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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-002688
Article Type:	Research
Date Submitted by the Author:	05-Feb-2013
Complete List of Authors:	Ekström, Nils; Sahlgrenska Academy at the University of Gothenburg, Department of Medicine Cederholm, Jan; Uppsala University, Department of Public Health and Caring Sciences / Family Medicine and Preventive Medicine Zethelius, Bjorn.; Uppsala University, Department of Public Health and Caring Sciences / Geriatrics Eliasson, Björn; Sahlgrenska Academy at the University of Gothenburg, Department of Medicine Fhärm, Eva; Umeå University, Department of Public Health and Clinical Medicine Rolandsson, Olov; Umeå University, Department of Public Health and Clinical Medicine Miftaraj, Mervete; Centre of Registers in Region Västra Götaland, Svensson, Ann-Marie; Centre of Registers in Region Västra Götaland, Gudbjörnsdottir, Soffia; Sahlgrenska Academy at the University of Gothenburg, Department of Medicine
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Cardiovascular medicine, Epidemiology
Keywords:	DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, Vascular medicine < INTERNAL MEDICINE

Aspirin treatment and risk of first incident cardiovascular diseases in patients with type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR)

Authors: Nils Ekström[1] (MD, PhD-student), Jan Cederholm[2] (MD, PhD, Associate professor), Björn Zethelius[3] (MD, PhD, Associate professor), Björn Eliasson[1] (MD, PhD, Adjunct professor), Eva Fhärm[4] (MD, PhD) Olov Rolandsson[4] (MD, PhD), Mervete Miftaraj[5] (M.S.), Ann-Marie Svensson[5] (PhD), Soffia Gudbjörnsdottir[1, 5] (MD, PhD, Associate professor)

Affiliations

1 Department of Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden

2 Department of Public Health and Caring Sciences / Family Medicine and Preventive Medicine, Uppsala University, Sweden

3 Department of Public Health and Caring Sciences / Geriatrics, Uppsala University and Medical Products Agency, Uppsala, Sweden

4 Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

5 Centre of Registers in Region Västra Götaland, Gothenburg, Sweden

Corresponding author:

Nils Ekström

Address: Olivedalsgatan 18, 41310 Göteborg, Sweden

E-mail: nils.ekstrom@gu.se

Phone: +46(0)702890121

Word count: 3010

References: 29

Tables: 5

Abstract

Objectives: To investigate the effects of aspirin for primary prevention of cardiovascular disease (CVD), in patients with type 2 diabetes, in clinical practice.

Design: Population-based cohort study between 2005 and 2009, mean follow-up 3.9 years.

Setting: Hospital outpatient clinics and primary care in Sweden.

Participants: Men and women with type 2 diabetes, free from CVD, including atrial fibrillation and congestive heart failure, at baseline, registered in the Swedish National Diabetes Register, with continuous low-dose aspirin treatment (n=4,608) or no aspirin treatment (n=14,038).

Main outcome measures: Risks of CVD, coronary heart disease (CHD), stroke, mortality and bleedings, associated with aspirin compared to no aspirin, were analysed in all patients and in subgroups by gender and estimated cardiovascular risk. Propensity scores were used to adjust for several baseline risk factors and characteristics at Cox regression.

Results: No beneficial effects on cardiovascular outcomes or death were seen with aspirin. Rather, there was an increased risk of nonfatal/fatal CHD associated with aspirin; HR 1.19 (95% CI 1.01 – 1.41), p=0.04. The increased risk of cardiovascular outcomes associated with aspirin was seen when analysing women separately; HR 1.41 (95% CI 1.07 – 1.87), p=0.02 and HR 1.28 (95% CI 1.01 – 1.61), p=0.04 for CHD and CVD respectively, but not for men separately. There was a trend towards increased risk of a composite of bleedings associated with aspirin, n=157; HR 1.41 (95% CI 0.99 – 1.99).

Conclusions: The results oppose routine use of aspirin in patients with type 2 diabetes and no previous CVD. More research is needed to explore the differences in aspirin's effects in women and men.

Article summary

Article focus:

To evaluate the effects of primary prevention with long term aspirin treatment in a large cohort of patients with type 2 diabetes and in subgroups by gender and estimated cardiovascular risk.

Key messages:

No beneficial effects on cardiovascular outcomes or death were seen with aspirin.

The results oppose routine use of aspirin in patients with type 2 diabetes and no previous CVD.

Strengths and limitations:

A large cohort with comprehensive data on patient characteristics was studied.

Despite extensive adjustments for relevant covariates, including balancing the groups for previous hospitalization as a marker for important co-morbidities, covariates of possible importance could have been missed.

Introduction

The great burden of cardiovascular disease (CVD) in patients with type 2 diabetes is well known. In patients with established CVD, long-term aspirin treatment (secondary prevention) has proven beneficial, with cardiovascular risk reductions clearly outbalancing the increased risk of bleedings. (1, 2) Irrespective of diabetes diagnosis, the net benefit of aspirin treatment in patients with no previous CVD (primary prevention) is more controversial, partly because a relatively low incidence of CVD in this population makes the absolute risk reduction small. (3, 4)

Current knowledge of the effects of aspirin treatment for primary prevention in patients with diabetes is to a large extent based on subgroup analyses in trials designed to evaluate its effects in a general population, which increases the risk of bias. (5) Concerns have also been expressed over insufficient power in the available trials. (5) The scarce evidence is reflected in the diverging recommendations from international expert organizations. The European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) do not recommend primary prevention with aspirin, while the American Diabetes Association (ADA) recommend primary prevention in patients with diabetes and high estimated cardiovascular risk. (6, 7)

Altogether, several questions regarding the net benefit of aspirin treatment for primary prevention of CVD in patients with diabetes remain, including the effect of factors such as gender, cardiovascular risk, and dosing. Against this background, further investigation with high quality randomized controlled trials (RCTs) and epidemiological studies, powered to detect clinically significant effects, are needed. The objective of this study was to investigate benefits and harms associated with aspirin for primary prevention of CVD in a large cohort of patients with type 2 diabetes in clinical practice.

Subjects and methods

The Swedish National Diabetes Register

The Swedish NDR was initiated in 1996 as a tool for local quality assurance in diabetes care. Annual reporting to the NDR is carried out by trained physicians and nurses via the Internet or clinical records databases, during patient visits at hospitals and primary health care centres nationwide. All included patients have agreed by informed consent to register before inclusion. The Regional Ethics Review Board at the University of Gothenburg approved this study. Several reports concerning risk factor control and risk prediction in patients with diabetes have been published previously. (8-13)

Subjects

This observational study included 18,646 patients with type 2 diabetes, aged 30-80 years, and with data available for all analysed variables at baseline. Two study groups consisted of 4,608 patients with aspirin treatment at baseline and 14,038 patients with no aspirin treatment. Exclusion criteria were other anticoagulant drugs except aspirin, cardiac glycosides, organic nitrates, history before baseline of CHD (ICD-10 I20-I25 or PCI or CABG), stroke including cerebral bleeding (I60-I64), heart failure (CHF) (I50), atrial fibrillation (AF) (I48), peripheral vascular disease (PVD), amputation, renal failure (N17-N19), gastric/duodenal/peptic ulcer (K25-K27), ventricular bleeding (K92.0-K92.2), respiratory bleeding (R04), unspecified bleeding (R58), and all forms of cancer (C00-C927), as well as BMI <18 kg/m^2 and plasma creatinine >150 µmol/l. The definition of type 2 diabetes was treatment with diet only, oral hypoglycaemic agents only, or onset age of diabetes ≥40 years and insulin only or combined with oral agents.

Study information was linked from four national registers in Sweden: the National Diabetes Register (NDR), the Prescribed Drug Register, (14) the Cause of Death Register, and the Hospital Discharge Register. (15, 16) Patients had to be registered in the NDR from 1st July 2005 to 30th June 2006 with regard to prescription of aspirin and other drugs. In each patient, baseline was defined as occurring after 12 months of

continuous use of aspirin. Only patients who had filled at least three prescriptions or 19 fills of multi-dose dispensed drugs during this 12-month period were included. Thus, 12 months of continuous aspirin medication at baseline was ensured.

Examination at baseline

Clinical characteristics included at baseline 1st July 2005 – 30th June 2006 were: Aspirin treatment, age, gender, diabetes duration, previous hospitalization (for at least three consecutive days within 6 months prior to baseline), type of hypoglycaemic treatment, HbA1c, weight, height, smoking, systolic blood pressure, total cholesterol, HDL cholesterol, cumulative microalbuminuria, use of antihypertensive drugs, statins and other lipid-lowering drugs, multi-dose dispensation. Aspirin treatment was defined as a daily oral intake of 75 mg acetyl salicylic acid per day. BMI (kg/m^2) was calculated as $weight/height^2$. The Swedish standard for blood pressure recording, used in the NDR, is the mean (mmHg) of two readings (Korotkoff 1–5) with a cuff of appropriate size, after at least 5 minutes of rest. A smoker was defined as a patient smoking one or more cigarettes/day, or smoking tobacco using a pipe, or stopped smoking within the past three months.

