Table 2. Costs and Health Utility Estimates

Variables	Baseline Value	Lower Range	Upper Range	Reference
Costs (2003 $)*				
Exercise electrocardiography	140	98	182	53
Exercise echocardiography	334	234	434	53
Exercise SPECT	730	511	949	53
Coronary angiography	6,035	4,225	7,846	53
PTCA	15,884	11,119	20,650	53
CABG	42,125	29,487	54,762	53
Annual cost				
Symptomatic myocardial ischemia	1,224	857	1,591	56
History of MI	1,431	1,002	1,860	56
Conventional diabetes care	1,113	779	1,447	52
Simvastatin	1,293	905	1,680	58
Aspirin	16	11	21	48
One-time cost				
Symptomatic myocardial ischemia	2,992	2,094	3,889	56
MI death	23,843	16,690	30,996	56
MI survival	21,161	14,813	27,509	56
Health utility†				
Symptomatic myocardial ischemia (SG)‡	0.947	0.663	1.0	61
History of MI (TTO)‡	0.880	0.616	1.0	62

* *Ranges for cost estimates represent ± 30% of baseline estimate.*
† *Ranges for health utility based on ± 30% of base-case estimates.*
‡ *SG, standard gamble; TTO, time tradeoff.*
SPECT, single-photon emission-tomography; CAD, coronary artery disease; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting.

Control) Diabetes Cost-effectiveness Group. This included drug costs based on the experience of the United Kingdom Prospective Diabetes Study (UKPDS) and costs of outpatient visits, self-testing, and care management based on U.S. clinical practice.[52] We used the costs of diagnostic tests and interventions based on the other cost-effectiveness model of CAD, and verified the original citations. Exercise test costs were obtained from Medicare-allowed charges, including both technical and professional fees. Hospital costs for coronary angiography and revascularization were taken from Medicare administrative data, and professional costs associated with cardiac interventions came from the Medicare schedule.[53-55] Annual costs of outpatient treatment for CAD were taken from the published literature that estimated the direct medical costs of CAD.[56,57] The cost of aspirin was derived from the cost-effectiveness model for these drugs,[48] and the cost of simvastatin was calculated by using the average wholesale prices[58]; we then adjusted for the adherence rate of the primary prevention trials.[21,44,59] The costs of patient travel, waiting, and treatment time associated with office visits were also estimated using average hourly earnings of employed persons reporting earnings from the Current Population Survey in the United States.[55] We did not assign any CAD-specific costs for silent myocardial ischemia.

All costs were converted to 2003 U.S. dollars using the medical care component of the Consumer Price Index. All costs and years of life were discounted at 3% per year to reflect time preference, because people are more likely to prefer having money and material goods sooner rather than later.[60]

Health Utility

Health utility values, running between 1 for perfect health and 0 for death, were used to calculate QALYs for patients. The utilities for symptomatic myocardial ischemia and myocardial infarction were based on information from a literature search. Health utilities for an individual who experienced angina and MI are shown in Table 2. The health utility for symptomatic myocardial ischemia was a weighted average of the two most severe groups with angina, based on the data obtained from the literature.[61,62] All other live statuses were set to 1 in health utility.

Sensitivity Analysis

We performed one-way sensitivity analyses on all of the variables within clinically plausible ranges. The ranges used for this are shown in Table 1. Ninety-five percent confidence intervals (CI) were used as the range of the variables in the sensitivity analysis where applicable; otherwise a ±30% range was used. There were two exceptions: we used the range of sensitivities and specificities of diagnostic tests reported in the meta-analysis because the 95% CIs reported

in the meta-analysis were extremely narrow[28,29]; and we allowed the lower range of risk reduction in late MI with PTCA to be 0%, because in diabetics with asymptomatic 1- or 2-vessel disease there is little evidence to support the effect of PTCA.

The results of one-way sensitivity analysis on diagnostic test performance could be misleading, because sensitivity and specificity are liable to move at the same time depending on the positivity threshold, that is, the sensitivity increases and the specificity falls when we take lenient positivity criteria (smaller ST depression as positive). We therefore conducted two-way sensitivity analysis on diagnostic test performance. We plotted 1 – specificity on the x-axis and sensitivity on the y-axis for comparison with the ROC curve. Straight lines indicate possible thresholds for allocating health care resources. For a particular cost-effectiveness threshold, points to the upper left of the lines indicate that these tests have a lower cost-effectiveness ratio relative to no screening than that depicted by the line. The asterisk indicates the combination of sensitivity and specificity for the base case. The point corresponding to sensitivity and 1 – specificity was expected to move around along the ROC curve through the asterisk, from the point (x = 0, y = 0) to the point (x = 1, y = 1) as the positivity criterion becomes lenient. For the usual diagnostic tests, the combination of sensitivity and specificity failed to take the point below the straight line that connects the point (x = 0, y = 0) and the point (x = 1, y = 1).

Analyses were also conducted for cohorts of different ages and/or different pairs of additional atherogenic risk factors. We also evaluated the effect of the discounting rate in the range recommended by the Panel on Cost-effectiveness in Health and Medicine (0% to 5%).[60]

RESULTS

Baseline Analysis

Table 3 shows the quality-adjusted life expectancy, lifetime cost, and incremental cost-effectiveness ratio in asymptomatic 55- and 60-year-old diabetic men with hypertension and smoking. Compared to no screening strategy, the incremental cost-effectiveness ratio of exercise electrocardiography was $93,500/QALY and that of exercise echocardiography was $88,400/QALY in 55-year-old men. The incremental cost-effectiveness ratio of exercise electrocardiography was within the acceptable range ($41,600/QALY), but was weakly dominated by that of exercise echocardiography ($40,800/QALY) in 60-year-old men. The exercise SPECT strategy had higher cost and smaller benefit than exercise echocardiography, and was therefore dominated by other strategies.

Patients with Different Characteristics

The incremental cost-effectiveness varied depending on age and the pairing of additional atherogenic risk factors. The cost-effectiveness of exercise echocardiography relative to a no screening strategy was sensitive to the age of patients at screening. It fell from $327,400/QALY to $25,600/QALY as the age at the initial screening rose from 50 to 70 years (Fig. 2). Figure 3 shows incremental cost-effectiveness ratios for exercise echocardiography and exercise electrocardiography compared with no screening for two age groups (55 and 60 years of age), and the 10 possible pairs of additional atherogenic risk factors. The incremental cost-effectiveness ratio of exercise echocardiography

Table 3. Quality-adjusted Life Expectancy, Cost, and Cost-effectiveness Ratios for Asymptomatic 55- and 60-Year-old Diabetic Men with Hypertension and Smoking

Screening Strategy	Expected Value		Incremental Value		Incremental Cost-effectiveness Ratio*
	Cost	QALYs	Cost	QALYs	
	$	Y	$	y	$/y
55-year-old					
No screening	135,447	11.754			
Exercise electrocardiography	142,179	11.826	(6,732)	(0.072)	(93,500)
Exercise echocardiography	143,847	11.849	8,400	0.095	88,400
Exercise SPECT	144,806	11.841			Dominated
	Y	$	y	$/y	$
60-year-old					
No screening	123,301	9.911			
Exercise electrocardiography	129,617	10.063	(6,316)	(0.152)	(41,600)
Exercise echocardiography	131,180	10.104	7,879	0.193	40,800
Exercise SPECT	132,129	10.100			Dominated

** Incremental cost-effectiveness ratios for each strategy are calculated compared with the next strategy other than the weakly dominated/dominated strategy shown in the table, and are rounded to the nearest $100. In this case, the incremental cost-effectiveness ratio of electrocardiography was weakly dominated by echocardiography, and thus was put in parentheses. Incremental cost-effectiveness ratio of echocardiography was calculated compared with no screening. (Note: cost-effectiveness ratios calculated directly by quality-adjusted life expectancies and costs from the table may differ due to rounding.)*

SPECT, single-photon emission-tomography; QALY, quality-adjusted life-year.

