Table 5 Combinations of drugs and symptoms

Drugs	Symptoms
ACE inhibitors	Cough, hypotension, angioedema
α_1 blockers	Asthenia, dizziness, hypotension, nausea, palpitations
Antiadrenergic agents	Asthenia, dry mouth, somnolence, dizziness, constipation, sexual dysfunction, hypotension
Antiarrhythmic agents	Blurred vision, cinchonism, constipation, dizziness, dry mouth, dyspepsia, dysuria, epigastric pain, headache, hearing disturbance, nausea, palpitations, somnolence, tinnitus, vomiting
Antibiotics	Diarrhea, eruption
Antidepressants	Anorexia, anxiety, confusion, constipation, dizziness, dry mouth, fainting, falls, hypotension, impotence, insomnia, irritability, nervousness, visual problems, weight loss
Antiplatelet agents	Dizziness, dyspepsia, epigastric pain, nausea, pruritis, vomiting
Antipsychotic agents	Akathisia, constipation, dry mouth, dysuria, somnolence, palpitations
Antiseizure agents	Confusion, dizziness, fatigue, impaired motor skills
Antithyroid agents	Dyspepsia, epigastric pain, nausea, rash, vomiting
Benzodiazepines	Confusion, falls, fatigue, impaired motor skills
β blockers	Bradycardia, dyspnea, bronchospasm, depression, dizziness, fainting, fatigue, heart block, heart failure
β_2 agonists	Palpitations, tachycardia, tremor
Bile acid sequestrants	Constipation, dyspepsia, epigastric pain, nausea, vomiting
Calcium channel blockers	Hypotension, peripheral edema
Digoxin	Nausea
Diuretics	Dizziness, fainting, falls, hypotension, renal failure, weakness
Fibric acids	Dyspepsia, epigastric pain, myalgia, nausea, rash, vomiting
HMG-CoA reductase inhibitors	Dyspepsia, epigastric pain, nausea, myalgia, vomiting
Hypoglycemics	Dizziness, fainting, falls, seizure
Insulin	Dizziness, fainting, falls, palpitations, seizure, tremor
Lithium	Bradycardia, confusion, dry mouth, dyspepsia, edema, epigastric pain, nausea, palpitations, polyuria, polydipsia, seizure, somnolence, tremor, vomiting
Narcotics	Confusion, constipation
Niacin	Dyspepsia, epigastric pain, nausea, vomiting
Nitrates	Dizziness, edema, hypotension, rebound tachycardia
NSAIDS	Dyspepsia, edema, epigastric pain, nausea, vomiting
Oral steroids	Dyspepsia, eye pain, epigastric pain, nausea, visual impairment, vomiting
Proton pump inhibitors	Diarrhea
Thyroid hormones	Palpitations

Table 6 Combinations of diagnoses and drugs

Diagnoses	Drugs
Agranulocytosis	Antiarrhythmic agents
Akathisia	Antipsychotic agents
Angioedema	ACE inhibitors
Anxiety	β_2 agonists
Arrhythmia	Antipsychotic agents, lithium
Arrhythmia (other)	Antiarrhythmic agents
Asthenia	α_1 blockers, antiadrenergic agents
Asthma	β blockers
Bleeding	Antiplatelet agents, warfarin
Bradycardia	β blockers
Cataract	Oral steroids
Cinchonism	Antiarrhythmic agents
Confusion	Insulin
Constipation	Antiadrenergic agents, antiarrhythmic agents, antidepressants, antipsychotic agents, bile acid sequestrants, narcotics
Coronary heart disease	Antipsychotic agents, lithium
Depression	β blockers
Diabetes or hyperglycemia	Oral steroids
Dry mouth	Antiadrenergic agents, lithium
Falls	Antidepressants, benzodiazepines, diuretics, hypoglycemics, insulin
Gastroduodenitis or gastroduodenal ulcer	Antiplatelet agents, antithyroid agents, oral steroids, lithium, niacin, NSAIDs, warfarin
Gastrointestinal bleeding	Antiplatelet agents, oral steroids, NSAIDs, warfarin
Glaucoma	Oral steroids
Heart failure	Antiadrenergic agents, antiarrhythmic agents, antipsychotic agents, β blockers, lithium
Heat block	β blockers
Hyperkalemia	ACE inhibitors, potassium supplement, potassium sparing diuretics, NSAIDs, COX II inhibitors, trimethoprim
Hypoglycemia	Hypoglycemics, insulin
Hypokalemia	Digoxin, non-potassium sparing diuretics
Hyponatremia	Diuretics
Hypotension	ACE inhibitors, α_1 blockers, antiadrenergic agents, antidepressants, calcium channel blockers, diuretics, nitrates
Impotence	Antidepressants
Insomnia	Antidepressants, β_2 agonists
Leukocytopenia	Carbamazepine, clozapine, ganciclovir
Long QTc interval	Amiodarone, bepridil, chlorpromazine, clarithromycin, desipramine, disopyramide, dofetilide, doxepin, erythromycin, erythromycin estolate, erythromycin ethyl succinate, felbamate, flecanide, fluoxetine, halofantrine, haloperidol, imipramine, indapamide, isradipine, levofloxacin, mesoridazine, moexipril/hydrochlorothiazide, moxifloxacin, naratriptan, nicardipine, paroxetine, pentamidine, pimozide, probucol, procainamide, quetiapine, quinadine, risperidone, salmeterol, sertraline, sotalol, sparfloxacin, sumatriptan, tacrolimus, tamoxifen, thioridazine, tizanidine, venlafaxine, ziprasidone, zolmitriptan
Myopathy	HMG-CoA reductase inhibitors
Pruritus	Antiplatelet agents
Rash	Antithyroid agents
Renal failure	ACE inhibitors, allopurinol, ARBs, atenolol, azathioprine, cyclosporine, digoxin, diuretics, enoxaparin, ganciclovir, metformin, NSAIDs, procainamide, tacrolimus
Seizure	Hypoglycemics, insulin, lithium
Sexual dysfunction	Antiadrenergic agents
Somnolence	Antiadrenergic agents, antipsychotic agents, antithyroid agents, insulin, lithium
Tachycardia	β_2 agonists, nitrates
Thrombocytopenia	Antiarrhythmic agents, ticlopidine, sulfonamide diuretics, sulfonamide antibiotics, H_2 blockers
Thyroid dysfunction	Antiarrhythmic agents, lithium
Tremor	β_2 agonists, hypoglycemics, insulin, lithium

are especially important. These include direct interviews in the office or patient's home, mail surveys, telephone surveys, and web based surveys. We conducted a telephone survey in outpatients to collect the incidents which patients experienced.[4] Patients were sent a letter describing the study and requesting their participation in a telephone survey. Within 10–14 days after an index visit, research assistants asked patients who agreed to participate about specific symptoms (table 5). If symptoms were present, structured questions followed about the timing and action taken. A similar telephone interview was conducted again 3 months later. All possible incidents collected by self-reports or surveys were sent to and screened by research pharmacists or assistants. Those unlikely to be associated with drugs were excluded and the rest were sent to the physician reviewers.

Table 7 Combinations of drugs and miscellaneous factors

Factors	Drugs
Sex: female	Finasteride
Age >65 years	Amitriptyline, carisoprodol, chlordiazepoxide, chlorpropamide, cyclobenzaprine, diazepam, flurazepam, haloperidol, indomethacin, meprobamate, methocarbamol, orphenadrine, pentazocine, pentobarbital, propoxyphene, secobarbital
Dose: 2 or more drugs containing same drug	Acetaminophen (paracematol)
Duration: treatment >5 days or >20 tablets	Ketorolac
Condition:	
Dialysis	Atenolol, enoxaprin, allopurinol, azathioprine, ganciclovir
Pregnancy	Isotretinoin, leflunomide, methotrexate, misoprostol, thalidomide
Procedures: oesophagogastroduodenoscopy	NSAIDs, COX II inhibitors

