC-NHLBI Lipid Standardization Program of the Center for Diseases Control and Prevention[16]. Trained research nurses measured the blood pressure of the seated subject using a standard mercury sphygmomanometer on the right arm after five minutes of rest. Hypertension was defined as a systolic blood pressure of ≥140 mmHg, diastolic blood pressure of ≥90 mmHg, use of antihypertensive drugs, history of hypertension or any combination of these findings. The serum glucose level was measured using the cupric-neocuproine method. Since the serum glucose level is more commonly measured using the hexokinase method, this parameter was adjusted using the following formula: [0.047× (glucose concentration in mg/dL) − 0.541][17]. Diabetes was defined as a non-fasting serum glucose level of ≥11.1 mmol/L, history of diabetes or both. Height in stocking feet and weight in light clothing were measured. Questionnaires responses regarding smoking and drinking habits and medical history were analyzed by public health nurses.

Statistical Analysis

The serum TC levels were categorized into the following seven categories: <4.14, 4.14-4.65, 4.66-5.16, 5.17-5.68, 5.69-6.20, 6.21-6.71 and ≥6.72 mmol/L. The participants with a serum TC level of 4.14-4.65 mmol/L formed the reference group. These categories were determined based on the results of our previous study, which provided key evidence for the guidelines for the diagnosis and prevention of atherosclerosis and CVD in the Japanese population issued by the Japan Atherosclerosis Society (JAS)[8]. Cox proportional hazard models were used to estimate the relative risk as the hazard ratio (HR) for death due to CVD according to one standard deviation (SD), i.e., a

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Table 2. Number of deaths and multivariable-adjusted HRs for CVD, CHD, cardiac death, stroke and cerebral infarction during the 24-year follow-up period

	1SD increment of serum TC (per 0.87 mmol/L increment)	Category of baseline serum TC level (mmol/L)						
		<4.14	4.14-4.65	4.66-5.17	5.18-5.68	5.69-6.20	6.21-6.71	6.72-
No of Persons	9209	1799	2182	2078	1573	881	442	254
Person-Years	193021.5	37099.5	46260.5	43685.5	33025.5	18612.5	9199	5139
CVD								
No deaths	884	152	189	181	169	101	48	44
HR	1.08	1.04	1.00	1.03	1.15	1.06	1.00	1.76
95%CI	1.00-1.16	0.84-1.30	-	0.84-1.26	0.93-1.43	0.83-1.36	0.73-1.39	1.25-2.47
CHD								
No deaths	172	23	34	28	36	24	11	16
HR	1.33	0.87	1.00	0.89	1.42	1.39	1.25	3.52
95%CI	1.14-1.55	0.51-1.48	-	0.54-1.47	0.87-2.31	0.81-2.39	0.62-2.51	1.89-6.57
Cardiac Death								
No deaths	348	52	69	72	68	42	22	23
HR	1.21	0.99	1.00	1.16	1.35	1.25	1.33	2.68
95%CI	1.08-1.35	0.68-1.42	-	0.83-1.62	0.95-1.91	0.84-1.86	0.81-2.17	1.64-4.38
Stroke								
No deaths	411	72	94	81	82	48	18	16
HR	1.01	0.99	1.00	0.90	1.08	1.00	0.74	1.25
95%CI	0.90-1.12	0.72-1.34	-	0.67-1.22	0.79-1.47	0.70-1.43	0.44-1.24	0.73-2.15
Cerebral infarction								
No deaths	241	40	59	45	48	35	8	6
HR	1.02	0.83	1.00	0.84	1.03	1.20	0.55	0.81
95%CI	0.89-1.18	0.55-1.25	-	0.57-1.25	0.69-1.54	0.77-1.85	0.26-1.16	0.35-1.92

SD: standard deviation, HR: hazard ratio, 95% CI: 95% confidence interval, CVD: cardiovascular disease, CHD: coronary heart disease, HF: heart failure
The HRs were adjusted according to age, sex, the serum albumin level, body mass index, hypertension, diabetes, smoking status and drinking status.

0.87 mmol/L increment in the baseline serum TC level. We evaluated the HRs for total CVD, CHD, cardiac death, stroke and cerebral infarction. In the Cox regression model, age, serum albumin, body mass index (BMI), hypertension, diabetes, smoking status (never-smoker as the reference, ex-smoker, current smoker ≤20 and smoker ≥20 cigarettes/day) and drinking status (never-drinker as the reference, ex-drinker, occasional drinker and daily drinker) were adjusted. We also estimated the HRs according to a Cox model assessing the serum TC level with reference to the seven categories described above. Violation of the proportional hazard assumption was determined using Schoenfeld residuals. Tests for interactions between sex, age (<65 or ≥65 years), hypertension, current smoking and BMI (<25 or ≥25 kg/m^2) were conducted with an interaction term generated by multiplying the continuous serum TC level by the cardiovascular risk factors described above. Tests for interactions were performed for death due to CVD, CHD and cardiac death. In addition, multivariable HRs were calculated following the classification of the subjects into the following groups: age (<65 or ≥65 years), sex, hypertension, current smoking and BMI (<25 or ≥25 kg/m^2).

