Prospective Study of Calcium Channel Blocker Use, Cardiovascular Disease, and Total Mortality Among Hypertensive Women : The Nurses' Health Study

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The Nurses' Health Study

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Background—In several observational studies, patients prescribed calcium channel blockers had higher risks of cardiovascular diseases and mortality than those prescribed other antihypertensive medications. We explored these associations in the Nurses' Health Study.

Methods and Results—A total of 14 617 women who reported hypertension and regular use of diuretics, β-blockers, calcium channel blockers, ACE inhibitors, or a combination in 1988 were included in the analyses. Cardiovascular events and deaths were ascertained through May 1, 1994. We documented 234 cases of myocardial infarction. Calcium channel blocker monodrug users had an age-adjusted relative risk (RR) of myocardial infarction of 2.36 (95% CI, 1.43 to 3.91) compared with those prescribed thiazide diuretics. Women prescribed calcium channel blockers had a higher prevalence of ischemic heart disease. After adjustment for these and other coronary risk factors, the RR was 1.64 (95% CI, 0.97 to 2.77). Comparing the use of any calcium channel blocker (monodrug and multidrug users) with that of any other antihypertensive agent, the adjusted RR was 1.42 (95% CI, 1.01 to 2.01). An association between calcium channel blocker use and myocardial infarction was apparent among women who had ever smoked cigarettes (covariate-adjusted RR, 1.81; 95% CI, 1.20 to 2.72) but not among never-smokers (RR, 0.94; 95% CI, 0.48 to 1.84).

Conclusions—In analyses adjusted only for age, we found a significant elevation in RR of total myocardial infarction among women who used calcium channel blockers compared with those who did not. After adjustment for comorbidity and other covariates, the RR was reduced. Whether the remaining observed elevated risk is real, or a result of residual confounding by indication, or chance, or a combination of the above cannot be evaluated with certainty on the basis of these observational data. (***Circulation.* 1998;97:1540-1548.**)

Key Words: calcium channels ■ cardiovascular diseases ■ mortality ■ epidemiology

In some but not all observational studies, both case-control and cohort, patients prescribed calcium channel blockers for hypertension had higher risks of cardiovascular diseases and mortality than those prescribed other antihypertensive medications.

See p 1529

In a large case-control study of hypertensives initially free of cardiovascular disease, those who suffered an MI were significantly more likely to have been treated with calcium channel blockers (primarily short-acting formulations) than hypertensives who did not suffer an MI (covariate-adjusted risk ratio, 1.62; 95% CI, 1.11 to 2.34).[1] In two other case-control studies,[2,3] no increased risk was seen for hypertensive patients on calcium channel blockers. In a recent case-control study, 27 hypertensive patients who received short-acting calcium channel blockers had a higher risk of cardiovascular events than patients on the long-acting formulation.[4]

In a prospective cohort study from the Established Populations for Epidemiologic Studies of the Elderly (EPESE), among 906 hypertensives ≥71 years old, there were 30 deaths among those who self-reported use of (mainly short-acting) nifedipine compared with 91 among those who used β-blockers, yielding an RR of 1.7 (95% CI, 1.1 to 2.7).[5] There was no apparent association for other calcium channel blockers (verapamil or diltiazem) or for ACE inhibitors relative to β-blockers.

A number of potential mechanisms for an increased risk associated with calcium channel blockers have been pro-

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Selected Abbreviations and Acronyms

CABG = coronary artery bypass graft
JNC = Joint National Committee
MI = myocardial infarction
PTCA = percutaneous transluminal coronary angioplasty
RR = relative risk

posed: proischemic, negative inotropic, proarrhythmic, or prohemorrhagic effects, or marked hypotension.[6]

The Nurses' Health Study provides the opportunity to explore the associations between calcium channel blockers used to treat hypertension and subsequent cardiovascular events and mortality in a large prospective cohort of women. As was the case for all previous populations, this cohort study was not designed a priori to address these questions but did provide a larger number of end points than reported previously and allowed us to assess whether and how confounding by indication (calcium channel blockers having been prescribed preferentially for women at higher risks) may have influenced the results.[7,8]

Methods

Study Population and Data Collection

The Nurses' Health Study cohort was established in 1976, when 121 701 female registered US nurses 30 to 55 years old returned completed questionnaires sent by mail. Participants are followed through biennial self-administered questionnaires. On baseline and follow-up questionnaires, nurses have been asked to provide demographic and lifestyle information as well as their disease status.[9]

In 1988, information was requested on the regular use of cardiovascular medication, including thiazide diuretics, β-blockers, calcium channel blockers, and ACE inhibitors. Participants were asked: "Are you currently taking any of the following medications at least once a week?" On the questionnaire, medications were identified only by drug class. Information on use of calcium channel blockers was not updated until 1994; therefore, medication use was not updated in this analysis. In 1994, 58% of women who reported use of calcium channel blockers in 1988 still reported calcium channel blocker use. Between 1988 and 1994, 16% of women switched from other medications to calcium channel blockers in our study population; 15% of women switched from diuretics to calcium channel blockers and 2% switched from calcium channel blockers to diuretics. Overall, the total use of calcium channel blockers in our study population almost doubled. Because the use of long-acting calcium channel blockers was rare in 1988, mostly short-acting formulations were likely to have been prescribed in this population.

