Aspirin Use Among Adults With Diabetes

Estimates from the Third National Health and Nutrition Examination Survey

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OBJECTIVE — Since 1997, the American Diabetes Association has recommended that aspirin therapy be considered for adults with diabetes who have cardiovascular disease (CVD) or CVD risk factors. We examined the prevalence of regular aspirin use among adults in the U.S. with diagnosed diabetes.

RESEARCH DESIGN AND METHODS — The Third National Health and Nutrition Examination Survey (1988–1994) used a probability sample of the U.S. population and included an interview, physical examination, and laboratory studies. Among the survey participants were 1,503 adults (age ≥21 years) with self-reported diabetes. We defined regular aspirin use as reported having taken aspirin ≥15 times in the previous month. CVD conditions were self-reported heart attack and stroke and symptoms of angina and claudication. CVD risk factors included smoking, hypertension, obesity, albuminuria, lipid abnormalities, and family history of heart attack.

RESULTS — An estimated 27% of adults with diabetes had CVD, and an additional 71% had one or more CVD risk factors. Aspirin was used regularly by 37% of those with CVD and by 13% of those with risk factors only. Adjusted odds of regular aspirin use were significantly greater for individuals with CVD than for those with one CVD risk factor (odds ratio [OR] = 4.3); for non-Hispanic whites than for blacks, Mexican-Americans, and others (OR = 2.5); and for individuals age 40–59 years than for those <40 years (OR = 33.3).

CONCLUSIONS — Nearly every adult in the U.S. with diabetes has at least one risk factor for CVD and thus may be considered a potential candidate for aspirin therapy. During 1988–1994, only 20% (95% CI 16–23) took aspirin regularly. Major efforts are needed to increase aspirin use.

Diabetes Care 24:197–201, 2001

Aspirin therapy to prevent cardiovascular disease (CVD) may be particularly beneficial for people with diabetes. First, people with diabetes are two to four times as likely to develop CVD as people without diabetes (1). Second, people with diabetes have been observed to have altered platelet function with increased production of thromboxane (2,3), and the primary way in which aspirin reduces the risk of CVD is through its effects on platelet function resulting in reduced thromboxane synthesis (4).

Aspirin has been shown to be an effective and relatively safe treatment for people with diabetes. Trials have demonstrated that aspirin therapy can prevent the first heart attack, stroke, or other indication of CVD (primary prevention) (5,7,8) and also subsequent cardiovascular events (secondary prevention) (6–8) without any significant increase in retinal or vitreous hemorrhage, gastrointestinal bleeding, or hemorrhagic stroke (7).

The American Diabetes Association (ADA) published guidelines for aspirin therapy in adults with diabetes in 1997 (8,9) and reissued them, with minor revisions, in 2000 (10). The ADA recommends that, in the absence of specific contraindications, aspirin should *1*) be used for secondary prevention by men and women with evidence of large vessel disease (myocardial infarction, vascular bypass procedure, stroke, transient ischemic attack, or angina) and *2*) be considered for primary prevention in adults who have one or more risk factors for CVD (family history of coronary heart disease, smoking, hypertension, obesity, albuminuria, or lipid abnormalities) or who are ≥30 years of age. Doses of 81–325 mg/day of enteric-coated aspirin are advised. Specific contraindications cited by the ADA include aspirin allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding, and clinically active liver disease. The ADA notes that the use of aspirin has not been studied in individuals with diabetes who are <30 years of age and that aspirin should not be recommended for those <21 years because of the risk of Reye's syndrome (10).

In this report, we use the ADA guidelines and a nationally representative sample to estimate the percentage of adults with diabetes who are potential candidates for aspirin therapy and the prevalence of regular aspirin use among such individuals.

RESEARCH DESIGN AND METHODS

— The Third National Health and Nutrition Examination Survey (NHANES III) was conducted in 1988–1994 and used a probability sample of the U.S. civilian noninstitutionalized population (11). Participants were asked to complete a household interview and then a physical examination that included the collection of blood and urine samples (12). In all, 18,460 individuals ≥21 years of age (81% of those eligible) completed the household interview.