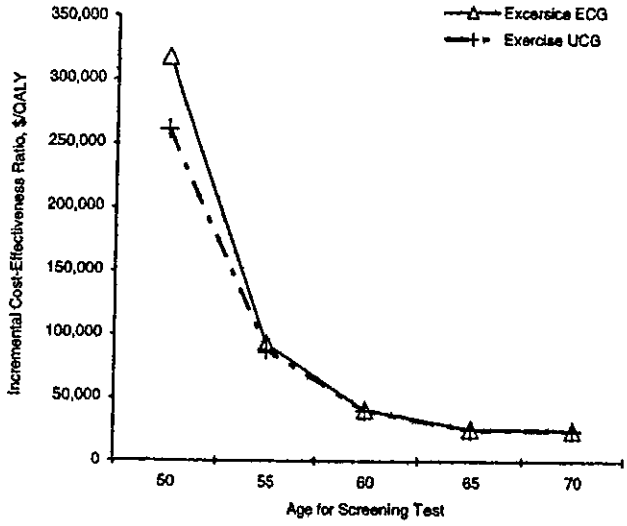

FIGURE 2. Cost-effectiveness of screening strategies relative to no screening strategy as a function of age at screening. Triangles (Δ) represent exercise electrocardiography compared with no screening; plus signs (+) represent exercise echocardiography compared with no testing.

compared with no screening ranged from $83,700/QALY (HTN [hypertension]/low HDL) to $126,300/QALY (high LDL/proteinuria) in 55-year-old men, depending on the additional atherogenic risk factors. In 60-year-old men, our model was fairly insensitive to the difference between pairs of risk factors; the incremental cost-effectiveness ratio of exercise echocardiography compared to no screening ranged from $38,600/QALY (HTN/low HDL) to $50,500/QALY (high LDL/proteinuria), and from $39,400/QALY to $53,700/QALY (high LDL/proteinuria) for exercise electrocardiography compared to no screening.

Sensitivity Analysis

We performed sensitivity analyses on other variables in 60-year-old men, because the incremental cost-effectiveness ratio was within the acceptable range in this cohort. Our results were sensitive to sensitivity and specificity of diagnostic tests in one-way analysis, but were not sensitive to the discount rate, the cost of CABG, the mortality risk reduction by CABG or PTCA, the risk reduction of MI by CABG or PTCA, the cost of screening tests, the proportion of patients with silent myocardial ischemia, or the health utility of CAD.

Our results were also sensitive to diagnostic test performance in two-way sensitivity analysis (Fig. 4). For both exercise echocardiography and electrocardiography, the incremental cost-effectiveness ratio exceeded $50,000/QALY if the sensitivity was very high, so that the specificity was very low. The incremental cost-effectiveness for echocardiography was always below $60,000/QALY for any combination of sensitivity and specificity; in the case of electrocardiography, the incremental cost-effectiveness could exceed $60,000/QALY, but this is very unlikely

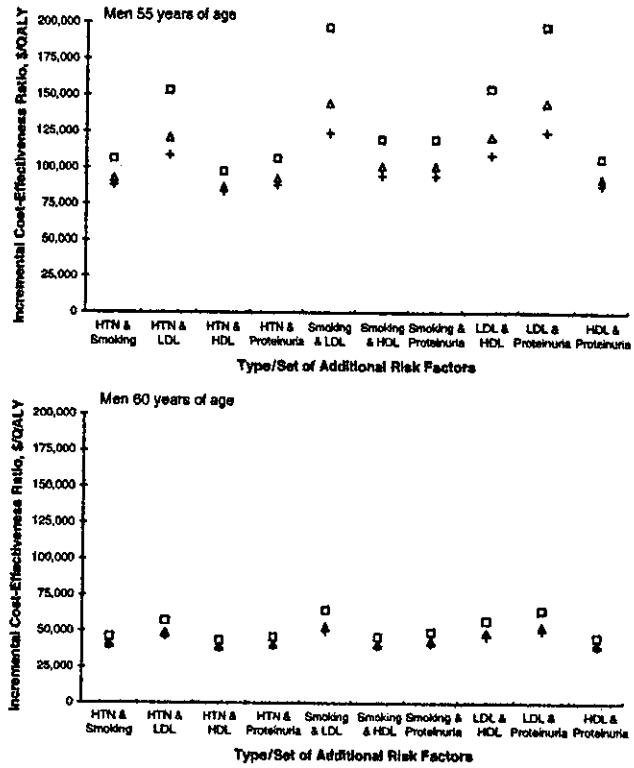

FIGURE 3. Cost-effectiveness ratio for alternative patient cohorts. Squares (□) represent SPECT compared with no screening; triangles (Δ) represent exercise electrocardiography compared with no screening; and plus signs (+) represent exercise echocardiography compared with no screening.
SPECT, single-photon emission-tomography; QALY, quality-adjusted life expectancy; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HTN, hypertension.

because the cost-effectiveness threshold of $60,000/QALY was close to the straight line connecting (x = 0, y = 0) to (x = 1, y = 1), below which no combination of sensitivity and specificity can fall.

DISCUSSION

No studies currently exist of the long-term costs and the effectiveness of CAD screening strategies in asymptomatic patients with diabetes. We have therefore developed a decision- analytic model to conduct cost-effectiveness analysis using published data to simulate patients in diverse situations. Our results suggest that screening of asymptomatic 60-year-old diabetic men with hypertension and smoking for CAD is cost-effective (relative to no screening). Exercise echocardiography dominated over electrocardiography and exercise SPECT. The initial screening cost advantage might be partially offset by the subsequent costs of medical care for patients with silent myocardial ischemia who eluded this screening test, although exercise electrocardiography is less expensive than exercise echocardiography. Its incremental cost-effectiveness ratio, however,