Table 8 Laboratory triggers

Laboratory triggers	Drugs
Anemia	Antiplatelet agents, antithyroid agents, oral steroids, lithium, niacin, nsaids, warfarin
Leukocytopenia	Carbamazepine, clozapine, ganciclovir
Thrombocytopenia	Diuretics, H_2 blockers, procainamide, quinidine, sulfonamide, sulfonamide antibiotics, ticlopidine
Raised bilirubin	Cyclosporine
Raised bilirubin and ALP	Allopurinol, amoxicillin/clavulanate, azathioprine, chlorpromazine, chlorpropamide, tolazamide, tolbutamide
Raised ALT or AST	Amiodarone, atorvastatin, carbamazepine, celecoxib, cerivastatin, cyclophosphamide, divalproex, erthromycin estolate, fluoxetine, fluvastatin, ibuprofen, isoniazide, lovastatin, methotrexate, methyldopa, metformin, nefazadone, nevirapine, paroxetine, pioglitazone, pravastatin, rifampin, ritonavir, rofecoxib, rosiglitazone, sertraline, simvastatin, sulfamethoxazole, sulfasalazine, sulfisoxazole, tetracycline, valproic acid, venlafaxine
Hyperkalemia	ACE inhibitors, COX II inhibitors, NSAIDs, potassium sparing diuretics, potassium supplement, trimethoprim
Hypokalemia	Digoxin, non-potassium sparing diuretics
Hyponatremia	Diuretics
Hyperglycemia	Oral steroids
Hypoglycemia	Hypoglycemics, insulin
Raised creatinine	ACE inhibitors, allopurinol, ARBs, atenolol, azathioprine, cyclosporine, digoxin, diuretics, enoxaparin, ganciclovir, metformin, NSAIDs, procainamide, tacrolimus
Raised BUN	Diuretics
Falling TSH	Levothyroxine
Raised CPK	HMG-COA reductase inhibitors
Positive UHCG for female aged <45	Atorvastatin, benazepril, captopril, cerivistatin, clozapine, clomiphene, danazol, desogestrel, dienestrol, diethylstilbesterol, dihydroergotamine, enalapril, ephedrine, ergotamine, estazolam, estradiol, estrogens conjugated, estrogens, esterified, estrone, estropipate, ethinyl estradiol, etretinate, finesteride, fluoxymesterone, fluvastatin, fosinopril, goserelin, isotretinoin, levonorgestrel, lisinopril, lovastatin, medroxyprogesterone, megestrol, mestranol, methotrexate, methylthestosterone, misoprostol, moexipril, naferelin, nandrolone, norethinodrone, norgestrel, oxandrolone, perindopril, pravastatin, quazepam, quinapril, quinestrol, quinine, ramipril, raloxefine, ribavirin, simvastatin, temazepam, testosterone, trandolapril, triazolam, urofollitropin, vitamin A, warfarin
Raised blood level	Lithium
Raised blood level or no test for 12 months	Carbamazepine, cyclosporine, digoxin, phenobarbitol, primidone, phenytoin, procainamide, quinidine, theophylline, valproate
Raised INR	Warfarin
Positive fecal occult blood	Antiplatelet agents, antithyroid agents, oral steroids, lithium, niacin, NSAIDs, warfarin
Positive *C difficile* toxin or culture	Antibiotics
No WBC test for 1 month	Clozapine
No creatinine test for 3 months	Allopurinol, azathioprine

Comparison of methods

The above mentioned four methods (chart reviews, computer based triggers, self-reports, and patient surveys) are complementary. In the inpatient setting, computer based triggers detected 45% of all ADEs, chart reviews detected 65%, and self-reports 4%.[11] The overlap of chart reviewing and computer based triggers was 12% while that of chart reviewing, computer based triggers, and self-reports was only 1%. On the other hand, patient surveys identified 92% of ADEs in the outpatient setting and chart reviewing identified 28%; the overlap was only 19%.[4] Thus, the proportion of overlap is typically minor and combinations of these methods can be useful in research to determine the true underlying rate of these events.

Methods for classifying incidents

In classifying incidents the reviewers consider the timing of findings (symptoms, abnormal laboratories, diagnoses), whether the physician in charge or the patient attributed the findings to the drug, and the strength of published data based on the relationship between the findings and the drug.

Once possible incidents are deemed actual incidents, they are classified according to the following categories: if a medication error is present, if a potential ADE is present, or if an ADE without an error is present. In addition, severity, preventability, ameliorability, the level of disability, the stage in the medication use process at which the error occurred, and the category of healthcare personnel responsible for the error can be classified (figs 2 and 3). The reviewers assess preventability or ameliorability on the basis of the physician's presumed knowledge at the time the drug was prescribed. If insufficient information is available the reviewers assume that the physician's decision was correct. When the incident is preventable or ameliorable, the reviewers specify the type of error and how it might be prevented. What is preventable may change over time because many ADEs judged non-preventable or non-ameliorable in the past might become preventable or ameliorable with new approaches such as genetic testing. We consider some laboratory abnormalities to be ADEs even if there are no symptomatic problems—for example, extreme hyperkalemia without arrhythmia or markedly raised INR without apparent bleeding (table 8). If an error is associated with the abnormal laboratory result—for example, failure to check a creatinine level within a 12 month period while the patient is receiving a medication known to increase creatinine levels—the incident would be considered a medication error.

Each ADE and potential ADE is classified as fatal, life threatening, serious, or significant (table 9). If a medication error is present, the stage of the process where the error occurred and the person responsible for the error considered are: ordering (physician, nurse practitioner, or physician assistant); transcribing (a secretary or nurse); dispensing (pharmacist); administration (nurse, pharmacist, or patients); and monitoring (physicians or patients).

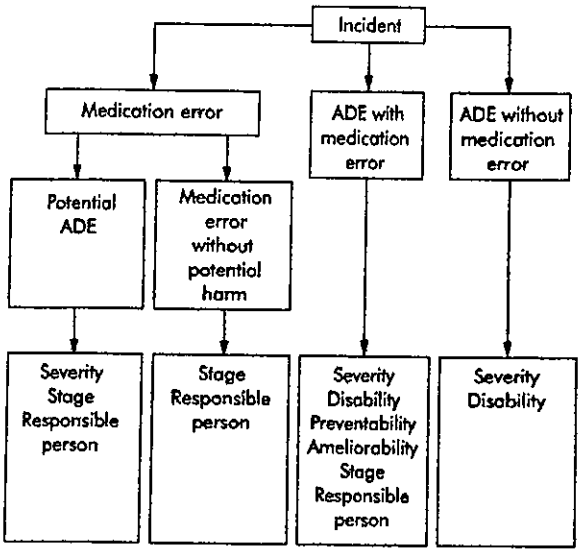

Figure 3 Flow diagram to classify the incidence of adverse drug events (ADEs) and medication errors.

Confidence about the classification of incidents is rated on a scale such as a 6 point scale (1 = little or no confidence; 2 = slight to moderate confidence; 3 = <50% confidence but a close call; 4 = >50% confidence but a close call; 5 = strong confidence; and 6 = virtually certain). Exclusion is made by a cut off point selected a priori and we considered 50% or more as indicating an actual incident.[4]

The rating method developed by Naranjo *et al*[18] is another reliable way to estimate the confidence about the classification. This rating method assigns point values of from −1 to +2 to each of the following 10 attributes: (1) previous conclusive report on the reaction, (2) ADE appeared after the suspected drug was administered, (3) adverse reaction improved when the drug was discontinued or a specific antagonist was administered, (4) adverse reaction reappeared when the drug was readministered, (5) alternative causes other than the drug could cause the reaction, (6) reaction appeared when a placebo was given, (7) the drug was detected in the blood or other fluids in concentration known to be toxic, (8) severity of reaction changed when the dose was changed, (9) patient had a similar reaction to the same or similar drugs in any previous exposure, and (10) ADE was confirmed by any objective evidence. Each possible incident with the summed score is categorized as a definite, probable, possible, or doubtful case.[18]

Table 9 Severity categories for incident classification

Severity	Examples
Fatal	Patient died due to the incident
Life threatening	Patient transferred to ICU Respiratory failure requiring intubation Mental status change: patient falls and gets intracranial hemorrhage Tongue swelling/anaphylactic shock due to medication
Serious	Gastrointestinal bleed Altered mental status/excessive sedation due to medication Increased creatinine due to medication Decrease in blood pressure, patient feels lightheaded Allergic reaction: shaking chills/fever Additional visit to clinic for treatment or additional medications
Significant	Rash Diarrhea due to antibiotics Thrombocytopenia due to histamine type 2 antagonist Nausea resulting from oral potassium Nausea and vomiting due to erythromycin Any significant event that is identified by the patient but not requiring a change in therapy

Training reviewers and assessment of reliability

Research nurses, pharmacists, and research assistants usually take part in the case identification step and physician reviewers in the case classification step. The standard training of reviewers is therefore crucial for reliability of the methods. We have developed training manuals with definitions of incidents, description of the case identification process, case examples, and practice exercises with regard to ADEs and other drug related incidents. Reviewers are trained in advance using the manual and are also trained by pilot reviewing using the actual practice data. The results of the exercise and pilot reviewing are evaluated in terms of accuracy and inter-reviewer variability and the reviewers receive feedback. This process has been well received and understood by reviewers in training and has produced consistent results.

Inter-rater reliability for reviewer judgments is calculated using percentage of agreement and the kappa (κ) statistic.[19] The percentage of agreement is calculated by dividing the number of agreed cases by the total cases. κ is calculated from (Po − Pc)/(1 − Pc) where Po = proportion of observed agreement and Pc = proportion of agreement expected by chance and ranges from −1 (complete disagreement) to +1 (perfect agreement). Differences between the two reviewers' judgments about the decisions and classification are usually resolved by discussion. If consensus cannot be reached, a third reviewer evaluates the incident.

DISCUSSION

Our approach used in previous and ongoing studies on ADEs involves three steps: case identification, classification of incidents, and assessment of reliability. Other identification approaches can be used depending upon the target population, the area of the medication use process being evaluated, and the data available. For example, for detecting a small proportion of ADEs inexpensively using administrative data, the patient safety indicators developed by the AHRQ represent one option.[12] For detecting medication administration errors Barker *et al*[8] have shown that direct observation can detect large numbers of errors and is highly reliable in the inpatient and long term care settings. This approach can also be used for detecting dispensing errors.

Reliability of classification is the crucial factor for the science of research collecting information about "soft" outcomes such as ADEs and errors. Many have raised concerns about the reliability of the process. In the process of identifying adverse clinical outcomes Sanazaro and Mills[9] suggested several concerns about screening methods in medical quality assessment including (1) screening could have a high error rate and high false positive rate up to 95%, even by specially trained personnel; (2) physicians substantially vary in conducting peer reviewing; and (3) peer review is more likely to ascribe adverse outcomes to medical care if the outcomes are serious. These criticisms are an important issue

in research in healthcare quality and should be considered carefully. A common way to address such criticism is assessment of inter-rater agreement using kappa statistics. The κ value indicates the extent to which the observational probability of agreement is in excess of the probability of agreement hypothetically expected under the baseline constraints. A κ score of 0.4–0.6 has been considered as moderate agreement, 0.6–0.8 as substantial, and 0.8–1.0 as almost perfect.[19] In our studies in inpatients the κ score for the presence of ADEs was 0.98, exclusion was 0.81, preventability was 0.92, fatal or life threatening *v* serious or significant was 0.37, and significant *v* fatal or life threatening or serious was 0.32.[3] Gandhi *et al*[4] obtained κ scores for exclusion of 0.89, severity 0.72, and preventability 0.70 in an outpatient setting. These figures suggest that the approach we have used is generally reliable.