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Received for publication 29 February 2000 and accepted in revised form 19 September 2000.
Abbreviations: ADA, American Diabetes Association; CVD, cardiovascular disease; ETDRS, Early Treatment Diabetic Retinopathy Study; HOT, Hypertension Optimal Treatment; NHANES III, Third National Health and Nutrition Examination Survey; OR, odds ratio.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Estimated prevalence of CVD and regular aspirin use among U.S. adults with diabetes*

Condition*	Percent with condition†	Percent using aspirin
Heart attack	14 (12–17)	39 (27–50)
Stroke	11 (8–13)	42 (32–53)
Angina	8 (6–9)	24 (13–35)
Claudication	3 (1–4)	70 (41–99)

Data are % (95% CI). *Categories are not mutually exclusive. †Unweighted sample size 1,503.

Our primary sample for this study consisted of the 1,503 interview participants (658 men, 845 women) age ≥21 years with diagnosed diabetes (11). Women who reported that they were diagnosed only during pregnancy were not included.

Participants were classified as regular aspirin users if they reported taking aspirin ≥15 times in the month before the interview. This definition was designed to capture alternate-day as well as daily use, both of which have been found effective for preventing CVD (5,7). The two relevant questions were, "In the past month have you taken any aspirin, Anacin, Bufferin, Ecotrin, Ascriptin, or Midol?" and a follow-up question, "How often did you take [aspirin] during the past month?" The distribution of "how often" had a prominent spike at 30, which is consistent with daily therapeutic use. We believe that those who did not know whether or how much aspirin they had taken were unlikely to have been regular users. Therefore, we classified individuals who did not answer both the initial and follow-up questions as nonregular users along with those who took aspirin 0–14 times in the previous month.

We defined CVD as the presence of one or more of four conditions (heart attack, stroke, possible angina, and lower-extremity claudication). Heart attack and stroke were both identified by self-report of a previous diagnosis; history of possible angina and lower-extremity claudication were determined from responses to the Rose questionnaire (13). We included six CVD risk factors in our analysis (family history of heart attack, smoking, obesity, hypertension, albuminuria, and dyslipidemia) and defined them to mirror their definitions in the ADA guidelines (10) (see footnote to Table 2). Age ≥30 years was treated as a separate risk factor, as it was in the ADA guidelines. Individuals with a missing or "unknown" response for a CVD condition or risk factor were considered to not have that condition.

We used the interview sample (n = 1,503 individuals with diabetes) to estimate the percentage of all adults with diabetes who had each of the four CVD conditions and the prevalence of aspirin use among those with each condition. Among individuals with diabetes but without any of the four CVD conditions, we estimated the percentage that had each of the six CVD risk factors, or age ≥30 years, and the prevalence of aspirin use among those with each risk factor. Here we used interview, physical examination, laboratory, and morning (fasting) subsamples (n = 1,092, 974, 932, and 429 individuals, respectively, with diabetes but without CVD).

We used the subsample (n = 1,265) of all diabetic participants with laboratory results available to estimate the distribution of adults with diabetes across four categories distinguished in the ADA guidelines and the prevalence of aspirin use in each of those groups. BMI, urinary albumin, HDL, and total cholesterol were available for most of these participants, but LDL and triglyceride values were available only for those examined in the morning after fasting.

We used logistic regression to test whether CVD or number of CVD risk factors, age, sex, race or ethnicity, family income, education, and health insurance coverage (any vs. none) were associated with regular aspirin use among adults with diabetes and CVD or one or more risk factors. Diabetes duration (in years), self-reported insulin use, and HbA_{1c} (levels <8, 8–10, or >10) were included in the analysis as indicators of disease severity that might be associated with the prescription of aspirin therapy. Additionally, we modeled regular aspirin use among all adults, with and without diabetes, who had CVD, one or more CVD risk factors, or age ≥30 years (n = 15,718) and tested whether diabetes was significantly associated with aspirin use after adjusting for the effects of age, race or ethnicity, CVD, and other demographic variables. We used the Wald F statistic to test main effects and interactions, and computed odds ratios (ORs) with 95% CIs to compare levels of explanatory variables. To assess whether there was a temporal trend, we compared the first 3-year phase of the survey with the second (each phase provided an independent national estimate).

We used SUDAAN (14) for estimation and regression modeling. All of our analyses account for the clustered design and planned oversampling and adjust for differential noncoverage and nonresponse (12). Separate weights were used for the interview, examination, laboratory, and morning (fasting) samples, permitting appropriate inference from every sample to the population of adults in the U.S. with diagnosed diabetes.