Hypertension, MI, angina pectoris, CABG and PTCA, stroke, and diabetes have been assessed every 2 years since 1976. Nurses were classified as hypertensive on the basis of self-reports of physician-diagnosed high blood pressure. Because patients with pulmonary disease are less likely to be prescribed β-blockers, we assessed the prevalence of pulmonary disorders. Pulmonary disease was defined as asthma, chronic bronchitis, or emphysema reported through 1988. Data on cigarette smoking (smoking status, amount of current smoking), self-reported blood pressure and cholesterol level, height, weight, and menopausal status were derived from the 1988 questionnaire.

The end points were first nonfatal MI or death due to coronary disease, nonfatal or fatal stroke, total cardiovascular events (consisting of the above plus sudden death), and total and CVD mortality from the return of the 1988 questionnaire through May 1, 1994. Nurses who reported a nonfatal MI or stroke were asked for permission to obtain and review their medical records. Confirmed MIs had to meet the criteria of the World Health Organization[10] (symptoms and either typical ECG changes or elevation of serum cardiac enzyme levels; ICDA-8 code 410). Nonfatal strokes were confirmed if they were characterized in the medical records as typical neurological deficits that were rapid in onset and lasted at least 24 hours and if they met the criteria of the National Survey of Stroke.[11] According to our review of the medical records, we classified strokes as ischemic strokes [defined as thrombotic (with assigned ICDA-8 code 433) or embolic (ICDA-8 code 434) occlusion of a cerebral artery or transient cerebral ischemia (ICDA-8 code 435)] or hemorrhagic strokes [defined as subarachnoidal hemorrhages (ICDA-8 code 430) or intraparenchymal hemorrhages (ICDA-8 code 431)]. We excluded subdural hematomas and strokes caused by infection or neoplasia.

Most deaths are reported by the participants' families. Mortality surveillance includes the National Death Index to identify deaths among nonresponders during each questionnaire cycle. Mortality follow-up is 98% complete in this cohort.[12]

When a death was identified, we requested written permission from the next of kin to review medical records and obtain pathology records. Cardiovascular mortality was defined as death from coronary disease, stroke, or sudden death. Coronary disease was considered the cause of death if the medical records or autopsy report confirmed a fatal MI or if coronary heart disease was listed as the underlying cause on the death certificate without another more plausible cause and the woman was known to have had coronary heart disease (ICDA 410 or 412). In no case was the cause listed on the death certificate used as the sole criterion for death due to coronary disease. Fatal strokes were confirmed on the basis of autopsy reports, hospital records, or death certificates listing stroke as the underlying cause. Sudden death was classified as death within 1 hour of symptoms in an apparently healthy woman without evidence of coronary heart disease or MI (ICDA-8 code 795).

All interviews and reviews of medical records were conducted by investigators without knowledge of exposure status.

Statistical Analysis

Analyses were restricted to women who reported physician-diagnosed hypertension in 1988 or on any previous questionnaire and who reported in 1988 that they regularly took diuretics, β-blockers, calcium channel blockers, or ACE inhibitors or any combination. Women who reported use of both calcium channel blockers and ACE inhibitors were excluded because of a sample size (n=196) that was too small to provide us with reliable estimates. Women were also excluded from the analysis if their covariate information was incomplete (n=91), leaving a study population of 14 617 women. During the 6-year observation period, 551 women (3.8%) died and 400 (2.7%) were lost to follow-up.

Only first events confirmed by medical record review were counted; therefore, women who suffered a second MI or a second stroke were excluded from the corresponding analysis. Self-reports of disease not confirmed by our review of the medical records (because they were reported before baseline, the medical records did not confirm that the women really had an MI, or we were unable to obtain medical records) were not ignored but rather adjusted for in the analysis. For example, 662 women reported an MI in or before 1988; of these, 259 were confirmed by medical records. The 259 women with confirmed prior MI were excluded from the analysis of the end points MI and cardiovascular disease between 1988 and 1994. An additional 37 women were excluded from these analyses who had reported other cardiovascular diseases in or before 1988, but a review of their medical records indicated that they had had an MI. Thus, our baseline population for the analysis of MI was reduced from 14 617 to 14 321. The 403 cases of MI self-reported in or before 1988 but not confirmed were adjusted for in the analysis. In addition, we also conducted analyses excluding all women with self-reported prior cardiovascular disease (nonfatal MI, stroke, CABG, PTCA, and angina).

Person-time of follow-up was allocated to each participant starting with the return of the 1988 questionnaire and accumulated either to May 31, 1994, the occurrence of one of the end points, or death, whichever occurred first. Incidence or mortality rates were calcu-

TABLE 1. Risk Factor Profile and Regular Use of Thiazide Diuretics (TD), β-Blockers (BB), Calcium Channel Blockers (CCB), ACE Inhibitors (ACE), and Their Combinations Self-Reported in 1988 Among 14 617 Participants of the Nurses' Health Study Who Had Reported Hypertension in 1988 or Before (Column Percentages in Parentheses)