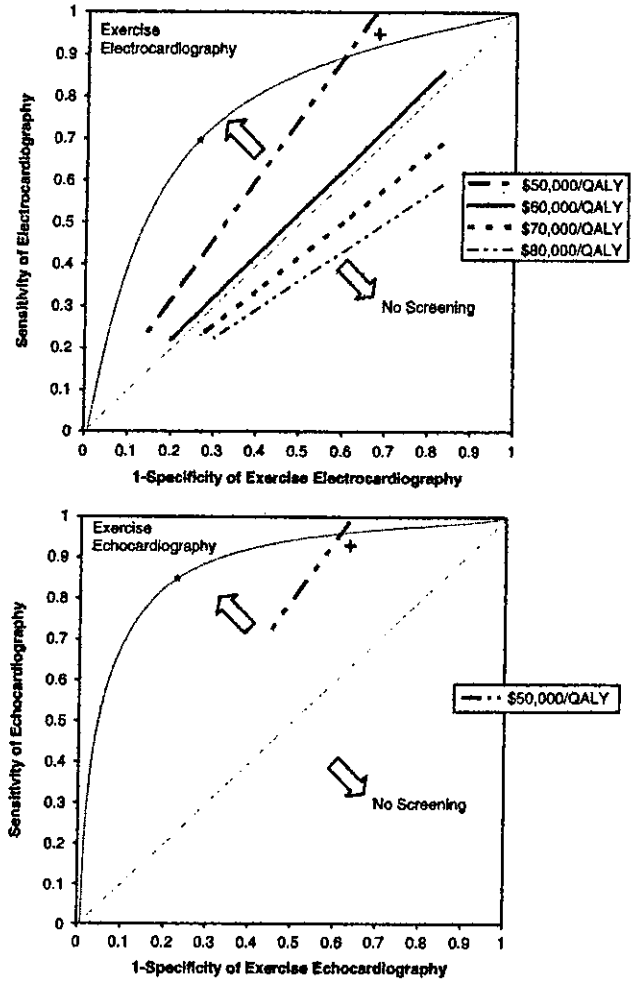

FIGURE 4. Two-way sensitivity analysis of the diagnostic performance of exercise electrocardiography and exercise echocardiography. Results of the two-way sensitivity analysis of the sensitivity and specificity of exercise electrocardiography and echocardiography, and the acceptable cost-effectiveness threshold for 60-year-old diabetic men with hypertension and smoking. We plotted 1 – specificity on the x-axis and sensitivity on the y-axis. Lines indicate four possible thresholds for allocating health care resources, and were confined to the actual data of sensitivity and specificity. For a particular cost-effectiveness threshold, points to the top left of the lines indicate that these tests, compared with no screening, have a lower cost-effectiveness ratio than that depicted by the line. The asterisks (*) indicate the pair of sensitivity and specificity for the base case; incremental cost-effectiveness of both tests was lower than $50,000 compared with no screening. Plus signs (+) indicate other possible examples; incremental cost-effectiveness of both tests was between $50,000 and $60,000 compared with no screening.

was in the acceptable range in cases where exercise echocardiography would not be available for practical reasons. Exercise SPECT was less cost-effective than the other two screening strategies, and thus dominated the other strategies as its cost was disproportionately higher than that for exercise echocardiography in spite of its favorable life-year saving effect.

Sox et al. suggested that the cost-effectiveness of exercise electrocardiography screening of CAD in 60-year-old men with one or more risk factors was $20,504 per additional year of life, and concluded that it might be cost-effective in a high-risk population, though the decision is close.[13] This conclusion would support our results, though we could not directly compare this with our results because that model did not consider utility, time preference, or the high mortality risk ratio for diabetics, and was not adjusted for the doubled consumer price index since then. The present results should also be interpreted in the context of other generally accepted screening strategies for various diseases. For example, screening mammography for women aged 50 years or older costs from $3,400/QALY to $84,830/QALY; annual screening for cervical cancer for women aged 21 years or older is $50,000/QALY; and hypertension screening for asymptomatic 20-year-olds costs $48,000/QALY for men and $87,000/QALY for women.[63–65] Thus, screening for CAD with exercise echocardiography in asymptomatic diabetic men with hypertension and smoking seems to be acceptable from a societal perspective.

Our model was sensitive to the age of patients and different pairs of additional atherogenic risk factors. Any screening strategy generally becomes more cost-effective by targeting groups of patients with a higher prevalence and lifetime incidence of CAD. In the present work, in a hypothetical cohort of 60-year-old diabetic men with proteinuria and high LDL, the incremental cost-effectiveness of exercise electrocardiography was $53,400/QALY, but in 60-year-old diabetic men with HTN and smoking it falls to $41,000/QALY.

Our model was also sensitive to diagnostic test performance. We explained the results of two-way sensitivity analysis in relation to the ROC curve; the sensitivity and specificity combination pair moves along the curve depending on the test threshold. By relaxing the threshold the point moves toward the right top; by tightening the threshold it moves to the bottom left. There are also other factors that could shift the ROC itself toward the point (x = 0, y = 1), such as younger age and high prevalence of disease, or away from this point.[66,67] We should therefore interpret our results in the context of these factors. Our results suggest that the incremental cost-effectiveness ratio exceeds $50,000/QALY if the sensitivity and specificity combination is close to the point (x = 1, y = 1). Our result was robust in terms of this point being so far from that of the base case, but we should realize the situations where the cost-effectiveness ratio is likely to fall into an unacceptable range; relaxing the positivity criteria (high-sensitivity test; e.g., use smaller ST depression as positive for exercise electrocardiography) makes the point shift to the top right; the ROC curve itself shifts toward the diagonal line if patients are older and/or at high risk. A test of high sensitivity is usually used for "screening," and a high-specificity test for "confirming" diagnoses.[66] From the standpoint of resource allocation, we

should therefore avoid a "screening" approach with very high sensitivity by tightening the positivity criteria (e.g., use larger ST depression as positive for exercise electrocardiography), especially when an older and/or lower risk population is being tested.

Assumptions were made in order to simplify the complex decision-making process of the real clinical setting and develop an understandable model. The present results must therefore be interpreted in light of the limitations of using heterogeneous data sources and these simplifying assumptions. For example, we did not incorporate the effects of intensive diabetes control, which should be encouraged when CAD is detected in asymptomatic patients with diabetes. In view of the increased morbidity and mortality from CAD in these patients, and the striking influence of diabetes mellitus observed in large-scale trials,[68,69] the cost-effectiveness of CAD screening might be underestimated in our model.

Cost-effectiveness analyses of the present type assist not only in assessing the economic impact of a significant intervention, such as screening for CAD in patients with diabetes, but also in identifying areas of uncertainty to improve decision making. The present analysis has exposed uncertainty surrounding probability estimates. First, it was assumed that the prevalence of CAD in asymptomatic diabetic men and two other atherogenic risk factors was comparable to that in symptomatic diabetic men with the same atherogenic risk factors. The prevalence of CAD in asymptomatic patients with diabetes and the influence of atherogenic risk factors in these cases were not clear, and the reported prevalence of CAD in asymptomatic patients with diabetes ranged widely depending on the patients' characteristics.[19] Recently, Bacci et al. studied the prevalence of myocardial ischemia using coronary angiography as a reference standard in asymptomatic type 2 diabetic patients having two or more additional atherogenic risk factors.[70] The prevalence data they found were not directly applicable to our analysis because they were not stratified by atherogenic risk factors, but our estimates were nevertheless broadly similar. Second, the effect of aspirin was assumed to continue for only 3 years, because of the lack of relevant data in secondary prevention of CAD. In cases of longer duration of the beneficial effect of aspirin, an initial screening strategy with exercise echocardiography might be more attractive. Third, we assumed that PTCA reduces MI in asymptomatic patients with 1- or 2-vessel disease, but there is little evidence to support this. We resolved this uncertainty by conducting strict sensitivity analysis assuming that the effect of PTCA was zero, and our model proved to be insensitive to this effect; this area of uncertainty, however, should be resolved for asymptomatic patients tests. Fourth, there were still few good data available on the degree of statins' risk reduction of CAD in those with diabetes in the primary care setting, especially for second-generation statins, such as atorvastatin. We therefore utilized currently available data, but the estimated cost-effectiveness of screening strategies might be less attractive if data on more potent statins were available and incorporated into our model. Last, we did not specify race/ethnicity, because equations to estimate the incidence of CAD from the Framingham study did not allow us to incorporate the difference between racial and ethnic groups, and there were not sufficient race-specific data on differences in prevalence, therapy/intervention, or disease-specific mortality ratios.[17]

We also assumed that the prognosis of patients with asymptomatic ischemia was the same as for those with symptomatic ischemia. The prognostic importance of asymptomatic ischemia is still controversial despite a wealth of data on the subject, perhaps because the term loosely encompasses a wide range of findings from different investigative modalities (e.g., continuous electrocardiography monitoring).[14,71] To find suitable estimates for our analysis, the prognosis of silent ischemia should be viewed from the standpoint of two groups of patients: those with and without a history of angina/MI, taking diagnostic modalities into account. Romeo et al. directly compared the prognoses between those without asymptomatic ischemia and those in whom it was detected by exercise tolerance testing, and found that the mortality risk ratios between the two groups were not different. Another way is to compare the mortality risk ratios of asymptomatic patients with that of the symptomatic.[35] The mortality risk ratios of hypercholesterolemic men with asymptomatic ischemia detected by exercise tolerance tests have been reported in two studies, and these ratios (5.2 and 5.9) are very similar to the mortality risk ratio of 5.9 estimated from the study on symptomatic patients and the U.S. life tables.[16,36-38] Although these data support our assumption, we believe that further studies are needed to derive more accurate direct evidence by focusing more on the range of subjects and diagnostic modalities.

