

Incidence and Prognostic Implications of Stable Angina Pectoris Among Women and Men

Harry Hemingway, FRCP

Alison McCallum, MB,BS

Martin Shipley, MSc

Kristiina Manderbacka, PhD

Pekka Martikainen, PhD

Ilmo Keskimäki, MD, PhD

THE PUBLIC HEALTH IMPACT OF stable angina, particularly among women, is poorly understood. In the United States¹ and many developed countries, coronary disease is the most common cause of death in women,² and among women, stable angina is the most common initial symptomatic presentation.³ Despite the declining incidence of myocardial infarction, the prevalence of angina remains high,^{4,5} and direct costs in the United States in 2000 have been estimated at up to \$75 billion.⁶ Major population studies of coronary disease in women^{7,8} have focused on patients hospitalized for acute coronary syndromes or fatal coronary disease, to the near exclusion of chronic stable angina. Because most angina patients are treated symptomatically with nitrates,⁵ and because prescribing data are more complete and standardized than diagnostic coding in primary care, nitrate use is a commonly used measure of the burden of treated angina in the community.^{5,9} However, there is an apparent paradox; angina prevalence in women is similar to that in men,^{10,11} in contrast with the marked male excess of myocardial infarction in-

Context Stable angina pectoris in women has often been considered a "soft" diagnosis, with less-severe prognostic implications than in men, but large-scale population studies are lacking.

Objective To determine sex differences in the incidence and prognosis of stable angina in a large ambulatory population.

Design Prospective cohort study using linked national registers.

Setting All municipal primary health care centers, hospital outpatient clinics, occupational health care services, and the private sector in Finland.

Participants Among ambulatory patients aged 45 to 89 years who had no history of coronary disease, we defined new cases of "nitrate angina" based on nitrate prescription (56 441 women and 34 885 men) or "test-positive angina" based on abnormal invasive or noninvasive test results (11 391 women and 15 806 men). Potentially eligible patients were evaluated between January 1, 1996, and December 31, 1998. Follow-up ended in December 2001.

Main Outcome Measures Coronary mortality at 4 years (n=7906 deaths) and fatal and nonfatal myocardial infarction at 1 year (n=3129 events).

Results The age-standardized annual incidence per 100 population of all cases of angina was 2.03 in men and 1.89 in women, with a sex ratio of 1.07 (95% confidence interval [CI], 1.06-1.09). At every age, nitrate angina in women and men was associated with a similar increase in risk of coronary mortality relative to the general population. Women with test-positive angina who were younger than 75 years had higher coronary-standardized mortality ratios than men; for example, among those aged 55 to 64 years, it was 4.69 (95% CI, 3.60-6.11) in women compared with 2.40 (95% CI, 2.11-2.73) in men ($P<.001$ for interaction). There was a strong, graded relationship between amount of nitrates used and event rates; women using higher doses of nitrates had prognoses comparable with those of men. Among patients with diabetes and test-positive angina, age-standardized coronary event rates were 9.9 per 100 person-years in women vs 9.3 in men ($P=.69$), and the fully adjusted male-female sex ratio was 1.07 (95% CI, 0.81-1.41).

Conclusions Women have a similarly high incidence of stable angina compared with men. Furthermore, stable angina in women is associated with increased coronary mortality relative to women in the general population and, among easily identifiable clinical subgroups, has similarly high absolute rates of prognostic outcomes compared with men.

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cidence¹² and angiographically demonstrated coronary artery disease.¹³ This has led some to consider population estimates of angina in women as

Author Affiliations are listed at the end of this article.
Corresponding Author: Harry Hemingway, FRCP, Department of Epidemiology and Public Health, University College London Medical School, 1-19 Torrington Pl, London WC1E 6BT, England (h.hemingway@ucl.ac.uk).

“soft,”¹⁴ not reflecting coronary pathologic findings.

Population studies that might elucidate this paradox have been lacking, with no national or community-based surveillance programs reporting incidence and prognosis of angina in women compared with men. Epidemiological studies^{3,15} have recruited and followed up patients over the course of decades, precluding inferences about contemporary practice. Studies set in cardiologists' outpatient clinics¹⁶ do not include the wider pool of patients presenting to internists or primary care.¹⁷ All studies have been limited by the small number of cases of angina and subsequent coronary events in women, as well as by exclusion of older patients. Sex disparities in access to specialist referral and investigation of angina have been widely demonstrated,¹⁸⁻²⁴ yet no study has determined sex differences in the incidence and prognostic effect of angina patients with and without an investigation abnormality. Nor has any study investigated how the severity^{25,26} of incident angina or the presence of coexisting conditions²⁷ might influence sex differences in prognosis.

Our objective was to determine sex differences in chronic stable angina with respect to (1) incidence in the general population, (2) coronary mortality compared with the general population, and (3) absolute coronary event rates, by angina severity and coexisting conditions. We used national linked registries in Finland, a country with a previously documented general population prevalence of angina similar to that of the United States (5.4% vs 6.3% in women and 4.4% vs 4.3% in men, respectively).^{10,11}

METHODS

Populations

Finland has a comprehensive health care system provided to all citizens, funded from general taxation. Using personal identity numbers, we linked data held in national registers in Finland to create a register of patients with angina and their coexisting conditions, hospitalizations, and mortality, as previously de-

scribed.²⁸ The denominator population used for the calculation of incidence risk was defined as the resident population of Finland, based on the 1990 census, who were aged 45 to 89 years in 1996. Demographic details on age, sex, living alone, and low education (<10 years full-time) were obtained from the census. All analyses were carried out on anonymized data and were approved by the Research Ethics Committee of STAKES, the National Research and Development Centre for Welfare and Health. STAKES (Sosiaali-ja Terveysalan Tutkimus-ja Kehittämiskeskus) is a research institute funded by the national government as part of the Ministry of Social Affairs and Health. Under Finnish law, individual patient informed consent is not required for the analyses presented here.