Laboratory analyses of HbA_{1c} and serum lipids were carried out at local laboratories. HbA1c analyses are quality assured nationwide by regular calibration with the HPLC Mono-S method. HbA1c values were converted to the DCCT standard values. (17) Albuminuria was defined as cumulative microalbuminuria: urine albumin excretion >20 µg/min in two out of three consecutive tests.

We also estimated 5-year risk (%) for fatal/nonfatal CVD with use of the NDR risk model, based on 12 predictors at baseline, as previously described. (13) All patients were divided in two subgroups based on high or lower risk, 3,688 patients with risk ≥15% and 15,842 patients with risk <15%.

Follow-up, definition of endpoints

All patients were followed from baseline examination until a first incident event or death, or otherwise until censor date 31st December 2009. Mean follow-up was 3.9 years. Nonfatal coronary heart disease (CHD) was defined as nonfatal myocardial infarction (ICD-10 code I21), percutaneous coronary intervention and/or coronary artery bypass grafting, and fatal CHD defined as ICD-10 codes I20-I25. Nonfatal or fatal stroke (nonfatal/fatal cerebral infarction, intracerebral haemorrhage) had ICD-10 codes I61, I63, I64). Cardiovascular disease (CVD) was a composite of CHD or stroke, whichever occurred first. Nonfatal or fatal intracerebral haemorrhage was defined as ICD-10 code I60-I62, ventricular bleeding as ICD-10 K92.0-K92.2, bleeding UNS including respiratory bleeding as ICD-10 R04 or R58. A composite variable, any bleeding, comprised these three bleeding endpoints. Ventricular ulcer was defined as ICD-10 code K25-27. History of atrial fibrillation was defined as ICD-10 code I48, and History of heart failure as ICD-10 code I50. All events were retrieved by data linkage with the Swedish Cause of Death and Hospital Discharge Registers, which is a reliable validated alternative to revised hospital discharge and death certificates. (15, 16)

Statistical methods

Baseline characteristics are presented as means ± 1 SD (standard deviation) or frequencies in Table 1, with crude significance levels of differences in patients with or without aspirin treatment, when analysed using student's t-test or X^2-test.

Propensity scores, in all patients and also in analysed subgroups, were estimated for each patient with logistic regression, (18) including the following variables: age, gender, diabetes duration, previous hospitalization, baseline HbA1c, BMI, systolic blood pressure, smoking, ratio total-to-HDL cholesterol, cumulative albuminuria, type of hypoglycaemic treatment, statins, other lipid-lowering drugs, antihypertensive drugs, oestrogen, and multi-dose dispensation. Table 1 shows significance levels in the covariate variables between the two groups in all patients, after adjustment by

stratification with deciles of the propensity score, when analysed using GLM (general linear modelling).

Cox regression analysis was used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for risk of the outcomes with aspirin compared to no aspirin (Tables 2, 3, 4 and 5). The propensity scores were used for adjustment in all Cox regression analyses, by stratification with deciles of the scores.

The proportional hazards assumption at Cox regression was confirmed with the test of all time-dependent covariates simultaneously introduced. Interactions between aspirin treatment and covariates were analysed with maximum likelihood estimation, and were found to be non-significant for all included covariates.

All statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC, USA). A p-value <0.05 at two-sided test was considered statistically significant.

Results

18,646 men and women, aged between 30 and 80 years, with type 2 diabetes, and no previous CVD were included in the study. 4,608 of the patients received low-dose aspirin treatment while 14,038 patients did not receive aspirin treatment, corresponding to 69,743 aspirin person-years, and 102,754 non-aspirin person-years. Table 1 gives clinical characteristics at baseline. In both groups, there were approximately 55% men and 15% smokers. Mean HbA1c was about 7% (53 mmol/mol), mean BMI about 30 kg/m^2, mean systolic blood pressure about 140 mmHg, and mean total cholesterol about 5 mmol/L.

The small p-values for differences in baseline characteristics between the groups were to a large extent a consequence of the large cohort included in the analysis. Nevertheless, there were important differences between the groups. Patients receiving aspirin were older and had longer diabetes duration compared to patients receiving no

aspirin. They also more often received glucose-lowering treatment with multiple-drug combinations, lipid lowering and blood pressure lowering treatment, indicating that these patients generally were treated more aggressively and were more likely to receive lipid-lowering treatment for primary prevention as well. However, after adjustment by stratification with a propensity score, the groups were balanced regarding the baseline variables.

Table 2 gives HR with 95% CIs for all endpoints with aspirin treatment compared to no aspirin in the whole sample, adjusted for covariates as given in the table by stratification with a propensity score. As HbA1c and sex remained significantly different between the two groups, these variables were also added as covariates in the Cox regression. Aspirin treatment was associated with a significantly increased risk of nonfatal/fatal CHD; HR 1.19 (95% CI 1.01 – 1.41), p=0.04. Regarding the other analysed endpoints, including nonfatal/fatal CVD, fatal CVD, nonfatal/fatal stroke, fatal stroke, and total mortality, there were no significant differences between the groups. In a corresponding analysis of subgroups by gender (Table 3), the increased risk of nonfatal/fatal CHD associated with aspirin seen in Table 2 was confirmed in women; HR 1.41 (95% CI 1.07 – 1.87), p=0.02, but not in men; HR 1.09 (95% CI 0.89 – 1.35), p=0.4. Furthermore, there was a significantly increased risk of nonfatal/fatal CVD associated with aspirin treatment in women; HR 1.28 (95% CI 1.01 – 1.61), p=0.04, which was not seen in men; HR 0.98 (95% CI 0.82 – 1.17), p=0.8.

The effects of aspirin on the analysed endpoints were similar in patients at high estimated cardiovascular risk (5-year CVD risk ≥15%) and patients at low estimated cardiovascular risk (5-year CVD risk <15%). No significant difference, regarding risks of the analysed endpoints, were seen between patients receiving aspirin and patients receiving no aspirin in either the group with high cardiovascular risk or the group with low cardiovascular risk when analysed separately (Table 4).

There was a borderline statistically significant increased risk of nonfatal/fatal total haemorrhages; HR 1.41 (95% CI 0.99 – 1.99), p=0.05 and nonfatal/fatal other haemorrhages; HR 2.49 (95% CI 1.00 – 6.20), p=0.05 in patients treated with aspirin (Table 5). When the sample was broken down by gender the statistical significance for these risk estimates slightly weakened due to wider CIs. HRs for nonfatal/fatal cerebral haemorrhage, fatal cerebral haemorrhage and nonfatal/fatal ventricular haemorrhage with aspirin compared to no aspirin were generally well above one, but the CIs were wide and none of the risk estimates were statistically significant. Aspirin was associated with a significantly increased risk of ventricular ulcer in the whole sample and in women; HR 1.64 (95% CI 1.06 – 2.53), p=0.02 and HR 2.32 (95% CI 1.24 – 4.36), p=0.009 respectively, but not in men; HR 1.23 (95% CI 0.67 – 2.26), p=0.4.

Discussion

We found no evidence of beneficial effects of primary prevention with aspirin on cardiovascular outcomes or death in patients with type 2 diabetes. Rather, there was a significantly increased risk of nonfatal/fatal CHD, although not of stroke, associated with aspirin compared to no aspirin. The increased risk associated with aspirin was seen when analysing women separately, but not for men separately. The risk for adverse events of cerebral or ventricular bleeding did not differ between aspirin or no aspirin, although a significantly increased risk of ventricular ulcer was associated with aspirin, especially in women

Our results indicating a modest increased risk of nonfatal/fatal CHD, although merely of tendency significance, are somewhat in contrast with previous findings. Meta-analyses evaluating the effects of primary prevention with aspirin consistently indicate modest risk reductions, although not statistically significant, of CVD with aspirin. (3, 5, 19-21) These finding, however, rely on subgroup analyses within trials designed to evaluate the effects of aspirin in a general population.