We have reported the incidence of ADEs, potential ADEs, and medication errors in a variety of clinical settings.[3–5 20] For example, the incidence of ADEs was 6.5 per 100 adult admissions[3] and 2.3 per 100 pediatric admissions.[5] In nursing homes ADEs were found at a rate of 1.89 per 100 resident-months,[20] while the incidence of ADEs among outpatients was 27.4 per 100 adult patients.[4] The incidence of potential ADEs was also reported to be 5.5 per 100 adult admissions,[3] 10 per 100 pediatric admissions,[5] and 0.65 per 100 nursing home resident-months.[20] ADEs and potential ADEs are common in any setting but vary substantially in incidence, and the causes of errors and ADEs vary greatly by setting. Adult inpatients tend to receive a larger number of drugs than pediatric inpatients or nursing home residents. In addition, outpatients are more likely to be exposed to drugs for a longer interval than inpatients, and administration is obviously under patient control.

The differences in the methods used varied primarily because different approaches work better in specific settings and for specific purposes. Generally, prescription review is better for identifying medication errors while patient surveys are better for identifying outpatient ADEs. Chart review can identify both medication errors and ADEs. In inpatients or nursing homes incidents were found by reviewing records and self-reports from health professionals because no other approach was practical, although surrogate or family interviews would be of interest.

These research methodologies can be used to identify and prioritize strategies for preventing medication errors and preventing or ameliorating ADEs in daily practice. One approach that has become particularly attractive is computerized prescribing. CPOE associated with decision support has been shown to reduce medication error rates by up to 81%.[21 22] The triggers and text screening based on computerized systems can be a foundation for the development of an ADE monitor.[15] The possible incidents detected through such triggers are then evaluated by a drug safety pharmacist for actual or potential ADEs on a daily basis. The drug safety pharmacist can make clinical recommendations to physicians or pharmacists working in conjunction with physicians. Silverman *et al*[15] reported that 78% of such recommendations based on real time ADE monitoring were accepted and resulted in changes in medication orders. Schiff and colleagues[23] have also suggested a framework for multiple ways to link laboratory and pharmacy data. Such linkages can be divided into drug selection (laboratory based indications or contraindications), drug dosing (renal or hepatic, blood level guided adjustment), laboratory monitoring (laboratory signals of toxicity, baseline, and ongoing monitoring), laboratory result interpretation (drug interfering with test), and other quality improvement (surveillance for unrecognized toxicity, monitoring clinician response delays). Because information technology progresses quickly, it would be straightforward to use new devices as tools for patient safety.[24]

Key messages

- Adverse drug events (ADEs) and medication errors are frequent in many clinical settings and can occur at any point in the medication use process. Medication errors are much more common than ADEs. Depending on the setting, about a third to half of ADEs are typically associated with medication errors.
- There are three ways to collect drug related events: review of practice data, self-reports by health professionals, and patient surveys. These methods are complementary and a combination of them is useful.
- Practice data review can be done manually but is much more efficient with computerized searching. Even with computerized searching, manual review is needed. Computerized detection will probably soon replace the all-manual approach, although substantial refinement of it is needed.
- ADEs can be classified according to preventability, ameliorability, disability, severity, stage of the process, and person or group responsible.
- The feasibility and reliability of the described classification methods range from good to excellent.

Although we have used state of the art methods for identifying ADEs, potential ADEs, and medication errors in non-experimental settings with available resources at this time, the methodology described here has several limitations and should be further refined. We believe the future improvement of patient safety research will focus on the computerized approach. Jha *et al*[11] reported that computerized monitoring could detect 45% of ADEs and 42% of potential ADEs in an inpatient setting. However, the efficacy of computerized monitoring was not satisfactory and its positive predictive value was only 17%. Thus, the remaining 83% of alerts were not associated with ADEs, potential ADEs, or medication errors and might result in unnecessary physician actions or resource utilization. Continuous refinement of computerized monitoring rules based on research findings is necessary.

In conclusion, a multidimensional case identification process followed by physician review provides the current best estimates of rates of ADEs, potential ADEs, and medication errors, although this approach is expensive and using all the approaches is probably only practical in the research setting. Each incident can be assessed for preventability, ameliorability, disability, severity, staging, and responsible persons. The classification scheme has acceptable reliability and feasibility. The use of computerized ADE screening and monitoring systems as well as CPOE and EMR systems will undoubtedly improve the efficacy of ADE identification in addition to real time patient safety, but there is still substantial room for improvement of these applications.

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Supported in part by grants from the Pfizer Health Research Foundation, the Health Care Science Institute, grant-in-aid from the Ministry of Health, Labour and Welfare of Japan, and grant R01-HS11169 from the Agency for Healthcare Research and Quality.

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Application of U.S. Guidelines in Other Countries: Aspirin for the Primary Prevention of Cardiovascular Events in Japan

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PURPOSE: Clinical guidelines developed in the United States are used frequently in other countries without assessment of their appropriateness in non-U.S. populations. We explored the relevance of recent U.S. guidelines for the use of aspirin for the primary prevention of cardiovascular events in the Japanese population.

METHODS: From a systematic search of published data, estimates were derived for rates of coronary heart disease, hemorrhagic stroke, and major gastrointestinal bleeding for the Japanese population and for subgroups with different risk factors. Odds ratios derived from meta-analyses were used to assess the potential benefits and risks of aspirin use.

RESULTS: The estimated incidence of coronary heart disease in middle-aged men in Japan is lower than in the United States (1.57 vs. 6.0 per 1000 person-years), while that of hemorrhagic stroke is higher (1.14 vs. 0.37 per 1000 person-years). Because of higher baseline rates of hemorrhagic diseases, the expected reduction in cardiovascular events with aspirin use would be offset by a greater increase in hemorrhagic complications for women and most men in Japan, except for those with both hypertension and diabetes. To achieve the same 2:1 ratio of coronary heart disease events avoided to hemorrhagic events caused that is implied by the 3% threshold for 5-year coronary disease risk in U.S. guidelines, a 6% to 14% risk threshold, depending on patient age, seems appropriate for recommending aspirin in Japanese patients.

CONCLUSION: The thresholds of antiplatelet therapy for Asian populations should be two to five times higher than those for the U.S. population because of higher risks of hemorrhagic complications. The assumptions and implications of U.S. guidelines should be evaluated before use in other countries. **Am J Med. 2004;117: 459–468.** ©2004 by Elsevier Inc.

Evidence-based guidelines in the United States (1) are usually based on research conducted in the United States and Europe, but they influence clinical care throughout the world. However, researchers in many other countries lack the resources to replicate the clinical trials upon which guidelines have been based, or the funding to assess the appropriateness of guidelines for their respective populations.

The U.S. Preventive Service Task Force's guidelines for the use of aspirin to prevent cardiovascular events among patients without a history of cardiovascular disease (2,3) recommend that aspirin be considered in patients with a 3% or more 5-year risk of coronary heart disease. They also suggest that aspirin in this group of patients would prevent at least twice as many as cardiovascular events as the number of hemorrhagic complications caused. In contrast, the Joint Research Committee for Cardiac Disease in Japan advises physicians to "consider the use of aspirin for those with risk factors" without stating any specific risk threshold (4). Further, cardiovascular disease is the most common health problem in the United States (5), whereas the incidence of coronary heart disease in Japan is lower than in the United States (6), and that of cerebrovascular diseases, especially hemorrhagic stroke, is higher (7).

Although the incidence of coronary heart disease has been increasing and that of stroke has been decreasing in Japan in recent years (8), the potential consequences of implementing U.S. guidelines in Japan and other Asian countries are still likely to differ (9,10). We therefore analyzed the predicted effects of aspirin for primary prevention to establish a threshold for aspirin use in Japan.

METHODS

We estimated the risks and benefits of aspirin use from data on the rates of coronary heart disease, hemorrhagic stroke, and major gastrointestinal bleeding in the Japanese population. There have been no Japanese trials assessing the effectiveness of aspirin for primary prevention. The sole trial (11) on aspirin use for secondary prevention did not report any hemorrhagic strokes in the treatment and control groups, and the sample was too small to provide estimates of the effects of various strategies, particularly when compared

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This study was supported by grant 15659159 from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

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Manuscript submitted October 16, 2003, and accepted in revised form April 15, 2004.

0002-9343/04/$–see front matter 459
doi:10.1016/j.amjmed.2004.04.017

with the data used to develop the U.S. Preventive Service Task Force guidelines (3,12). Because the incidence of subarachnoid hemorrhage is much higher in Japan than in the United States (13), and the U.S. guidelines included subarachnoid hemorrhage in hemorrhagic stroke (14–18), we analyzed data for intracranial hemorrhage and subarachnoid hemorrhage separately and combined them to estimate the incidence of hemorrhagic stroke. We assumed aspirin use had no effect on the risk of ischemic stroke, as per the conclusions of the U.S. guidelines (3,12). We used odds ratios for the risks and benefits of aspirin derived from meta-analyses to estimate the effects of aspirin use in the Japanese population, assuming that aspirin has similar pharmacologic effects as in published investigations.