Angina Case Definitions

Two mutually exclusive case definitions of incident, uncomplicated angina were used, based on linking records of reimbursement of charges for medications in the Social Insurance Institution during recruitment from January 1, 1996, to December 31, 1998. This register covers all prescriptions reimbursed by the mandatory national health insurance irrespective of the ambulatory care provider. All patients were identified in an ambulatory setting, which included municipal primary health care centers, hospital outpatient clinics, occupational health care services, and the private sector. To identify angina as the first symptomatic presentation of coronary disease, we excluded all patients with a prior special reimbursement right for coronary heart disease (CHD) or prior admission with acute myocardial infarction, unstable angina, or other coronary disease (*International Classification of Diseases, Tenth Revision [ICD-10]*²⁹ codes I20-25; *International Classification of Diseases, Ninth Revision* codes 410-414) or for coronary revascularization during the 5 years before the date of angina.

The first case definition (“nitrate angina”) was based on reimbursement for dispensed (filled) prescriptions for gly-

ceryl trinitrate, isosorbide dinitrate, and isosorbide mononitrate (including sublingual, aerosol, transdermal, and oral preparations) during the 3-year recruitment period. We excluded all patients who were taking a nitrate medication in the calendar year before recruitment. Nitrate use is a valid measure of angina in primary care,^{5,30} being a moderately sensitive (73%) and highly specific (96%) marker of a physician diagnosis of angina identified by case record review.⁹

The second case definition (“test-positive angina”) was based on a special reimbursement right requiring a medical certificate by the attending physician, usually an internist or a cardiologist, which was then reviewed and approved by a specialist physician at the Social Insurance Institution. Such a reimbursement right is awarded only to patients with chronic angina pectoris symptoms responding to antianginal medication in the presence of unequivocal electrocardiographic changes (on exercise or at rest) or angiographic coronary artery disease. Patients who made the transition from nitrate angina to test-positive angina at any time during the recruitment period were counted only once, as test-positive cases. We used the amount of reimbursed nitrate prescriptions filled during the year of incidence, expressed in defined daily doses,³¹ as a marker of angina severity. For example, the defined daily dose of sublingual glyceryl trinitrate is set at 2.5 mg; thus, a package containing thirty 0.25-mg tablets (total, 7.5 mg) corresponds to 3 defined daily doses. The defined daily dose of oral isosorbide dinitrate is 60 mg and that of isosorbide mononitrate is 40 mg.

Cardiovascular and Noncardiovascular Coexisting Conditions

The presence of coexisting conditions was ascertained from Social Insurance Institution data on entitlements to reimbursement of medicine costs according to a prespecified list of 43 chronic diseases at the time of angina diagnosis, each of which required confirmation by a specialist or hospital investi-

gations. This list included cardiovascular disorders (hypertension, diabetes, heart failure [ICD-10 codes I11.0, I13, I50, or I97.1], and arrhythmias [ICD-10 codes I47-149]) and noncardiovascular disorders, including respiratory (asthma and chronic obstructive pulmonary disease), musculoskeletal (rheumatoid arthritis and other systemic connective tissue disorders, gout), psychiatric (severe mental illness), and neoplastic. Coexisting condition codes validate well against hospital case records.³²

Mortality and Nonfatal Myocardial Infarction Follow-up

All patients were linked to the Causes of Death Register at Statistics Finland, which provided details of the date and underlying cause of death, according to ICD-10 codes, until December 31, 2001 (median follow-up, 4 years). The post-mortem examination rate in Finland during this period was approximately 60% among those younger than 65 years. Coronary heart disease mortality was defined by ICD-10 codes I20-I25, and 7906 coronary deaths occurred during follow-

up. Details of nonfatal acute myocardial infarction (defined as ICD-10 codes I21-I22), percutaneous coronary intervention, and coronary artery bypass graft surgery were obtained from linkage to the hospital discharge register. The completeness and accuracy of the death and discharge registers for CHD have previously been demonstrated.³³