RESULTS — We estimated that among all U.S. adults with diabetes, 63% took aspirin 0 times in the previous month; 16%, 1–14 times; 2%, 15–29 times; 16%, 30 times, and 2%, 30–122 times (2% had an unknown level of use). Therefore, by our definition, 18% of adults with diabetes were regular aspirin users in 1988–1994.

Among adults with diabetes, heart attack was the most prevalent (14%) of four CVD conditions (Table 1). Only 39% of those with diabetes and a history of heart attack were regular aspirin users. The estimated prevalence of aspirin use was highest (70%) among individuals with symptoms of claudication, but only 30 individuals in our sample reported such symptoms.

Among adults with diabetes who did not have CVD (Table 2), the prevalence of individual CVD risk factors ranged from 8% (family history of heart attack) to 92% (dyslipidemia) and 98% (age ≥30 years). Aspirin was used regularly by <17% of those with each of these risk factors.

We estimated that 27% of U.S. adults with diabetes had CVD (one or more of four conditions) and that 37% of those with CVD used aspirin regularly (Table 3). Among those without CVD but with one or more of six CVD risk factors (71% of all adults with diabetes), 13% used aspirin regularly. We found that >99% of the U.S. adult diabetes population fell into one of the three categories (CVD, one or more CVD risk factors, or age ≥30 years) of individuals for whom the ADA recommends that aspirin therapy be used or considered. In this combined group, only 20% (95% CI 16–23) used aspirin regularly.

CVD, race or ethnicity, and age were significantly associated with regular aspirin use among individuals with diabetes who could be considered candidates for aspirin therapy per the ADA recommendation

Table 2—*Estimated prevalence of risk factors and regular aspirin use among adults with diabetes but without CVD*

Risk factor*	Percent with risk factor†	Percent aspirin use
Family history of heart attack‡	8 (5–11)	16 (1–31)
Obesity§ (n = 974)	61 (57–66)	13 (8–19)
Hypertension¶	55 (50–59)	16 (11–21)
Smoking‖	21 (15–28)	13 (6–19)
Albuminuria# (n = 932)	34 (29–38)	11 (5–18)
Dyslipidemia** (n = 429)	92 (89–95)	15 (10–20)
Age ≥30 years	98 (97–99)	13 (9–17)

Data are % (95% CI). *Categories are not mutually exclusive. †Unweighted sample size 1,092 except as noted. ‡Mother or father had a heart attack before age 50 years. §BMI ≥27.8 kg/m^2 for men and ≥27.3 kg/m^2 for women. ¶Elevated blood pressure (systolic ≥140 mmHg or diastolic ≥90 mmHg) or ever prescribed medication for hypertension. Blood pressure value is arithmetic mean of up to six readings obtained during the interview or examination. ‖Current smoker and smoked ≥100 cigarettes during lifetime. #Urinary albumin ≥30 μg/ml (microalbuminuria). Value not adjusted for creatinine. **HDL <45 mg/dl (1.16 mmol/l) in men or HDL <55 mg/dl (1.42 mmol/l) in women or total cholesterol ≥200 mg/dl (5.17 mmol/l) or LDL ≥100 mg/dl (2.59 mmol/l) or fasting triglycerides ≥200 mg/dl (2.28 mmol/l) or ever prescribed medication for high cholesterol.

(Table 4). The odds of regular aspirin use were 4.3 times as great for people with CVD as for those with zero or one CVD risk factors, but having a larger number of CVD risk factors was not significantly associated with increased odds of aspirin use. Non-Hispanic whites were 2.5 times as likely to use aspirin regularly as non-Hispanic blacks, Mexican-Americans, or individuals of other races. The odds of regular aspirin use, which increased with age, were greater for individuals ≥40 years than for those 21–39 years of age.

We found no statistically significant differences in regular aspirin use by sex, educational attainment, or family income. Insulin use, duration of diabetes, HbA_{1c}, and health insurance coverage were not found to be associated with aspirin use and were not included in the final model. None of the two-way interactions between CVD, age, race, and sex was significant; the sample size was inadequate for testing higher-order interactions. There was no evidence of a temporal trend: among people with diabetes who had CVD or risk factors, 19.3% used aspirin regularly during the first phase, and 19.9% used it during the second phase.