In conclusion, screening of asymptomatic diabetic men age 60 years or older with two additional atherogenic high-risk factors for CAD should be cost-effective from the societal perspective. Exercise echocardiography offers the most rational use of health care resources, followed by exercise electrocardiography.

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APPENDIX I - Incidence of CAD

Transition probabilities associated with the incidence of CAD were calculated using the methods of the CDC Diabetes Cost-effectiveness Group.[52] The probability of moving from the Normal state to CAD (P(CAD)), adjusted for coronary risk factors, was derived from a Framingham Heart Study. The equations used to calculate P(CAD) are described in Anderson et al. in detail.[17] The probability that initial CAD was MI (P(MI|CAD)) was obtained from Hunink et al. (0.6171 for 35–44 year-old, 0.544 for 45–54, 0.4739 for 55–64, 0.4929 for 65–74, and 0.5101 for 75+).[18]

The probability that initial CAD was myocardial ischemia (P(Myocardial ischemia | CAD)) was calculated by substituting the P(MI|CAD) (1- P(MI|CAD)), and the probability that initial myocardial ischemia was asymptomatic was assigned; then was multiplied by the probability that myocardial ischemia was in an certain disease category (1-vessel, 2-vessel, 3-vessel, or left main trunk disease) stratified by age groups based on data from the Coronary Artery Surgery Study (CASS) registry.[20]

APENDIX II - Prevalence of CAD

The prevalence of CAD (P_0) in a particular age group with a particular risk factor was calculated as follows:

$$P_0 \text{ (age, risk)} = \text{Pam}*RR_r$$

In this formula,

- age indicates the age group (55-64, 65-74, 75+)
- risk indicates the type of risk factor
- Pam indicates calibrated age-specific prevalence of CAD in the general male population. The original age- and sex-specific estimates of prevalence of CAD (Pas) were obtained from the Third National Health and Nutrition Examination Survey (NHANES III).[23] These self-reported data are liable to be influenced by self-reporting bias[24]; therefore, to derive the prevalence of CAD (Pam), we calibrated Pas to match the estimated number of patients with stable angina (16,500,000) by the American College of Cardiology/American Heart Association,[25] using the following formula:

$$Pam_{ij} = Pas_{ij} * \frac{16{,}500{,}000}{\sum Pas_{ij} * Pop\_as_{ij}}$$

In this equation, Pas_{ij} denotes the age and sex specific prevalence of CAD from NHANES III (i=25–34, 35–44 45–54, 55–64, 65–74, or 75+; j=male or female), Pop_as_{ij} denotes the corresponding age and sex specific population (U.S. census 2000), and $\sum Pas_{ij} * Pop\_as_{ij}$ is the sum of the numbers of patients with stable angina in different age and sex groups estimated from NHANES III prevalence data.

- RR_r denotes the ratio of the prevalence of CAD for those with a particular risk factor **r** to those without **r**. RR_r was estimated from the odds ratio (OR) using the following formula,[26] because we could only find ORs relevant to these risk factors:
  Values of ORs for HTN (2.1), HDL<35mg/dl (2.1), Smoking (1.7), Proteinuria (1.7), LDL (1.0), and diabetes mellitus (1.4) were obtained from Alexander et al.[27]

$$RRr = \frac{OR}{(1-P_{am})+(P_{am}*OR)}$$

APPENDIX III – Mortality

We estimated the cycle specific mortality in each health state based on a falling exponential approximation to life expectancy (DEALE) method.[39-41] This method assumes that the mortality rate is constant (one year in our analysis), and thus the survival probability declines exponentially over a certain period of time. The patient specific probability of death in one year (P_3) is then given by:

$$P_3 \text{ (age, risk)} = 1 - \exp[-\mu_{am} * RR_r * (1-RRR_t)]$$

In this equation,

- age indicates a patient's age
- risk indicates types of risk factors
- μ_{am} indicates the baseline age-specific mortality rate per year in males derived from U.S. life tables (2000).[38]
- RR_r indicates the relative mortality ratio of a particular risk factor **r** compared with the baseline age-specific mortality rate. We used 1.5 as the standardized mortality ratio derived from the population-based Framingham Heart Study. The relative mortality ratio for patients with one-vessel (2.35), two-vessel (4.11), and three vessels/ left-main coronary artery disease (6.61) were extracted from the CASS registry.[20]
- RRR_t denotes the relative mortality risk reduction by a particular therapy or intervention **t**.

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An evaluation of risk factors for adverse drug events associated with angiotensin-converting enzyme inhibitors

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Abstract

Rationale, aims and objectives To identify potential factors leading to discontinuation of angiotensin-converting enzyme (ACE) inhibitors because of adverse drug events. **Methods** Retrospective cohort study was conducted at outpatient clinics affiliated with an urban tertiary care hospital. ACE inhibitors were administered to 2225 consecutive outpatients. **Results** In 19% of the total cohort, ACE inhibitors were discontinued because of adverse drug events. Cox proportional hazard model identified the following independent risk factors for discontinuation because of adverse drug events: age, female gender, ethnicity other than African American or Latino, no history of previous ACE inhibitor use, history of cough caused by another ACE inhibitor, hypertension, anxiety or depression, no hemodialysis, and elevated creatinine. History of smoking was shown to be a risk factor for cough [hazard ratio (HR): 2.5; 95% confidence interval (CI): 1.1–5.7], angioedema (HR: 2.7; 95% CI: 1.1–7.0), and hyperkalaemia (HR: 5.4; 95% CI: 1.3–23.2). History of ACE inhibitor-induced cough was not only a risk factor for cough (HR: 12.9; 95% CI: 7.5–22.3) but also for angioedema (HR: 9.1; 95% CI: 2.1–39.9). Patients with creatinine ≥ 1.6 mg dL^{-1} were likely to discontinue ACE inhibitors because of renal dysfunction (HR: 4.7; 95% CI: 1.5–12.7) and hyperkalaemia (HR: 10.9; 95% CI: 3.1–39.0). East Asians were more likely to develop cough (HR: 2.5; 95% CI: 1.1–5.7) and hyperkalaemia (HR: 80.3; 95% CI: 5.4–1190) and African Americans to develop angioedema (HR: 3.5; 95% CI: 1.3–8.9). **Conclusions** Although further validation is necessary, these risk factors should help doctors identify patients with elevated risk for adverse drug events because of ACE inhibitors.

Introduction

Patient safety is an important issue in medical practice today. Many adverse events are caused by medications, and such events are called adverse drug events (ADEs) (Bates & Gawande 2000). ADEs are common in the ambulatory setting with a reported incidence of 25% (Gandhi *et al.* 2003). These ADEs have important consequences, and cause admissions, additional utilization, and time

away from work, and they have also been associated with lower patient satisfaction (Gandhi *et al.* 2000). Reducing ADE rates by more careful prescription and monitoring would undoubtedly improve patient safety (Leape *et al.* 2002). Identification of those with a high risk for ADEs represents a potentially effective approach for reducing ADE rates (Bates *et al.* 1999).