Statistical Analysis

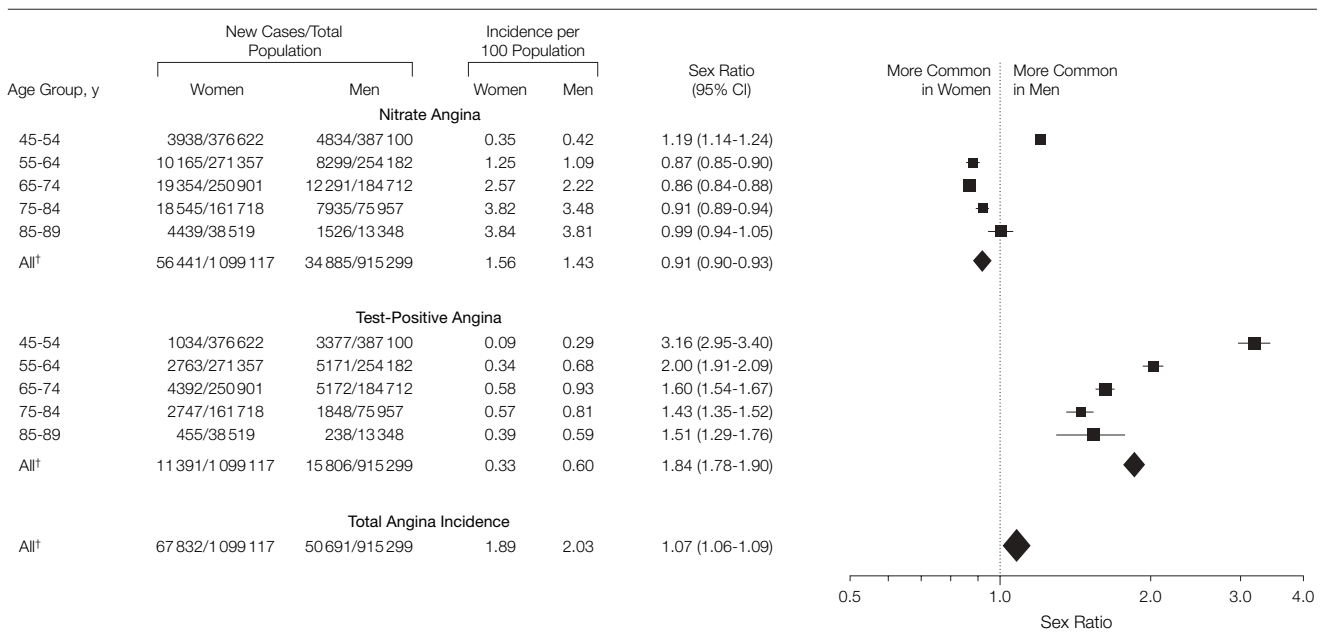
Annual incidence risks of angina were calculated as the ratio of the average number of new cases per year to the total 1996 Finnish population. To allow comparisons between sexes, incidence risks and the prevalence of coexisting conditions were adjusted for age using direct standardization to the entire Finnish population. Standardized mortality ratios (SMRs) were calculated as the ratio of observed to expected deaths. The expected number of deaths was calculated using age (5-year categories), sex, and calendar year-specific coronary mortality rates from the total Finnish population. When the observed number of deaths numbered fewer than 50, 95%

confidence intervals (CIs) for the SMRs were calculated using the exact Poisson distribution, with an approximation used for larger numbers of deaths.

Absolute rates of the composite end point of fatal and nonfatal myocardial infarction at 1-year follow-up (n = 3129 events) were calculated per 100 person-years at risk. Entry into the register was defined by month and year for test-positive angina and by year for nitrate angina, and a midmonth or midyear date used for time-to-event and person-year analysis, respectively. When death occurred during the year of recruitment, entry was deemed to have occurred halfway between January 1 and the date of death. For nonfatal myocardial infarction and coronary revascularization, all patients were followed up for 1 calendar year after their incidence date.

Within the 2 angina case definitions, all-cause mortality and coronary event rates were compared between women and men with and without coexisting conditions using multivariable hazard ratios computed from Cox proportional hazards models, adjusting for the

Figure 1. Age- and Sex-Specific Annual Incidence Risk* of Nitrate Angina and Test-Positive Angina and Sex Ratios Among Incident Cases



CI indicates confidence interval. The size of the data markers represents the number of angina cases.

*Annual risk per 100 population, using estimated total population of Finland in 1996. Because the case definitions of angina are mutually exclusive, the same population denominator was used for each.

†Age-standardized to the combined (women and men) population.

potential confounders of age in the combined (women and men) population, education (<10, 10-11, or ≥12 years), marital status (married, divorced/separated, single, or widowed), nitrate type (none, glyceryl trinitrate, isosorbide mononitrate or isosorbide dinitrate, or both), nitrate use (0, 1-7, 8-30, 31-90, or >90 defined daily doses), number of noncardiovascular coexisting conditions (0, 1, or ≥2) and receipt of percutaneous coronary intervention or coronary artery bypass graft surgery during the first year of follow-up. We assessed the proportional hazards assumption by fitting exposure × log time interaction terms and by examining the effects separately within each year of follow-up. These analyses showed that the proportionality assumption was robust. All *P* values are 2-tailed. All analyses were carried out in SAS software, version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

As shown in FIGURE 1, the age-standardized annual incidence of nitrate angina was higher in women than in men, but for test-positive angina the incidence was lower in women. The latter effect was most marked in the youngest age group, which included perimenopausal women. Among all cases combined, total incidence risks were similar in women (1.89 per 100) and men (2.03 per 100), with a sex ratio of 1.07 (95% CI, 1.06-1.09).