Three randomized trials have evaluated the effects of aspirin for primary prevention of CVD exclusively in patients with diabetes, and do not support routine use in these patients. (22-24) The Early Treatment of Diabetic Retinopathy Study (ETDRS) of 3711 patients with diabetes (half of them had previous CVD) showed a non-significant 15% lower risk of nonfatal or fatal MI with 650 mg of aspirin a day compared to placebo after 5 years. (22) The small Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial of 1276 patients with diabetes (no previous CVD) presented similar results for two primary composite endpoints after median 7 years of follow-up: fatal/nonfatal CVD or amputation above the ankle (HR: 0.98, 95% CI: 0.76 – 1.26), and fatal CVD (HR 1.23, 95% CI: 0.79 – 1.93) comparing the aspirin to the placebo groups. (23) In the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial, among 2539 patients with type 2 diabetes and no CVD at baseline, followed for mean 4 years, aspirin (81–100 mg daily) compared to placebo had no significant effect on the primary composite endpoint of fatal or nonfatal CHD, fatal or nonfatal stroke, and peripheral arterial disease. Only one of several secondary endpoints, fatal CHD and stroke, showed a significantly lower risk with aspirin. (24)

Interestingly, our results indicated a difference in the effect of aspirin between women and men, which also has been shown in previous studies. Women's Health Study (WHS) found a significantly reduced risk of stroke in female diabetes patients receiving aspirin, but no beneficial effect on CHD. (25) Similar results were seen in the ETDRS and in several meta-analyses. (3, 20, 21, 26) Altogether in the general population, the effect of aspirin on cardiovascular events has been suggested to be similar in women and men, but with a reduced risk of myocardial infarction in men and a reduced risk of stroke in women. (26) However, these differences have been regarded as uncertain, (5) since the findings are strongly affected by the results from one trial (WHS) and because such sex differences have not been found in studies investigating the effect of aspirin for secondary prevention. (3) Our study suggest somewhat different results in the effect of aspirin between women and men with type 2 diabetes, as women but not men

showed more harmful effects of aspirin on risk for CHD, while both women and men showed a non-significant effect of aspirin on risk for stroke.

In line with previous findings in the general population, (3) we found a non-significant effect of aspirin on CVD outcomes in patients with higher baseline cardiovascular risk estimated by a risk model. The finding in the general population of a weak risk-reducing effect of aspirin in patients at lower baseline cardiovascular risk (3) was not verified in our patients with type 2 diabetes. Furthermore, previous studies have suggested factors associated with increased cardiovascular risks to be associated with increased risks of bleedings as well, (3, 27) and a recently published meta-analysis showed that the benefits of primary prevention with aspirin in a general population was independent of baseline cardiovascular risk. (28)

As in several previous studies on patients with diabetes, (20, 23, 24) the present study showed no increased risk of major cerebral- or ventricular haemorrhages associated with aspirin treatment, while a recent meta-analysis concluded that primary prevention with aspirin in the general population caused equal amounts of major bleedings as it prevented major cardiovascular events. (28) A large observational study found an increased risk of major bleedings associated with long-term aspirin treatment in a general population, but not in the subgroup of patients with diabetes. (27) Why patients with diabetes seem to react differently to aspirin is not fully understood, but several mechanisms including an accelerated platelet turn over has been suggested as contributing factors. (29) However, in the present study, there was a significantly increased risk of ventricular ulcer and borderline significantly increased risks of other haemorrhages and total haemorrhages associated with aspirin treatment. When broken down by gender, the increased risk of ventricular ulcer associated with aspirin treatment was confirmed in women but not in men.

The large sample size of 18,646 patients with type 2 diabetes is an apparent strength of the present survey. Data are collected from the NDR database with a currently estimated coverage of more than 90% of all patients in hospital outpatient clinics and almost 80% of all patients in primary care in Sweden, suggesting it to be highly representative of clinical practice. The use of propensity score for adjustments enabled us to balance the two groups regarding numerous important covariates. However, despite extensive adjustments for reasonably relevant covariates, including balancing the groups for previous hospitalization as a marker for important co-morbidities, other covariates of possible importance could have been missed. In this study, patients with no recorded diagnosis of CVD from previous hospital visits at baseline were considered to be free from CVD. A small portion of these patients may have had a mild CVD not requiring any hospital visits. If so, some patients treated with aspirin for secondary prevention may have been included in this study, which would result in an overestimation of the benefits of aspirin.

In conclusion, the present study shows no beneficial effects of aspirin for primary prevention in patients with diabetes and no previous CVD, and opposes routine use of aspirin in these patients, also underlined by the increased risk of ventricular ulcer with aspirin. When analysed by gender, the results indicated even harmful effects associated with aspirin use in women, although not verified in men. More research is needed to explore and better understand the differences in aspirin's effects in women and men.

Author contributions: NE, JC, BZ, BE, EF, OR, MM, AMS, and SG contributed to the conception and design. JC, MM, and AMS contributed to the acquisition of data. JC and NE performed the statistical analyses. NE, JC, BZ, BE, EF, OR, MM, AMS, and SG contributed to the analysis and interpretation of data. NE, JC, and BZ contributed to drafting the article. NE, JC, BZ, BE, OR, MM, AMS, and SG contributed to revising the article critically for important intellectual content and final approval of the version to be submitted.

Acknowledgements

We thank all regional NDR coordinators, contributing nurses, physicians, and patients. The patient organization Swedish Diabetes Association, and the Swedish Society of Diabetology support the NDR. The Swedish Association of Local Authorities and Regions funds the NDR.

Funding

The Region Västra Götaland and the Swedish Association of Local Authorities and Regions fund the National Diabetes Register (NDR). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Conflicts of interest

The authors declared no conflicts of interest.

Disclaimer

Results and views of the presented study represent the authors and are not necessarily any official views of the Swedish Medical Products Agency where one author is employed (BZ).

Table 1. Baseline characteristics in 18,646 patients with type 2 diabetes, aged 30-80 years.

	Aspirin	No Aspirin	P value [1]	P value [2]
Numbers	4,608	14,038		
Age, years	65.2±8.3	61.4±9.8	<0.001	0.85
Diabetes duration, years	8.1±6.5	6.6±6.0	<0.001	0.11
HbA1c, % (mmol/mol)	7.1±1.1 (54)	7.0±1.2 (53)	0.03	0.035
Systolic BP, mmHg	142±16	139±16	<0.001	0.41
BMI, kg/m^2	29.8±5.0	29.6±5.3	0.02	0.68
Total cholesterol, mmol/l	4.80±0.92	5.06±0.97	<0.001	-
HDL cholesterol, mmol/l	1.36±0.40	1.38±0.41	0.003	-
Ratio total:HDL cholesterol	3.77±1.16	3.93±1.27	<0.001	0.07
Male gender	56.1	55.0	0.2	0.005
Smoking	15.0	15.5	0.3	0.60
Albuminuria >20 µg/min	24.2	18.5	<0.001	0.90
Previous hospitalization	4.5	4.4	0.8	0.68
Hypoglycaemic treatment				
Oral agents only	46.2	44.5	0.004	0.51
Oral agents and insulin	20.1	12.3	<0.001	0.72
Insulin only	12.6	14.0	0.02	0.44
ACE inhibitors	32.8	18.8	<0.001	0.70
ACE inhibitors + diuretics	5.3	2.6	<0.001	0.56
ACE inhib + Ca antagonists	0.04	0.02	0.4	0.04
AT2 antagonists	15.2	9.9	<0.001	0.91
AT2 antagonists + diuretics	9.8	5.2	<0.001	0.40
Ca antagonists	26.3	14.2	<0.001	0.23
Beta receptor blockers	38.3	21.7	<0.001	0.29
Diuretics	26.6	15.0	<0.001	0.35
Alpha receptor blockers	1.5	0.7	<0.001	0.68
Statins	55.7	29.1	<0.001	0.19
Other lipid lowering drugs	2.5	1.6	<0.001	0.39
Oestrogen	5.2	5.4	0.6	0.42
Multidose dispensation	1.1	0.8	0.07	0.35

Means ± SD and frequencies (%) are given. [1] Significance using t-test or X^2 test. [2] Significance using GLM after adjustment by stratification with a propensity score.

Table 2. Hazard ratios for outcomes with aspirin treatment compared to no aspirin treatment at Cox regression, in 18,646 patients with type 2 diabetes followed for 4 years.

	Patients N	Events N (%)	Events / 1000 person-years	Hazard ratio* (95% CI)	P value
Nonfatal/fatal CVD	18,646	1003 (5.4)	15.3	1.08 (0.93 – 1.24)	0.3
Fatal CVD	18,646	205 (1.1)	3.1	0.84 (0.61 – 1.14)	0.3
Nonfatal/fatal CHD	18,646	698 (3.7)	10.6	1.19 (1.01 – 1.41)	0.041
Fatal CHD	18,646	176 (0.9)	2.6	0.78 (0.56 – 1.10)	0.2
Nonfatal/fatal stroke	18,646	338 (1.8)	5.1	0.91 (0.71 – 1.16)	0.5
Fatal stroke	18,646	33 (0.2)	0.5	1.24 (0.60 – 2.57)	0.3
Total mortality	18,646	655 (3.5)	9.8	0.88 (0.74 – 1.06)	0.2

Abbreviations: CHD: coronary heart disease. CVD: cardiovascular disease. CI: confidence interval.