	TD	BB	CCB	ACE	TD+BB	CCB+TD or BB	ACE+TD or BB
No.	5594	2745	806	1073	2543	868	988
Mean age, y	57.8	56.7	57.9	56.7	57.7	58.7	57.2
Mean weight, lb	163.7	159.6	158.4	163.0	166.8	166.3	168.2
Mean height,* in	64.3	64.4	64.4	64.4	64.5	64.3	64.5
Mean cholesterol,† mg/dL	214.0	212.7	219.6	216.0	215.8	224.0	217.5
Mean systolic BP,† mm Hg	138.7	137.4	140.0	141.3	139.2	140.5	141.8
Mean diastolic BP,† mm Hg	86.3	85.6	86.0	87.3	86.5	86.2	87.6
Current smoker, %	876 (15.7)	439 (16.0)	138 (17.1)	171 (15.9)	434 (17.1)	147 (16.9)	154 (15.6)
Former smoker, %	2133 (38.1)	1074 (39.1)	315 (39.1)	440 (41.0)	998 (39.2)	377 (43.4)	426 (43.1)
Amount smoked,†‡ cigs/d	18.8	18.4	19.5	19.1	18.4	19.9	19.1
Years since stopped smoking	15.9	16.7	14.0	14.9	17.6	15.1	14.9
Alcohol intake,§ g/d	6.2	6.7	6.1	6.5	6.7	5.7	6.7
Regular physical activity,¶ %	2217 (39.6)	1064 (38.8)	304 (37.7)	412 (38.4)	975 (38.3)	322 (37.1)	357 (36.1)
Postmenopausal, %	4946 (88.4)	2321 (84.6)	723 (89.7)	927 (86.4)	2237 (88.0)	806 (92.9)	856 (86.6)
Current postmenopausal hormone use for ≥5 years, %	860 (15.4)	380 (13.8)	114 (14.1)	131 (12.2)	396 (15.6)	122 (14.1)	130 (13.2)
Aspirin intake,‖ %	1957 (35.0)	1013 (36.9)	318 (39.5)	365 (34.0)	961 (37.8)	392 (45.2)	381 (38.6)
Diabetes, %	505 (9.0)	212 (7.7)	123 (15.3)	134 (12.5)	266 (10.5)	146 (16.8)	126 (12.8)
Pulmonary disease,# %	644 (11.5)	221 (8.1)	134 (16.6)	149 (13.9)	206 (8.1)	143 (16.5)	145 (14.7)

*In 1976.
†Mean number of cigarettes smoked per day among current smokers in 1988.
‡Self-reported values; average values were calculated as means from prespecified categorical responses.
§In grams per day in 1986; includes women who do not drink alcohol.
‖Regular aspirin intake was defined as use on at least 5 days each month.
¶Assessed in 1980; regular physical activity was defined as working up a sweat at least once a week.
#Pulmonary disease was defined as asthma, chronic bronchitis, or emphysema as of 1988.

lated for each medication by dividing the number of events by the person-time of follow-up for that agent. RRs were estimated as the ratio of incidence rates comparing different medications. To control simultaneously for confounding variables and risk factors for disease, we used a pooled logistic regression model in which risk sets were updated every 2 years.[13]

We used data on cardiovascular disease history in two different ways: (1) we included in the baseline population women who reported a diagnosis of MI or stroke that was not confirmed by our review of the medical records or a diagnosis of CABG/PTCA or angina pectoris and adjusted for this history in the analysis, or, in alternative analyses, (2) we excluded all women who had reported stroke, MI, CABG, PTCA, or angina pectoris in or before the 1988 questionnaire, thus starting with a cohort free of self-reported cardiovascular disease in 1988. For statistical adjustment of prior cardiovascular disease, women who suffered more than one form of cardiovascular disease in or before 1988 were classified according to the following hierarchy: (1) stroke, (2) MI, (3) CABG/PTCA, (4) angina pectoris. The rationale for the hierarchical approach is that the risk for a subset is most likely based on the most severe condition; hence, a subject who reports both an MI and angina pectoris has the same risk as a woman with an MI alone.

Results

The distribution of risk factors among women prescribed antihypertensive medications is given in Table 1. Women who reported the use of calcium channel blockers also reported somewhat higher cholesterol levels, diabetes, and pulmonary disease. Calcium channel blockers were preferentially prescribed for higher-risk hypertensive patients diagnosed with ischemic heart disease (MI or angina pectoris) (Table 2).

Of the 14 617 women included in this analysis, 385 suffered a first fatal or nonfatal cardiovascular event between 1988 and 1994 (234 MIs, 162 strokes, and 12 sudden deaths, not mutually exclusive) (Tables 3A and 4). The age-adjusted risk of a first MI was increased among women who reported use of calcium channel blockers alone (RR, 2.36; 95% CI, 1.43 to 3.91) or in combination with diuretics or β-blockers (RR, 3.43; 95% CI, 2.23 to 5.27) relative to women on thiazide diuretics alone (Table 3A). Adjustment for a history of stroke, CABG/PTCA, angina, diabetes, pulmonary disease, and numerous other risk factors for cardiovascular disease reduced the association considerably, but it remained elevated (calcium channel blocker monotherapy: RR, 1.64; 95% CI, 0.97 to 2.77; combination therapy: RR, 1.88; 95% CI, 1.18 to 3.01). A similar observation was made for total cardiovascular events, although associations were less strong (Table 3A). RRs for stroke were not significantly different for users of calcium channel blockers from those for users of other medications, but numbers of events were smaller (Table 4).