Baseline Risks

A systematic search was conducted of articles written in English and Japanese on the incidence of coronary heart disease, intracranial hemorrhage, subarachnoid hemorrhage, and gastrointestinal bleeding among Japanese. The MEDLINE database (January 1990 to December 2002) was searched and a manual search was performed. To qualify as relevant, the article had to be a prospective cohort study with a fixed population at risk and to report the number of events or deaths and person-years of the base population. Two investigators (TM and KM) independently conducted the literature search and assessed the relevance of each article. Disagreement was resolved by discussion.

The literature search for data on population-based risks yielded four articles each for coronary heart disease (19–22), intracranial hemorrhage (20–23), and subarachnoid hemorrhage (20–23). Agreement between the investigators on the relevance of the articles was 100%. After review of the studies, we decided to base assumptions about mortality on a prospective cohort study of 73,424 Japanese with 580,378 person-years of follow-up (22). This study provided mortality data for coronary heart disease, intracranial hemorrhage, and subarachnoid hemorrhage with subgroup data for age, sex, hypertension, and diabetes status (Table 1). Because this study provided only mortality data, we estimated incidences of combined fatal and nonfatal events using mortality rates combined with case-fatality rates from a study by Kimura et al (24). For example, if the data indicated that 100 deaths from acute myocardial infarction were expected for a given population over a 5-year period, the total number of combined fatal and nonfatal acute myocardial infarctions would be estimated by dividing the number of deaths (n = 100) by a published mortality rate (e.g., 13%). By dividing the estimated number of fatal and nonfatal cases by the person-years of the population at risk, we estimated the incidence of coronary heart disease, intracranial hemorrhage, and subarachnoid hemorrhage for 16 subgroups: men/women, hypertensive men/women, diabetic men/women, and hypertensive and diabetic men/women in the 40- to 64-year and 65- to 79-year age groups.

The incidences of coronary heart disease and hemorrhagic stroke in the United States were derived from the Framingham Study (25,26). Because the risk score for stroke could not be used to predict the incidence of hemorrhagic stroke (25), the incidence ratio for ischemic stroke and hemorrhagic stroke was used to estimate the rate of hemorrhagic stroke (27). The predicted 5-year rates for coronary heart disease and hemorrhagic stroke per 1000 patients was estimated in subsets of the Japanese and U.S. populations (Figure). We considered base case patients in the two age strata (40-64 years and 65-79 years) to be patients aged 50 or 70 years without a history of dyslipidemia or smoking. For example, a 50-year-old U.S. male patient without hypertension or diabetes would have a 3% risk of coronary heart disease and a 0.2% risk of hemorrhagic stroke in the next 5 years, whereas the Japanese counterpart would have risks of 0.8% for coronary heart disease and 0.6% for hemorrhagic stroke.

There were no data on the incidence of mortality due to major gastrointestinal bleeding with or without use of aspirin among Japanese. Therefore, we used data from a Japanese study of aspirin for secondary prevention (11). In this study, there was 1 case of major gastrointestinal bleeding among 250 patients who were taking aspirin and no cases of gastrointestinal bleeding among the 230 patients who were not on antiplatelet therapy. We therefore used the same odds ratio (1.7) for bleeding associated with aspirin use as in the U.S. guidelines (28). Consequently, the incidence of major gastrointestinal bleeding among Japanese patients was estimated to be 1.8 compared with 0.86 per 1000 person-years in U.S. patients (3).

Effects of Aspirin

The odds ratios for the effects of aspirin use on coronary heart disease, hemorrhagic stroke, and major gastrointestinal bleeding that were used in the U.S. guidelines were applied to the Japanese population (3,28). These odds ratios were 0.72 (95% confidence interval [CI]: 0.60 to 0.87) for coronary heart disease, 1.4 (95% CI: 0.9 to 2.0) for hemorrhagic stroke, and 1.7 (95% CI: 1.4 to 2.1) for major gastrointestinal bleeding (3). We calculated the net benefit of aspirin therapy by subtracting the predicted increases in cases of hemorrhagic stroke and major gastrointestinal bleeding from the expected avoided cases of coronary heart disease for 1000 Japanese patients over a 5-year period, as was done in the U.S. guidelines (3). We also estimated the net benefit of aspirin therapy in terms of fatal cases because the consequence of cardiovascular events and major gastrointestinal events were not equal. In addition, we conducted sensitivity analyses to assess the effects of varying our estimates of the benefits and

Table 1. Mortality among Japanese Patients

Characteristic	Original Cohort	Coronary Heart Disease*	Myocardial Infarction		All Stroke	Ischemic Stroke	Intraparenchymal Hemorrhage		Subarachnoid Hemorrhage	
	Person-Years†	No. of Deaths†	No. of Deaths†	Case-Fatality Rate‡	No. of Deaths†	No. of Deaths†	No. of Deaths†	Case-Fatality Rate‡	No. of Deaths†	Case-Fatality Rate‡
Gender										
Male	236,726	168	133	0.13 (age <65 years) 0.25 (age ≥65 years)	341	206	95	0.17 (age <65 years) 0.18 (age ≥65 years)	40	0.36 (age <65 years) 0.44 (age ≥65 years)
Female	343,652	113	89	0.17 (age <65 years) 0.32 (age ≥65 years)	316	172	66	0.14 (age <65 years) 0.15 (age ≥65 years)	78	0.25 (age <65 years) 0.35 (age ≥65 years)
Age										
40–64 years	442,441	79	NA	NA	200	NA	NA	NA	NA	NA
65–79 years	137,937	202	NA	NA	457	NA	NA	NA	NA	NA
Hypertension										
Positive	90,764	117	NA	NA	282	NA	NA	NA	NA	NA
Negative	469,110	164	NA	NA	375	NA	NA	NA	NA	NA
Diabetes										
Positive	25,571	32	NA	NA	54	NA	NA	NA	NA	NA
Negative	554,807	32	NA	NA	603	NA	NA	NA	NA	NA

* Defined as angina pectoris, and acute/chronic myocardial infarction.
† Data from Iso et al (22).
‡ Data from Kimura et al (24).
NA = data not available.

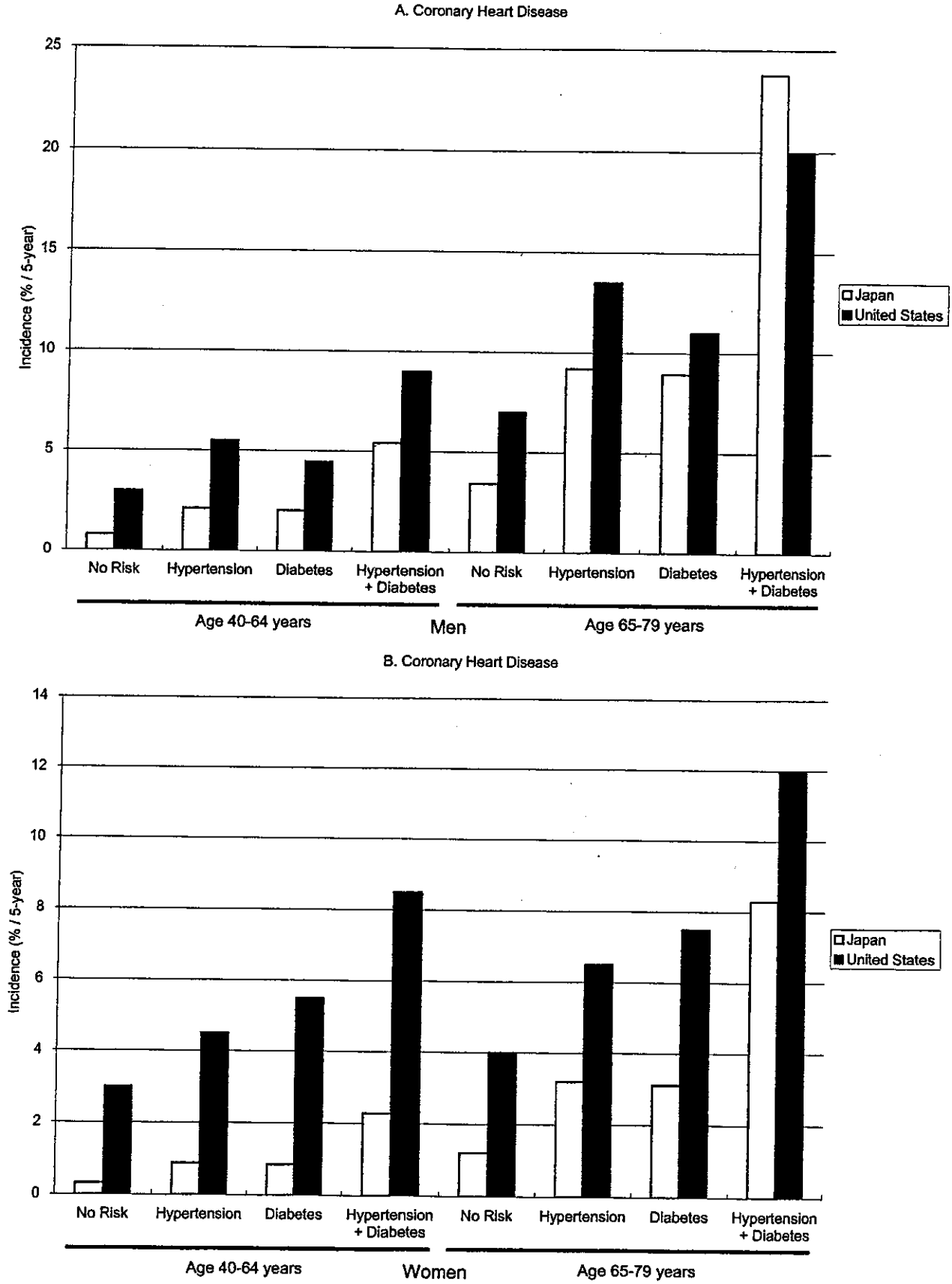

Figure. Estimated incidences of coronary heart disease (A and B) and hemorrhagic stroke (C and D) in Japan and the United States, by sex, age group, and risk factor.

