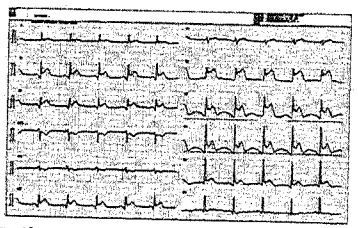
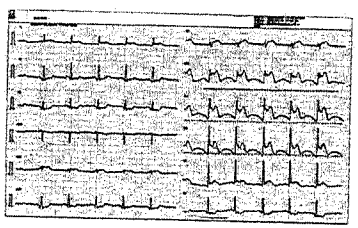
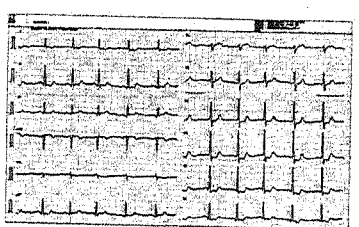
subtotal stenosis were seen in segment 6 and 13, we performed PCI successfully.
We are able to diagnose acute myocardial infarction during the transfer and useful for preparation for acceptance.
Only 12-lead ECG detects the precardial leads' ST elevation and its change.
At the arrival, ST returned to the baseline: it would have been difficult to diagnose ST-elevation acute coronary syndrome with high-risk by only seeing the last ECG. After admission without prehospital continuous 12-lead ECG, this patient will be stratified into no ST change with low-risk and without emergency coronary angiography. These observations will show the new concept for the risk stratification for ACS, because standard stratification is performed using ECG changes in emergency department or after admission.
Thus, the continuous 12-lead ECG transmission using the mobile telemedicine is useful for the management of acute coronary syndrome in the emergency system.
AHA/ACC guidelines recommend routine use of 12-lead ECG and advance notification for patients with acute coronary syndrome [6].



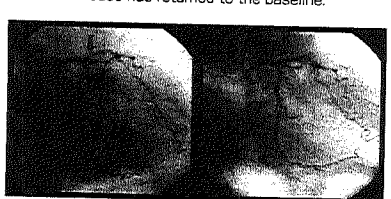
【Fig.3】 Three minutes later, the ST segment of the II III aVF leads has re-elevated.



【Fig.4】 Four minutes later, the ST segment of the II III aVF leads has returned once more to the baseline.



【Fig.5】 Seven minutes later, the ST segment of the precardial leads has returned to the baseline.



【Fig.6】 Emergency coronary angiography was performed (left). As thrombus and severe stenosis were seen in segment 6 and 13 (arrows), we performed intervention using coronary stenting to those sites (right).

4. Conclusion

This may be the first report of live-ECGs showing varying ST changes transmitted from a moving ambulance. Mobile doctor car and helicopter will surely play a significant role as virtual-doctor mobile in future.

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REVIEW

Cardiovascular clinical trials in Japan and controversies regarding prospective randomized open-label blinded end-point design

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Recently, results of several cardiovascular clinical trials conducted in Japan were published. Most of them were designed as prospective randomized open-label blinded end-point (PROBE)-type trials, in which patients were randomly allocated to different regimens and both the patients and doctors are aware of the regimen being administered. Although the PROBE design enables performing trials resembling real-world practices, entails low costs and renders patient recruitment easier, it presents several conditions that have to be satisfied to acquire accurate results, due to its open-label nature. Principally, the so-called hard end points, which are judged by objective criteria, should be used as primary end points in order to prevent biases. In this article, a general description of various designs of clinical studies is provided, followed by a description of the PROBE design, and the precautions to be taken while conducting PROBE-designed trials by comparing trials conducted in Japan and the West.
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Keywords: clinical trials; PROBE design; hard end point; soft end point