Compared with people who did not have diagnosed diabetes, people with diabetes were somewhat more likely to take aspirin regularly (20 vs. 10% overall, 37 vs. 31% among those with CVD, and 13 vs. 9% among those with CVD risk factors). We found no significant association, however, between regular aspirin use and having diabetes (OR = 1.02; 95% CI 0.78–1.35) after adjusting for CVD, race, and age. Here, as in the diabetes subgroup, CVD, white race, and older age were most strongly associated with regular aspirin use. We also found that in this expanded population, aspirin was significantly more likely to be used by men than by women. Once again, there was no evidence of a temporal trend.

CONCLUSIONS — Based on a nationally representative sample, we estimated that >99% of U.S. adults with diagnosed diabetes in 1988–1994 had CVD or at least one CVD risk factor. Aspirin was used regularly by 20% of such individuals. Among those with established CVD (27% of people with diabetes), for whom the value of aspirin therapy for secondary prevention is unequivocal (6,7,10,15), 37% reported regular use. Among those without CVD but with one or more CVD risk factors (71% of adults with diabetes), a group for whom aspirin therapy should be considered for primary prevention (5,7,10,16), 13% were regular users.

Diabetes-specific guidelines for aspirin therapy (10) were not published until 1997. However, the potential benefits of aspirin therapy for primary prevention of CVD were widely publicized beginning with the release, in January 1988, of a preliminary report on the Physician's Health Study (5), and more general guidelines for secondary prevention were developed and published during the study period (17,18). In this context, our estimates of the prevalence of regular aspirin use seem quite low, and it is somewhat surprising that aspirin use did not increase during the second phase of the survey.

The argument in favor of aggressive efforts to prevent CVD in people with diabetes is overwhelming. The risk of myocardial infarction is as high for diabetic patients who have never had an infarction as it is for other patients who have (1). People with diabetes are not only at greater risk for CVD than those without the disease, but they are also more likely to die from CVD (19,20). In our study, the presence of diabetes was not associated with increased odds of regular aspirin use among U.S. adults after accounting for differences in the distributions of CVD, race, and age. A study conducted in Israel in 1990–1992 among individuals aged 45–74 years with coronary artery disease supports our finding: researchers there found similarly little difference in the prevalence of aspirin use between those with diabetes (52%) and others (56%) (21). Also, a

Table 3—*Estimated prevalence of regular aspirin use among U.S. adults with diabetes according to four mutually exclusive categories distinguished in the ADA guidelines for aspirin therapy*

Risk category	n*	Percent in category	Percent aspirin use	ADA recommendation for aspirin therapy
CVD	333	27 (24–31)	37 (30–44)	Use for secondary prevention
One or more of six CVD risk factors	917	71 (68–74)	13 (9–17)	Consider for primary prevention
Neither CVD nor risk factor, age ≥30 years	13	1.5 (0–3)	13†	Consider for primary prevention
Neither CVD nor risk factor, age <30 years	2	0.3†	0†	No specific recommendation

Data are n or % (95% CI). *Total unweighted sample size 1,265. Among the 917 with one or more CVD risk factor are 15 individuals <30 years of age. †No CI because estimate based on less than five sample cases. CVD includes heart attack, stroke, angina, and claudication. CVD risk factors include family history of heart attack, obesity, hypertension, smoking, albuminuria, and dyslipidemia.

Table 4—*Prevalence and odds of regular aspirin use among adults with CVD, one or more CVD risk factors, or age ≥30 years*

Variable	Percent of population	Percent aspirin use	Adjusted odds of aspirin use*	95% CI for OR
CVD or number of CVD risk factors				
0–1 risk factors	12	9	1.0	—
2–3 risk factors	42	14	1.2	0.4–3.1
4–6 risk factors	18	14	1.4	0.4–5.1
CVD	27	37	4.3	1.6–11.8
Age (years)				
21–39	9	1	0.03	0.01–0.17
40–59 (reference level)	34	16	1.0	—
≥60	56	25	1.5	0.9–2.5
Race or ethnicity				
Non-Hispanic white	74	23	1.0	—
Non-Hispanic black	15	9	0.4	0.3–0.5
Mexican-American	6	8	0.4	0.2–0.8
Other race	6	10	0.4	0.1–1.3
Sex				
Female	55	18	1.0	—
Male	45	21	1.1	0.7–1.8
Education				
<High school	43	18	1.0	—
High school	33	22	1.3	0.7–2.2
>High school	24	18	1.1	0.5–2.3
Income				
<$20,000	47	17	1.0	—
≥$20,000	53	22	1.5	0.9–2.8

Total unweighted sample size 1,263. *Computed from a logistic regression model that included all variables listed in this table; 31 observations were excluded from the logistic regression analysis because of missing values for education or income.

recent survey of members of a U.S. health maintenance organization found that those with diagnosed diabetes had significantly lower adjusted odds of using aspirin to prevent heart disease than those without diabetes (22).