We also compared the risk of a first MI for hypertensive women who reported regular calcium channel blocker use (as monotherapy or combination therapy) with that for hypertensive women who received other antihypertensive medication(s) (Table 3A). RRs adjusted only for age (2.10; 95% CI,

TABLE 2. Profile of Self-Reported Diseases Before or in 1988 and Use of TD, BB, CCB, ACE Inhibitors, and Their Combinations Self-Reported in 1988 Among 14 617 Participants of the Nurses' Health Study Who Had Reported Hypertension in 1988 or Before

	Total	TD	BB	CCB	ACE	TD+BB	CCB+TD or BB	ACE+TD or BB
Stroke	249	70 (1.3)*	39 (1.4)	16 (2.0)	17 (1.6)	50 (2.0)	31 (3.6)	26 (2.6)
		(28.1)†	(15.7)	(6.4)	(6.8)	(20.1)	(12.4)	(10.4)
MI	662	137 (2.5)	107 (3.9)	99 (12.3)	29 (2.7)	103 (4.1)	140 (16.1)	47 (4.8)
		(20.7)	(16.2)	(15.0)	(4.4)	(15.6)	(21.1)	(7.1)
CABG/PTCA	171	17 (0.3)	29 (1.1)	35 (4.3)	15 (1.4)	16 (0.6)	47 (5.4)	12 (1.2)
		(9.9)	(17.0)	(20.5)	(8.8)	(9.4)	(27.5)	(7.0)
Angina pectoris	1135	223 (4.0)	194 (7.1)	149 (18.5)	53 (4.9)	203 (8.0)	239 (27.5)	74 (7.5)
		(19.6)	(17.1)	(13.1)	(4.7)	(17.9)	(21.1)	(6.5)

Abbreviations as in Table 1. Categories are mutually exclusive with the following hierarchy: (1) stroke, (2) MI, (3) CABG/PTCA, (4) angina pectoris.
*Prevalence rates, eg, percent of women with stroke among all women on TD (does not add up to 100% because not all women had prior CVD in 1988).
†Row percentages, ie, distribution of drug use among women with a particular prior disease.

1.53 to 2.89) decreased to 1.42 (95% CI, 1.01 to 2.01) after adjustment for prior disease and pertinent covariates.

When only women who were free of cardiovascular disease (stroke, MI, CABG, PTCA, angina pectoris) in 1988 were considered, age- and covariate-adjusted RRs differed considerably less (Table 3B). The age-adjusted RR for MI among calcium channel blocker monodrug users compared with women on diuretics was 1.82 (95% CI, 0.89 to 3.70), and the covariate-adjusted value was 1.65 (95% CI, 0.81 to 3.38); the corresponding estimates among multidrug users were 2.48 (95% CI, 1.26 to 4.90) and 2.29 (95% CI, 1.15 to 4.54).

To account for possible effects of duration of use of calcium channel blockers as well as misclassification due to discontinuation of the drug, we considered women who

TABLE 3A. RR (95% CI) of Total (Fatal and Nonfatal) MI and Cardiovascular Disease (CVD) Between 1988 and 1994 According to Medication Status Self-Reported in 1988 Among Women of the Nurses' Health Study Who Had Reported Hypertension in 1988 or Before

	No. of Events	Person-Years	Age-Adjusted RR (95% CI)	Covariate-Adjusted RR (95% CI)*
Total MI (n=14 321)†	234	82 030		
TD	64	31 939	1.0	1.0
BB	37	15 516	1.26 (0.84-1.89)	1.29 (0.85-1.94)
CCB	20	4219	2.36 (1.43-3.91)	1.64 (0.97-2.77)
ACE	18	6072	1.56 (0.93-2.64)	1.27 (0.75-2.16)
TD+BB	49	14 385	1.72 (1.19-2.49)	1.51 (1.03-2.20)
CCB+TD or BB	31	4328	3.43 (2.23-5.27)	1.88 (1.18-3.01)
ACE+TD or BB	15	5572	1.38 (0.79-2.42)	1.03 (0.58-1.83)
CCB vs. no CCB§	51	8547	2.10 (1.53-2.89)	1.42 (1.01-2.01)
Total CVD‡ (n=14 183)‖	385	80 944		
TD	124	31 569	1.0	1.0
BB	63	15 357	1.12 (0.83-1.52)	1.13 (0.83-1.54)
CCB	28	4155	1.73 (1.15-2.62)	1.31 (0.85-2.00)
ACE	27	5997	1.23 (0.81-1.87)	1.01 (0.66-1.55)
TD+BB	74	14 190	1.35 (1.01-1.80)	1.24 (0.93-1.66)
CCB+TD or BB	39	4231	2.25 (1.57-3.24)	1.49 (1.00-2.20)
ACE+TD or BB	30	5445	1.46 (0.98-2.18)	1.18 (0.78-1.77)
CCB vs no CCB§	67	8386	1.64 (1.25-2.15)	1.23 (0.92-1.65)

*The RR and 95% CI estimates are adjusted for age, self-reported weight, height, cholesterol level, systolic and diastolic blood pressure in 1988, smoking status and amount of smoking among women who smoked in 1988, alcohol intake in 1988, physical activity, menopausal status in 1988, postmenopausal hormone use, aspirin intake, diabetes, and pulmonary disease. MI estimates additionally adjusted for history of stroke, CABG/PTCA, or angina.
†Includes fatal and nonfatal MI, fatal and nonfatal stroke, and sudden death.
‡296 women with prior MI were excluded from this analysis.
§Additionally adjusted for multidrug use.
‖434 women with prior MI or prior stroke were excluded from this analysis.