INTRODUCTION

Evidence-based medicine is thought to be extremely important in contemporary medicine.[1] However, until recently, actual evidence with Japanese subjects has not been sufficiently produced. It is known that despite the westernized lifestyle of the Japanese population, the incidence rate of myocardial infarction remains relatively low.[2] Thus, generation of scientific evidence based on data from Japanese patients is warranted. However, owing the fact that the Japanese healthcare system covers the entire population in principle, and that people have free access to almost any kind of medical institution,[3] it has been rather difficult to recruit patients into clinical trials, especially into randomized, double-blind studies, in which the patients and doctors are required to be unaware of what medicines are being administered. This is the reason why many recent clinical trials conducted in Japan adopted the prospective randomized open-label blinded end-point evaluation (PROBE) design,[4] in which both the patient and the doctor are aware of what medicines are being administered. However, if not designed carefully, the accuracy of the PROBE-style study results can be compromised. In this review, we would first like to discuss the designs used in various studies and then describe the design of PROBE; thereafter, we would like to provide referral to the merits and demerits of the PROBE design trials, accompanied by recent examples.

STUDY DESIGNS USED IN EPIDEMIOLOGICAL STUDIES

Epidemiology is the study of factors affecting the health and illness of a certain population. It does not usually encompass the assessment of the efficacy of drugs or medical devices. However, the principal concepts and methodology used in clinical trials have been generated in epidemiology, and understanding them is important.

Retrospective cohort studies

In retrospective cohort studies, a population set (cohort) is defined and the risks and outcomes are investigated retrospectively. This design of epidemiological studies can be adopted when there is already a database of risks and outcomes of sufficient size. With the recent evolution of information technology, patients' demographic data, laboratory data, prescription data, and morbidity and mortality data are sometimes available over the course of several years. For example, to elucidate the relationship between chronic kidney disease and mortality, a study was conducted by referring to a registry database of coronary revascularization and valve procedures, which revealed that patients having moderate to severe acute kidney injury after CABG surgery showed worse 5-year survival compared with those who having normal or near-normal renal function.[5] However, not all confounding factors might be stored in the database, which limits the use of the results of such a study. If a promising result is obtained, it should be confirmed by performing a prospective randomized control study.

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Retrospective case–control studies

In the case of rare diseases, standard cohort studies will entail long time periods and high costs for identifying the cause, because of the low incidence rates of the diseases. To overcome this challenge, a case–control study might be useful, in which individuals with the disease (case) are compared with those without the disease (control) and are matched with several demographic factors such as age, sex and place of dwelling. The study will retrospectively investigate the exposure to risks in both groups to identify the cause of the disease.

Prospective cohort studies

In this study design, patient background information is collected at the start of the study or when a subject is newly recruited into the cohort and followed up by collecting information on risk exposures and incidence of morbidity and mortality; thereby, the relationships between the presumptive risk factors and disease are investigated. This type of study (for example, the Framingham study[6,7]) has established cardiovascular risk factors such as hypertension, hyperlipidemia resulting from smoking, age and diabetes mellitus. Although it is the most scientifically accurate design, it is laborious and usually involves extremely high costs.

STUDY DESIGNS USED IN CLINICAL TRIALS

In the past, single-blind prospective trials were conducted. However, due to its limited advantage over open prospective trials, currently this type of trial is conducted rarely.

Double-blind, prospective, placebo-controlled trials

Double-blind, prospective, placebo-controlled trials were the standard type of clinical trials that were considered to provide the most reliable results. Numerous trials have been conducted based on this design; such studies showed the value of antihypertensive therapy[8,9] or the efficacy of statins in the primary or secondary prevention of coronary heart diseases.[10,11] One of the major flaws of this design is that, once the efficacy of a treatment is established, it becomes unethical to conduct a placebo-controlled study; another flaw is that it is relatively difficult to recruit patients into this type of trial. Further, it is also difficult to use this type of trials in the assessment of interventional therapies such as comparison of coronary stents or pacemakers.

