Aspirin Is Associated With Reduced Cardiovascular and All-Cause Mortality in Type 2 Diabetes in a Primary Prevention Setting

The Fremantle Diabetes Study

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OBJECTIVE — To determine whether regular aspirin use (≥75 mg/day) is independently associated with cardiovascular disease (CVD) and all-cause mortality in community-based patients with type 2 diabetes and no history of CVD.

RESEARCH DESIGN AND METHODS — Of the type 2 diabetic patients recruited to the longitudinal observational Fremantle Diabetes Study, 651 (50.3%) with no prior CVD history at entry between 1993 and 1996 were followed until death or the end of June 2007, representing a total of 7,537 patient-years (mean ± SD 11.6 ± 2.9 years). Cox proportional hazards modeling was used to determine independent baseline predictors of CVD and all-cause mortality including regular aspirin use.

RESULTS — There were 160 deaths (24.6%) during follow-up, with 70 (43.8%) due to CVD. In Kaplan-Meier survival analysis, there was no difference in either CVD or all-cause mortality in aspirin users versus nonusers ($P = 0.52$ and 0.94, respectively, by log-rank test). After adjustment for significant variables in the most parsimonious Cox models, regular aspirin use at baseline independently predicted reduced CVD and all-cause mortality (hazard ratio [HR] 0.30 [95% CI 0.09–0.95] and 0.53 [0.28–0.98[, respectively; $P \leq 0.044$). In subgroup analyses, aspirin use was independently associated with reduced all-cause mortality in those aged ≥65 years and men.

CONCLUSIONS — Regular low-dose aspirin may reduce all-cause and CVD mortality in a primary prevention setting in type 2 diabetes. All-cause mortality reductions are greatest in men and in those aged ≥65 years. The present observational data support recommendations that aspirin should be used in primary CVD prevention in all but the lowest risk patients.

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The value of low-dose aspirin as primary prevention for cardiovascular disease (CVD) in patients with type 2 diabetes remains to be established. The American Diabetes Association (ADA) (1) and the European Society of Cardiology (ESC) and European Society for the Study of Diabetes (EASD) (2) recommend the use of aspirin in this situation, but there is no consistent supportive evidence of reductions in CVD events or mortality (3–6). In population-based primary prevention trials reported to date, only 4% of patients had type 2 diabetes (7). This low percentage raises the question of whether the diabetic subjects were representative. There have been few such studies in diabetic subjects specifically (4,5).

There is a clear need for more data on the benefits and risks of aspirin for primary prevention in diabetes. We have, therefore, examined the relationship between CVD death and all-cause mortality in a large, well characterized Australian community-based cohort of type 2 patients with no history of CVD.

RESEARCH DESIGN AND METHODS

The Fremantle Diabetes Study (FDS) was a longitudinal observational cohort study of patients from a postal code–defined urban community of 120,097 people. Descriptions of recruitment, sample characteristics including classification of diabetes type, and details of nonrecruited patients have been published elsewhere (8). Of 2,258 diabetic patients identified between 1993 and 1996, 1,426 (63%) were recruited to the FDS and 1,294 had type 2 diabetes. Eligible patients who declined participation were a mean of 1.4 years older than participants, but their sex distribution, the proportion with type 2 diabetes, and their use of blood glucose–lowering therapies were similar (8). The FDS protocol was approved by the Human Rights Committee at Fremantle Hospital, and all subjects gave informed consent before participation.

Baseline and annual assessments

The assessment of each patient at study entry and at each annual review included a comprehensive questionnaire and physical examination (8). In addition to details of all medical conditions and their management, demographic, socioeconomic, and lifestyle data were recorded. Patients were requested to bring all medications to each visit and details, including doses, were recorded. Regular aspirin use was defined as a minimum of 75 mg/day or 300 mg every 2nd day (9). Biochemical tests were performed on fasting blood and urine samples using standard automated methods in a single laboratory (8).