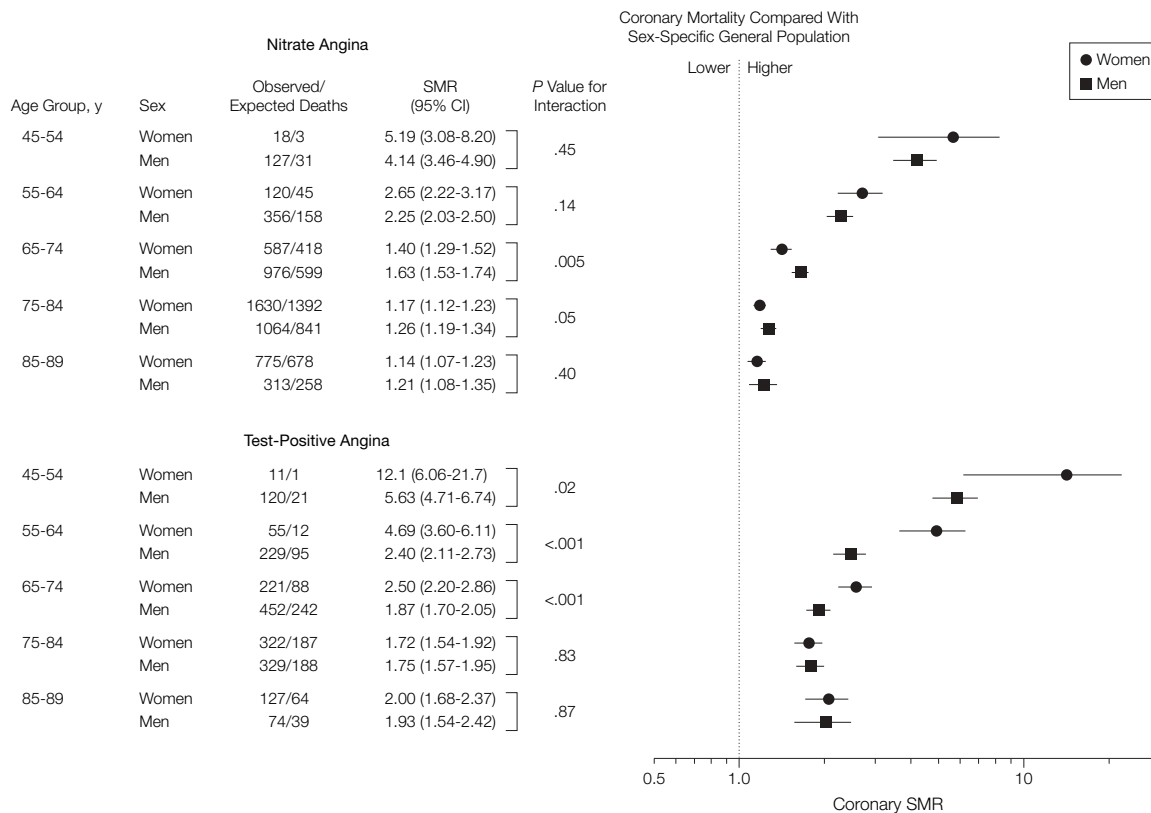
Into the ninth decade of life, age was strongly associated with higher incidence of nitrate angina (*P*<.001 for linear trend), but for test-positive angina, incidence declined after age 75 years (Figure 1). Among all cases of angina, women were less likely to be test-positive than men consistently within each age group (*P*<.001 for all), with proportions in women/men of 21%/

41% at age 45 to 54 years, 21%/38% at 55 to 64 years, 18%/30% at 65 to 74 years, 13%/19% at 75 to 84 years, and 9%/13% at 85 to 89 years.

In every age group, nitrate angina in women was associated with increased coronary SMRs similar in magnitude to those observed in men (FIGURE 2). In contrast, women with test-positive angina aged 45 to 74 years had higher coronary SMRs than men (Figure 2). For example, among those aged 55 to 64 years, the SMR was 4.69 (95% CI, 3.60-6.11) in women and 2.40 (95% CI, 2.11-2.73) in men (*P*<.001 for interaction). Within strata defined by age and sex, associations with coronary mortality were stronger for test-positive angina than for nitrate angina.

As shown in TABLE 1, women with angina were older than men and, in age-adjusted analyses, were slightly more likely to be using short-acting nitrates

Figure 2. Prognosis of Nitrate and Test-Positive Angina: Standardized Mortality Ratios (SMRs) for Coronary Heart Disease, by Sex, Within Age Groups



CI indicates confidence interval.

and lower defined daily doses. Test-positive angina patients were prescribed more nitrates than those with nitrate angina, but there was little difference between sexes in amount used; 14.7% of women and 17.2% of men were taking no nitrates (but may have been taking other antianginal medication). Noncardiovascular coexisting conditions were more common among women and, in both sexes, were more common in nitrate angina cases than in test-positive cases.

Among nitrate angina cases in women and men, the amount of nitrates used showed a very strong, graded relationship with coronary event rates after adjustment for demographic factors, cardiovascular and noncardiovascular conditions, and receipt of coronary re-

vascularization (TABLE 2). This dose-response effect was present among women who were taking short-acting nitrates only, with hazard ratios of 1.48 (95% CI, 1.31-1.67), 2.25 (95% CI, 1.84-2.73), and 2.72 (95% CI, 1.99-3.73) for 8 to 30, 31 to 90, and more than 90 defined daily doses, respectively (reference category, 1-7 defined daily doses).

In general, predictors of coronary events also tended to predict all-cause mortality. Absolute rates of fatal and nonfatal myocardial infarction tended to be lower in women than in men. However, women using higher doses of nitrates had comparable prognoses with men, and among test-positive cases, there were no sex differences in prognosis among patients with 2 or more noncardiovascular conditions. Diabetes was

strongly associated with event rates, narrowing sex differences among cases of nitrate angina and abolishing them in test-positive angina. Among patients with diabetes and test-positive angina, age-standardized event rates were 9.9 per 100 person-years in women vs 9.3 in men ($P = .69$); in fully adjusted models, the male-to-female sex ratio for coronary events was 1.07 (95% CI, 0.81-1.41). Among women, the presence of heart failure was associated with increased coronary event rates, similar to those seen in men without these disorders.