Double-blind, prospective trials without placebo control

This design allows the evaluation of a new mode of treatment against an established one. Numerous studies have established the efficacy of treating hypertension[8,9] and hypercholesterolemia[10,11] in the management of cardiovascular diseases, the benefits of employing β-blockers[12–15] or angiotensin-converting enzyme inhibitors[16,17] in the management of congestive heart failure, and so on. Thus, as stated above, it is unethical to avoid using these agents under conditions in which they are proven to be effective; in such cases, this trial design is used. The disadvantage of this design is that, because an already proven treatment is used, the difference between the new one and the established one might be marginal; this usually leads to the requirement of a larger number of patients and longer duration of studies.

PROBE DESIGN

The PROBE study was designated by Dr Hansson in 1992 as an alternative to the double-blind, prospective study design.[4] In this type of study, patients are allocated to different treatment regimens in a strictly random fashion. Unlike double-blind studies, the regimens are made obvious to both physicians and patients. An important aspect is that strictly defined end points are adjudicated by an independent committee that is unaware of the treatment allocation, which guarantees the unbiased comparison of therapies and evaluation of study results.

Table 1 Advantages and disadvantages of the PROBE design compared with double-blinded design

	Double-blinded studies	*PROBE studies*
Randomization	+	+
Cost	−	+
Investigator bias	+	−
Patient compliance	−	+
Reliability of end point evaluation	+	+
Similarity to clinical practice	−	+

The + sign denotes that the design has the property, the minus sign denotes that the design lacks the property.
Modified from Blood Press, 1992; 1: 113–119.

Other conditions that require a PROBE design study include cases in which the drug warfarin is administered.[18–20] Warfarin requires strict titration, and thus cannot be used in a double-blind study. Studies that involve the use of interventional devices are also usually designed in an open-label fashion.

As shown in Table 1, the merits of the PROBE design include better patient acceptance, lower cost, and the existence of similarities between PROBE studies and regular clinical practice.

PRECAUTIONS TO BE TAKEN WITH THE PROBE DESIGN

As described in the Introduction, in Japan, it is generally difficult to conduct a randomized, controlled, double-blind study in which both the doctors and patients are unaware of the medicines being administered. Therefore, realistically, large clinical trials have to be conducted in a PROBE fashion in Japan. If PROBE studies are designed and conducted properly, the results will not be biased. One of the ways to ensure accuracy is to use only 'hard end points' in primary end-point assays. Hard end points are end points that can be defined solely by objective criteria; sudden death of any cause, non-fatal myocardial infarction and non-fatal stroke are examples of hard end points. Soft end points, on the other hand, are end points that may be affected by subjective judgements, such as hospitalization due to unstable angina, congestive heart failure or coronary revascularization procedures. These end points might be defined by objective criteria, but if the attending physician deems the patient requires hospitalization or can be medically controlled in an outpatient setting is, for example, at the discretion of the physician. As shown in Table 2, most cardiovascular clinical trials with PROBE designs conducted in the West[18,19,21–33] use only hard end points. In contrast, four major Japanese PROBE-designed trials with clinical outcomes specified as primary end points used soft end points such as unstable angina, exacerbation of heart failure or coronary revascularization procedures.[34–37] One of the reasons might be that the Japanese tend to have lower incidence rates of cardiovascular diseases compared with the westerners[2] and thus, soft end points are required to produce statistically significant differences with a reasonable cohort size. If these end points are reported and adjudicated in an unbiased fashion, the reliability of the results will be the same as those acquired from double-blind studies. In this context, the results of the JIKEI-Heart Study[35] interested the Japanese Medical Society. One reason was that it was one of the few large clinical studies successfully conducted in Japan. This study was conducted to investigate whether addition of an angiotensin receptor

Table 2 Cardiovascular clinical trials conducted in PROBE fashion and their primary end points