Baseline complications were identified using standard definitions (10). In brief, microalbuminuria was defined as a

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urine albumin-to-creatinine ratio (ACR) of ≥3.0 mg/mmol. The estimated glomerular filtration rate was calculated from the serum creatinine (11). Neuropathy was defined using the clinical portion of the Michigan Neuropathy Screening Instrument. Retinopathy was defined as one microaneurysm in either eye or worse and/or evidence of previous laser treatment on direct and/or indirect ophthalmoscopy through dilated pupils and/or more detailed ophthalmological data in patients assessed for photocoagulation. Patients were classified as having coronary heart disease if there was a history of myocardial infarction, angina, coronary artery bypass grafting, or angioplasty and as having cerebrovascular disease if there was a history of stroke and/or transient ischemic attack. Peripheral arterial disease was defined as an ankle brachial index ≤0.90 or the presence of a diabetes-related lower-extremity amputation.

Mortality ascertainment

All deaths and hospital admissions in the state of Western Australia are recorded in the Western Australian Data Linkage System (12), which was used to provide FDS patient outcomes from the beginning of the study until the end of June 2007. Causes of death were reviewed independently by two physicians and classified under the system used in the UK Prospective Diabetes Study (13). In cases of discrepant coding, case notes were consulted and a consensus was obtained. Death from CVD was defined as death from cardiac or cerebrovascular causes or peripheral arterial disease or sudden death.

Statistical analysis

The computer package SPSS for Windows (version 15.0) was used for statistical analysis. Data are presented as proportions, mean ± SD, geometric mean (SD range), or, in the case of variables that did not conform to a normal or log-normal distribution, median (interquartile range). For independent samples, two-way comparisons for proportions were performed by Fisher exact test, for normally distributed variables by Student *t* test, and for nonnormally distributed variables by Mann-Whitney *U* test. Multiple comparisons for proportions were performed by Fisher exact test or χ^2 test, for normally distributed variables by one-way ANOVA, and for nonnormally distributed variables by Kruskal-Wallis H-test. A two-tailed significance level of $P < 0.05$ was used throughout.

Kaplan-Meier analysis was used to assess all-cause mortality and CVD death with respect to aspirin use. Cox proportional hazards modeling (forward conditional variable entry and removal with $P < 0.05$ and $P > 0.10$, respectively) was used to determine independent baseline predictors of all-cause and CVD mortality. All clinically plausible variables were considered for entry into the models, including demographic and diabetes-related factors, the presence of other diabetes complications, and cardiovascular risk factors. The validity of the proportional hazards assumption was assessed from log (−log[survival]) curves and examination of time-dependent covariates.

Table 1—*Baseline characteristics of 1,294 FDS participants with type 2 diabetes classified by primary or secondary CVD prevention status*

	Primary prevention	Secondary prevention	*P* value
n	651	625	
Age (years)	60.7 ± 11.2	67.6 ± 10.1	<0.001
Male sex (%)	45.3	52.8	0.008
Ethnic background (%)			
Anglo-Celt	62.1	65.0	
Southern European	20.0	16.5	
Other European	7.8	9.0	0.66
Asian	3.2	3.2	
Aboriginal	1.5	1.3	
Other	5.4	5.1	
Education beyond primary level (%)	73.8	74.6	0.75
Not fluent in English (%)	16.7	13.6	0.14
Currently married/de facto relationship (%)	67.2	64.7	0.38
Smoking status (%)	52.4	36.7	
Never			
Former	34.4	46.8	<0.001
Current	13.3	16.6	
Any exercise in past 2 weeks (%)	75.2	69.0	0.014
Alcohol consumption (standard drinks/day)	0 [0–0.8]	0 [0–0.3]	0.020
Diabetes duration (years)	3.0 [0.8–7.0]	5.0 [1.4–11.0]	<0.001
Fasting serum glucose (mmol/l)	8.4 [6.8–10.9]	8.5 [6.9–10.7]	0.69
A1C (%)	7.4 [6.3–8.7]	7.5 [6.5–8.9]	0.054
Diabetes treatment (% diet/oral agents/insulin ± oral agents)	35.9/55.3/8.8	27.7/57.2/15.1	<0.001
BMI (kg/m^2)	29.9 ± 5.4	29.1 ± 5.3	0.007
Abdominal obesity (%; by waist circumference*)	66.2	62.4	0.18
Systolic blood pressure (mmHg)	146 ± 22	156 ± 24	<0.001
Diastolic blood pressure (mmHg)	80 ± 11	81 ± 11	0.08
Taking antihypertensive medication (%)	37.5	65.1	<0.001
Total serum cholesterol (mmol/l)	5.4 ± 1.1	5.5 ± 1.2	0.45
Serum HDL cholesterol (mmol/l)	1.08 ± 0.33	1.04 ± 0.32	0.015
Serum triglycerides (mmol/l)	1.8 (1.1–3.2)	2.0 (1.1–3.4)	0.039
Lipid-lowering therapy (%)	7.2	14.0	<0.001
Regular aspirin use (≥75 mg/day)	7.7	36.6	<0.001
Urinary ACR (mg/mmol)	2.4 (0.6–9.7)	4.0 (0.9–18.0)	<0.001
Estimated glomerular filtration rate <60 ml/min per 1.73 m^2 (%)	13.0	29.2	<0.001
Peripheral neuropathy (%)	25.0	37.1	<0.001
Any retinopathy (%)	12.7	20.3	<0.001
Coronary heart disease (%)	0	57.1	<0.001
Cerebrovascular disease (%)	0	21.0	<0.001
Peripheral arterial disease (%)	0	60.5	<0.001