COMMENT

To our knowledge, this study represents the first large-scale investigation of angina as an initial symptomatic manifestation of CHD. We found that

Table 1. Baseline Patient Characteristics According to Sex and Type of Angina*

Characteristics	Nitrate Angina			Test-Positive Angina		
	Women (n = 56 441)	Men (n = 34 885)	P Value	Women (n = 11 391)	Men (n = 15 806)	P Value
Age, mean (SD), y	71.6 (9.9)	67.9 (10.5)	<.001	68.9 (9.6)	63.8 (9.7)	<.001
Education <10 y	42 780 (64.9)	24 811 (64.4)	.25	8378 (64.6)	10 253 (61.4)	<.001
Living alone	33 741 (45.5)	11 248 (34.6)	<.001	5885 (43.7)	4094 (27.8)	<.001
Nitrate type						
None	0	0	<.001	1493 (14.7)	2633 (17.2)	<.001
Glyceryl trinitrate	31 049 (58.5)	18 085 (54.0)		1993 (18.8)	2600 (16.9)	
Isosorbide†	17 368 (29.0)	10 870 (30.0)		2892 (24.3)	3714 (23.3)	
Glyceryl trinitrate + isosorbide†	8024 (12.6)	5930 (15.9)		5013 (42.2)	3859 (42.7)	
Nitrate use, defined daily doses filled per y						
0	0	0	<.001	1493 (14.7)	2633 (17.2)	<.001
1-7	19 504 (40.8)	10 670 (33.8)		1091 (11.1)	1365 (8.8)	
8-30	20 258 (35.4)	12 479 (36.2)		1608 (15.1)	2337 (15.3)	
31-90	9416 (13.7)	6296 (16.4)		2554 (21.8)	3418 (21.8)	
>90	7263 (10.0)	5440 (13.6)		4645 (37.3)	6053 (36.9)	
Cardiovascular conditions						
Diabetes	5417 (7.5)	3426 (9.0)	<.001	1139 (9.9)	1474 (9.1)	.11
Hypertension	22 293 (33.8)	12 143 (32.9)	.03	3568 (29.3)	3976 (24.3)	<.001
Heart failure	7660 (7.2)	3468 (7.2)	.70	1495 (8.9)	1540 (9.3)	.24
Arrhythmias	2465 (3.0)	1917 (4.6)	<.001	518 (3.4)	673 (3.8)	.08
Comorbidity						
Respiratory	4371 (8.6)	2708 (6.7)	<.001	683 (6.1)	765 (4.3)	<.001
Mental	2081 (5.0)	1131 (3.9)	<.001	267 (2.5)	291 (1.9)	.01
Musculoskeletal	3315 (4.9)	1706 (4.2)	<.001	614 (4.3)	553 (3.4)	<.001
Neoplastic	721 (1.0)	390 (0.8)	.002	101 (0.8)	98 (0.6)	.09
No. of noncardiovascular coexisting conditions‡						
0	40 190 (72.9)	27 108 (80.1)	<.001	8712 (78.5)	13 455 (85.9)	<.001
1	13 644 (22.9)	6785 (17.4)		2326 (18.7)	2110 (12.7)	
≥2	2607 (4.2)	992 (2.5)		353 (2.8)	241 (1.4)	

*Data are expressed as No. (%) unless otherwise specified. Percentages are age-standardized to the combined (women and men) population.

†Isosorbide dinitrate or isosorbide mononitrate.

‡From a prespecified list of 43 chronic conditions diagnosed using objective test criteria.

overall incidence was similarly high in women and men among contemporary, unselected patients in primary care. Angina in women was associated with increased coronary mortality relative to women in the general population and, in absolute terms, high coronary event rates. Indeed, among easily identifiable clinical subgroups, angina in women had similarly high absolute rates of prognostic outcomes compared with men.

The total incidence risk of angina in primary care reported herein is substantially (1 order of magnitude) higher than the rate of first admissions for acute myocardial infarction in Finland³⁴ and in any of the age, sex, and race subgroups in the Atherosclerosis Risk in Communities study.³⁵ Indeed, our estimates for an-

gina may be conservative; not all angina is diagnosed and treated, particularly among women.^{36,37} Among those whose angina is treated, not all receive nitrates³⁰; furthermore, among those taking nitrates, not all pursue reimbursement. Finally, the general population denominator in this study inevitably included some cases of angina.

Women had a total incidence of angina that was similar to that of men, which is consistent with numerous population-based studies assessing angina prevalence with the Rose questionnaire.^{10,11} Taken together, these findings are likely to be robust, as the former is free of instrument and reporting biases and the latter is free of diagnostic and treatment biases. We found that women with nitrate angina had a

markedly increased risk of coronary mortality compared with women in the general population, an effect similar in magnitude to that observed in men.

Women had a lower incidence than men of test-positive cases of angina, consistent with previous US studies that, although not based on primary care, report underuse of investigation in women with chest pain.^{18-20,22,24} This may relate to sex differences in symptom description³⁸ or physician perception of risk. Of further concern was that these selected women had particularly high sex-specific coronary SMRs, exceeding those of men, up to age 75 years. This may reflect a combination of factors in women, including lower absolute rates of CHD mortality in the population, selection of sicker pa-

Table 2. Sex Differences in Prognostic Impact of the Severity of Angina and Coexisting Conditions on All-Cause Mortality and Fatal CHD and Nonfatal MI Among Angina Cases*