The PAFs of CVD, CHD and cardiac death were calculated using the formula below[18]:

[Proportion of cases exposed to risk factor × (Adjusted HR-1)/Adjusted HR].

The PAFs for the TC categories ≥5.69 mmol/L (according to the definition of "hypercholesterolemia" provided by the JAS)[19] and ≥6.21 mmol/L (according to the definition provided by the adult treatment panel III by the National Cholesterol Education Program, United States: ATP III) were estimated as the excess death fractions due to a high TC level. We recalculated the adjusted HR for each hypercholesterolemia case in order to estimate the PAFs.

All statistical analyses were performed using the

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Table 3. The multivariable-adjusted HRs for CVD, CHD and cardiac death, classified according to age and sex, over the 24-year follow-up period

A. Age

Age <65 years old	No of Persons	Person-years	CVD			CHD			Cardiac Death		
			No deaths	HR	95%CI	No deaths	HR	95%CI	No deaths	HR	95%CI
1SD increment of serum total cholesterol	7713	172219	363	1.09	0.98-1.22	83	1.29	1.04-1.61	132	1.22	1.03-1.46
Category of baseline serum total cholesterol level (mmol/L)											
<4.14	1527	33848	60	1.04	0.75-1.46	12	1.05	0.49-2.23	19	1.04	0.57-1.88
4.14-4.65	1856	41724	79	1.00		16	1.00		26	1.00	
4.66-5.17	1751	39145	65	0.79	0.57-1.10	10	0.60	0.27-1.33	22	0.82	0.46-1.45
5.18-5.68	1302	29144	73	1.20	0.86-1.66	18	1.36	0.68-2.73	26	1.28	0.73-2.25
5.69-6.20	724	16092	48	1.21	0.83-1.75	14	1.54	0.73-3.23	22	1.60	0.89-2.88
6.21-6.71	353	7897	19	0.88	0.52-1.47	5	0.99	0.35-2.79	8	1.06	0.47-2.42
6.72-	200	4369	19	1.63	0.97-2.74	8	3.00	1.23-7.35	9	2.22	1.01-4.89
Age >=65 years old	No of Persons	Person-years	CVD			CHD			Cardiac Death		
			No deaths	HR	95%CI	No deaths	HR	95%CI	No deaths	HR	95%CI
1SD increment of serum total cholesterol	1496	20803	521	1.06	0.96-1.16	89	1.32	1.05-1.65	216	1.17	1.01-1.36
Category of baseline serum total cholesterol level (mmol/L)											
<4.14	272	3252	92	1.13	0.85-1.50	11	0.80	0.37-1.74	33	1.03	0.65-1.65
4.14-4.65	326	4537	110	1.00		18	1.00		43	1.00	
4.66-5.17	327	4541	116	1.25	0.95-1.63	18	1.22	0.63-2.38	50	1.41	0.93-2.14
5.18-5.68	271	3882	96	1.15	0.87-1.54	18	1.46	0.73-2.93	42	1.38	0.88-2.16
5.69-6.20	157	2521	53	0.98	0.70-1.37	10	1.15	0.52-2.55	20	0.98	0.57-1.70
6.21-6.71	89	1302	29	1.16	0.76-1.77	6	1.63	0.63-4.25	14	1.61	0.86-2.99
6.72-	54	770	25	1.92	1.23-3.02	8	3.93	1.62-9.52	14	2.96	1.58-5.57

R version 2.15 software program (R Foundation for Statistical Computing, Vienna, Austria). All confidence intervals (CIs) were estimated at the 95% level, and statistical significance was defined as a p value of <0.05.

Results

The means and prevalence of the baseline characteristics of all subjects in each TC category based on sex are summarized in **Table 1**. The mean serum TC level was 4.88±0.87 mmol/L overall (mean±SD), 4.93±0.88 mmol/L in women and 4.81±0.85 mmol/L in men. The mean age of the subjects in this study was 50.0±13.2 years overall, 50.1±13.3 years in women and 49.7±13.1 years in men. Age, the serum albumin level, BMI and the prevalence of hypertension and diabetes were statistically different in each TC category for both sexes, whereas the proportion of current smokers and drinkers was significantly different among the TC categories only in men.

The total person-years were 193,022 years and the mean follow-up period was 21.0±5.8 years (mean±SD). During the follow-up period, there were 2,566 total deaths (1,365 men and 1,201 women), with 884 deaths due to CVD (34%), including 172 deaths due to CHD (7%), 176 deaths due to heart failure (7%) and 411 deaths due to stroke (16%). The deaths due to stroke also included 241 cerebral infarction-related deaths (9%).