ADEs among outpatients were frequently associated with the use of angiotensin-converting enzyme (ACE) inhibitors and in fact 8% of ADEs among outpatients were attributed to ACE inhibitors (Gandhi *et al.* 2003). ACE inhibitors have been shown to improve the prognosis of patients with a variety of cardiovascular diseases, and are prescribed for a substantial number of patients (Khalil *et al.* 2001). ADEs because of ACE inhibitors include cough (incidence: 5–25%), angioedema (<1%), renal dysfunction (1–4%), hyperkelaemia (<1%), dysgeusia (1–7%), and cytopenia (<1%), resulting in drug discontinuation for a significant fraction of patients (Israili & Hall 1992; Alderman 1996; Kostis *et al.* 1996; Squire 2002). It should be noted that most of the epidemiological data regarding ADEs attributed to ACE inhibitors came from clinical trials and that the characteristics and behaviour of patients enrolled in these trials were different from those of general patients (Cleland & Clark 1999).

Angiotensin II receptor blockers (ARBs) have recently come into the market and are often substituted for ACE inhibitors for those experiencing cough as an ADE (Grossman *et al.* 2000). However, accumulated evidence suggests that ARBs are not as effective as ACE inhibitors and are 1.5–3 times more costly in the US (Grossman *et al.* 2000), so that switching from ACE inhibitors to ARBs unnecessarily results in less good clinical outcomes and higher medication costs. Furthermore, ARBs are not appropriate as a remedy for ADEs related to ACE inhibitors other than cough (Tabibiazar *et al.* 2001). Thus, it would be useful to identify patients with a high risk of discontinuing ACE inhibitors because of ADEs, especially such life-threatening ADEs as angioedema and hyperkalaemia.

Because few data are available regarding the epidemiology and the risk factors for discontinuation of ACE inhibitors because of ADEs among general patients, we undertook a study to address this issue. Our goals were (i) to identify the incidence of discontinuation of ACE inhibitors because of ADEs in ambulatory settings; (ii) to identify the type and frequency of ADEs because of ACE inhibitors; and (iii) to identify by means of multivariate analyses the independent risk factors for discontinuation of ACE inhibitors because of ADEs.

Methods

Study design and patient population

We performed a retrospective cohort study of consecutive patients at the outpatient clinic of Brigham and Women's Hospital in Boston, MA. The cohort included all outpatients who were prescribed an ACE inhibitor for the first time between January 2000 and December 2001. Follow-up data were obtained until May 2002. We excluded patients who had received the same kind of ACE inhibitors in the past, for whom doctors had refilled ACE inhibitors previously prescribed at other clinics, in whom starting date of the drug administration was not identified, and those who were not followed up after the prescription of ACE inhibitors. The Human Research Committee at Brigham and Women's Hospital approved this study.

Data collection

All new prescriptions of ACE inhibitors were extracted from electronic medical records and manually reviewed to determine whether they met inclusion criteria.

ADEs because of ACE inhibitors were defined as follows: ADEs that developed after the prescription of ACE inhibitors; those without any other causative reasons; and those recognized as ACE inhibitor-induced and for which medication was discontinued. We selected four ADEs (dry cough, angioedema, renal dysfunction, and hyperkalaemia) to explore their risk factors. We classified renal dysfunction or hyperkalaemia as ADEs when the doctor had discontinued the ACE inhibitor because of an increase in creatinine or serum potassium (i.e. we did not set threshold values).

Potential risk factors for ADEs caused by ACE inhibitors included demographic characteristics,

medical comorbid conditions, smoking status, history of using other types of ACE inhibitors, history of cough caused by other types of ACE inhibitors, history of angioedema caused by other types of ACE inhibitors, and medications used at the time of prescription of an ACE inhibitor (antihypertensive drugs, non-steroidal anti-inflammatory drugs, aspirin, and cyclo-oxygenase-2 inhibitors). We treated age in two ways, as continuous and in four categories (<50, 50–59, 60–69, and ≥70). We also treated the creatinine value in two ways, as continuous and binary (<1.6 mg dL^{-1}, ≥1.6 mg dL^{-1}). Smoking status was categorized into two groups (current and past smoker vs. never smoker) and ethnicity into six groups (White, African American, Latino, East Asian, Non-East Asian, and others).

Statistical analysis

The number of days from the prescription of ACE inhibitor to its withdrawal because of ADEs was considered the right-censored outcome. We first calculated the Kaplan-Meier estimates of the proportion of patients who discontinued the ACE inhibitor because of any form of ADEs. Cox proportional hazards models were used to determine variables independently associated with the time to discontinuation of the ACE inhibitor because of any ADE and drug-induced cough, angioedema, renal dysfunction, and hyperkalaemia. Strength of association was represented with the hazard ratio (HR) and 95% confidence intervals (CIs). To identify independent risk factors, we developed multivariate models for potential risk factors, including variables associated with withdrawal because of ADEs ($P < 0.2$) identified in the univariate models. History of other ACE inhibitors was included in the model to evaluate whether this information would be a negative risk (protective) factor. These variables were then entered with a backward elimination approach to retain factors with $P < 0.05$. The chi-square test was used to evaluate the effects of type of ADEs on substitution with ARBs.

SAS software version 8.02 (SAS Institute Inc., Cary, NC, USA) and S-plus software version 6.0 (Insightful Corp., Seattle, WA, USA) were used for all statistical analyses.

Results

Patient characteristics

During the study period, 2225 patients were found to be eligible. The mean age was 58 years, and 41% were men (Table 1). About half of the patients were White, followed by African American and Latino. Asians accounted for 2.5%. A history of use of other ACE inhibitors was present in 491 patients (22%), 36 patients had a history of cough and five angioedema because of ACE inhibitors. Patients with hypertension made up 86% of the total and those with diabetes mellitus, 34%. About one-third of the patients were taking at least one of diuretics, beta blockers, or low dose aspirin when the ACE inhibitors were prescribed. The median follow-up for patients without ADEs was 336 days (95% CI: 318–351).

Discontinuation of ACE inhibitors because of ADEs

Among the patients who were prescribed ACE inhibitors, 422 (19%) stopped taking ACE inhibitors because of any kind of ADEs, and this rate was similar for all ACE inhibitors except benazepril (Table 2). Lisinopril was the most frequently prescribed ACE inhibitor, accounting for 81% (1809/2225). Cough was the most frequently recorded ADE, followed by angioedema and dizziness. Renal dysfunction and hyperkalaemia were the reasons to discontinue ACE inhibitors in 0.6% of patients. Thirteen per cent of the patients also stopped ACE inhibitors because of other reasons than ADEs, and 1506 (68%) continued ACE inhibitors until the end of the study. Kaplan-Meier estimates showed that 80% (95% CI: 78–82) of the patients remained on ACE inhibitors for 1 years and 74% (95% CI: 71–76) for 2 years (Fig. 1).

Risk factors for ADEs

Univariate correlates of discontinuation because of any kind of ADEs included older age, female gender, ethnicity other than African American or Latino, history of smoking, history of ACE inhibitor-induced cough, hypertension, diabetes mellitus, anxiety or depression or no other psychiatric diseases, no hemodialysis, and creatinine (mg dL^{-1}). History of other

Table 1 Patient characteristics at baseline

Characteristic	n	*% or SD*
Age (years)	58.2	14.2
Male	905	40.7
Ethnicity		
White	969	47.8
African American	607	29.9
Latino	362	17.9
East Asian	28	1.4
Non-East Asian	23	1.1
Other	39	1.9
Smoking status		
Current smoker	265	11.9
Past smoker	552	24.8
Never smoker	1408	63.3
History of other ACE inhibitors	491	22.1
History of ACE inhibitor-induced cough	36	1.6
History of ACE inhibitor-induced angioedema	5	0.2
Medical conditions		
Hypertension	1906	85.7
Diabetes mellitus	752	33.8
Coronary artery disease	437	19.6
Congestive heart failure	179	8
Chronic obstructive pulmonary disease	84	3.8
Asthma	208	9.4
Depression or anxiety	612	27.5
Any psychiatric diseases except for anxiety or depression	86	3.9
Hemodialysis	28	1.3
Creatinine ≥1.6 mg dL^{-1}	130	5.9
Concurrent medications		
Diuretics	843	37.9
Beta blockers	827	37.2
Calcium antagonists	330	14.8
Low dose (≤325 mg day^{-1}) aspirin	733	32.9
High dose (>325 mg day^{-1}) aspirin	3	0.1
Non-steroidal anti-inflammatory drugs	342	15.4
Cyclo-oxygenase-2 inhibitors	131	5.9
Withdrawal of ACE inhibitor because of any kind of ADE	422	19

ACE, angiotensin-converting enzyme; ADE, adverse drug events; CI, confidence interval.