Data are means ± SD, %, median [interquartile range], or geometric mean (SD range). *Men ≥94 cm; women ≥80 cm.

RESULTS

Baseline patient characteristics

Of the 1,294 type 2 patients recruited to the FDS, 1,276 (98.6%) had complete details of baseline aspirin use and CVD status as well as outcomes of interest during follow-up. Of these 651 (51.0%) had no prior history of coronary heart disease, cerebrovascular disease, or peripheral arterial disease. Compared with the remaining 625 participants with prevalent CVD at baseline, they were significantly younger, were less likely to be male, had shorter diabetes duration, and were less likely to be taking aspirin regularly (7.7 vs. 36.6%; $P < 0.001$) (Table 1). Of the primary prevention subgroup, 50 (7.7%) were taking aspirin regularly, and all of these patients were taking a daily dose of ≥75 mg/day.

Cardiovascular and all-cause mortality

Between study entry and the end of June 2007, there were 160 deaths (24.6%) in the primary prevention group during a total of 7,537 patient-years (11.6 ± 2.9 years) of follow-up, of which 70 (43.8%) were attributed to CVD. In Kaplan-Meier survival analysis, there were no significant differences between aspirin users and nonusers in terms of CVD or all-cause mortality ($P = 0.52$ and $P = 0.94$, respectively, by log-rank test). After adjustment for other significant variables, regular aspirin use was independently associated with reduced all-cause and CVD mortality (Table 2).

In patients aged at least 65 years, aspirin use was not significantly associated with CVD or all-cause mortality in unadjusted Kaplan-Meier analyses ($P \geq 0.09$ by log-rank test), but, after adjustment for the most parsimonious Cox model of time to death, it was a significant, independent predictor of reduced all-cause mortality (Table 3). In Cox proportional hazards models, there were no independent associations between aspirin use and either CVD or all-cause mortality in patients aged <65 years ($P > 0.56$).

The regular use of aspirin had different effects by sex. In both men and women, aspirin use was not significantly associated with CVD or all-cause mortality in unadjusted Kaplan-Meier analyses ($P > 0.09$ by log-rank test). In Cox models, aspirin use was independently associated with reduced all-cause mortality in men but not in women (Table 4). No such reduction was seen for CVD mortality in men or women ($P \geq 0.12$).

Table 2—*Independent determinants of time to CVD and all-cause mortality in FDS primary prevention subjects*

	HR (95% CI)	*P* value
Cardiovascular mortality		
Age (increase of 10 years)	3.09 (2.27–4.21)	<0.001
Diabetes duration (increase of 5 years)	1.27 (1.09–1.49)	0.003
Not fluent in English	0.17 (0.07–0.47)	0.001
BMI (increase of 1 kg/m^2)	0.92 (0.87–0.97)	0.002
ln(urine ACR)*	1.21 (1.02–1.44)	0.034
Regular aspirin use	0.30 (0.09–0.95)	0.041
All-cause mortality		
Age (increase of 10 years)	2.15 (1.76–2.62)	<0.001
Male sex	1.47 (1.06–2.03)	0.022
Southern European ethnicity	0.63 (0.40–0.98)	0.041
BMI (increase of 1 kg/m^2)	0.93 (0.90–0.97)	<0.001
Lipid-modifying therapy	0.30 (0.11–0.82)	0.018
ln(urinary ACR)*	1.36 (1.21–1.52)	<0.001
Peripheral neuropathy	1.79 (1.27–2.53)	0.001
Regular aspirin use	0.53 (0.28–0.98)	0.044