We can suggest several possible reasons for the low rates of aspirin use among people with diabetes. We have mentioned the absence, before 1997, of diabetes-specific guidelines. It is conceivable that physicians have had an exaggerated perception of the risks of aspirin therapy for people with diabetes, particularly those with retinopathy or hypertension. Results from the Early Treatment Diabetic Retinopathy Study (ETDRS) and the Hypertension Optimal Treatment (HOT) trial should be noted. The ETDRS used a relatively high dose of aspirin (650 mg/day) in people with diabetes and retinopathy, yet showed no significant increase in the risk of severe complications (7). In the HOT study, which included 1,501 patients with diabetes, 75 mg/day of aspirin reduced the risk of myocardial infarction, with no effect on stroke or fatal bleeds (23). It is also possible that patients with more severe diabetes may be less motivated to comply with recommendations for medications. Such patients are often prescribed multiple therapies, among which aspirin may be perceived as relatively unimportant. However, in our study, we examined several markers for diabetes severity (duration, HbA_{1c} level, and insulin use) and found that none was associated with regular aspirin use.

Among our most important findings, in the population of individuals with diabetes and CVD or risk factors, aspirin was less likely to be used by blacks and Mexican-Americans than by non-Hispanic whites, even after adjusting for differences in age, CVD, and number of CVD risk factors. This difference was not explained by measured differences in income or education. In addition, younger people were much less likely to use aspirin than older people. Among all adults (those with diabetes and others) with CVD or risk factors, aspirin was less likely to be used by women than by men. Others have observed similar differences in aspirin use (24–26), and we note reports that other CVD treatments may be underused by ethnic minorities in the U.S. (27,28).

Several factors could have biased our results. Although it is likely that some of the regular aspirin users in our sample did not use aspirin expressly for CVD benefit (29), it is important to note that the risk of CVD is reduced by regular use of aspirin for any purpose (including arthritis and pain relief). It is also possible that we counted as regular aspirin users a few people who took frequent doses of aspirin for a short time, but not for most of the month, or misclassified as nonregular users some who did not know how much aspirin they took. Our measure of CVD did not include history of vascular bypass or transient ischemic attack, and some of our lipid measures were available only for NHANES III participants who had fasted overnight, yet we still found that 98% of all adults with diabetes had CVD or one or more CVD risk factors. Unfortunately, we were unable to estimate the prevalence of specific contraindications to aspirin therapy.

The NHANES III data provide national baseline estimates for measuring improvements in the quality of care received by people with diabetes. Approximately 10.2 million U.S. adults have diagnosed diabetes (34). Low cost (about $1.50/month for enteric-coated preparations) and ready availability make aspirin practical for widespread use. Our study suggests that as many as 8 million people with diabetes who are potential candidates for aspirin therapy are not using this effective treatment. Clearly, extensive efforts are needed to increase aspirin use among people with diabetes, and racial and ethnic minorities should be targeted in these efforts. Using guidelines, educating patients, involving opinion leaders, and carrying out other similar interventions can potentially achieve the goal of increasing aspirin use (30). Preventive measures should be monitored, and the effectiveness of existing guidelines should be evaluated (31). Including aspirin in the Diabetes Quality Improvement Program measure sets (32) and in the Health Plan Employer Data and Information Set (33) as a measure of the quality of care received by people with diabetes might also encourage regular use.

There are important contraindications to aspirin use, and even in the absence of these, the individual's level of cardiovascular risk must be weighed against the small

but serious risks of aspirin therapy, particularly among those <30 years of age. Still, our data suggest that nearly every U.S. adult with diagnosed diabetes has at least one measurable risk factor for CVD and thus may be considered a potential candidate for aspirin therapy (10).

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