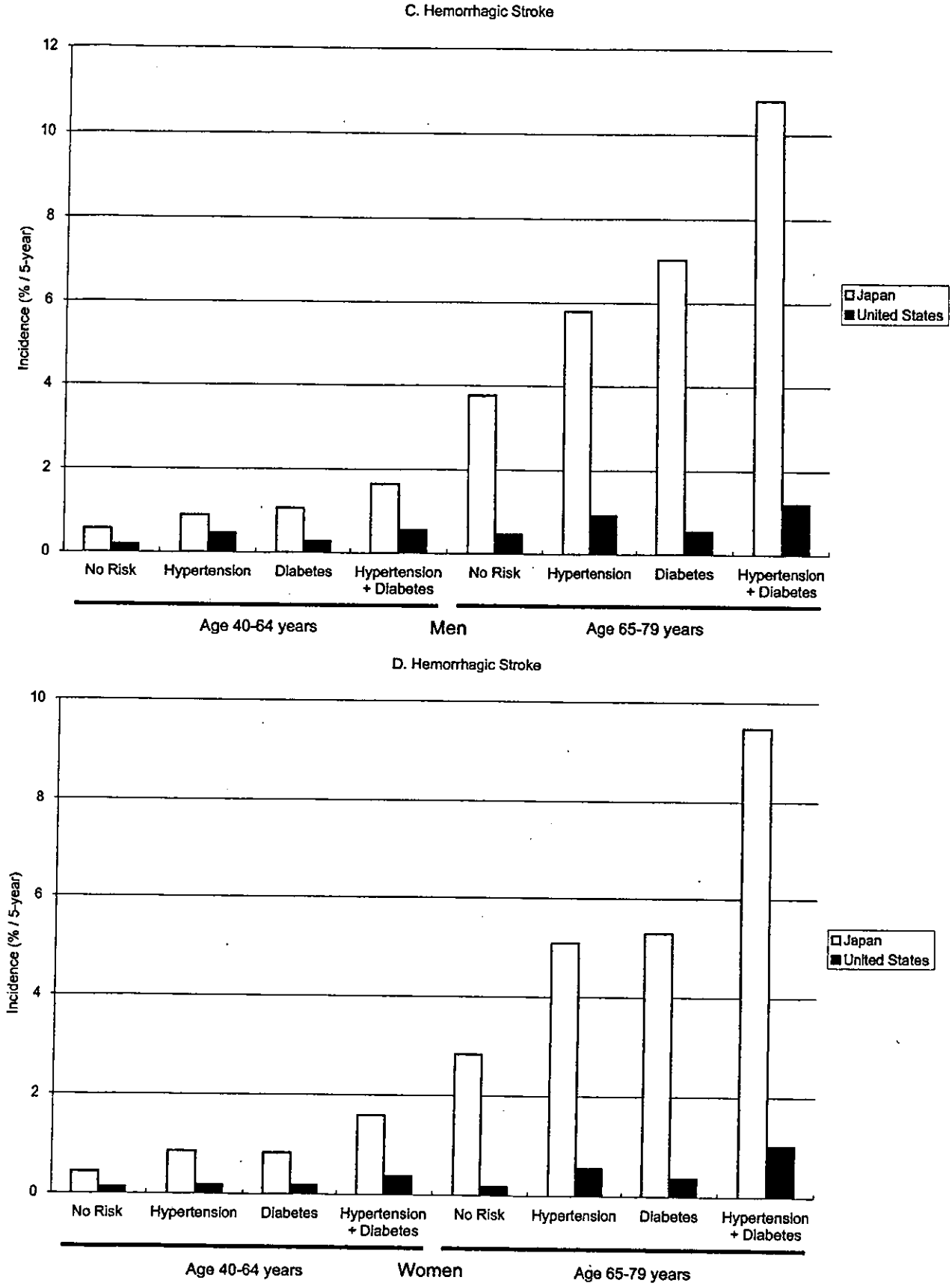

FIGURE 1. *(Continued)*

risks by up to 100% on net benefit. Finally, we calculated a threshold 5-year risk of coronary heart disease for a hypothetical cohort of 1000 Japanese patients that would be expected to yield the same 2:1 ratio of coronary heart disease events avoided to hemorrhagic events caused as was used in the U.S. guidelines to identify the recommended 3% threshold (3).

Analyses were performed using DATA (TreeAge Software, Williamstown, Massachusetts) and Excel (Microsoft Corporation, Redmond, Washington).

RESULTS

In analyses of the effects of aspirin use on the rates of coronary heart disease, hemorrhagic stroke, and major gastrointestinal bleeding, the expected harm from aspirin exceeded the benefits for most of the Japanese population (Table 2). In contrast to the U.S. guidelines, our analyses showed that Japanese men aged 40 to 64 years have a 5-year coronary heart disease risk of only 0.8% and would be harmed by, rather than benefit from, aspirin use. Only Japanese men with both hypertension and diabetes would benefit from aspirin as a primary preventive measure. When considering fatal cases only, the expected harm from aspirin use was attenuated, and the benefits and harmful effects appeared similar.

In sensitivity analyses, in which the estimated risk of coronary heart disease increased by up to 100% while the risk of hemorrhagic stroke decreased by up to 100%, the harmful effects of aspirin use continued to exceed the benefits for all women and for middle-aged men. Aspirin was beneficial only in elderly men (age ≥65 years) when the estimated incidence of hemorrhagic stroke was decreased by 80% or that of hemorrhagic stroke was decreased by 50%, with a simultaneous 50% increase in coronary heart disease incidence.

To identify a risk threshold that would be associated with a 2:1 ratio of events prevented to complications caused, the 5-year risk of coronary heart disease would have to be at least 6% for middle-aged (age 40-64 years) normotensive patients, 7% for hypertensive patients (Table 3), and 14% for those ≥65 years old. As a result, the Japanese population for whom aspirin would be appropriate would be middle-aged or elderly men with both hypertension and diabetes, or women with hypertension, diabetes, and other additional risk factors.

DISCUSSION

U.S. guidelines for the use of aspirin have been developed without specifications for use in other countries. In this analysis, we demonstrate that such guidelines, at least for antiplatelet therapy, should not be used in other countries without careful consideration of the implications. When we applied U.S. guidelines to most subsets of Japanese patients, the expected increase in hemorrhagic events exceeded the number of coronary heart disease events avoided, suggesting that the threshold for 5-year coronary heart disease risk that is used to determine candidates for aspirin prophylaxis should be higher in Japan.

The validity of our analysis depends on the accuracy of our estimates of the risks of coronary heart disease and hemorrhagic events among Japanese. These estimates are consistent with prior reports demonstrating that mortality from coronary heart disease for Japanese men is about one quarter that for men in the United States (9). One prospective cohort study in Japan showed that the age-categorized incidence of hemorrhagic stroke for men was 0.5 to 2.2 per 1000 person-years and that for women was 0.33 to 6.3 per 1000 person-years (23). These and other risk estimates in our analysis are comparable.

One major reason why the U.S. Preventive Service Task Force guidelines may be inappropriate in Japan is that mortality from coronary heart disease is 4.3 times higher in a standardized U.S. population (6). Similarly, the baseline risk of coronary heart disease in the five studies used in the U.S. guidelines was 2.3 to 7.9 times higher than our estimates.

The higher incidence of hemorrhagic stroke in Japan also strongly influenced the net benefit of aspirin and the thresholds for considering primary prevention with aspirin. In addition to the approximately twofold greater incidence of stroke in Japan as compared with the United States (7), the proportion of hemorrhagic stroke among Asians is also much higher (29).

Our risk factor analysis is also consistent with other data. For example, the Seven Countries Study showed that Japanese hypertensive men are at 3.4 times greater risk of coronary heart disease than are Japanese men with normal blood pressure (6). Furthermore, Japanese hypertensive elderly men and women have a three times greater risk of coronary heart disease than normotensive counterparts (30). These results are comparable with our estimated hazard risk ratio of 2.7. In terms of hemorrhagic stroke, the Honolulu Heart Program reported hazard risk ratios of 3.1 for hypertensive men and 1.4 for diabetic men (27), whereas our estimates were 1.6 for hypertensive men and 1.9 for diabetic men. The higher estimated incidence of major gastrointestinal bleeding is consistent with the higher prevalence of *Helicobacter pylori* infection in Japan (31), and the finding that upper gastrointestinal bleeding in patients taking aspirin is associated with *H. pylori* infection (32).