ACE inhibitors did not significantly correlate with ACE inhibitor-induced cough ($P > 0.2$), but we included these variables in the multivariate analysis because of our predetermined hypothesis. In the Cox proportional hazard model for discontinuation because of any kind of ADE, the following variables were retained as independent risk factors ($P < 0.05$): age 60–69 or older than 70 compared to age less than 50, female gender, ethnicity other than African American or Latino, history of smoking, no history of other ACE inhibitors, history of ACE inhibitor-induced cough, hypertension, anxiety or depression or no other psychiatric diseases, no hemodialysis, and creatinine (Table 3).

Table 4 shows risk factors for cough, angioedema, renal dysfunction, and hyperkalaemia. Independent risk factors for cough because of ACE inhibitors were age 60–69 (HR: 1.7 compared to age < 50; 95% CI: 1.3–2.3) or older than 70 (HR: 1.5 compared to age < 50; 95% CI: 1.1–2.1), female gender (HR: 2.2;

Table 2 Reasons for discontinuation of ACE inhibitors

Variable	*Benazepril (n = 5)*	*Captopril (n = 93)*	*Enalapril (n = 82)*	*Fosinopril (n = 15)*	*Lisinopril (n = 1809)*	*Moexipril (n = 80)*	*Quinapril (n = 36)*	*Ramipril (n = 62)*	*Trandolapril (n = 43)*	*All (n = 2225)*
Discontinuation because of ADEs, *n* (%)	0 (0)	21 (22.6)	17 (20.7)	3 (20)	341 (18.9)	13 (16.3)	8 (22.2)	12 (19.4)	7 (16.3)	422 (19.0)
Cough, *n* (%)	0 (0)	11 (11.8)	12 (14.6)	2 (13.3)	222 (12.3)	11 (13.8)	5 (13.9)	7 (11.3)	5 (11.6)	275 (12.4)
Angioedema, *n* (%)	0 (0)	1 (1.1)	1 (1.2)	0 (0)	15 (0.8)	1 (1.3)	0 (0)	0 (0)	1 (2.3)	19 (0.9)
Dizziness, *n* (%)	0 (0)	1 (1.1)	1 (1.2)	0 (0)	15 (0.8)	0 (0)	0 (0)	1 (1.6)	0 (0)	18 (0.8)
Gastrointestinal symptoms,* *n* (%)	0 (0)	2 (2.2)	0 (0)	0 (0)	12 (0.7)	0 (0)	1 (2.8)	0 (0)	0 (0)	15 (0.7)
Renal dysfunction, *n* (%)	0 (0)	1 (1.1)	1 (1.2)	0 (0)	9 (0.5)	0 (0)	1 (2.8)	1 (1.6)	1 (2.3)	14 (0.6)
Hyperkalaemia, *n* (%)	0 (0)	0 (0)	0 (0)	1 (6.7)	12 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	13 (0.6)
Fatigue, *n* (%)	0 (0)	1 (1.1)	0 (0)	0 (0)	8 (0.4)	0 (0)	1 (2.8)	2 (3.2)	0 (0)	12 (0.5)
Skin rash, *n* (%)	0 (0)	1 (1.1)	0 (0)	0 (0)	8 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	9 (0.4)
Hives, *n* (%)	0 (0)	1 (1.1)	0 (0)	0 (0)	6 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	7 (0.3)
Headache, *n* (%)	0 (0)	1 (1.1)	0 (0)	0 (0)	6 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	7 (0.3)
Myalgia or arthralgia, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.2)	0 (0)	0 (0)	1 (1.6)	0 (0)	4 (0.2)
Orthostatic hypotension, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	4 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	4 (0.2)
Sexual dysfunction, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	4 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	4 (0.2)
Anxiety, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.2)	0 (0)	1 (2.8)	0 (0)	0 (0)	3 (0.1)
Others,† *n* (%)	0 (0)	2 (2.2)	1 (1.2)	0 (0)	16 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	19 (0.9)
Unknown adverse events,‡ *n* (%)	0 (0)	0 (0)	1 (1.2)	0 (0)	2 (0.2)	1 (1.3)	0 (0)	0 (0)	0 (0)	4 (0.2)
Discontinuation without ADEs, *n* (%)	1 (20.0)	29 (31.2)	14 (17.1)	4 (26.7)	211 (11.7)	12 (15.0)	5 (13.9)	8 (12.9)	13 (30.2)	297 (13.4)
Failure to control high blood pressure, *n* (%)	0 (0)	3 (3.2)	2 (2.4)	0 (0)	20 (1.1)	2 (2.5)	0 (0)	1 (1.6)	1 (2.3)	29 (1.3)
Unnecessary to control blood pressure, *n* (%)	0 (0)	2 (2.2)	0 (0)	0 (0)	56 (3.1)	1 (1.3)	0 (0)	1 (1.6)	2 (4.7)	62 (2.8)
Loss of follow-up, *n* (%)	0 (0)	6 (6.5)	4 (4.9)	1 (6.7)	58 (3.2)	3 (3.8)	2 (5.6)	1 (1.6)	2 (4.7)	77 (6.5)
Change medications because of insurance, *n* (%)	1 (20.0)	16 (17.2)	7 (8.5)	3 (20.0)	32 (1.8)	6 (7.5)	2 (5.6)	4 (6.5)	6 (14.0)	77 (3.5)
Poor compliance, *n* (%)	0 (0)	2 (2.2)	0 (0)	0 (0)	30 (1.7)	0 (0)	0 (0)	0 (0)	1 (2.3)	33 (1.5)
Medical reasons, *n* (%)	0 (0)	0 (0)	1 (1.2)	0 (0)	11 (0.6)	0 (0)	1 (2.8)	1 (1.6)	0 (0)	14 (0.6)
Undetermined reasons, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	4 (0.2)	0 (0)	0 (0)	0 (0)	1 (2.3)	5 (0.2)
Continue until study end, *n* (%)	4 (80.0)	43 (46.2)	51 (62.2)	8 (53.3)	1257 (69.5)	55 (68.8)	23 (63.9)	42 (67.7)	23 (53.5)	1506 (67.7)

ACE, angiotensin-converting enzyme; ADEs, adverse drug events.

*Gastrointestinal symptoms included nausea, diarrhoea gastric upset, and abdominal distress.

†Others included hair loss, palpitation, tingling fingers, leg spasms, hand swelling, throat irritation, cytopenia, bad taste, somnolence, flushing, pancreatitis, visual discomfort, and short of breath.

‡Unknown adverse events represented that doctor discontinued ACE inhibitor because of adverse events but no details in record.