Trial name	*Publication year*	*Comparison*	*Primary end point description*	*Hard end points*						*Soft endpoints*					*Significant difference in the primary endpoint*
				Non-fatal MI	*Non-fatal stroke*	*Fatal MI*	*Fatal stroke*	*Sudden death/ resuscitated cardiac arrest*	*Other cardio-vascular deaths*	*All-cause deaths*	*Worsening angina/ unstable angina*	*Exacer-bation of heart failure*	*Any-cause hospital-ization*	*PCI*	
Western trials															
HOT[a]	1998	Three levels of theapeutic BP targets	Major cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death)	○	○	○	○		○						No
STOP-hypertension2[b]	1999	BP lowering new vs. old drugs	Fatal stroke, fatal myocardial infarction, sudden death and other cardiovascular deaths			○	○	○	○						No
CAPPP[c]	1999	Captopril vs. conventional drugs	Combination of fatal and nonfatal myocardial infarction and stroke, and other cardiovascular deaths	○	○	○	○		○						No
NORDIL[d]	2000	Diltiazem vs. β-blockers and/or diuretics	Fatal and nonfatal stroke, fatal and non-fatal myocardial infarction and other cardiovascular death	○	○	○	○		○						No
ANBP2[e]	2003	ACE-I vs. diuretics	All fatal events+non-fatal cardiovascular events	○	○	○	○	○	○	○	○	○			Yes
SPORTIF III[f]	2003	Ximelagatran vs. warfarin	All strokes (ischemic and hemorrhagic) and systemic embolic events		○		○								No
INVEST[g]	2003	Ca blocker vs. non-Ca blocker	All cause mortality, nonfatal MI or nonfatal stroke	○	○					○					No
LoWASA[h]	2004	Fixed low dose warfarin+aspirin vs aspirin	Cardiovascular event (cardiovascular death or reinfarction or stroke) and cardiovascular death	○	○				○						No
IDEAL[i]	2005	Statin therapy usual vs. intensive	MACE (nonfatal AMI, coronary death or resuscitated cardiac arrest)	○		○		○							No
CIBIS III[j]	2005	Enalapril→bisoprolol vs bisoprolol→enalapril	Combined end point of mortality (death from any cause) and first all-cause hospitalization							○			○		No
ASCOT-BPLA[k]	2005	CCB/ACE-I vs. β-blocker/ diuretics	Non-fatal MI fatal CHD	○		○									No
MOSES[l]	2005	Eprosartan vs. nitrendipine	Composite of all-cause mortality and the number of cardiovascular and cerebrovascular events including all recurrent events	○	○	○	○			○					No
ACTIVE W[m]	2006	Aspirin+clopidogrel vs. warfarin	First occurrence of stroke, non-CNS systemic embolism, myocardial infarction or vascular death	○	○	○	○		○						Yes*
ESPRIT[n]	2006	Aspirin+dypiridamole vs. aspirin	Combined event of 'death from all vascular causes', non-fatal stroke, non-fatal myocardial infarction or major bleeding complication	○	○	○	○		○						Yes
BAFTA[o]	2007	Adjusted dose warfarin vs. aspirin	Incidence of fatal or non-fatal disabling stroke (ischemic or hemorrhagic), infra-cranial hemorrhage or significant arterial embolism		○		○								Yes
Japanese trials															
MEGA[p]	2006	diet vs. diet+pravastatin			○			○			○			○	Yes