* Adjusted by stratification with deciles of a propensity score including the covariates age, sex, diabetes duration, type of hypoglycaemic treatment, HbA1c, smoking, BMI, systolic blood pressure, ratio total-to-HDL cholesterol, albuminuria >20 µg/min, antihypertensive drugs, statins, other lipid lowering drugs, oestrogen, multidose dispensation, previous hospitalization. Sex and HbA1c were also added as covariates.

Table 3. Hazard ratios for outcomes with aspirin treatment compared to no aspirin treatment at Cox regression, by gender in 18,646 patients with type 2 diabetes followed for 4 years.

	Patients N	Events N (%)	Events / 1000 person-years	Hazard ratio* (95% CI)	P value
Nonfatal/fatal CVD					
Women	8341	349 (4.2)	11.8	1.28 (1.01 – 1.61)	0.04
Men	10305	654 (6.4)	18.2	0.98 (0.82 – 1.17)	0.8
Fatal CVD					
Women	8341	65 (0.8)	2.2	1.22 (0.73 – 2.06)	0.6
Men	10305	140 (1.4)	3.8	0.70 (0.48 – 1.04)	0.08
Nonfatal/fatal CHD					
Women	8341	231 (2.8)	7.8	1.41 (1.07 – 1.87)	0.02
Men	10305	467 (4.5)	12.9	1.09 (0.89 – 1.35)	0.4
Fatal CHD					
Women	8341	54 (0.7)	1.8	1.09 (0.61 – 1.93)	0.7
Men	10305	122 (1.2)	3.3	0.69 (0.45 – 1.05)	0.08
Nonfatal/fatal stroke					
Women	8341	128 (1.5)	4.3	1.02 (0.68 – 1.52)	0.9
Men	10305	210 (2.0)	5.8	0.85 (0.62 – 1.16)	0.3
Fatal stroke					
Women	8341	12 (0.1)	0.4	1.71 (0.51 – 5.69)	0.7
Men	10305	21 (0.2)	0.6	1.02 (0.41 – 2.55)	0.9
Total mortality					
Women	8341	249 (3.0)	8.3	1.07 (0.81 – 1.40)	0.6
Men	10305	406 (3.9)	11.1	0.81 (0.64 – 1.02)	0.07

Abbreviations: CHD: coronary heart disease. CVD: cardiovascular disease. CI: confidence interval.

* Adjusted by stratification with deciles of a propensity score including the covariates age, diabetes duration, previous hospitalization, type of hypoglycaemic treatment, HbA1c, smoking, BMI, systolic blood pressure, ratio total-to-HDL cholesterol, albuminuria >20 µg/min, antihypertensive drugs, statins, other lipid lowering drugs, oestrogen, multidose dispensation. HbA1c was also added as covariate.

Table 4. Hazard ratios for outcomes with aspirin treatment compared to no aspirin treatment at Cox regression, by level of 5-year CVD risk, in 18,646 patients with type 2 diabetes followed for 4 years.

	Patients N	Events N (%)	Events / 1000 person-years	Hazard ratio* (95% CI)	P value
Nonfatal/fatal CVD					
5-y CVD risk <15%	15,296	593 (3.9)	10.8	1.07 (0.88 – 1.30)	0.5
5-y CVD risk ≥15%	3,350	410 (12.2)	34.9	1.09 (0.88 – 1.35)	0.4
Fatal CVD					
5-y CVD risk <15%	15,296	89 (0.6)	1.6	0.83 (0.51 – 1.36)	0.5
5-y CVD risk ≥15%	3,350	116 (3.5)	9.9	0.86 (0.57 – 1.28)	0.5
Nonfatal/fatal CHD					
5-y CVD risk <15%	15,296	409 (2.7)	7.5	1.21 (0.96 – 1.51)	0.1
5-y CVD risk ≥15%	3,350	289 (8.6)	25.2	1.18 (0.92 – 1.51)	0.2
Fatal CHD					
5-y CVD risk <15%	15,296	74 (0.5)	1.3	0.73 (0.42 – 1.28)	0.3
5-y CVD risk ≥15%	3,350	102 (3.0)	8.7	0.85 (0.55 – 1.30)	0.5
Nonfatal/fatal stroke					
5-y CVD risk <15%	15,296	200 (1.3)	3.6	0.83 (0.59 – 1.17)	0.3
5-y CVD risk ≥15%	3,350	138 (4.1)	11.8	1.03 (0.71 – 1.50)	0.9
Fatal stroke					
5-y CVD risk <15%	15,296	15 (0.1)	0.3	1.45 (0.49 – 4.31)	0.5
5-y CVD risk ≥15%	3,350	18 (0.5)	1.5	1.09 (0.40 – 2.95)	0.8
Total mortality					
5-y CVD risk <15%	15,296	370 (2.4)	6.7	0.94 (0.74 – 1.20)	0.6
5-y CVD risk ≥15%	3,350	285 (8.5)	24.3	0.88 (0.68 – 1.14)	0.3

Abbreviations: CHD: coronary heart disease. CVD: cardiovascular disease. CI: confidence interval.

* Adjusted by stratification with deciles of a propensity score including the covariates age, sex, diabetes duration, previous hospitalization, type of hypoglycaemic treatment, HbA1c, smoking, BMI, systolic blood pressure, ratio total-to-HDL cholesterol, albuminuria >20 µg/min, antihypertensive drugs, statins, other lipid lowering drugs, oestrogen, multidose dispensation. Sex and HbA1c were also added as covariates.

Table 5 Hazard ratios for haemorrhages or ventricular ulcer with aspirin treatment compared to no aspirin treatment at Cox regression, in 18,646 patients with type 2 diabetes followed for 4 years.

	Patients N	Events N (%)	Events / 1000 person-years	Hazard ratio* (95% CI)	P Value
Total haemorrhages, fatal/nonfatal					
All	18,646	157 (0.8)	2.4	1.41 (0.99 – 1.99)	0.05
Women	8,341	71 (0.9)	2.4	1.32 (0.79 – 2.21)	0.3
Men	10,305	86 (0.8)	2.3	1.53 (0.95 – 2.45)	0.08
Cerebral haemorrhage, fatal/nonfatal					
All	18,646	59 (0.3)	0.9	1.26 (0.70 – 2.25)	0.4
Women	8,341	23 (0.3)	0.8	1.42 (0.57 – 3.58)	0.6
Men	10,305	36 (0.3)	1.0	1.13 (0.54 – 2.38)	0.7
Cerebral haemorrhage, fatal					
All	18,646	14 (0.1)	0.2	1.60 (0.51 – 6.05)	0.4
Women	8,341	3 (0.04)	0.1	1.26 (0.11 – 14.3)	0.9
Men	10,305	11 (0.1)	0.3	1.68 (0.46 – 6.15)	0.4
Ventricular haemorrhage, fatal/nonfatal					
All	18,646	79 (0.4)	1.2	1.27 (0.77 – 2.09)	0.4
Women	8,341	40 (0.5)	1.3	1.05 (0.52 – 2.13)	0.9
Men	10,305	39 (0.4)	1.1	1.69 (0.83 – 3.42)	0.1
Other haemorrhages, fatal/nonfatal					
All	18,646	20 (0.1)	0.3	2.49 (1.00 – 6.20)	0.05
Women	8,341	8 (0.1)	0.3	2·99 (0.68 – 13.2)	0.1
Men	10,305	12 (0.1)	0.3	2.37 (0.73 – 7.71)	0.2
Ventricular ulcer					
All	18,646	93 (0.5)	1.4	1.64 (1.06 – 2.53)	0.02
Women	8,341	41 (0.5)	1.4	2.32 (1.24 – 4.36)	0.009
Men	10,305	52 (0.5)	1.4	1.23 (0.67 – 2.26)	0.4

Abbreviations: CI: confidence interval. Other haemorrhages: respiratory or unspecified.