	Nitrate Angina				Test-Positive Angina			
	All-Cause Mortality		Fatal CHD and Nonfatal MI		All-Cause Mortality		Fatal CHD and Nonfatal MI	
	Women (9564 Deaths)	Men (8430 Deaths)	Women (982 Events)	Men (877 Events)	Women (1453 Deaths)	Men (2329 Deaths)	Women (460 Events)	Men (810 Events)
Mean age†	1.07 (1.07-1.07)	1.11 (1.10-1.11)	1.10 (1.09-1.11)	1.06 (1.05-1.07)	1.11 (1.10-1.12)	1.08 (1.08-1.09)	1.05 (1.04-1.06)	1.03 (1.03-1.04)
Nitrate use, defined daily doses filled per year								
0					1.00 (3.39)‡	2.33 (1.94-2.81)	1.00 (4.95)‡	2.22 (1.66-2.96)
1-7	1.00 (2.64)‡	2.37 (2.22-2.53)	1.00 (0.72)‡	2.68 (2.11-3.42)	0.91 (0.69-1.20)	2.51 (2.01-3.13)	1.32 (0.92-1.91)	1.50 (1.05-2.15)
8-30	1.28 (1.20-1.35)	2.89 (2.72-3.07)	1.76 (1.42-2.18)	3.55 (2.84-4.44)	1.15 (0.91-1.44)	2.48 (2.01-3.04)	1.16 (0.81-1.66)	1.80 (1.29-2.51)
31-90	1.71 (1.60-1.84)	3.89 (3.62-4.18)	2.69 (2.12-3.42)	5.64 (4.42-7.20)	1.66 (1.32-2.08)	3.14 (2.52-3.91)	1.09 (0.74-1.60)	1.62 (1.12-2.34)
>90	2.07 (1.92-2.22)	3.85 (3.57-4.16)	3.52 (2.76-4.49)	5.75 (4.48-7.39)	1.45 (1.17-1.81)	2.95 (2.37-3.66)	0.94 (0.65-1.36)	1.47 (1.02-2.11)
Cardiovascular conditions								
Diabetes								
Absent	1.00 (3.32)‡	2.26 (2.19-2.34)	1.00 (1.28)‡	2.16 (1.93-2.41)	1.00 (3.19)‡	2.18 (2.01-2.36)	1.00 (3.74)‡	1.74 (1.51-2.00)
Present	1.84 (1.74-1.94)	3.42 (3.22-3.65)	2.54 (2.19-2.93)	3.88 (3.26-4.63)	2.11 (1.86-2.40)	3.61 (3.19-4.09)	2.40 (1.93-2.99)	2.57 (2.06-3.20)
Hypertension								
Absent	1.00 (3.37)‡	2.30 (2.21-2.40)	1.00 (1.23)‡	2.10 (1.83-2.40)	1.00 (3.37)‡	2.06 (1.89-2.25)	1.00 (3.89)‡	1.64 (1.41-1.91)
Present	1.14 (1.10-1.19)	2.33 (2.22-2.44)	1.43 (1.26-1.62)	2.70 (2.33-3.13)	1.15 (1.04-1.28)	2.46 (2.21-2.73)	1.32 (1.09-1.59)	1.98 (1.65-2.38)
Heart failure								
Absent	1.00 (3.31)‡	2.21 (2.14-2.30)	1.00 (1.37)‡	1.97 (1.76-2.21)	1.00 (3.00)‡	2.04 (1.88-2.22)	1.00 (3.79)‡	1.63 (1.42-1.88)
Present	1.39 (1.33-1.46)	2.96 (2.79-3.14)	1.41 (1.23-1.63)	2.94 (2.48-3.48)	2.01 (1.79-2.25)	4.43 (3.97-4.93)	1.84 (1.49-2.28)	2.67 (2.17-3.28)
Arrhythmias								
Absent	1.00 (3.62)‡	2.22 (2.15-2.30)	1.00 (1.57)‡	2.01 (1.81-2.23)	1.00 (3.57)‡	2.05 (1.91-2.22)	1.00 (4.34)‡	1.59 (1.40-1.81)
Present	1.29 (1.19-1.40)	2.40 (2.20-2.62)	1.12 (0.86-1.46)	2.09 (1.59-2.74)	1.02 (0.84-1.23)	2.51 (2.15-2.94)	0.88 (0.58-1.31)	1.39 (1.00-1.94)
No. of coexisting noncardiovascular conditions								
0	1.00 (3.23)‡	2.19 (2.10-2.28)	1.00 (1.39)‡	2.08 (1.84-2.35)	1.00 (3.32)‡	2.06 (1.90-2.25)	1.00 (4.02)‡	1.67 (1.45-1.93)
1	1.37 (1.31-1.43)	3.05 (2.90-3.21)	1.37 (1.19-1.57)	2.43 (2.06-2.87)	1.33 (1.18-1.49)	2.88 (2.57-3.22)	1.29 (1.04-1.60)	1.90 (1.55-2.35)
≥2	1.80 (1.67-1.95)	3.95 (3.57-4.37)	1.67 (1.31-2.13)	3.69 (2.74-4.96)	1.90 (1.51-2.40)	3.69 (2.87-4.75)	2.01 (1.36-2.98)	1.57 (0.88-2.80)

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction.

*Data are expressed as multivariable hazard ratios (95% confidence intervals) unless otherwise noted. Women without the coexisting condition or with the lowest use of nitrates are the reference category. All hazard ratios are adjusted for age in the combined (women and men) population, education (<10, 10-11, or ≥12 years), marital status (married, divorced/separated, single, or widowed), nitrate type, nitrate use, number of noncardiovascular coexisting conditions, and receipt of percutaneous coronary intervention or coronary artery bypass graft surgery during first year of follow-up.

†Hazard ratios for the effect of age are estimated per year of increase.