Our recommendations are consistent with, but would refine, Japanese guidelines for primary prevention of coronary heart disease (4). The guidelines recommend aspirin for primary prevention in patients with risk factors for coronary heart disease without specifying any risk thresh-

Table 2. Estimated Benefits and Harmful Effects of Aspirin Therapy in the Japanese Population

Patient Group	Baseline Coronary Heart Disease Risk	Coronary Heart Disease		Hemorrhagic Stroke		Major Gastrointestinal Bleeding		Net Benefit	
		Avoided Cases	Avoided Fatal Cases	Increased Cases	Increased Fatal Cases	Increased Cases	Increased Fatal Cases	Cases	Fatal Cases
	% Per 5 Years	Number Per 1000 Patients* (95% Confidence Interval)							
Men									
Age 40–64 years									
No risk factors	0.8	2 (1 to 3)	0.3 (0.1 to 0.4)	2 (0 to 5)	0.5 (0 to 1.1)	6 (4 to 8)	0.2 (0.1 to 0.2)	−6 (−12 to −1)	0 (−1 to 0)
Hypertensive	2.1	5 (2 to 8)	0.8 (0.4 to 1.1)	3 (0 to 8)	1.3 (0 to 3.1)	6 (4 to 8)	0.2 (0.1 to 0.2)	−4 (−14 to 4)	0 (−2 to 1)
Diabetic	2.0	5 (2 to 8)	0.8 (0.3 to 1.1)	4 (0 to 10)	0.8 (0 to 2.1)	6 (4 to 8)	0.2 (0.1 to 0.2)	−5 (−16 to 4)	0 (−2 to 1)
Hypertensive and diabetic	5.4	15 (7 to 21)	2 (1 to 3)	6 (0 to 16)	2 (0 to 6)	6 (4 to 8)	0.2 (0.1 to 0.2)	3 (−17 to 17)	0 (−5 to 2)
Age 65–79 years									
No risk factors	3.5	9 (4 to 13)	2 (1 to 3)	15 (0 to 37)	3 (0 to 8)	6 (4 to 8)	0.4 (0.3 to 0.5)	−12 (−41 to 9)	−1 (−7 to 2)
Hypertensive	9.2	25 (11 to 36)	6 (3 to 9)	23 (0 to 57)	9 (0 to 23)	6 (4 to 8)	0.4 (0.3 to 0.5)	−4 (−54 to 32)	−3 (−20 to 8)
Diabetic	8.9	25 (11 to 35)	6 (3 to 9)	28 (0 to 70)	6 (0 to 16)	6 (4 to 8)	0.4 (0.3 to 0.5)	−9 (−63 to 31)	0 (−13 to 8)
Hypertensive and diabetic	23.8	66 (30 to 95)	16 (8 to 23)	43 (0 to 108)	17 (0 to 43)	6 (4 to 8)	0.4 (0.3 to 0.5)	17 (−86 to 91)	−1 (−35 to 22)
Women									
Age 40–64 years									
No risk factors	0.33	0 (0 to 1)	0.1 (0.1 to 0.2)	1 (0 to 4)	0.3 (0 to 0.8)	6 (4 to 8)	0.2 (0.1 to 0.2)	−7 (−12 to −3)	0 (0 to 0)
Hypertensive	0.88	2 (1 to 3)	0.4 (0.2 to 0.5)	3 (0 to 8)	0.9 (0 to 2)	6 (4 to 8)	0.2 (0.1 to 0.2)	−7 (−15 to −1)	0 (−2 to 0)
Diabetic	0.85	2 (1 to 3)	0.3 (0.2 to 0.5)	3 (0 to 8)	0.6 (0 to 2)	6 (4 to 8)	0.2 (0.1 to 0.2)	−7 (−15 to −1)	0 (−2 to 0)
Hypertensive and diabetic	2.3	6 (2 to 9)	0.9 (0.4 to 1.3)	6 (0 to 15)	2 (0 to 4)	6 (4 to 8)	0.2 (0.1 to 0.2)	−6 (−21 to 5)	−1 (−3 to 1)
Age 65–79 years									
No risk factors	1.2	3 (1 to 4)	1 (0.5 to 2)	11 (0 to 28)	2 (0 to 6)	6 (4 to 8)	0.4 (0.3 to 0.5)	−14 (−35 to 0)	−1 (−6 to 1)
Hypertensive	3.2	8 (4 to 12)	3 (1 to 4)	20 (0 to 50)	7 (0 to 17)	6 (4 to 8)	0.4 (0.3 to 0.5)	−18 (−54 to 8)	−4 (−16 to 3)
Diabetic	3.1	8 (4 to 12)	3 (1 to 4)	21 (0 to 53)	5 (0 to 11)	6 (4 to 8)	0.4 (0.3 to 0.5)	−19 (−57 to 8)	−2 (−10 to 3)
Hypertensive and diabetic	8.3	23 (10 to 33)	8 (4 to 11)	37 (0 to 94)	13 (0 to 31)	6 (4 to 8)	0.4 (0.3 to 0.5)	−20 (−92 to 29)	−5 (−27 to 10)

* Estimated based on 1000 patients receiving aspirin for 5 years.

Table 3. Estimated Benefits and Harmful Effects of Aspirin Therapy for Japanese Middle-Aged Patients at Different Levels of Risk for Coronary Heart Disease Events

	Estimated 5-Year Risk of Coronary Heart Disease Events at Baseline Number Per 1000 Patients* (95% Confidence Interval)		
	3%	6%	9%
Normotensive patients			
Effect on all-cause mortality	No change	No change	No change
Coronary heart disease events avoided	8 (4 to 12)	16 (7 to 24)	25 (11 to 36)
Ischemic strokes avoided	0	0	0
Hemorrhagic strokes precipitated	2 (0 to 5)	2 (0 to 5)	2 (0 to 5)
Major gastrointestinal bleeding events precipitated	6 (4 to 8)	6 (4 to 8)	6 (4 to 8)
	3%	7%	10%
Hypertensive patients			
Effect on all-cause mortality	No change	No change	No change
Coronary heart disease events avoided	8 (4 to 12)	19 (9 to 28)	28 (13 to 40)
Ischemic strokes avoided	0	0	0
Hemorrhagic strokes precipitated	3 (0 to 8)	3 (0 to 8)	3 (0 to 8)
Major gastrointestinal bleeding events precipitated	6 (4 to 8)	6 (4 to 8)	6 (4 to 8)

* Estimated based on 1000 middle-aged (age 40–64 years) patients receiving aspirin for 5 years and a relative risk reduction of 28% for coronary heart disease events in those who received aspirin.

olds. Furthermore, patients with diabetes are considered strong candidates for aspirin except for those with contraindications.

In contrast, U.S. guidelines recommend a 5-year coronary heart disease risk of 3% as the threshold for considering the use of aspirin, while also stating that patient preferences should be considered (2). Similarly, Lauer suggested that recommendations for patients with a 5-year risk of between 3% and 7.5% should take into account patient preferences and comorbid conditions (33). Because our analysis did not take into account other risk factors such as smoking or dyslipidemia, our estimates may need to be adjusted to reflect these risk factors and patients' preferences.

Our analysis raises concerns about the application of U.S. guidelines to other populations, particularly guidelines involving the use of antiplatelet agents or anticoagulation, such as those that recommend anticoagulation in patients with atrial fibrillation (34). Our results should also be interpreted with several limitations in mind. First, we had to estimate the baseline risks of coronary heart disease, hemorrhagic stroke, and major gastrointestinal bleeding owing to a lack of directly measured data, and we often had to combine estimates to derive incidence rates. However, as did the U.S. Preventive Service Task Force, we fixed the precipitated hemorrhagic stroke cases and did not vary this risk with increasing coronary heart disease risk. Second, there were no direct data on the effect of daily aspirin use on the risk of subarachnoid hemorrhage among Japanese, and actual effects are likely to differ by race/ethnicity. The proportion of subarachnoid hemorrhage in all strokes in Japan is 32% compared with 9% in the United States (22,35); available data show an increased risk of subarachnoid hemorrhage only for women who took a much higher dose of aspirin than that used for coronary disease prevention (36). As a result, the association between aspirin use and the risk of hemorrhagic stroke might be overestimated. Third, we assumed that aspirin has the same effects on the risks of coronary heart disease and hemorrhagic complications among patients in the United States and Japan. The commonly used dose of aspirin in Japan is 81 to 100 mg/d, compared with 75 to 325 mg/d in the United States. Fourth, the high incidence of ischemic stroke among Japanese did not affect our main results (22); a meta-analysis showed that aspirin had no effect on the risk of ischemic stroke (12). Since aspirin therapy has been shown to be effective for secondary prevention of ischemic stroke in the United States (37), our results could change if aspirin were shown to be effective for primary prevention of ischemic stroke among Japanese. Fifth, we had to estimate the incidence of major gastrointestinal bleeding based on only 1 case in 250 patients from a single study (11). Finally, we constructed the coronary heart disease risk threshold based on the incidence of fatal and nonfatal cases. Although the U.S. guidelines utilized this method, the consequences of coronary heart disease, hemorrhagic stroke, and major gastrointestinal bleeding are not equivalent, and, as noted in the U.S. guidelines, patient preferences and attitudes toward the various outcomes might influence the threshold at which a patient desired to use aspirin.

We recognize that, due to the lack of primary data, our assessment of the risks of application of U.S. guidelines

for the use of aspirin in Japanese and other Asian populations must be considered speculative. However, in the absence of such data, the assumption that these guidelines are safe and appropriate must be considered speculative as well. We conclude that our analyses support the need for caution when implementing foreign guidelines. In addition, our limitations point to the lack of well-designed randomized trials among Asians for important clinical issues, as well as the paucity of fundamental epidemiologic data in Japan.