* Adjusted by stratification with deciles of a propensity score including the covariates age, sex,

diabetes duration, previous hospitalization, type of hypoglycaemic treatment, HbA1c, smoking, BMI, systolic blood pressure, ratio total-to-HDL cholesterol, albuminuria >20 µg/min, antihypertensive drugs, statins, other lipid lowering drugs, oestrogen, multidose dispensation. Sex (when applicable) and HbA1c were also added as covariates.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	2, 4, 5-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2, 5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	2, 5-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6, 7
Bias	9	Describe any efforts to address potential sources of bias	7, 8, 13
Study size	10	Explain how the study size was arrived at	5, 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7, 8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5, 6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, 9, 15
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	17-20
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, 10, 17-20
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Aspirin treatment and risk of first incident cardiovascular diseases in patients with type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR)

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-002688.R1
Article Type:	Research
Date Submitted by the Author:	12-Mar-2013
Complete List of Authors:	Ekström, Nils; Sahlgrenska Academy at the University of Gothenburg, Department of Medicine Cederholm, Jan; Uppsala University, Department of Public Health and Caring Sciences / Family Medicine and Preventive Medicine Zethelius, Bjorn.; Uppsala University, Department of Public Health and Caring Sciences / Geriatrics Eliasson, Björn; Sahlgrenska Academy at the University of Gothenburg, Department of Medicine Fhärm, Eva; Umeå University, Department of Public Health and Clinical Medicine Rolandsson, Olov; Umeå University, Department of Public Health and Clinical Medicine Miftaraj, Mervete; Centre of Registers in Region Västra Götaland, Svensson, Ann-Marie; Centre of Registers in Region Västra Götaland, Gudbjörnsdottir, Soffia; Sahlgrenska Academy at the University of Gothenburg, Department of Medicine
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Cardiovascular medicine, Epidemiology, Pharmacology and therapeutics
Keywords:	DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, Vascular medicine < INTERNAL MEDICINE

Aspirin treatment and risk of first incident cardiovascular diseases in patients with type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR)

Authors: Nils Ekström[1] (MD, PhD-student), Jan Cederholm[2] (MD, PhD, Associate professor), Björn Zethelius[3] (MD, PhD, Associate professor), Björn Eliasson[1] (MD, PhD, Adjunct professor), Eva Fhärm[4] (MD, PhD) Olov Rolandsson[4] (MD, PhD), Mervete Miftaraj[5] (M.S.), Ann-Marie Svensson[5] (PhD), Soffia Gudbjörnsdottir[1, 5] (MD, PhD, Associate professor)

Affiliations

1 Department of Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden

2 Department of Public Health and Caring Sciences / Family Medicine and Preventive Medicine, Uppsala University, Sweden

3 Department of Public Health and Caring Sciences / Geriatrics, Uppsala University and Medical Products Agency, Uppsala, Sweden

4 Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

5 Centre of Registers in Region Västra Götaland, Gothenburg, Sweden

Corresponding author:

Nils Ekström

Address: Olivedalsgatan 18, 41310 Göteborg, Sweden

E-mail: nils.ekstrom@gu.se

Phone: +46(0)702890121

Word count: body: 3247, abstract: 280

References: 30

Tables and Figures: 5 tables, 1 supplementary table and 1 figure

Abstract

Objectives: To investigate benefits and risks associated with aspirin treatment in patients with type 2 diabetes and no previous cardiovascular disease (CVD), in clinical practice.

Design: Population-based cohort study between 2005 and 2009, mean follow-up 3.9 years.

Setting: Hospital outpatient clinics and primary care in Sweden.

Participants: Men and women with type 2 diabetes, free from CVD, including atrial fibrillation and congestive heart failure, at baseline, registered in the Swedish National Diabetes Register, with continuous low-dose aspirin treatment (n=4,608) or no aspirin treatment (n=14,038).

Main outcome measures: Risks of CVD, coronary heart disease (CHD), stroke, mortality and bleedings, associated with aspirin compared to no aspirin, were analysed in all patients and in subgroups by gender and estimated cardiovascular risk. Propensity scores were used to adjust for several baseline risk factors and characteristics at Cox regression, and the effect of unknown covariates was evaluated in a sensitivity analysis.

Results: There was no association between aspirin use and risks of CVD or death. Rather, there was an increased risk of nonfatal/fatal CHD associated with aspirin; HR 1.19 (95% CI 1.01 – 1.41), p=0.04. The increased risk of cardiovascular outcomes associated with aspirin was seen when analysing women separately; HR 1.41 (95% CI 1.07 – 1.87), p=0.02 and HR 1.28 (95% CI 1.01 – 1.61), p=0.04 for CHD and CVD respectively, but not for men separately. There was a trend towards increased risk of a composite of bleedings associated with aspirin, n=157; HR 1.41 (95% CI 0.99 – 1.99).

Conclusions: The results support the trend towards more restrictive use of aspirin in patients with type 2 diabetes and no previous CVD. More research is needed to explore the differences in aspirin's effects in women and men.

Article summary

Article focus:

To evaluate benefits and risks associated with aspirin treatment in a large cohort of patients with type 2 diabetes and no previous cardiovascular disease, as well as in subgroups by gender and estimated cardiovascular risk.

Key messages:

There were no beneficial effects on cardiovascular outcomes or death associated with aspirin treatment.

The results support the trend towards more restrictive use of aspirin in patients with type 2 diabetes and no previous cardiovascular disease.

Strengths and limitations:

A large cohort with comprehensive data on patient characteristics, where groups of aspirin users and aspirin non-users were balanced regarding relevant covariates with use of propensity score, was studied.

Although sensitivity assessment showed that the effect of an unknown covariate had to be of considerable magnitude to affect the study results, the possibility of residual confounding cannot be ruled out.

Introduction

The great burden of cardiovascular disease (CVD) in patients with type 2 diabetes is well known. In patients with established CVD, long-term aspirin treatment (secondary prevention) has proven beneficial, with cardiovascular risk reductions clearly

outbalancing the increased risk of bleedings. (1, 2) Irrespective of diabetes diagnosis, the net benefit of aspirin treatment in patients with no previous CVD (primary prevention) is more controversial, partly because a relatively low incidence of CVD in this population makes the absolute risk reduction small. (3, 4)

Current knowledge of the effects of aspirin treatment for primary prevention in patients with diabetes is to a large extent based on subgroup analyses in trials designed to evaluate its effects in a general population, which increases the risk of bias. (5) Concerns have also been expressed over insufficient power in the available trials. (5) The scarce evidence is reflected in the diverging recommendations from international expert organisations. The European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) do not recommend primary prevention with aspirin, while the American Diabetes Association (ADA) recommend primary prevention in patients with diabetes and high estimated cardiovascular risk. (6, 7)

Altogether, several questions regarding the net benefit of aspirin treatment for primary prevention of CVD in patients with diabetes remain, including the effect of factors such as gender, cardiovascular risk, and dosing. Against this background, further investigation with high quality randomised controlled trials (RCTs) and epidemiological studies, powered to detect clinically significant effects, are needed. The objective of this study was to investigate benefits and harms associated with aspirin for primary prevention of CVD in a large cohort of patients with type 2 diabetes in clinical practice.

Subjects and methods

The Swedish National Diabetes Register

The Swedish NDR was initiated in 1996 as a tool for local quality assurance in diabetes care. Annual reporting to the NDR is carried out by trained physicians and nurses via the Internet or clinical records databases, during patient visits at hospitals and primary health care centres nationwide. All included patients have agreed by informed consent

to register before inclusion. The Regional Ethics Review Board at the University of Gothenburg approved this study. Several reports concerning risk factor control and risk prediction in patients with diabetes have been published previously. (8-13)

Subjects

This observational study included 18,646 patients with type 2 diabetes, aged 30-80 years, and with data available for all analysed variables at baseline in 2006 (Figure 1). The cohort was divided into two study groups consisting of 4,608 patients with aspirin treatment and 14,038 patients with no aspirin treatment based on aspirin exposure at baseline. Exclusion criteria, measured at baseline, were other anticoagulant drugs except aspirin, cardiac glycosides, organic nitrates, history before baseline of CHD (ICD-10 I20-I25 or PCI or CABG), stroke including cerebral bleeding (I60-I64), heart failure (CHF) (I50), atrial fibrillation (AF) (I48), peripheral vascular disease (PVD), amputation, renal failure (N17-N19), gastric/duodenal/peptic ulcer (K25-K27), ventricular bleeding (K92.0-K92.2), respiratory bleeding (R04), unspecified bleeding (R58), and all forms of cancer (C00-C927), as well as BMI <18 kg/m^2 and plasma creatinine >150 µmol/l. The definition of type 2 diabetes was treatment with diet only, oral hypoglycaemic agents only, or onset age of diabetes ≥40 years and insulin only or combined with oral agents.

Study information was linked from four national registers in Sweden: the National Diabetes Register (NDR), the Prescribed Drug Register, (14) the Cause of Death Register, and the Hospital Discharge Register. (15, 16) Patients had to be registered in the NDR and the Prescribed Drug Register from 1st July 2005 to 30th June 2006 with regard to prescription of aspirin and other drugs. Only patients, on aspirin treatment, who had filled at least three prescriptions or 19 fills of multi-dose dispensed drugs during this 12-month period, were included. Thus, 12 months of continuous medication in aspirin-treated patients was ensured at baseline in 2006.