‡The age-standardized absolute event rate per 100 person-years is given in parentheses for each reference category.

tients, and undertreatment. If there is a bias whereby men are more likely to be tested than women, it might explain the higher incidence of test-positive angina in men in contrast with the higher incidence of nitrate angina in women. The fact that long-term coronary mortality rates were higher in younger women with test-positive angina than in men suggests that sicker women were being tested—that is, there is a higher threshold for testing in women than in men. However, the similarity of the coronary SMRs in women and men with nitrate angina demonstrates that even if this bias exists, it is unlikely to have seriously affected our estimates of overall incidence.

The rate of coronary revascularization was higher in men than women, but adjustment for receipt of revascularization had no effect on sex differences in coronary event rates. Sex differences in secondary prevention are small in this population; in a companion study of 2650 patients carried out in 2001, we found that the proportion taking 3 agents (aspirin, a β -blocker, and a statin) was 49% for women and 51.6% for men (K.M., I.K., Antti Reunanen, MD, and Timo Klaukka, MD, PhD; unpublished data; 2006). In women and men older than 75 years, there were no sex differences in coronary SMRs and the incidence of test-positive angina declined, consistent with older age influencing access to testing.

We found a strong stepwise relationship between the amount of filled nitrate prescriptions over the year of incidence and subsequent coronary event rates. Angina follows an intermittent, relapsing-remitting course, and amount of nitrate use may thus be a valid marker of anginal severity over time.²⁶ The prognostic clinical validity of a pragmatic measure of treated angina, demonstrated here, suggests a method of surveillance and identification of target populations in future randomized trials.

Absolute rates of coronary events in women were high when compared with thresholds for initiating secondary prevention treatment.³⁹ Estimated 10-year risks of fatal and nonfatal myocardial in-

farction exceeded 10% (“moderately high”) for women with nitrate angina, even among those without cardiovascular or noncardiovascular comorbidity; absolute risks were considerably higher for women with test-positive angina. When compared with men, women overall tended to have lower coronary event rates. This effect was present among those with test-positive angina, suggesting that it is not explained by diagnostic error. However, the female advantage was diminished or absent among clinical subgroups. Women with diabetes and angina had particularly high event rates, reducing sex differences in prognosis in nitrate angina and eliminating them in test-positive angina.

Sex differences in the nature and severity of the underlying cardiac pathophysiology in angina may explain these prognostic differences. Further research is required to understand which patients with nitrate angina had never been investigated and which had been investigated and tested negative on conventional noninvasive ischemic testing or coronary angiography. Novel functional imaging studies suggest that among women with angina and nonobstructed coronary arteries (a finding considerably more common in women than in men with chest pain¹³), nuclear magnetic resonance spectroscopy reveals hitherto undetected evidence of ischemia, which is associated with increased coronary event rates.^{13,40} Impaired coronary endothelial function in women with nonobstructive coronary disease is associated with adverse prognosis.

Randomized trials of angina select a large excess of men vs women (eg, with ratios of 3.8 in the ACTION [A Coronary Disease Trial Investigating Outcome With Nifedipine Gastrointestinal Therapeutic System],⁴¹ 4.2 in the TNT [Treating to New Targets],⁴² and 4.9 in the PEACE [Prevention of Events with Angiotensin Converting Enzyme Inhibition]⁴³ trials). This does not reflect the sex burden of angina in the population, and influential trials may perpetuate the unsubstantiated notion that “real” angina predominantly affects men. Nor are low event rates in women a reason for

recruiting disproportionately low numbers of women into trials. We found that even among women aged 45 to 54 years with test-positive angina, the rate of fatal and nonfatal myocardial infarction was 2.52 per 100 person-years, higher than that observed in the aforementioned trials (with rates of 1.67,⁴¹ 1.76,⁴² and 1.86⁴³ per 100 person-years). Our results extend to angina the previous findings on underrepresentation of women in trials of acute coronary syndromes⁴⁴ and the worse prognosis in “real-world” vs trial populations.⁴⁵ Major studies among women, such as the Women’s Health Initiative and the Nurses’ Health Study, have reported predictors of hospitalized unstable angina^{7,8} but not chronic stable angina.

There have been no trials among incident cases of angina as the initial symptomatic manifestation of coronary disease; half or more of all patients in the existing angina trials have had previous myocardial infarction and many patients have already survived years since first presentation. In the absence of randomized comparisons of different investigational strategies for angina,⁴⁶ formal methods⁴⁷ of defining appropriate investigation and the prognostic consequences of its underuse in women are required.

The subject of long-standing⁴⁸ debate, angina in women occurs in the general population as commonly as in men, and its prognostic impact suggests that it should not be discounted as a benign or soft diagnosis. These findings demonstrate the public health importance of angina in women and underscore the importance of both understanding the biological mechanisms of the angina-sex paradox and ensuring fair access to investigation and treatment services.

Author Affiliations: Department of Epidemiology and Public Health, University College London Medical School, London, England (Dr Hemingway and Mr Shipley); and Outcomes and Equity Research, National Research and Development Centre for Welfare and Health (Drs McCallum, Manderbacka, and Keskimäki), and Population Research Unit, Department of Sociology, University of Helsinki (Dr Martikainen), Helsinki, Finland.

Author Contributions: Dr Hemingway had full access to all of the data in the study and takes respon-

sibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hemingway, McCallum, Manderbacka, Martikainen, Keskimäki.

Acquisition of data: Hemingway, Manderbacka, Martikainen, Keskimäki.

Analysis and interpretation of data: Hemingway, McCallum, Shipley, Manderbacka, Martikainen, Keskimäki.

Drafting of the manuscript: Hemingway, McCallum, Shipley, Manderbacka.