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Cost-effectiveness of Screening for Coronary Artery Disease in Asymptomatic Patients with Type 2 Diabetes and Additional Atherogenic Risk Factors

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OBJECTIVE: **Screening for coronary artery disease (CAD) in asymptomatic diabetic patients with two additional atherogenic risk factors has been recommended by the American College of Cardiology/American Diabetes Association, but its cost-effectiveness is yet to be determined. The present study aims to evaluate the cost-effectiveness of screening and determine acceptable strategies.**

DESIGN: **Cost-effectiveness analysis using a Markov model was performed from a societal perspective to measure the clinical benefit and economic consequences of CAD screening in asymptomatic men with diabetes and two additional atherogenic risk factors. We evaluated cohorts of patients stratified by different age groups, and 10 possible combination pairs of atherogenic risks. Incremental cost-effectiveness of no screening, exercise electrocardiography, exercise echocardiography, or exercise single-photon emission-tomography (SPECT) was calculated. Input data were obtained from the published literature. Outcomes were expressed as U.S. dollars per quality-adjusted life-year (QALY).**

MEASUREMENTS AND MAIN RESULTS: **Compared with no screening, incremental cost-effectiveness ratio of exercise electrocardiography was $41,600/QALY in 60-year-old asymptomatic diabetic men with hypertension and smoking, but was weakly dominated by exercise echocardiography. Exercise echocardiography was most cost-effective, with an incremental cost-effectiveness ratio of $40,800/QALY. Exercise SPECT was dominated by other strategies. Sensitivity analyses found that results varied depending on age, combination of additional atherogenic risk factors, and diagnostic test performance.**

CONCLUSIONS: **Incremental cost-effectiveness ratio of CAD screening in asymptomatic patients with diabetes and two or more additional atherogenic risk factors is shown to be acceptable from a societal perspective. Exercise echocardiography was the most cost-effective strategy, followed by exercise electrocardiography.**

KEY WORDS: **silent myocardial ischemia; ischemic heart disease; cost-effectiveness analysis; screening strategy; diabetes mellitus.**

J GEN INTERN MED 2004;19:1181–1191.

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Coronary artery disease (CAD) is the major cause of morbidity and mortality in patients with diabetes.[1,2] More than half of all diabetic patients die from problems associated with coronary arteries.[3,4] In diabetic patients, CAD is usually diagnosed at an advanced stage, with a correspondingly dismal prognosis.[5,6] The delay in diagnosing CAD is due partly to the presence of silent myocardial ischemia, which is more frequently recognized angiographically in diabetic than nondiabetic patients. The reported prevalence of silent myocardial ischemia ranges from 10% to 60% in diabetic patients, possibly reflecting the differing numbers of atherogenic risk factors in differing studies.[7–11]

The American College of Cardiology/American Diabetes Association recommends that cardiac testing be done irrespective of the presence of CAD symptoms in diabetic patients with two or more atherogenic risk factors, in view of the high prevalence of CAD.[12] Various screening methods are available including exercise electrocardiography, exercise echocardiography, and exercise single-photon emission-tomography (SPECT). From the point of view of health care policy, the value of a screening strategy is determined not only by diagnostic accuracy and risk but also by the cost associated with it. Sox et al. evaluated the cost-effectiveness of screening asymptomatic patients for CAD, and concluded that the effect of exercise testing was too small to justify screening in healthy persons.[13] In high-risk patients with diabetes, however, the cost-effectiveness of screening strategies for CAD in patients has not yet been evaluated.

We have therefore performed a cost-effectiveness analysis of different screening strategies from the societal perspective, using a Markov model to examine the benefits and costs of screening for CAD in asymptomatic patients with diabetes and two additional atherogenic risk factors.

METHODS

We evaluated cohorts of patients stratified by age (50, 55, 60, 65, and 70 years of age), and 10 possible pairs of atherogenic risk factors (hypertension, smoking, low-density lipoprotein [LDL] level above 160 mg/dl, high-density lipoprotein [HDL] level below 35 mg/dl, and proteinuria) that are recommended by American College of Cardiology/American Diabetes Association.[12] The base-case cohort were asymptomatic men with type 2 diabetes mellitus and two additional atherogenic risk factors. Cohn has classified silent ischemia into 3 categories: 1) asymptomatic ischemia without a history of angina/myocardial infarction (MI); 2) asymptomatic ischemic episode with a history of angina; and 3) asymptomatic ischemia with a history of MI.[14] We

define silent myocardial ischemia as the first of these categories, because individuals suffering the second or third were taken already to be receiving specific medication or intervention, and not to benefit from screening. Because most of the available data relate to men of around 55 years of age with hypertension and smoking,[1] base-case analysis was conducted on this patient group. A Markov model was used to estimate the lifetime costs and the quality-adjusted life expectancy.[15] We set the time horizon at 30 years because any effects of treatment should be apparent by 85 years of age.

DATA 3.5.9 software (TreeAge Software, Inc., Williamstown, Mass) was used to calculate costs and outcomes. Costs were estimated from a societal perspective, and outcomes were measured in quality-adjusted life-years (QALYs). We then calculated the incremental cost-effectiveness for all competing strategies. The cost-effectiveness ratio for SPECT compared with echocardiography, for example, is the difference between costs of the two strategies divided by the difference between the QALYs produced by each. A strategy that was less effective and had a higher incremental cost-effectiveness ratio than another strategy was ruled out by weak dominance. A weakly dominated strategy was retained in the list and its cost-effectiveness ratio compared with the next strategy was put in parentheses in the tables, but the incremental cost-effectiveness ratios of the dominant strategy were recalculated using data other than the weakly dominated strategy. This method allowed us to examine whether extending therapy given a new indication is cost-effective. Components of effects or costs that did not differ among the alternative strategies (e.g., giving up smoking) were not evaluated in detail, because we employed incremental cost-effectiveness analysis.

Decision-analytic Model

We assumed that a diagnostic screening test was performed once only, at the first stage. Screening strategies included: 1) no screening; 2) exercise electrocardiography followed by coronary angiography (CAG) if positive; 3) exercise echocardiography followed by CAG if positive; and 4) exercise SPECT followed by CAG if positive. Patients with negative screening test results did not undergo CAG.

Our model was a revised version of the Coronary Heart Disease Policy Model proposed by Weinstein et al.[16] We first simplified the model by incorporating cardiac arrest (CA) into death state, in view of the very low survival rates associated with CA. We then considered the states associated with coronary artery bypass grafting (CABG) and post-percutaneous transluminal coronary angioplasty (PTCA). Because of the nature of our study, we divided the angina state into silent ischemia and symptomatic ischemia. The original 12 CAD states were thereby modified and reduced to 7 CAD states: normal, silent ischemia, symptomatic ischemia, history of MI, post-PTCA, post-CABG, and death. An individual in the normal state at the time of the initial screening may remain in the normal state or move to the CAD event state in the next year, with probabilities determined by demographic and epidemiological factors such as age, gender, and other atherogenic risk factors, including diabetes mellitus. These transition probabilities were calculated using Framingham data estimated from equations developed by Anderson et al.[17] The method used to calculate the transition probabilities is described in detail in Appendices I to III (available online at www.jgim.org). Figure 1 shows a schematic representation of the decision tree.

If an individual in the normal state experiences a first CAD event, the event would be either myocardial ischemia (symptomatic or silent) or a non-fatal MI. Probabilities of myocardial ischemia or MI were assigned to these events.[18] The probability that initial myocardial ischemia was asymptomatic was estimated from a review of the literature dealing with silent ischemia in patients with diabetes (Table 1).[19] Those with myocardial ischemia then had the probability of falling in a particular disease category (1-, 2-, 3-vessel, or left-main trunk disease) in a certain age group assigned from the Coronary Artery Surgery Study (CASS) registry.[20]

The following assumptions were made concerning medications/interventions in this model: 1) patients with negative screening test results received no specific therapy; 2) all patients received one 325 mg-tablet of aspirin per day (U.S. Preventive Service Task Force Recommendation); 3) patients received simvastatin (40 mg/day) irrespective of baseline LDL levels based on the latest studies or guidelines[21,22]; 4) management after angiography was based on the anatomic pattern of vessel obstruction, and patients without vessel obstruction on angiography received no specific treatment; 5) patients with 1- or 2-vessel CAD on angiography underwent PTCA; 6) patients with 3-vessel or left-main trunk disease (LMD) on angiography underwent CABG; 7) patients who developed restenosis after PTCA underwent PTCA only one more time, so that PTCA was performed not more than twice—if they subsequently experienced restenosis, they underwent CABG; 8) patients with myocardial infarction developed relevant symptoms and received the appropriate treatment; 9) patients with silent myocardial ischemia did not receive specific anti-anginal therapy; and 10) PTCA reduced late MI in those with 1- or 2-vessel disease.