Examination at baseline

Clinical characteristics included at baseline were: Aspirin treatment, age, gender, diabetes duration, previous hospitalisation (for at least three consecutive days within 6 months prior to baseline), type of hypoglycaemic treatment, HbA1c, weight, height, smoking, systolic blood pressure, total cholesterol, HDL cholesterol, cumulative microalbuminuria, use of antihypertensive drugs, statins and other lipid-lowering drugs, multi-dose dispensation. Aspirin treatment was defined as a daily oral intake of 75 mg acetyl salicylic acid per day. BMI (kg/m^2) was calculated as weight/height^2. The Swedish standard for blood pressure recording, used in the NDR, is the mean (mmHg) of two readings (Korotkoff 1–5) with a cuff of appropriate size, after at least 5 minutes of rest. A smoker was defined as a patient smoking one or more cigarettes/day, or smoking tobacco using a pipe, or stopped smoking within the past three months.

Laboratory analyses of HbA_{1c} and serum lipids were carried out at local laboratories. HbA1c analyses are quality assured nationwide by regular calibration with the HPLC Mono-S method. HbA1c values were converted to the DCCT standard values. (17) Albuminuria was defined as cumulative microalbuminuria: urine albumin excretion >20 µg/min in two out of three consecutive tests.

We also estimated 5-year risk (%) for fatal/nonfatal CVD with use of the NDR risk model, based on 12 predictors at baseline, as previously described. (13) All patients were divided in two subgroups based on high or lower risk, 3,688 patients with risk ≥15% and 15,842 patients with risk <15%.

Follow-up, definition of endpoints

All patients were followed from baseline examination until a first incident event or death, or otherwise until censor date 31st December 2009. Mean follow-up was 3.9 years. Nonfatal coronary heart disease (CHD) was defined as nonfatal myocardial infarction (ICD-10 code I21), percutaneous coronary intervention and/or coronary artery bypass

grafting, and fatal CHD defined as ICD-10 codes I20-I25. Nonfatal or fatal stroke (nonfatal/fatal cerebral infarction, intracerebral haemorrhage) had ICD-10 codes I61, I63, I64). Cardiovascular disease (CVD) was a composite of CHD or stroke, whichever occurred first. Nonfatal or fatal intracerebral haemorrhage was defined as ICD-10 code I60-I62, ventricular bleeding as ICD-10 K92.0-K92.2, bleeding UNS including respiratory bleeding as ICD-10 R04 or R58. A composite variable, any bleeding, comprised these three bleeding endpoints. Ventricular ulcer was defined as ICD-10 code K25-27. History of atrial fibrillation was defined as ICD-10 code I48, and History of heart failure as ICD-10 code I50. All events were retrieved by data linkage with the Swedish Cause of Death and Hospital Discharge Registers, which is a reliable validated alternative to revised hospital discharge and death certificates. (15, 16)

Statistical methods

Baseline characteristics are presented as means ± 1 SD (standard deviation) or frequencies in Table 1, with crude significance levels of differences in patients with or without aspirin treatment, when analysed using student's t-test or X^2-test.

Propensity scores, in all patients and also in analysed subgroups, were estimated for each patient with logistic regression, (18) including the following variables: age, gender, diabetes duration, previous hospitalisation, baseline HbA1c, BMI, systolic blood pressure, smoking, ratio total-to-HDL cholesterol, cumulative albuminuria, type of hypoglycaemic treatment, statins, other lipid-lowering drugs, antihypertensive drugs, oestrogen, and multi-dose dispensation. Table 1 shows significance levels in the covariate variables between the two groups in all patients, after adjustment by stratification with deciles of the propensity score, when analysed using GLM (general linear modelling).

Cox regression analysis was used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for risk of the outcomes with aspirin compared to no aspirin (Tables 2, 3, 4 and 5). The propensity scores were used for adjustment in all Cox regression analyses,

by stratification with deciles of the scores.

The proportional hazards assumption at Cox regression was confirmed with the test of all time-dependent covariates simultaneously introduced. Interactions between aspirin treatment and covariates were analysed with maximum likelihood estimation, and were found to be non-significant for all included covariates.

Unmeasured confounders may affect the results if they are unrelated to or not fully accounted for by measured confounders, or if they affect the decision to prescribe aspirin. Therefore, we performed a sensitivity analysis by quantifying the effects of a hypothetical unmeasured confounder in comparison between patients with or without aspirin treatment, (Supplementary Table 1). (19)

All statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC, USA). A p-value <0.05 at two-sided test was considered statistically significant.

Results

18,646 men and women, aged between 30 and 80 years, with type 2 diabetes, and no previous CVD were included in the study. 4,608 of the patients received low-dose aspirin treatment while 14,038 patients did not receive aspirin treatment, corresponding to 69,743 aspirin person-years, and 102,754 non-aspirin person-years. Table 1 gives clinical characteristics at baseline. In both groups, there were approximately 55% men and 15% smokers. Mean HbA1c was about 7% (53 mmol/mol), mean BMI about 30 kg/m^2, mean systolic blood pressure about 140 mmHg, and mean total cholesterol about 5 mmol/L.

The small p-values for differences in baseline characteristics between the groups were to a large extent a consequence of the large cohort included in the analysis. Nevertheless, there were important differences between the groups. Patients receiving

aspirin were older and had longer diabetes duration compared to patients receiving no aspirin. They also more often received glucose-lowering treatment with multiple-drug combinations, lipid lowering and blood pressure lowering treatment, indicating that these patients generally were treated more aggressively and were more likely to receive lipid-lowering treatment for primary prevention as well. However, after adjustment by stratification with a propensity score, the groups were balanced regarding the baseline variables.

Table 2 gives HR with 95% CIs for all endpoints with aspirin treatment compared to no aspirin in the whole sample, adjusted for covariates as given in the table by stratification with a propensity score. As HbA1c and sex remained significantly different between the two groups, these variables were also added as covariates in the Cox regression. Aspirin treatment was associated with a significantly increased risk of nonfatal/fatal CHD; HR 1.19 (95% CI 1.01 – 1.41), p=0.04. Regarding the other analysed endpoints, including nonfatal/fatal CVD, fatal CVD, nonfatal/fatal stroke, fatal stroke, and total mortality, there were no significant differences between the groups. In a corresponding analysis of subgroups by gender (Table 3), the increased risk of nonfatal/fatal CHD associated with aspirin seen in Table 2 was confirmed in women; HR 1.41 (95% CI 1.07 – 1.87), p=0.02, but not in men; HR 1.09 (95% CI 0.89 – 1.35), p=0.4. Furthermore, there was a significantly increased risk of nonfatal/fatal CVD associated with aspirin treatment in women; HR 1.28 (95% CI 1.01 – 1.61), p=0.04, which was not seen in men; HR 0.98 (95% CI 0.82 – 1.17), p=0.8.

The effects of aspirin on the analysed endpoints were similar in patients at high estimated cardiovascular risk (5-year CVD risk ≥15%) and patients at low estimated cardiovascular risk (5-year CVD risk <15%). No significant difference, regarding risks of the analysed endpoints, were seen between patients receiving aspirin and patients receiving no aspirin in either the group with high cardiovascular risk or the group with

low cardiovascular risk when analysed separately (Table 4).

There was a borderline statistically significant increased risk of nonfatal/fatal total haemorrhages; HR 1.41 (95% CI 0.99 – 1.99), p=0.05 and nonfatal/fatal other haemorrhages; HR 2.49 (95% CI 1.00 – 6.20), p=0.05 in patients treated with aspirin (Table 5). When the sample was broken down by gender the statistical significance for these risk estimates slightly weakened due to wider CIs. HRs for nonfatal/fatal cerebral haemorrhage, fatal cerebral haemorrhage and nonfatal/fatal ventricular haemorrhage with aspirin compared to no aspirin were generally well above one, but the CIs were wide and none of the risk estimates were statistically significant. Aspirin was associated with a significantly increased risk of ventricular ulcer in the whole sample and in women; HR 1.64 (95% CI 1.06 – 2.53), p=0.02 and HR 2.32 (95% CI 1.24 – 4.36), p=0.009 respectively, but not in men; HR 1.23 (95% CI 0.67 – 2.26), p=0.4.

The sensitivity analysis (Supplementary Table 1) gives the quantified effects of a hypothetical confounder in the two groups of all aspirin users or aspirin non-users. To invalidate our findings in table 2 concerning fatal/nonfatal CVD (i.e., for aspirin to be significantly associated with CVD), a binary confounder with a HR for total CVD of 1.3 would have to be present in at least 40% (absolute) more non-users versus users. Concerning all other outcomes with non-significant aspirin effect in Table 2 (all except fatal/nonfatal CHD), a binary confounder with a HR for these outcomes of 1.3 would have to be present in over 80% more non-users versus users.