Table 2 Continued

Trial name	Publication year	Comparison	Primary end point description	Hard end points: Non-fatal MI	Non-fatal stroke	Fatal MI	Fatal stroke	Sudden death/ resuscitated cardiac arrest	Other cardio-vascular deaths	All-cause deaths	Soft endpoints: Worsening angina/ unstable angina	Exacer-bation of heart failure	Any-cause hospital-ization	PCI	Significant difference in the primary endpoint
			Fatal or nonfatal myocardial infarction, sudden cardiac death, development of unstable angina and coronary revascularization procedures, either coronary artery bypass grafting or percutaneous coronary intervention												
JIKEI-HEART[q]	2007	Valsartan vs. non-ARB	Stroke, new or recurrent transient ischemic attack, new or recurrent acute myocardial infarction, new occurrence or exacerbation of heart failure, new occurrence or exacerbation of angina pectoris, dissecting aneurysm of the aorta, lower limb arterial obstruction, transition to dialysis, doubling of plasma Cr levels	○	○	○	○				○	○			Yes
JELIS[r]	2007	EPA+statin vs. statin	Sudden cardiac death, fatal and nonfatal MI, unstable angina pectoris including hospitalization for documented ischemic episodes, and events of angioplasty/stenting or CABG	○		○		○			○			○	Yes
CASE-J[s]	2008	Candesartan vs. amlodipine	Sudden death, new occurrence or recurrence of stroke or TIA, new occurrence, aggravation or recurrence of heart failure, angina pectoris or acute myocardial infarction, renal dysfunction, new occurrence or aggravation of dissecting aneurysm of aorta, arteriosclerotic occlusion of peripheral artery	○	○	○	○	○			○	○			No

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BP, blood pressure; CABG, coronary artery bypass graft; CCB, calcium blocker; CNS, central nervous system; EPA, eicosapentaenoic acid; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous intervention; PROBE, prospective randomized open-label blinded end-point.

[a]Hypertension Optimal Treatment Study.[21]

[b]Swedish Trial in Old Patients with Hypertension-2 Study.[22]

[c]Captopril Prevention Project.[23]

[d]Nordic Diltiazem Study.[24]

[e]Australian National Blood Pressure Study 2.[25]

[f]Stroke Prevention using an ORal Thrombin Inhibitor in patients with atrial Fibrillation III Study.[18]

[g]International Verapamil-Trandolapril Study.[26]

[h]Low-dose Warfarin and Aspirin Study.[27]

[i]Incremental Decrease in End Points Through Aggressive Lipid Lowering Study.[28]

[j]Cardiac Insufficiency Bisoprolol Study III.[29]

[k]Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm.[30]

[l]Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention Study.[31]

[m]Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events.

[n]European/Australian Stroke Prevention in Reversible Ischaemia Trial.[32]

[o]Birmingham Atrial Fibrillation Treatment of the Aged Study.[19]

[p]Management of Elevated Cholesterol in the Primary Prevention Group of the Adult Japanese Study.[33]

[q]35

[r]Japan EPA Lipid Intervention Study.[36]

[s]Candesartan Antihypertensive Survival Evaluation in Japan.[37]

*The result was significantly in favor of warfarin.

Table 3 The number of end points in JIKEI HEART Study

	Number of events valsartan group (%)	Number of events non-ARB treatment group (%)	P-value
Primary end point			
Composite end point of stroke, new or recurrent transient ischemic attack, new or recurrent acute myocardial infarction, new occurrence or exacerbation of heart failure, new occurrence or exacerbation of angina pectoris, dissecting aneurysm of the aorta, lower limb arterial obstruction, transition to dialysis, doubling of plasma Cr levels	92 (6.0)	149 (9.7)	0.0002
Secondary end points			
Stroke or transient ischemic attack	29 (1.9)	48 (3.1)	0.0280
New or recurrent acute myocardial infarction	17 (1.1)	19 (1.2)	0.7545
New occurrence or exacerbation of angina pectoris needing hospitalization[a]	19 (1.2)	53 (3.4)	0.0001
New occurrence or exacerbation of heart failure needing hospitalization[a]	19 (1.2)	36 (2.3)	0.0293
Dissecting aneurysm of the aorta	2 (0.1)	10 (0.6)	0.0340
Transition to dialysis, doubling of serum creatinine levels	7 (0.5)	8 (0.5)	0.8966
All-cause mortality	28 (1.8)	27 (1.8)	0.7537
Cardiovascular mortality	9 (0.6)	9 (0.6)	0.9545

[a]End points that are considered to be 'soft end points'.
Modified from *Lancet*. 2007 April 28; **369** (9571):1431–1439.