Baseline Prevalence of Coronary Artery Disease

We assumed that the prevalence of CAD in asymptomatic diabetic patients is determined by atherogenic risk factors age and gender to the same extent as in the general population; this was estimated from data provided by a review of the literature.[19] The prevalence of CAD in each risk state was calculated from the prevalence of CAD in the general population and the odds ratio for associated atherogenic risk factors for CAD, stratified by age and gender (Appendix II, available online at www.jgim.org). The baseline prevalence of CAD in different age groups of diabetics was derived from the Third National Health and

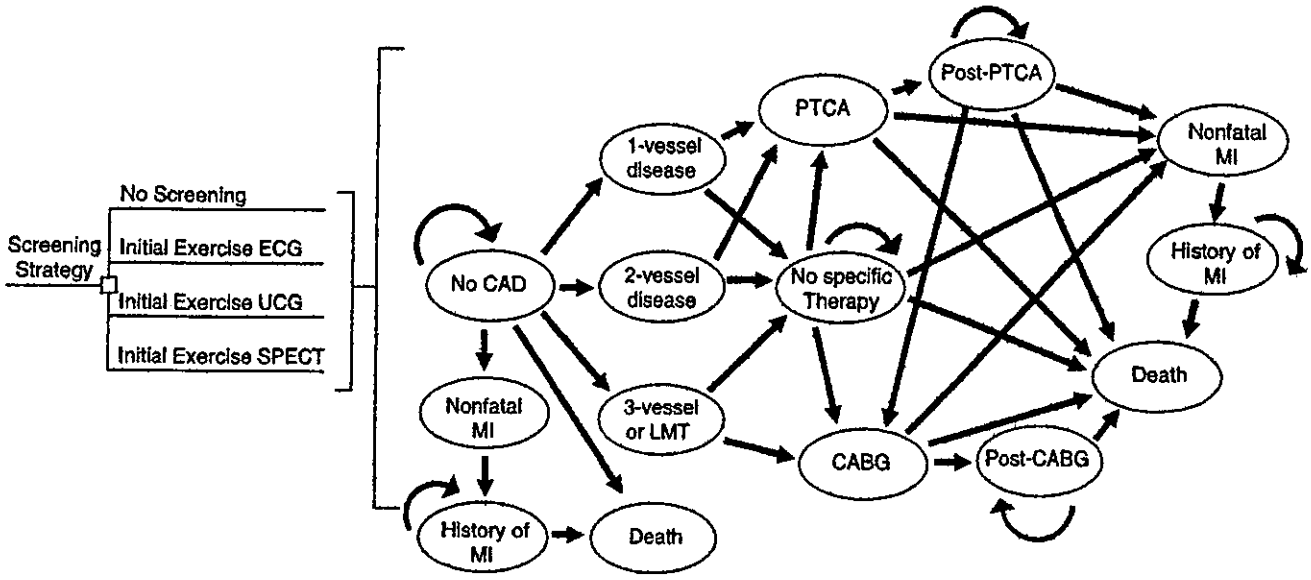

FIGURE 1. A Markov model of screening strategies for CAD in diabetic patients with additional atherogenic risk factors. Patients with silent myocardial ischemia detected by initial screening and patients with symptomatic myocardial ischemia developing in the years following received PTCA or CABG according to the number or location of their diseased vessels. Patients with false negative results by screening tests and those with silent myocardial ischemia developing in the years following do not receive specific therapy. ECG, electrocardiography; UCG, echocardiography; SPECT, single-photon emission-tomography; LMT, left-main trunk disease; CAD, coronary artery disease; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting.

Nutrition Examination Survey (NHANES III).[23] We then calibrated the prevalence data to match the estimated number of patients with stable angina (16,500,000) according to the American College of Cardiology/American Heart Association, as NHANES data are self-reported and likely to be influenced by self-reporting bias.[24,25] Relative risks were taken from the published literature, and were estimated by multivariate logistic regression using NHANES III data.[26,27] Table 1 shows the baseline prevalence of CAD.

Number of Diseased Vessels

The extent of CAD is expressed by the number of diseased vessels (0 to 3), with a separate category for left-main trunk disease as revealed by CAG. Probability data for different numbers of diseased vessels and LMD stratified by age were derived from the CASS registry.[20]

Characteristics of Screening Tests

The performances of screening tests were obtained from a meta-analysis of diagnostic tests, and are shown in Table 1. The sensitivity and specificity of exercise electrocardiography for detecting CAD were obtained from data pooled from 150 studies[28]; sensitivity and specificity of exercise echocardiography and exercise SPECT came from another meta-analysis, based on a summary of receiver operating characteristics (ROC) curve analysis.[29]

Complications of Intervention

We made the following assumptions concerning short-term sequels to intervention. CAG was associated with a 0.1% probability of death and a 0.06% of nonfatal MI, regardless of the extent of CAD.[30] PTCA was associated with mortality rates of 0.2% in 1-vessel disease and 0.9% in 2-vessel disease; the mortality rate of nonfatal MI was 3.5% in 1-vessel disease and 5.2% in 2-vessel disease.[31] CABG was associated with a mortality rate of 3.2%, and the probability of nonfatal MI was 7.0%.[32-34]

Long-term Prognosis

We assumed that the prognosis of patients with asymptomatic ischemia is the same as for patients with symptomatic ischemia.[16,35-38] We estimated the cycle-specific mortality in each health state based on a declining exponential approximation to life expectancy (DEALE; Appendix III, available online at www.jgim.org).[39-41] This method takes the mortality hazard as constant over a certain period of time (1 year in our analysis), and thus the survival probability declines exponentially over a certain period of time. Mortality rates were then determined according to patient characteristics (e.g., age, gender, extent of CAD, and treatment) using all-cause mortality from U.S. life tables, together with the standardized mortality ratio for patients with diabetes, the relative mortality ratio for the specific extent of disease from the CASS registry, and the mortality risk

Table 1. Baseline Values and Ranges in Sensitivity Analysis

Variables	Baseline Value	Lower Range	Upper Range	Reference
Prevalence of asymptomatic ischemia in base case (estimated)*	0.39	0.27	0.51	27, 38
Annual incidence of CAD in base case, per 1,000 (estimated)*	23.4	16.4	30.4	17
Proportion of silent ischemia in patients with myocardial ischemia†	0.4	0.38	0.62	19
Diagnostic performance of screening tests‡				
Exercise electrocardiography				
Sensitivity	0.68	0.23	1	28
Specificity	0.77	0.17	1	28
Exercise echocardiography				
Sensitivity	0.85	0.71	0.97	29
Specificity	0.77	0.37	0.96	29
Exercise SPECT				
Sensitivity	0.87	0.71	0.97	29
Specificity	0.64	0.27	1	29
Mortality risk reduction by CABG, %‡				
1- or 2-vessel disease	15	0	49	42
3-vessel disease	48	32	64	42
Left-main trunk disease	67	43	87	42
Risk reduction in late myocardial infarction with revascularization, %*				
PTCA	17	0	22	49
CABG	42	29	55	49
Risk reduction in the incidence of CAD by aspirin (primary prevention), %*	15	11	20	43
Risk reduction in late CAD events by aspirin (secondary prevention), %*	31	21	41	43
Risk reduction in all-cause mortality by aspirin (secondary prevention), %*	28	21	36	43
Risk reduction in the incidence of CAD by simvastatin (primary prevention), %*	25	18	33	21
Annual risk for revascularization by initial treatment and extent of disease*§				
Nonspecific therapy (1-vessel disease)	0.010	0.001	0.022	46, 50
Nonspecific therapy (2-vessel disease)	0.042	0.028	0.056	46, 50
Nonspecific therapy (3-vessel disease or left-main trunk disease)	0.075	0.061	0.089	46, 50
PTCA	0.036	0.026	0.046	29, 51
CABG	0.018	0.011	0.025	50, 51

* *Ranges based on ± 30% of base-case estimates. (Note: lower range of risk reduction in late myocardial infarction with PTCA was set to 0%.)*
† *Ranges based on reported proportions in the literature.*
‡ *Ranges based on the actual range among original studies in a meta-analysis.*
§ *The percentage of revascularizations that were CABG were as follows: 16% (1-vessel disease and initial nonspecific therapy); 58% (2-vessel disease and initial nonspecific therapy); 87% (3-vessel disease or left-main trunk disease and nonspecific therapy); 22% (initial PTCA); and 7% (initial CABG).*
SPECT, single-photon emission-tomography; CAD, coronary artery disease; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting.

reduction by medication or interventions.[20,21,38,42–44] The standardized mortality ratio for patients with diabetes was the ratio of the all-cause mortality rate in persons with diabetes to the mortality rate of the general population. We used 1.5 as the standardized mortality ratio derived from the population-based Framingham Heart Study.[45]

The mortality risk ratio for the extent of CAD and mortality risk reduction by CABG (the proportion of coronary artery disease-related mortality reduced by surgery) were derived so as to match the mean survival time at 10 years that was reported in a systematic review of 7 CABG trials.[42] We assumed that the risk reduction by CABG persisted for 10 years, because the initial efficacy of therapeutic interventions usually has a near-linear decline. We also assumed that the efficacy of PTCA in patients with single- or double-vessel disease was the same as that of CABG.[46,47] For the effect of medications, a 15% reduction for aspirin and 25% reduction for simvastatin in the relative risk for the incidence of major coronary events were applied to the incidence of CAD in our model; these data were derived from studies conducted in primary prevention settings.[21,44] In secondary prevention settings, a 31% reduction in the odds of nonfatal MI derived from pooled trials was applied to nonfatal MI and to death from chronic coronary disease.[43] Because the median follow-up time in the secondary prevention trials for high-risk patients was 3 years, the benefit of aspirin was taken to continue for 3 years.[48]

We took the rates of nonfatal MI and revascularization to vary depending on the initial treatment, and assumed that the risks of subsequent nonfatal MI, PTCA, or CABG depend on the extent of the CAD and the type of initial treatment (Table 1).[46,47,49–51]

Costs and Discounting

All cost estimates are shown in Table 2. For diabetes care, we used the costs of conventional diabetes control based on the U.S. scenario by the CDC (Centers for Disease