Discussion

We found no evidence of beneficial effects associated with aspirin on cardiovascular outcomes or death in patients with type 2 diabetes and no previous CVD. Rather, there was a significantly increased risk of nonfatal/fatal CHD, although not of stroke, associated with aspirin compared to no aspirin. The increased risk associated with aspirin was seen when analysing women separately, but not for men separately. The

risk for adverse events of cerebral or ventricular bleeding did not differ between aspirin or no aspirin, although a significantly increased risk of ventricular ulcer was associated with aspirin, especially in women

Our results indicating a modest increase in risk of nonfatal/fatal CHD associated with aspirin, although merely of tendency significance, are somewhat in contrast with previous findings. Meta-analyses evaluating the effects of primary prevention with aspirin consistently indicate modest reductions in risk of CVD with aspirin, although not statistically significant. (3, 5, 20-22) These finding, however, rely on subgroup analyses within trials designed to evaluate the effects of aspirin in a general population.

Three randomised trials have evaluated the effects of aspirin for primary prevention of CVD exclusively in patients with diabetes, and do not support routine use in these patients. (23-25) The Early Treatment of Diabetic Retinopathy Study (ETDRS) of 3711 patients with diabetes (half of them with previous CVD) showed a non-significant 15% lower risk of nonfatal or fatal MI with 650 mg of aspirin a day compared to placebo after 5 years. (23) The small Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial of 1276 patients with diabetes (no previous CVD) presented similar results for two primary composite endpoints after median 7 years of follow-up: fatal/nonfatal CVD or amputation above the ankle (HR: 0.98, 95% CI: 0.76 – 1.26), and fatal CVD (HR 1.23, 95% CI: 0.79 – 1.93) comparing the aspirin to the placebo groups. (24) In the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial, among 2539 patients with type 2 diabetes and no CVD at baseline, followed for mean 4 years, aspirin (81–100 mg daily) compared to placebo had no significant effect on the primary composite endpoint of fatal or nonfatal CHD, fatal or nonfatal stroke, and peripheral arterial disease. Only one of several secondary endpoints, fatal CHD and stroke, showed a significantly lower risk with aspirin. (25)

Interestingly, our results indicated a difference in the effect of aspirin between women and men, which also has been shown in previous studies. Women's Health Study

(WHS) found a significantly reduced risk of stroke in female diabetes patients receiving aspirin, but no beneficial effect on CHD. (26) Similar results were seen in the ETDRS and in several meta-analyses. (3, 21, 22, 27) Altogether, in the general population, the effect of aspirin on cardiovascular events has been suggested to be similar in women and men, but with a reduced risk of myocardial infarction in men and a reduced risk of stroke in women. (27) However, these differences have been regarded as uncertain, (5) since the findings are strongly affected by the results from one trial (WHS) and because such sex differences have not been found in studies investigating the effect of aspirin for secondary prevention. (3) Our study, in a type 2 diabetes population, suggest somewhat different results as women but not men showed more harmful effects of aspirin on risk for CHD, while both women and men showed a non-significant effect of aspirin on risk for stroke.

In line with previous findings in the general population, (3) we found a non-significant effect of aspirin on CVD outcomes in patients with higher baseline cardiovascular risk estimated by a risk model. However, the finding in the general population of a weak risk-reducing effect of aspirin in patients at lower baseline cardiovascular risk (3) was not verified in our patients with type 2 diabetes. Furthermore, previous studies have suggested factors associated with increased cardiovascular risks to be associated with increased risks of bleedings as well, (3, 28) and a recently published meta-analysis showed that the benefits of primary prevention with aspirin in a general population was independent of baseline cardiovascular risk. (29)

As in several previous studies on patients with diabetes, (21, 24, 25) the present study showed no increased risk of major cerebral- or ventricular haemorrhages associated with aspirin treatment, while a recent meta-analysis concluded that primary prevention with aspirin in the general population caused equal amounts of major bleedings as it prevented major cardiovascular events. (29) A large observational study found an increased risk of major bleedings associated with long-term aspirin treatment in a

general population, but not in the subgroup of patients with diabetes. (28) Why patients with diabetes seem to react differently to aspirin is not fully understood, but several mechanisms including an accelerated platelet turn over has been suggested as contributing factors. (30) However, in the present study, there was a significantly increased risk of ventricular ulcer and borderline significantly increased risks of other haemorrhages and total haemorrhages associated with aspirin treatment. When broken down by gender, the increased risk of ventricular ulcer associated with aspirin treatment was confirmed in women but not in men.

The large sample size of 18,646 patients with type 2 diabetes is an apparent strength of the present survey. Data are collected from the NDR database with a currently estimated coverage of more than 90% of all patients in hospital outpatient clinics and almost 80% of all patients in primary care in Sweden, suggesting it to be highly representative of clinical practice. The use of propensity score for adjustments enabled us to balance the two groups regarding numerous important covariates. However, despite extensive adjustments for reasonably relevant covariates, including balancing the groups for previous hospitalisation as a marker for important co-morbidities, the possibility of residual confounding due to unknown and unmeasured covariates cannot be ruled out. According to the conducted sensitivity analysis such unmeasured confounding associated with the outcomes, independently of all known and relevant covariates included in our propensity score and independently of treatment, would have to be of reasonable magnitude (over 80% more present in aspirin non-users than in aspirin users for almost all outcomes) to invalidate the findings.

In this study, patients with no recorded diagnosis of CVD from previous hospital visits at baseline were considered to be free from CVD. A small portion of these patients may have had a mild CVD not requiring any hospital visits. If so, some patients treated with aspirin for secondary prevention may have been included in this study, which would result in an overestimation of the benefits of aspirin.

In conclusion, the present study shows no association between aspirin use and risks of CVD or mortality in patients with diabetes and no previous CVD, and supports the trend towards a more restrictive use of aspirin in these patients, also underlined by the increased risk of ventricular ulcer associated with aspirin. When analysed by gender, the results indicated more unfavourable benefit-risk ratios associated with aspirin treatment in women, but more research is needed to explore and better understand the differences in aspirin's effects in women and men.

Author contributions: NE, JC, BZ, BE, EF, OR, MM, AMS, and SG contributed to the conception and design. JC, MM, and AMS contributed to the acquisition of data. JC and NE performed the statistical analyses. NE, JC, BZ, BE, EF, OR, MM, AMS, and SG contributed to the analysis and interpretation of data. NE, JC, and BZ contributed to drafting the article. NE, JC, BZ, BE, OR, MM, AMS, and SG contributed to revising the article critically for important intellectual content and final approval of the version to be submitted.

Acknowledgements

We thank all regional NDR coordinators, contributing nurses, physicians, and patients. The patient organisation Swedish Diabetes Association, and the Swedish Society of Diabetology support the NDR. The Swedish Association of Local Authorities and Regions funds the NDR.

We also thank Linus Schiöler for assistance in statistical sensitivity analysis.

Funding

The Region Västra Götaland and the Swedish Association of Local Authorities and Regions fund the National Diabetes Register (NDR). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Conflicts of interest

The authors declared no conflicts of interest.

Disclaimer

Results and views of the presented study represent the authors and are not necessarily any official views of the Swedish Medical Products Agency where one author is employed (BZ).

Data sharing

No additional data available.

Table 1. Baseline characteristics in 18,646 patients with type 2 diabetes, aged 30-80 years.

	Aspirin	No Aspirin	P value [1]	P value [2]
Numbers	4,608	14,038		
Age, years	65.2±8.3	61.4±9.8	<0.001	0.85
Diabetes duration, years	8.1±6.5	6.6±6.0	<0.001	0.11
HbA1c, % (mmol/mol)	7.1±1.1 (54)	7.0±1.2 (53)	0.03	0.035
Systolic BP, mmHg	142±16	139±16	<0.001	0.41
BMI, kg/m^2	29.8±5.0	29.6±5.3	0.02	0.68
Total cholesterol, mmol/l	4.80±0.92	5.06±0.97	<0.001	-
HDL cholesterol, mmol/l	1.36±0.40	1.38±0.41	0.003	-
Ratio total:HDL cholesterol	3.77±1.16	3.93±1.27	<0.001	0.07
Male gender	56.1	55.0	0.2	0.005
Smoking	15.0	15.5	0.3	0.60
Albuminuria >20 µg/min	24.2	18.5	<0.001	0.90
Previous hospitalisation	4.5	4.4	0.8	0.68
Hypoglycaemic treatment				
Oral agents only	46.2	44.5	0.004	0.51
Oral agents and insulin	20.1	12.3	<0.001	0.72
Insulin only	12.6	14.0	0.02	0.44
ACE inhibitors	32.8	18.8	<0.001	0.70
ACE inhibitors + diuretics	5.3	2.6	<0.001	0.56
ACE inhib + Ca antagonists	0.04	0.02	0.4	0.04
AT2 antagonists	15.2	9.9	<0.001	0.91
AT2 antagonists + diuretics	9.8	5.2	<0.001	0.40
Ca antagonists	26.3	14.2	<0.001	0.23
Beta receptor blockers	38.3	21.7	<0.001	0.29
Diuretics	26.6	15.0	<0.001	0.35
Alpha receptor blockers	1.5	0.7	<0.001	0.68
Statins	55.7	29.1	<0.001	0.19
Other lipid lowering drugs	2.5	1.6	<0.001	0.39

Oestrogen	5.2	5.4	0.6	0.42
Multidose dispensation	1.1	0.8	0.07	0.35

Means ± SD and frequencies (%) are given. [1] Significance using t-test or X^2 test. [2] Significance using GLM after adjustment by stratification with a propensity score.