blocker (valsartan) to conventional treatment was effective in reducing cardiovascular events in Japanese patients with cardiovascular disease. Although the successful lowering of blood pressure was similar in both the valsartan and non-valsartan groups, it was shown that the addition of valsartan to conventional treatment prevented more cardiovascular events than conventional treatment. This superiority of valsartan to other blood pressure-lowering agents, which goes beyond its blood pressure-lowering effect, has not been shown in other clinical trials conducted in a double-blind fashion;[38,39] this is one of the other reasons that the results of this trial interested many individuals. When examined in greater detail, it is obvious that the differences in the number of soft end points are the factors that mainly contributed to the favorable results for valsartan in this study (Table 3). The primary end point of this study is a composite of several pre-specified events, and its components are not clearly shown. However, the number of each component is shown as secondary end points, which is a good indication of the composition of the primary end point. In fact, hard end points such as myocardial infarction or cardiovascular mortality did not differ significantly between the two groups. As is questioned in the editorial that accompanied the article,[40] it cannot be totally ruled out that there might have been underreporting of events in the valsartan group. It is also of great interest that although most studies conducted in the West produced no significant difference as regards the primary end point, results of three of the four studies conducted in Japan were significantly in favor of the study drug, the manufacturer of which was the sponsor (Table 2). These could be considered as examples showing that the results of PROBE-designed trials should be evaluated carefully, especially in cases wherein the results with soft end points are widely discrepant from those with hard end points.

CONCLUSION

Epidemiological studies conducted in prospective cohort design have established cardiovascular risk factors such as hypertension, hyperlipidemia, smoking and age. By applying the ideas and methodologies developed in epidemiological studies, many clinical trials have been conducted to prove the benefits of various medicines.

Randomized, controlled, double-blind clinical trials report the most scientifically accurate results. However, they usually entail high costs, render the recruitment of patients more difficult and are rather discrepant from usual clinical care. The PROBE study design is a feasible alternative to double-blind studies. However, if not designed and conducted properly, it will be more susceptible to biases. Thus, studies conducted with a PROBE design using soft end points included in the primary end point require the participating physicians to adhere to the guidelines for PROBE studies more strictly.

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EDITORIAL

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Eicosapentaenoic Acid (EPA) in Reducing Secondary Cardiovascular Events in Hypercholesterolemic Japanese Patients

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Epidemiological studies have shown that the disease pattern of the population of Inuit is quite different from that of the population of Denmark[1,2] The most evident difference is found in the incidence of coronary heart disease: compared with the Western population, Greenland Eskimos are less than one-tenth as likely to experience acute myocardial infarction.[1] One study showed that the 2 populations exhibit different fatty acid composition of the plasma lipids[3] the most notable difference being the significantly higher levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid observed in Greenland Eskimos compared with both Eskimos living in Denmark and the Danes. These 2 fatty acids are mainly of fish oil origin. Similarly, Japanese are also known to have a lower rate of mortality from cardiovascular disease than Westerners in industrialized countries[4] and the Japanese, like Eskimos, are known to consume large amounts of fish. This has led to the hypothesis that a higher rate of fish oil consumption results in a higher concentration of n-3 polyunsaturated fatty acids (PUFA) in the plasma lipids, which in turn results in a lower rate of cardiovascular disease.

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This hypothesis has led to several studies investigating whether an increase in fatty fish consumption or the administration of n-3 PUFA can actually decrease the rate of cardiovascular disease;[5,6] these studies have shown that both methods of intake decrease the mortality rate of patients who have suffered myocardial infarction.

These studies, however, were conducted in Western countries, where fish consumption levels are not as high as in Japan. To determine whether their results were also applicable to the Japanese population, a study, which was named JELIS, was conducted to investigate whether EPA, 1 of the n-3 PUFAs found in fish oil, was effective in reducing the incidence of cardiovascular events in hyperlipidemic Japanese patients? JELIS showed that EPA provides an additional benefit beyond that provided by statin treatment in reducing major coronary events.