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Table 3 Risk factors for discontinuation because of adverse drug events

Variable	*Unadjusted hazard ratio (95% CI)*	*Adjusted hazard ratio (95% CI)*
Age, years		
50–59	1.0 (0.7–1.3)	0.9 (0.6–1.2)
60–69	1.8 (1.4–2.4)	1.5 (1.2–2.0)
70 or more	1.6 (1.2–2.1)	1.4 (1.1–1.8)
Female	1.8 (1.5–2.2)	1.8 (1.4–2.3)
Ethnicity		
Non-African American	1.3 (1.0–1.6)	1.3 (1.0–1.6)
Non-Latino	1.5 (1.1–2.1)	1.4 (1.0–1.9)
	1.3 (1.1–1.6)	1.4 (1.1–1.7)
No history of other ACE inhibitors	1.1 (0.8–1.3)	1.5 (1.2–2.0)
History of ACE inhibitor-induced cough	6.9 (4.7–10.1)	6.9 (4.3–10.9)
Medical conditions		
Hypertension	1.6 (1.2–2.2)	1.5 (1.1–2.1)
Anxiety or depression or no other psychiatric diseases	1.7 (0.9–3.2)	2.2(1.0–4.6)
No hemodialysis	5.4 (0.8–36.6)	20.0 (1.6–251.7)
Creatinine, mg dL^{-1}	0.9 (0.8–1.1)	1.2 (1.0–1.5)

ACE, angiotensin-converting enzyme; CI, confidence interval.

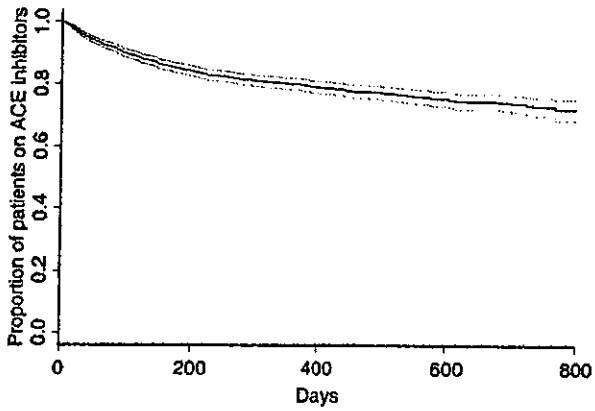

Figure 1 Withdrawal of angiotensin-converting enzyme (ACE) inhibitors because of adverse drug events and 95% confidence interval (CI). Solid line indicates the Kaplan-Meier estimate and dashed lines indicate its 95% CI.

95% CI: 1.6–3.0), East Asian ethnicity (HR: 2.5; 95% CI: 1.1–5.7), history of smoking (HR: 1.5; 95% CI: 1.2–1.9), no history of other ACE inhibitors (HR: 2.0; 95% CI: 1.3–2.9), and history of ACE inhibitor-induced cough (HR: 12.9; 95% CI: 7.5–22.3). Independent risk factors for angioedema were African American ethnicity (HR: 3.5; 95% CI: 1.3–8.9), history of smoking (HR: 2.7; 95% CI: 1.1–7.0), and history of ACE inhibitor-induced cough (HR: 9.1; 95% CI: 2.1–39.9). Independent risk factors for renal dysfunction were age (HR: 1.1/1-year; 95% CI: 1.0–1.1), creatinine of 1.6 mg dL^{-1} or more (HR: 4.7; 95% CI: 1.5–14.6), and concurrent use of a calcium antagonist (HR: 4.4; 95% CI: 1.5–12.7). Independent risk factors for hyperkalaemia were East Asian ethnicity (HR: 80.3; 95% CI: 5.4–1189.7), history of smoking (HR: 5.4; 95% CI: 1.3–23.2), coronary artery disease (HR: 11.5; 95% CI: 2.3–56.8), depression or anxiety (HR: 3.8; 95% CI: 1.1–13.9), creatinine of 1.6 mg dL^{-1} or more (HR: 10.9; 95% CI: 3.1–39.0), and concurrent use of cyclo-oxygenase-2 inhibitors (HR: 6.1; 95% CI: 1.2–31.2).

Substitution with ARBs

Among the 422 patients who discontinued ACE inhibitors because of ADEs, 191 received ARBs as a substitution. After the development of cough, 59% (162/275) took ARBs but almost none received them after the onset of angioedema, renal dysfunction, or hyperkalaemia (Table 5). Significantly more patients took ARBs after cough ($P < 0.0001$), but significantly less patients took ARBs after the onset of other ADEs.

Table 4 Risk factors for discontinuation because of specific side-effect

Variable	*Unadjusted hazard ratio (95% CI)*	*Adjusted hazard ratio (95% CI)*
Cough		
Age (years)		
50–59	1.3 (0.9–1.9)	1.1 (0.8–1.7)
60–69	2.3 (1.6–3.2)	1.7 (1.3–2.3)
70 or more	1.6 (1.1–2.4)	1.5 (1.1–2.1)
Female	2.3 (1.8–3.1)	2.2 (1.6–3.0)
Ethnicity		
East Asian	1.7 (0.8–3.9)	2.5 (1.1–5.7)
History of Smoking (current and past smoker)	1.4 (1.1–1.8)	1.5 (1.2–1.9)
No history of other ACE inhibitors	1.2 (0.9–1.5)	2.0 (1.3–2.9)
History of ACE inhibitor-induced cough	10.1 (6.7–15.1)	12.9 (7.5–22.3)
Angioedema		
Ethnicity		
African American	2.8 (1.0–7.6)	3.5 (1.3–8.9)
History of Smoking (current and past smoker)	2.3 (0.9–5.8)	2.7 (1.1–7.0)
No history of other ACE inhibitors	1.6 (0.5–5.6)	*
History of ACE inhibitor-induced cough	10.8 (2.5–47.0)	9.1 (2.1–39.9)
Renal dysfunction		
Age, years	1.1 (1.0–1.1)	1.1 (1.0–1.1)
Medical conditions		
Creatinine ≥1.6 mg dL^{-1}	8.8 (3.0–26.3)	4.7 (1.5–14.6)
Concurrent medications		
Calcium antagonists	5.6 (2.0–16.0)	4.4 (1.5–12.7)
Hyperkalaemia		
Ethnicity		
East Asian	7.3 (0.9–62.7)	80.3 (5.4–1189.7)
History of smoking (current and past smoker)	3.8 (1.2–12.5)	5.4 (1.3–23.2)
Coronary artery disease	9.4 (2.9–30.7)	11.5 (2.3–56.8)
Depression or Anxiety	3.1 (1.1–9.3)	3.8 (1.1–13.9)
Creatinine ≥1.6 mg dL^{-1}	10.1 (3.5–32.9)	10.9 (3.1–39.0)
Concurrent medications		
Cyclo-oxygenase-2 inhibitors	3.2 (0.7–14.4)	6.1 (1.2–31.2)

ACE, angiotensin-converting enzyme; CI, confidence interval.
*Hazard risk was not calculated because of convergence.

Table 5 Substitution of angiotensin receptor II blockers (ARBs)

Adverse drug events (n = 422)	*ARB (n = 191)*	*No ARB (n = 231)*	P-*value**
Cough, *n* (%)	162 (85)	113 (49)	<0.0001
Angioedema, *n* (%)	4 (2)	15 (6)	0.03
Renal dysfunction, *n* (%)	1 (0.5)	13 (6)	0.004
Hyperkalaemia, *n* (%)	0 (0)	13 (6)	0.0009

Discussion

We found that a large proportion of the general patient population who were prescribed ACE inhibitors discontinued them because of ADEs or other reasons. Overall, 19% of patients stopped ACE inhibitors because of ADEs and another 13% did so for other reasons. The independent risk factors for discontinuation of ACE inhibitors because of ADEs were age, gender, ethnicity, smoking status, history of other ACE inhibitors, history of ACE inhibitor-induced cough, and other medical conditions.