Critical revision of the manuscript for important intellectual content: Hemingway, Shipley, Manderbacka, Martikainen, Keskimäki.

Statistical analysis: Shipley, Martikainen.

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Table. Annual Number of Laparoscopic Cases

Procedure	Years Since Introduction														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Cholecystectomy	16 247	93 464	270 991	363 161	354 565	348 323	331 076	333 600	327 092	316 733	319 793	346 157	351 736	360 844	358 069
Fundoplication	19	184	1613	5299	11 245	13 111	15 802	18 399	23 993	24 761	24 188	18 981	19 042		
Hysterectomy	4838	6181	13 102	38 929	44 852	41 401	42 335	48 578	68 455	60 805	60 733	64 639	69 659	71 977	76 033
Nephrectomy indication															
Cancer	35	236	215	199	283	308	563	532	701	1226	1968	4221	5093		
Benign disease	452	454	573	614	767	898	1261	1055	1947	1662	1896	2823	3388		
Donor	11	4	19	21	40	154	473	449	510	1589	1305	1648	1789		

Critical revision of the manuscript for important intellectual content: Miller, Dunn, Wei, Hollenbeck.

Statistical analysis: Dunn.

Obtained funding: Hollenbeck.

Administrative, technical, or material support: Hollenbeck.

Study supervision: Wei, Hollenbeck.

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Incorrect Statements on Funding/Support and Role of the Sponsors and Incorrect and Incomplete Financial Disclosures: In the Review entitled "Anti-TNF Antibody Therapy in Rheumatoid Arthritis and the Risk of Serious Infections and Malignancies: Systematic Review and Meta-analysis of Rare Harmful Effects in Randomized Controlled Trials" published in the May 17, 2006, issue of *JAMA* (2006;295:2275-2285), the following errors appeared:

After this issue was printed and mailed, *JAMA* was informed by the authors that information reported on page 2284 of the article was incorrect.

The Funding/Support statement should have read "This study was supported by the Mayo Foundation. Additional data were provided by Abbott and Centocor. Data provided by Abbott were subject to a confidentiality agreement."

The Role of the Sponsors statement should have read "Abbott and Centocor did not have any role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation or approval of the manuscript. The manuscript was sent to Abbott for review prior to submission for publication."

The Financial Disclosures statement should have read: "Dr Bongartz reported that he has given lectures for Abbott as part of seminars for study nurses and received honorarium in the form of a medical textbook for the Internal Medicine library; he received an educational grant from Amgen in February 2006 to perform the same type of analysis of harmful events under anti-TNF treatment for etanercept; and he received the 2005 Fellow's Award of the American College of Rheumatology, which was supported by Amgen."

Dr Matteson reported that he has been a paid consultant for Centocor for work unrelated to this study and has been working with Wyeth and Amgen to perform a similar analysis for etanercept; he has been an Investigator for the American College of Rheumatology, Amgen, Asta, Biogen-IDEC, Burroughs-Wellcome, Centocor, Cypress, Endocyte Inc, Genentech, Hoffmann-LaRoche, Human Genome Sciences, Immunex, Protein Design Laboratories, Nasteck, Pharmacia & Upjohn, Schering, Wyeth, and Xoma Corp; he has received grant support from Amgen, Aventis, Centocor/Johnson & Johnson, Genentech, Immunex, Mayo Foundation, Novartis, and the National Institutes of Health; and he has been a consultant for Amgen, BoneandJoint.org, Burroughs-Wellcome, Centocor, Regeneron, Takeda, Upjohn, Watermark Research, and the Vasculitis Foundation."

This correction was published online on May 16, 2006. Because of the nature and extensiveness of this incorrect and incomplete reporting, *JAMA* has requested that the Mayo Clinic College of Medicine conduct an investigation. *JAMA* will publish another correction or clarification once the results of that investigation become available.

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The Role of the Sponsors statement should have read "Abbott and Centocor did not have any role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation or approval of the manuscript. The manuscript was sent to Abbott for review prior to submission for publication."

The Financial Disclosures statement should have read: "Dr Bongartz reported that he has given lectures for Abbott as part of seminars for study nurses and received honorarium in the form of a medical textbook for the Internal Medicine library; he received an educational grant from Amgen in February 2006 to perform the same type of analysis of harmful events under anti-TNF treatment for etanercept; and he received the 2005 Fellow's Award of the American College of Rheumatology, which was supported by Amgen."

Dr Matteson reported that he has been a paid consultant for Centocor for work unrelated to this study and has been working with Wyeth and Amgen to perform a similar analysis for etanercept; he has been an Investigator for the American College of Rheumatology, Amgen, Asta, Biogen-IDEC, Burroughs-Wellcome, Centocor, Cypress, Endocyte Inc, Genentech, Hoffmann-LaRoche, Human Genome Sciences, Immunex, Protein Design Laboratories, Nasteck, Pharmacia & Upjohn, Schering, Wyeth, and Xoma Corp; he has received grant support from Amgen, Aventis, Centocor/Johnson & Johnson, Genentech, Immunex, Mayo Foundation, Novartis, and the National Institutes of Health; and he has been a consultant for Amgen, BoneandJoint.org, Burroughs-Wellcome, Centocor, Regeneron, Takeda, Upjohn, Watermark Research, and the Vasculitis Foundation."

This correction was published online on May 16, 2006. Because of the nature and extensiveness of this incorrect and incomplete reporting, *JAMA* has requested that the Mayo Clinic College of Medicine conduct an investigation. *JAMA* will publish another correction or clarification once the results of that investigation become available.