A subsequent paper published in this Journal by Matsuzaki et al analyzes in detail a subpopulation of JELIS, all of whom had established coronary heart disease[8] This study shows that the administration of EPA to Japanese with hyperlipidemia and established coronary heart disease decreases the incidence of secondary major cardiovascular events, even though Japanese already consume large amounts of fish, a tendency which might have been expected to diminish the effect of the additional administration of EPA. It also shows that EPA confers its benefits to patients with various backgrounds, including those with prior myocardial infarction or prior coronary intervention, without significantly changing low-density lipoprotein-cholesterol (LDL-C) levels, as indicated by the similarity in LDL-C levels of the control group and the EPA group. The authors conclude that, even in a population that already consumes a large amount of fish, EPA is effective in reducing the incidence of secondary cardiovascular events, and it should be considered as an addition to conventional treatment.

However, there are several points to be made concerning this study. For one thing, when this study was conducted, cholesterol management was not as vigorous as it is today. The LDL-C level achieved in this study was 130 mg/dl, in both the control group and the EPA group, and while this may have been acceptable at the time, the Japan Atherosclerosis Society guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese published in 2007 states that persons with established coronary heart disease should lower their serum LDL-C level to less than 100 mg/dl[9] Further investigation may be necessary to determine whether EPA confers additional benefit in preventing secondary cardiovascular events in the context of modern dyslipidemia management. In addition, the insufficient use of antiplatelet/anticoagulant agents might have affected the results of this study. It is possible that the investigators used these agents less often than is typical for fear of inducing a high rate of adverse bleeding events, because EPA itself has been shown to have antiplatelet properties.[10] It has been reported, however, that of 148 n-3 PUFA studies that reported on adverse events, only 1, in which an unusually high dose of 6 g/day of n-3 PUFA was administered, reported an increased incidence of bleeding.[11] Moreover, the AHA/ACC guidelines for secondary prevention for patients with coronary and other forms of atherosclerotic vascular disease state that all patients with established coronary heart disease should be administered aspirin unless contraindicated.[12] The Japanese Circulation Society guidelines for

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management of anticoagulant and antiplatelet therapy in cardiovascular disease also state that all patients in the chronic phase of ischemic heart disease should be administered low doses of aspirin unless contraindicated. A large-scale observational study, which reported on Japanese patients with coronary artery disease diagnosed with coronary angiography, showed that approximately 87% were given antithrombotics[13] indicating that most physicians are conforming to the published guidelines. Thus another study may be necessary to demonstrate that EPA confers additional benefit in reducing secondary cardiovascular events beyond that conferred by the application of the strategies recommended in today's guidelines.

Another point to consider is the fact that, while this study was conducted in a PROBE (prospective randomized open-label blinded-endpoint) fashion, softer endpoints, such as unstable angina pectoris, angioplasty and stenting, were included in the primary endpoint. As we have observed previously[14] all major recently-published Japanese cardiovascular clinical trials have adopted the PROBE design and yet have included soft endpoints in their primary endpoints. Although adopting the PROBE design makes it easier to recruit more patients into a trial, the inclusion of soft endpoints may hamper the scientific rigor of the study. It would have been better to conduct the study either in a blinded fashion with soft endpoints or in an open-labeled fashion without soft endpoints, although, considering the low incidence of cardiovascular events among the Japanese, even among established coronary heart disease patients, as demonstrated by the study under discussion[8] it may not be realistic to conduct such a study either way.

The study conducted by Matsuzaki et al[8] provides us with the important information that EPA may be effective in reducing cardiovascular events in Japanese patients with established coronary heart disease. However, considering the rapid rate of change in clinical practice not all of its results may be directly applicable to the contemporary practice of cardiology in Japan. Further studies incorporating recent clinical changes, such as stricter LDL-C management and aggressive use of antiplatelet agents, may be necessary to corroborate its results.

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