The most parsimonious models are shown with HRs (95% CI). The HRs for regular aspirin use are those after adjustment for the significant variables in the models. *A 2.72-fold increase in ACR or triglycerides corresponds to an increase of 1 in ln(ACR) or ln(triglycerides), respectively.

CONCLUSIONS— We found that regular use of aspirin by community-based patients with type 2 diabetes and no prior history of CVD was independently associated with a reduction in subsequent CVD and all-cause mortality of at least 50%. The effect was most pronounced in subgroups comprising males and those patients aged ≥65 years. Although the present data are observational, they add weight to recommendations from bodies such as ESC, EASD, and ADA (1,2) that aspirin should be used in a primary prevention setting to reduce the potentially devastating effects of CVD complicating type 2 diabetes in all but the lowest risk patients (those who are young and without recognized vascular risk factors).

In the recent Antithrombotic Trialists' (ATT) Collaboration meta-analysis of primary prevention studies of samples drawn from the general population (6), "serious vascular events" (primarily nonfatal myocardial infarction) were reduced

Table 3—*Independent determinants of time to CVD and all-cause mortality in FDS primary prevention subjects aged ≥65 years*

	HR (95% CI)	*P* value
Cardiovascular mortality		
Age (increase of 10 years)	2.98 (1.76–5.04)	<0.001
Alcohol consumption	1.09 (1.01–1.17)	0.024
BMI (increase of 1 kg/m^2)	0.91 (0.85–0.97)	0.004
Diabetes duration (increase of 5 years)	1.28 (1.09–1.50)	0.002
Regular aspirin use	0.35 (0.11–1.13)	0.079
All-cause mortality		
Age (increase of 10 years)	2.69 (1.83–3.95)	<0.001
BMI (increase of 1 kg/m^2)	0.93 (0.89–0.97)	0.002
Diastolic blood pressure (increase of 1 mmHg)	0.98 (0.97–1.00)	0.050
Any exercise	0.59 (0.39–0.91)	0.016
Insulin therapy	1.87 (1.05–3.32)	0.033
ln(urinary ACR)*	1.26 (1.10–1.45)	0.001
Male sex	1.84 (1.22–2.78)	0.004
Southern European ethnicity	0.37 (0.20–0.68)	0.001
Regular aspirin use	0.40 (0.19–0.84)	0.015

The most parsimonious models are shown with HRs (95% CI). The HRs for regular aspirin use are those after adjustment for the significant variables in the models. *A 2.72-fold increase in ACR or triglycerides corresponds to an increase of 1 in ln(ACR).

Table 4—*Independent determinants of time to CVD and all-cause mortality in FDS primary prevention male subjects*

	HR (95% CI)	*P* value
Cardiovascular mortality		
Age (increase of 10 years)	2.58 (1.61–4.15)	<0.001
BMI (increase of 1 kg/m^2)	0.87 (0.80–0.95)	0.003
ln(urinary ACR)*	1.44 (1.14–1.81)	0.002
Aboriginal background	30.49 (2.72–341.82)	0.006
Not fluent in English	0.14 (0.02–1.04)	0.054
Regular aspirin use	0.20 (0.03–1.51)	0.12
All-cause mortality		
Age (increase of 10 years)	2.43 (1.82–3.24)	<0.001
BMI (increase of 1 kg/m^2)	0.94 (0.89–0.99)	0.019
ln(urinary ACR)*	1.34 (1.16–1.55)	<0.001
Aboriginal background	13.03 (1.52–111.54)	0.019
Southern European ethnicity	0.43 (0.22–0.83)	0.013
Regular aspirin use	0.34 (0.12–0.93)	0.035