The number of deaths, person-years and multivariable adjusted HRs for the CVD-related deaths according to a 1-SD increment in the serum TC level and the seven TC level categories in all subjects are summarized in **Table 2**. Consequently, a 1-SD increment in the serum TC level was found to be positively associated with an increased risk of CVD death (HR: 1.08, 95% CI: 1.00-1.16). The positive relationships between a 1-SD increment in the serum TC level and an increased risk of CHD death and cardiac death

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(Cont Table 3)

B. Sex

Women	No of Persons	Person-years	CVD			CHD			Cardiac Death		
			No deaths	HR	95%CI	No deaths	HR	95%CI	No deaths	HR	95%CI
1SD increment of serum total cholesterol	5180	111018	449	1.06	0.96-1.17	86	1.23	0.99-1.53	187	1.18	1.02-1.37
Category of baseline serum total cholesterol level (mmol/L)											
<4.14	951	20689	56	1.24	0.88-1.75	10	1.05	0.47-2.35	22	1.27	0.73-2.20
4.14-4.65	1183	25878	81	1.00		16	1.00		32	1.00	
4.66-5.17	1142	24431	88	0.94	0.70-1.28	12	0.67	0.32-1.44	35	1.00	0.62-1.62
5.18-5.68	925	19585	100	1.05	0.78-1.41	21	1.19	0.61-2.31	42	1.20	0.75-1.93
5.69-6.20	527	11164	63	1.03	0.74-1.45	12	1.05	0.49-2.25	26	1.20	0.71-2.03
6.21-6.71	275	5752	28	0.92	0.59-1.43	3	0.51	0.15-1.79	12	1.15	0.58-2.27
6.72-	177	3521	33	1.76	1.16-2.67	12	3.48	1.60-7.58	18	2.79	1.54-5.06
Men	**No of Persons**	**Person-years**	**CVD**			**CHD**			**Cardiac Death**		
			No deaths	HR	95%CI	No deaths	HR	95%CI	No deaths	HR	95%CI
1SD increment of serum total cholesterol	4029	82004	435	1.08	0.97-1.20	86	1.37	1.11-1.71	161	1.19	1.01-1.40
Category of baseline serum total cholesterol level (mmol/L)											
<4.14	848	16411	96	1.02	0.77-1.35	13	0.91	0.44-1.87	30	0.97	0.59-1.58
4.14-4.65	999	20383	108	1.00		18	1.00		37	1.00	
4.66-5.17	936	19255	93	1.10	0.83-1.46	16	1.07	0.54-2.11	37	1.28	0.81-2.03
5.18-5.68	648	13441	69	1.32	0.97-1.81	15	1.63	0.80-3.32	26	1.52	0.91-2.56
5.69-6.20	354	7449	38	1.09	0.74-1.59	12	1.73	0.81-3.67	16	1.25	0.69-2.29
6.21-6.71	167	3447	20	1.16	0.72-1.89	8	2.41	1.02-5.69	10	1.71	0.84-3.50
6.72-	77	1619	11	1.65	0.88-3.11	4	2.83	0.92-8.71	5	2.14	0.82-5.57

SD: standard deviation, HR: hazard ratio, 95% CI: 95% confidence interval, CVD: cardiovascular disease, CHD: coronary heart disease, HF: heart failure
The HRs were adjusted based on the following factors:
A. age, sex, the serum albumin level, body mass index, hypertension, diabetes, smoking status and drinking status
B. age, the serum albumin level, body mass index, hypertension, diabetes, smoking status and drinking status

were also noted. The HRs for CHD and cardiac death were 1.33 (95% CI: 1.14-1.55) and 1.21 (95% CI: 1.08-1.35), respectively. Alternatively, deaths due to stroke and cerebral infarction were not associated with a 1-SD increment in the serum TC level. In the analyses of the seven TC level categories, we found a positive association between the highest TC level category and an increased risk of CVD death (HR: 1.76, 95% CI: 1.25-2.47). An increased risk of CHD death and cardiac death was also observed in the highest TC level category. The HR was 3.52 (95% CI: 1.89-6.57) for CHD death and 2.68 (95% CI: 1.64-4.38) for cardiac death. Meanwhile, death due to stroke and/or cerebral infarction was not associated with any TC level category. There were no significant violations of the proportional hazard assumption in these models.

The results obtained after classifying the subjects by age and sex are summarized in **Table 3**. The relationship between a 1-SD increment in the serum TC level and death due to CHD and/or cardiac death was very similar to that observed in the overall analysis. Specifically, we showed that a 1-SD increment in the serum TC level was positively associated with cardiac death in both age categories (<65 or ≥65 years) and sexes (women and men). There were no interactions with age or sex in the associations between the TC level and each endpoint, i.e., CVD, CHD and cardiac death. In **Table 4**, we present the multivariable HRs obtained after stratifying the patients by other risk factors, including hypertension, smoking and BMI. The results of these analyses were similar to those of the over analysis and the analyses performed following classification based on age or sex. There were no interactions with hypertension or BMI in the associations