TABLE 3B. RR (95% CI) of Total (Fatal and Nonfatal) MI and Cardiovascular Disease (CVD) Between 1988 and 1994 According to Medication Status Self-Reported in 1988 Among Women of the Nurses' Health Study Who Had Reported Hypertension in 1988 or Before and Were Free of CVD (Stroke, MI, CABG/PTCA, Angina Pectoris) in 1988

	No. of Events	Person-Years	Age-Adjusted RR (95% CI)	Covariate-Adjusted RR (95% CI)*
Total MI (n=12 394)	154	71 266		
TD	52	29 621	1.00	1.00
BB	29	13 680	1.28 (0.81-2.02)	1.37 (0.86-2.16)
CCB	9	2880	1.82 (0.89-3.70)	1.65 (0.81-3.38)
ACE	12	5484	1.31 (0.70-2.47)	1.19 (0.63-2.23)
TD+BB	34	12 517	1.57 (1.02-2.42)	1.49 (0.96-2.30)
CCB+TD or BB	10	2306	2.48 (1.26-4.90)	2.29 (1.15-4.54)
ACE+TD or BB	8	4778	0.99 (0.47-2.09)	0.90 (0.43-1.91)
CCB vs. no CCB§	19	5186	1.70 (1.05-2.77)	1.54 (0.94-2.51)
Total CVD† (n=12 384)	288	70 925		
TD	107	29 462	1.00	1.00
BB	51	13 628	1.12 (0.80-1.56)	1.16 (0.83-1.62)
CCB	17	2861	1.70 (1.02-2.85)	1.45 (0.86-2.44)
ACE	20	5467	1.08 (0.67-1.75)	0.92 (0.57-1.49)
TD+BB	55	12 467	1.25 (0.90-1.73)	1.19 (0.86-1.66)
CCB+TD or BB	17	2294	2.07 (1.23-3.46)	1.77 (1.05-2.99)
ACE+TD or BB	21	4747	1.28 (0.80-2.05)	1.10 (0.69-1.77)
CCB vs. no CCB§	34	5155	1.64 (1.14-2.36)	1.46 (1.01-2.11)

Footnotes as in Table 3A.

answered both the 1988 and the 1994 questionnaires. Women who reported calcium channel blocker use in 1988 and 1994 had an RR of nonfatal MI of 1.82 (95% CI, 1.03 to 3.23) compared with those on other antihypertensive agents. Women who reported use in 1988 but not in 1994 had an RR of nonfatal MI of 2.72 (95% CI, 1.57 to 4.70), and those who reported use in 1994 but not in 1988 had an RR of 2.57 (1.78 to 3.74) compared with women on other antihypertensive agents.

Results for smoking-specific subgroups are presented in Table 5. When only women who ever smoked were considered, the disease- and covariate-adjusted RR of MI was 1.81 (95% CI, 1.20 to 2.72), compared with 0.94 (95% CI, 0.48 to 1.84) among never-smokers (Table 5) (test for statistical interaction: $2P=.12$). Because we could not determine smoking status at the start of calcium channel blocker prescription and we were interested in a possible pharmacological interaction between medication use and smoking, we present data for current and former smokers combined (ie, ever-smokers). Women who smoked in 1988, however, had a covariate-adjusted association between calcium channel blocker use and MI similar to that of women who were former smokers in 1988 (current smokers in 1988: RR, 1.83; 95% CI, 0.97 to 3.46; former smokers in 1988: RR, 1.92; 95% CI, 1.12 to 3.28). Among women free of self-reported cardiovascular disease in 1988, the difference in the association of risk with calcium channel blocker use between ever-smokers and never-smokers was even stronger and statistically significant: ever-smokers who reported the use of calcium channel blockers had a covariate-adjusted RR for MI of 2.23 (95% CI, 1.28 to 3.89), whereas the estimate among never-smokers was 0.65 (95% CI, 0.20 to 2.12) (test for statistical interaction: $2P=.045$).

Overall, 551 women died during the follow-up period (Table 6). Total mortality was higher for women who reported use of calcium channel blockers than for women on diuretics (monodrug users: RR, 1.64; 95% CI, 1.17 to 2.29), but this estimate was reduced in magnitude after adjustment for potential confounders (RR, 1.30; 95% CI, 0.91 to 1.85) (Table 6). The elevated RR was partly due to a somewhat higher cardiovascular mortality among women reporting calcium channel blocker use. Noncardiovascular mortality was also somewhat elevated for calcium antagonist users, which was largely due to deaths other than cancer. The covariate-adjusted RRs for total mortality for calcium channel blocker users (monodrug and multidrug users) was 1.44 (95% CI, 1.14 to 1.82) overall, 1.37 (95% CI, 1.03 to 1.83) among women who had ever smoked, and 1.54 (95% CI, 1.01 to 2.35) among never-smokers compared to women on other antihypertensive medication.