The most parsimonious models are shown with HRs (95%CI). The HRs for regular aspirin use are those after adjustment for the significant variables in the models. *A 2.72-fold increase in ACR or triglycerides corresponds to an increase of 1 in ln(ACR).

by the use of low-dose aspirin, but there was no effect on vascular mortality. In 376 diabetic patients allocated either aspirin or placebo, there was a nonsignificant trend toward benefit for serious vascular events with a rate ratio of 0.88 (95% CI 0.67–1.15) favoring aspirin, but mortality data were not reported for this small subgroup (6). In a randomized trial of aspirin in 3,711 patients with type 1 or type 2 diabetes and retinopathy with or without CVD recruited in the early 1980s and followed for 5 years (14), there were nonsignificant reductions of 13 and 9%, respectively, for CVD and all-cause mortality in aspirin-treated subjects.

Two more recent intervention trials have examined the role of aspirin as primary prevention for patients with diabetes. The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial in 1,276 Scottish patients with type 1 or 2 diabetes and asymptomatic peripheral vascular disease followed for a median of 6.7 years (4) and the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial in 2,539 Japanese with type 2 diabetes followed for a median of 4.4 years (5) did not show that aspirin therapy prevented a composite vascular end point. The JPAD trial provided some evidence that aspirin-treated patients had lower coronary and cerebrovascular mortality, but there was only one death from coronary or cerebrovascular causes in the aspirin group and 10 in the control group. Indeed, the low event rates in these trials and their consequently limited statistical power have been highlighted (15). In the present study, the numbers of total and CVD deaths were much greater, due mainly to the longer follow-up period.

Older individuals and men are at increased risk of vascular events (6), and our findings suggest that aspirin therapy is particularly beneficial in these subgroups in type 2 diabetes. In the general population trials included in the recent ATT meta-analysis of data from 95,000 subjects, there was no convincing evidence of an interaction between age or sex and aspirin effects on CVD or all-cause mortality (6,16). However, these analyses included a majority of women with almost 40,000 low CVD–risk subjects from the Women's Health Initiative (WHI) study (17,18). Consistent with our data, the JPAD study found that the reduction in incidence of atherosclerotic events with aspirin was seen mainly in patients with type 2 diabetes who were at least 65 years of age (5). However, neither the POPADAD (4) nor JPAD (5) study was able to identify any sex-specific differences.

The risk of aspirin-associated hemorrhage needs to be balanced against CVD and mortality benefits. In the present study, aspirin use was not associated with increased all-cause mortality. In addition, aspirin was not independently associated with hospitalization for complicated peptic ulcer disease in the FDS cohort as a whole (19). Although extracranial hemorrhage rates were increased in both the ATT meta-analysis (6) and the JPAD trial (5), these were mainly nonfatal episodes. Stroke-related mortality in the ATT meta-analysis (6), due mainly to hemorrhagic events, was only statistically significant if data from primary and secondary prevention studies were pooled. In the JPAD trial no significant increase in hemorrhagic stroke was identified (5). A recent Swedish record linkage study (20) showed an increase in all-cause mortality in aspirin-treated type 2 diabetic patients, especially in elderly patients, but the range of variable was not as extensive as in the present study.

Our study had limitations. The FDS data were observational, but there is little evidence that estimates of intervention effects in well conducted observational studies are consistently larger than or qualitatively different from those obtained in randomized controlled trials (21). We were unable to address the influence of changes in therapies, including aspirin, during follow-up. Nevertheless, if patients not taking aspirin at baseline started this therapy subsequently, this would have attenuated the protective effect of aspirin we identified. Our sample size was greater than that in some published analyses (6) but smaller than that in several intervention trials (4,5,14). However, the strengths of our study include the representative nature of the study sample and a relatively long duration of follow-up with a consequently high event rate. In addition, the Western Australian Data Linkage System captures both public and private hospital admissions in Western Australia (11) with low rates of coding errors (22) and migration out of the state of Western Australia (23).

In the absence of valid data from intervention trials conducted specifically in diabetic patients or in general population samples with an identified subgroup with diabetes (4–6), the marked protection against mortality seen in aspirin-treated patients in the present study supports use of the drug in patients with type 2 diabetes and no prior CVD history. Confirmatory data may come from large scale intervention trials currently in progress (24,25).

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