Our findings are consistent with and extend those from prior reports on the epidemiology of and individual risk factors for ADEs because of ACE inhibitors. The studies of left ventricular dysfunction (SOLVD) reported that 10% of patients discontinued enalapril because of ADEs except for hypotension and 3% because of cough during an average follow-up of 40 months (Kostis *et al.* 1996). However, these figures are underestimated because cough was not listed as an ADE during the first several months (Kostis *et al.* 1996). Although many randomized trials also reported incidences between 3 and 7% for cough because of ACE inhibitors (Squire 2002), participants in clinical trials are different from patients in general practice (Cleland & Clark 1999), and the incidences reported in surveys conducted after marketing of the medication are reportedly higher (8–11%) (Speirs *et al.* 1998). Our study may differ from other studies in terms of definition of outcome, study design, and patient population, but it is likely to reflect the actual incidences of ADEs among general outpatients and the response of doctors, that is 19% of the patients discontinued ACE inhibitors because of ADEs and 12% because of cough. The SOLVD found that the percentages for discontinuation of enalapril because of renal dysfunction, angioedema, and hyperkalaemia were 2%, 0.3%, and 0.7%, respectively. The incidences for angioedema and hyperkalaemia were similar to those in our study, but discontinuation because of renal dysfunction showed a lower incidence in our study. The reason seems to be that elevation of creatinine used to be considered a sign of deterioration of renal function, but now many doctors have recognized protective effects of ACE inhibitors on the kidneys and thus tend to tolerate mild elevation of creatinine. Thus, our findings are likely to reflect the incidence of ADEs in the current clinical setting.

We also explored the risk factors for discontinuation of ACE inhibitors because of ADEs and specific ADEs. Although no studies have reported the risk factors for discontinuation because of any type of ADEs, some risk factors have been reported for cough, angioedema, renal dysfunction, and hyperkalaemia. Clinical trials as well as observational studies have identified risk factors for cough, including female gender (Israili & Hall 1992; Os *et al.* 1994; Elliott 1996; Kostis *et al.* 1996; Speirs *et al.* 1998), advanced age (Kostis *et al.* 1996; Speirs *et al.* 1998), Chinese, Japanese, and African American ethnicity (Woo *et al.* 1995; Elliott 1996; Ishimitsu *et al.* 1997), renal insufficiency (Keane *et al.* 1997), diabetes mellitus (Malini *et al.* 1999), and non-smoking status (Os *et al.* 1994). Our findings supported advanced age, female gender, and Asian ethnicity but not African American ethnicity as risk factors. As an example, the SOLVD found that the risk of cough because of enalapril was 2.4 times higher for women than men (Kostis *et al.* 1996), which is close to the HR of 2.2 reported in our study. We also added two critical types of medical history, no history of other ACE inhibitors and ACE inhibitor-induced cough, as risk factors. Concurrent use of some drugs, including non-steroidal anti-inflammatory drugs (Fogari *et al.* 1992), aspirin (Tenenbaum *et al.* 2000), cyclo-oxygenase-2 inhibitors (Knox & Pang 1997), and nifedipine (Fogari *et al.* 1992), has been reported to decrease the risk of cough. However, none of these drugs was associated with lower incidence of ACE inhibitor-induced cough in this study.

Other ADEs, specifically angioedema, renal dysfunction, and hyperkalaemia, are rare but life-threatening. Their risk factors have not been reported in detail in the literature, but several characteristics associated with a higher incidence of ADEs have been identified. African American ethnicity has been reported to be a risk factor for angioedema with a relative risk of 4.5 (Brown *et al.* 1996), compared with our HR of 3.5. In addition, our multivariate model suggested that a history of smoking, no history of other ACE inhibitors, and a history of ACE inhibitor-induced cough were also risk factors for angioedema. It is of special interest that a history of ACE inhibitor-induced cough was found to be a risk factor for angioedema. Although the pathophysiology of cough and angioedema because of ACE inhibitors is not the same (Israili & Hall 1992), our finding suggests that these ADEs partly share a common pathway, such as increased kinins (Nussberger *et al.* 2002). Being elderly and pre-existing renal impairment have been previously proposed as risk factors for renal dysfunction (Alderman 1996; Knight *et al.* 1999), compatible with our findings. However, diabetes and concurrent use of diuretics and non-steroidal anti-inflammatory drugs were not identified as risk factors in our study (Alderman

1996), while calcium antagonists were. Although 86% of the participants were hypertensive and we did not adjust for baseline blood pressure level, this predictor may reflect the severity of hypertension. Diabetes, creatinine level, and congestive heart failure were reported to be risk factors for hyperkalaemia (Ahuja *et al.* 2000). In addition, concurrent use of cyclo-oxygenase-2 inhibitors and ACE inhibitors has been suggested as a cause of hyperkalaemia (Hay *et al.* 2002), while depressed patients were found to be more likely to have ADEs than non-depressed patients when they were prescribed ACE inhibitors (Onder *et al.* 2003). All these reported findings concur with ours except for diabetes and congestive heart failure. Additional potential predictors identified in this study were East Asian ethnicity, history of smoking, and coronary artery disease. However, a history of smoking reportedly correlates with hyperkalaemia even in the absence of ACE inhibitors (Wannamethee *et al.* 1997), so that our findings may simply reflect this phenomenon.

While it has been claimed that ACE inhibitors have a good safety and tolerability profile (Alderman 1996), our findings suggest that an important proportion of patients discontinued them because of ADEs. Taking the various risk factors into account when prescribing these medications in clinical practice can be expected to reduce the rate of ADEs resulting from the use of these drugs. For example, the need to discontinue ACE inhibitors for patients with a previous history of ACE inhibitor-induced cough can be expected to be seven times higher, for cough 13 times higher, and for angioedema nine times higher than for those without such history. For patients who develop a cough because of ACE inhibitors, changing to different class of antihypertensive medication, such as ARBs, seems to be safer than trying other ACE inhibitors. Although the incidences of angioedema, renal dysfunction, and hyperkalaemia were very low, patients with risk factors reported here should alert doctors to monitor them for these ADEs more closely than those without such risk factors. An additional tool for improving medication safety is computerized doctor order entry, which has been shown to reduce medication error rates (Bates *et al.* 1998). Although the risk factors in our study should be validated in other settings, they can easily be presented to clinicians using computerized prescribing applications, especially the items that are readily available. Such a system would make it easy for doctors to consider these risk factors in their daily practice (Bates *et al.* 2003).

This study has a number of limitations. First, we used a retrospective cohort study design, so that not all data, in terms of both outcomes and risk factors, may have been fully recorded. We defined the outcomes as not only ADE symptoms but also required that they be severe enough to require discontinuation of ACE inhibitors. The risk factors may also be biased as a result of incomplete records or subjective judgements by doctors. However, most of the risk factors in our study were simple demographics, including age, gender, ethnicity, history of smoking, history of other ACE inhibitors, and history of ACE inhibitor-induced cough, all of which are recorded on a regular basis and unlikely to be influenced by subjective judgement. Concurrent use of medication and creatinine values are also unlikely to be missed or biased. Second, because 65% of the ADEs were cough, the risk factors for discontinuation because of ADEs were strongly influenced by those for ACE inhibitor-induced cough. In addition, the number of cases of angioedema, renal dysfunction, and hyperkalaemia cases were relatively small. Although the independent risk factors for discontinuation because of these ADEs were determined with the multivariate model, the possibility of chance remains. Finally, our findings are based on a single urban tertiary care study, and prospective validation on a different patient population remains to be carried out.

In this study, we found that a large proportion of patients discontinued of ACE inhibitors because of ADEs in a general patient population, and identified the independent risk factors for discontinuation because of such ADEs as cough, angioedema, renal dysfunction, and hyperkalaemia. Taking these risk factors into consideration when prescribing ACE inhibitors may lead to changes in the prescription pattern and the follow-up strategy. Appropriate recognition of risk factors for ADEs in daily practice is expected to result in improved patient safety.

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