There was no evidence of effect modification by diabetes in our population (data not shown).

Discussion

In this prospective cohort study, a greater proportion of women prescribed calcium channel blockers had risk factors for cardiovascular disease and prior diseases, specifically ischemic heart disease, pulmonary disease, and diabetes. Our primary analysis included women with cardiovascular comorbidity, because this is representative of the patient population

TABLE 4. RR (95% CI) of Total (Fatal and Nonfatal) Stroke, Hemorrhagic (Fatal and Nonfatal) Stroke, and Ischemic (Fatal and Nonfatal) Stroke Between 1988 and 1994 According to Medication Status Self-Reported in 1988 Among 14 468 Women* of the Nurses' Health Study Who Had Reported Hypertension in 1988 or Before

Stroke	No. of Events	Person-Years	Age-Adjusted RR (95% CI)	Covariate-Adjusted RR (95% CI)†
Total stroke	162	82 900		
TD	56	31 870	1.0	1.0
BB	28	15 672	1.11 (0.70-1.75)	1.11 (0.70-1.76)
CCB	14	4515	1.78 (0.99-3.20)	1.45 (0.79-2.68)
ACE	9	6074	0.92 (0.46-1.86)	0.78 (0.38-1.58)
TD+BB	28	14 456	1.12 (0.71-1.77)	1.08 (0.68-1.71)
CCB+TD or BB	11	4761	1.23 (0.64-2.35)	1.00 (0.51-1.99)
ACE+TD or BB	16	5553	1.71 (0.98-2.99)	1.50 (0.85-2.63)
CCB vs no CCB‡	25	9276	1.32 (0.85-2.04)	1.12 (0.70-1.79)
Hemorrhagic stroke	18	83 225		
TD	6	31 992	1.0	1.0
BB	4	15 723	1.44 (0.41-5.13)	1.46 (0.41-5.27)
CCB	2	4541	2.38 (0.48-11.8)	3.87 (0.74-20.2)
ACE	2	6085	1.87 (0.38-9.3)	1.64 (0.32-8.46)
TD+BB	4	14 512	1.51 (0.43-5.35)	1.43 (0.40-5.15)
CCB+TD or BB	0	4790	NA	NA
ACE+TD or BB	0	5583	NA	NA
CCB vs no CCB‡	2	9331	1.05 (0.24-4.67)	1.95 (0.43-8.82)
Ischemic stroke	107	83 024		
TD	37	31 912	1.0	1.0
BB	12	15 704	0.73 (0.38-1.40)	0.71 (0.37-1.36)
CCB	10	4529	1.92 (0.95-3.86)	1.50 (0.72-3.13)
ACE	6	6082	0.94 (0.40-2.23)	0.79 (0.33-1.89)
TD+BB	22	14 468	1.34 (0.79-2.27)	1.26 (0.73-2.15)
CCB+TD or BB	10	4762	1.68 (0.84-3.39)	1.33 (0.63-2.83)
ACE+TD or BB	10	5568	1.63 (0.81-3.28)	1.42 (0.70-2.89)
CCB vs no CCB‡	20	9291	1.56 (0.95-2.57)	1.31 (0.77-2.25)

*149 women with prior stroke were excluded from this analysis.

†The RR and 95% CI estimates are adjusted for age, self-reported weight, height, cholesterol level, systolic and diastolic blood pressure in 1988, smoking status and amount of smoking among women who smoked in 1988, alcohol intake in 1988, physical activity, menopausal status in 1988, postmenopausal hormone use, aspirin intake, diabetes, pulmonary disease, and history of MI, CABG/PTCA, or angina.

‡Additionally adjusted for multidrug use.

actually treated with antihypertensive agents in clinical practice. In analyses adjusted only for age, we observed significant elevations in RRs for total MI and cardiovascular events as well as cardiovascular and total mortality among women prescribed calcium channel blockers. Statistical adjustment for comorbidity and other prevalent risk factors reduced the RRs for all endpoints.

In observational epidemiological studies, it is difficult to determine whether drugs that are considered more "potent" may be given to patients at higher risk for the outcome being evaluated. Such confounding by indication would make the more effective drugs appear more harmful simply because patients for whom they are prescribed were at higher risk because of other baseline risk factors or prior disease. It is generally difficult to exclude all such bias in an observational study as severity of disease may be difficult to assess with sufficient precision.

After women with prior stroke, MI, CABG, PTCA, or angina were excluded from our analyses, age-adjusted and covariate-adjusted RRs for calcium channel blocker users differed only marginally. The remaining elevation in risk could reflect a real effect, residual confounding by indication, the play of chance, or any combination of the above. For residual confounding by indication by prior disease to explain the remaining elevated RR, a considerable proportion of nurses who did not report cardiovascular disease or cardiovascular risk factors by 1988 would actually have to have had those, and such underlying unreported cardiovascular disease would have to be differential with respect to calcium channel blocker use. To explain the observed RR of 1.6 for MI, about

TABLE 5. RR (95% CI) of Total MI, Total Cardiovascular (CVD) Events, and Total Strokes Between 1988 and 1994 Comparing Women Who Reported Use of Calcium Channel Blockers (CCB) (Monodrug and Multidrug Users) With Women Who Reported Use of Other Antihypertensives in 1988 Stratified by Smoking Status

	CCB, No. of Events	CCB, Person-Years	No CCB, No. of Events	No CCB, Person-Years	Age-Adjusted RR (95% CI)	Age- and Prior Disease–Adjusted RR (95% CI)*	Covariate-Adjusted RR (95% CI)†	Covariate- and Prior Disease–Adjusted RR (95% CI)*†
MI (n=14 272)‡	51	8517	183	73 225	2.10 (1.53-2.89)	1.50 (1.07-2.11)	1.81 (1.31-2.51)	1.43 (1.01-2.02)
Ever-smokers (n=7860)	39	4788	120	40 000	2.40 (1.65-3.48)	1.72 (1.15-2.58)	2.25 (1.53-3.30)	1.81 (1.20-2.72)
Never-smokers (n=6412)	12	3729	63	33 225	1.50 (0.80-2.81)	1.08 (0.55-2.09)	1.14 (0.60-2.18)	0.94 (0.48-1.84)
Stroke (n=14 418)‡	25	9247	136	73 364	1.33 (0.86-2.05)	1.21 (0.76-1.93)	1.17 (0.75-1.82)	1.13 (0.71-1.81)
Ever-smokers (n=7972)	17	5322	86	40 124	1.29 (0.76-2.20)	1.19 (0.67-2.11)	1.20 (0.70-2.07)	1.17 (0.66-2.09)
Never-smokers (n=6446)	8	3924	50	33 240	1.37 (0.64-2.93)	1.27 (0.57-2.83)	1.22 (0.56-2.67)	1.21 (0.53-2.72)
CVD events (n=14 134)‡	67	8357	317	72 304	1.64 (1.25-2.15)	1.32 (0.99-1.76)	1.45 (1.10-1.91)	1.24 (0.93-1.67)
Ever-smokers (n=7767)	48	4684	205	39 380	1.75 (1.27-2.42)	1.39 (0.98-1.98)	1.63 (1.17-2.27)	1.39 (0.98-1.99)
Never-smokers (n=6367)	19	3673	112	32 924	1.41 (0.86-2.31)	1.15 (0.68-1.95)	1.16 (0.70-1.94)	1.01 (0.59-1.72)

*The RR and 95% CI estimates are adjusted for age, self-reported weight, height, cholesterol level, systolic and diastolic blood pressure in 1988, alcohol intake in 1988, physical activity, menopausal status in 1988, postmenopausal hormone use, aspirin intake, diabetes, and pulmonary disease; estimates among smokers are additionally adjusted for amount of current smoking among current smokers and years since stopped smoking among former smokers.

†Women with unknown values for years since stopped smoking were excluded from this analysis.

‡The RR and 95% CI estimates are adjusted for age and self-reported history of stroke, MI, CABG, and angina.

half the nurses on calcium channel blockers would have had to be so misclassified.

Although the sample size is large, this prospective cohort study was not designed specifically to test the hypotheses addressed. We had to rely on self-reported medication use; however, because the study population consists of health professionals, the reliability of such data can be assumed to be high. Doses and duration of use were not known. Furthermore, because the use of calcium channel blockers was assessed only in 1988 and 1994, new and preexisting prescriptions could not be separated, so we could not determine with certainty the indications for which the various drugs were prescribed. Because the total use of calcium-channel blockers in our study population almost doubled in that interval, and many more women switched from diuretics to calcium channel blockers than vice versa, the use of baseline classification of drug use as exposure may underestimate the association between calcium antagonists and disease incidence rather than overestimate it. The RR for nonfatal MI was not stronger among women who remained on calcium channel blockers between 1988 and 1994, however, than for women who reported use only in 1988 or in 1994. Although we also have no information on short-acting versus long-acting formulations of calcium channel blockers, in 1988 most formulations were almost certainly short-acting, as opposed to the situation today.

In subgroup data, a significantly elevated risk of MI among women who reported regular use of calcium channel blockers was apparent among ever- (current or former) but not among never-smokers. These findings could well be due to chance, but are also compatible with a possible pharmacological interaction between calcium channel blockers and smoking. It may also be the case that all the residual confounding is concentrated in the higher-risk group, the smokers. No important modification by smoking was observed for total mortality. In a prior large case-control study, there was no significant difference in the risk ratio of MI associated with the use of calcium channel blockers for current smokers (1.86) and nonsmokers (1.53); however, former smokers were combined with nonsmokers in the analysis.[1] Further investigations of the role of smoking with respect to the use of calcium channel blockers are needed.

Differential effects of antihypertensive drugs in smokers and nonsmokers have been reported previously. In the MRC trial of treatment of mild hypertension, the event rates for stroke and for all cardiovascular events among patients on propranolol were reduced only among nonsmokers but not among smokers ($P=.03$ and $P=.01$, respectively).[14]

Pharmacological treatment of mild to moderate hypertension with diuretics and β-blockers has been shown to reduce stroke, MI, and vascular mortality.[15-17] Although calcium channel blockers and ACE inhibitors have clear antihypertensive effects, almost two decades after their introduction their risk-to-benefit ratio has not been tested directly in large-scale, randomized trials. Nonetheless, because of their apparently lower side effects and some pharmacological benefits, the number of prescriptions for calcium channel blockers and ACE inhibitors for the treatment of hypertension has risen rapidly during the past decade.[18-21] Our study population reflected these changes in prescription pattern; women who reported new onset of hypertension in 1988 reported a relatively larger percentage of ACE inhibitor and calcium antagonist use than of diuretics and β-blockers (data not shown).

In 1988, the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure recommendations listed calcium channel blockers and ACE inhibitors as first-line choices, besides diuretics and β-blockers (JNC-IV).[22] Lack of data on morbidity and mortality for calcium channel blockers and ACE inhibitors led national committees such as the JNC in 1993 (JNC-V)[23] as well as the World Health Organization and the International Society of Hypertension[24] in 1997 to recommend initial monotherapy with diuretics and/or β-blockers for hypertension, and re-

TABLE 6. RR (95% CI) of Total (All-Cause) Mortality, Cardiovascular (CVD) Mortality, and Mortality From Other Causes Between 1988 and 1994 According to Medication Status Self-Reported in 1988 Among 14 617 Women of the Nurses' Health Study

	No. of Events	Person-Years	Age-Adjusted RR (95% CI)	Covariate-Adjusted RR (95% CI)*
Total mortality	551	84 093		
TD	185	32 251	1.0	1.0
BB	82	15 851	0.97 (0.75-1.26)	0.96 (0.73-1.25)
CCB	43	4600	1.64 (1.17-2.29)	1.30 (0.91-1.85)
ACE	40	6151	1.23 (0.87-1.73)	1.10 (0.78-1.57)
TD+BB	96	14 659	1.16 (0.91-1.49)	1.11 (0.86-1.43)
CCB+TD or BB	69	4894	2.35 (1.78-3.11)	1.67 (1.23-2.27)
ACE+TD or BB	36	5688	1.14 (0.80-1.64)	0.96 (0.67-1.39)
CCB vs no CCB	112	9494	1.82 (1.47-2.26)	1.44 (1.14-1.82)
CVD mortality	174	84 093		
TD	53	32 251	1.0	1.0
BB	17	15 851	0.71 (0.41-1.23)	0.66 (0.38-1.14)
CCB	16	4600	2.14 (1.22-3.74)	1.14 (0.63-2.06)
ACE	11	6151	1.19 (0.62-2.28)	0.88 (0.45-1.70)
TD+BB	32	14 659	1.36 (0.87-2.11)	1.07 (0.68-1.68)
CCB+TD or BB	33	4894	3.88 (2.50-6.00)	1.71 (1.06-2.78)
ACE+TD or BB	12	5688	1.33 (0.71-2.49)	0.88 (0.46-1.67)
CCB vs no CCB	49	9494	2.84 (2.03-3.97)	1.61 (1.11-2.33)
Non-CVD mortality	377	84 093		
TD	132	32 251	1.0	1.0
BB	65	15 851	1.08 (0.80-1.45)	1.07 (0.79-1.44)
CCB	27	4600	1.43 (0.94-2.17)	1.33 (0.86-2.05)
ACE	29	6151	1.24 (0.83-1.85)	1.20 (0.80-1.80)
TD+BB	64	14 659	1.08 (0.80-1.46)	1.09 (0.80-1.47)
CCB+TD or BB	36	4894	1.69 (1.17-2.45)	1.54 (1.04-2.31)
ACE+TD or BB	24	5688	1.06 (0.69-1.65)	1.02 (0.65-1.59)
CCB vs no CCB	63	9494	1.47 (1.11-1.94)	1.36 (1.01-1.83)

*The RR and 95% CI estimates are adjusted for age, self-reported weight, height, cholesterol level, systolic and diastolic blood pressure in 1988, smoking status and amount of smoking among women who smoked in 1988, alcohol intake in 1988, physical activity, menopausal status in 1988, postmenopausal hormone use, aspirin intake, diabetes, pulmonary disease, cancer, and history of stroke, MI, CABG/PTCA, angina, and hypertension in or before 1988.

served calcium channel blockers and ACE inhibitors as second-line choices when diuretics and β-blockers have proved unacceptable or ineffective. The National Heart, Lung, and Blood Institute recently stated that "... short-acting nifedipine should be used with great caution (if at all), especially at higher doses, in the treatment of hypertension, angina, and MI."[25] Recently, the JNC-VI recommendations have reaffirmed diuretics and β-blockers as first-line choices and reserved calcium channel blockers for special indications.[26]

In general, data on drug efficacy and safety from observational studies have to be interpreted with considerable caution, because residual confounding by indication may remain even after careful consideration of other risk factors and comorbidity. In these circumstances, for small to moderate effects, randomized trials specifically designed to compare efficacies and adverse effects of the various antihypertensive medications are advantageous. The recent Syst-Eur trial indicated net cardiovascular benefit of the medium-acting calcium channel blocker nitrendipine compared with placebo among patients with isolated systolic hypertension.[27] Because no comparison with other antihypertensives was made, inferences on the relative efficacy of calcium channel blockers cannot be made from this trial.

Because short-acting calcium channel blockers have largely been supplanted by long-acting formulations in clinical practice today, clinical trials that are currently under way are randomizing long-acting calcium channel blockers against other antihypertensive agents, including the first-line drugs, diuretics and β-blockers. Whether short-acting calcium channel blockers have harmful effects compared with other antihypertensive agents may never be completely resolved.

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