Table 2. Hazard ratios for outcomes with aspirin treatment compared to no aspirin treatment at Cox regression, in 18,646 patients with type 2 diabetes followed for 4 years.

	Patients N	Events N (%)	Events / 1000 person-years	Hazard ratio* (95% CI)	P value
Nonfatal/fatal CVD	18,646	1003 (5.4)	15.3	1.08 (0.93 – 1.24)	0.3
Fatal CVD	18,646	205 (1.1)	3.1	0.84 (0.61 – 1.14)	0.3
Nonfatal/fatal CHD	18,646	698 (3.7)	10.6	1.19 (1.01 – 1.41)	0.041
Fatal CHD	18,646	176 (0.9)	2.6	0.78 (0.56 – 1.10)	0.2
Nonfatal/fatal stroke	18,646	338 (1.8)	5.1	0.91 (0.71 – 1.16)	0.5
Fatal stroke	18,646	33 (0.2)	0.5	1.24 (0.60 – 2.57)	0.3
Total mortality	18,646	655 (3.5)	9.8	0.88 (0.74 – 1.06)	0.2

Abbreviations: CHD: coronary heart disease. CVD: cardiovascular disease. CI: confidence interval.

* Adjusted by stratification with deciles of a propensity score including the covariates age, sex, diabetes duration, type of hypoglycaemic treatment, HbA1c, smoking, BMI, systolic blood pressure, ratio total-to-HDL cholesterol, albuminuria >20 µg/min, antihypertensive drugs, statins, other lipid lowering drugs, oestrogen, multidose dispensation, previous hospitalisation. Sex and HbA1c were also added as covariates.

Table 3. Hazard ratios for outcomes with aspirin treatment compared to no aspirin treatment at Cox regression, by gender in 18,646 patients with type 2 diabetes followed for 4 years.

	Patients N	Events N (%)	Events / 1000 person-years	Hazard ratio* (95% CI)	P value
Nonfatal/fatal CVD					
Women	8341	349 (4.2)	11.8	1.28 (1.01 – 1.61)	0.04
Men	10305	654 (6.4)	18.2	0.98 (0.82 – 1.17)	0.8
Fatal CVD					
Women	8341	65 (0.8)	2.2	1.22 (0.73 – 2.06)	0.6
Men	10305	140 (1.4)	3.8	0.70 (0.48 – 1.04)	0.08
Nonfatal/fatal CHD					
Women	8341	231 (2.8)	7.8	1.41 (1.07 – 1.87)	0.02
Men	10305	467 (4.5)	12.9	1.09 (0.89 – 1.35)	0.4
Fatal CHD					
Women	8341	54 (0.7)	1.8	1.09 (0.61 – 1.93)	0.7
Men	10305	122 (1.2)	3.3	0.69 (0.45 – 1.05)	0.08
Nonfatal/fatal stroke					
Women	8341	128 (1.5)	4.3	1.02 (0.68 – 1.52)	0.9
Men	10305	210 (2.0)	5.8	0.85 (0.62 – 1.16)	0.3
Fatal stroke					
Women	8341	12 (0.1)	0.4	1.71 (0.51 – 5.69)	0.7
Men	10305	21 (0.2)	0.6	1.02 (0.41 – 2.55)	0.9
Total mortality					
Women	8341	249 (3.0)	8.3	1.07 (0.81 – 1.40)	0.6
Men	10305	406 (3.9)	11.1	0.81 (0.64 – 1.02)	0.07

Abbreviations: CHD: coronary heart disease. CVD: cardiovascular disease. CI: confidence interval.

* Adjusted by stratification with deciles of a propensity score including the covariates age, diabetes duration, previous hospitalisation, type of hypoglycaemic treatment, HbA1c, smoking, BMI, systolic blood pressure, ratio total-to-HDL cholesterol, albuminuria >20 µg/min, antihypertensive drugs, statins, other lipid lowering drugs, oestrogen, multidose dispensation. HbA1c was also added as covariate.

Table 4. Hazard ratios for outcomes with aspirin treatment compared to no aspirin treatment at Cox regression, by level of 5-year CVD risk, in 18,646 patients with type 2 diabetes followed for 4 years.

	Patients N	Events N (%)	Events / 1000 person-years	Hazard ratio* (95% CI)	P value
Nonfatal/fatal CVD					
5-y CVD risk <15%	15,296	593 (3.9)	10.8	1.07 (0.88 – 1.30)	0.5
5-y CVD risk ≥15%	3,350	410 (12.2)	34.9	1.09 (0.88 – 1.35)	0.4
Fatal CVD					
5-y CVD risk <15%	15,296	89 (0.6)	1.6	0.83 (0.51 – 1.36)	0.5
5-y CVD risk ≥15%	3,350	116 (3.5)	9.9	0.86 (0.57 – 1.28)	0.5
Nonfatal/fatal CHD					
5-y CVD risk <15%	15,296	409 (2.7)	7.5	1.21 (0.96 – 1.51)	0.1
5-y CVD risk ≥15%	3,350	289 (8.6)	25.2	1.18 (0.92 – 1.51)	0.2
Fatal CHD					
5-y CVD risk <15%	15,296	74 (0.5)	1.3	0.73 (0.42 – 1.28)	0.3
5-y CVD risk ≥15%	3,350	102 (3.0)	8.7	0.85 (0.55 – 1.30)	0.5
Nonfatal/fatal stroke					
5-y CVD risk <15%	15,296	200 (1.3)	3.6	0.83 (0.59 – 1.17)	0.3
5-y CVD risk ≥15%	3,350	138 (4.1)	11.8	1.03 (0.71 – 1.50)	0.9
Fatal stroke					
5-y CVD risk <15%	15,296	15 (0.1)	0.3	1.45 (0.49 – 4.31)	0.5
5-y CVD risk ≥15%	3,350	18 (0.5)	1.5	1.09 (0.40 – 2.95)	0.8
Total mortality					
5-y CVD risk <15%	15,296	370 (2.4)	6.7	0.94 (0.74 – 1.20)	0.6
5-y CVD risk ≥15%	3,350	285 (8.5)	24.3	0.88 (0.68 – 1.14)	0.3

Abbreviations: CHD: coronary heart disease. CVD: cardiovascular disease. CI: confidence interval.

* Adjusted by stratification with deciles of a propensity score including the covariates age, sex, diabetes duration, previous hospitalisation, type of hypoglycaemic treatment, HbA1c, smoking, BMI, systolic blood pressure, ratio total-to-HDL cholesterol, albuminuria >20 µg/min, antihypertensive drugs, statins, other lipid lowering drugs, oestrogen, multidose dispensation. Sex and HbA1c were also added as covariates.

Table 5 Hazard ratios for haemorrhages or ventricular ulcer with aspirin treatment compared to no aspirin treatment at Cox regression, in 18,646 patients with type 2 diabetes followed for 4 years.

	Patients N	Events N (%)	Events / 1000 person-years	Hazard ratio* (95% CI)	P Value
Total haemorrhages, fatal/nonfatal					
All	18,646	157 (0.8)	2.4	1.41 (0.99 – 1.99)	0.05
Women	8,341	71 (0.9)	2.4	1.32 (0.79 – 2.21)	0.3
Men	10,305	86 (0.8)	2.3	1.53 (0.95 – 2.45)	0.08
Cerebral haemorrhage, fatal/nonfatal					
All	18,646	59 (0.3)	0.9	1.26 (0.70 – 2.25)	0.4
Women	8,341	23 (0.3)	0.8	1.42 (0.57 – 3.58)	0.6
Men	10,305	36 (0.3)	1.0	1.13 (0.54 – 2.38)	0.7
Cerebral haemorrhage, fatal					
All	18,646	14 (0.1)	0.2	1.60 (0.51 – 6.05)	0.4
Women	8,341	3 (0.04)	0.1	1.26 (0.11 – 14.3)	0.9
Men	10,305	11 (0.1)	0.3	1.68 (0.46 – 6.15)	0.4
Ventricular haemorrhage, fatal/nonfatal					
All	18,646	79 (0.4)	1.2	1.27 (0.77 – 2.09)	0.4
Women	8,341	40 (0.5)	1.3	1.05 (0.52 – 2.13)	0.9
Men	10,305	39 (0.4)	1.1	1.69 (0.83 – 3.42)	0.1
Other haemorrhages, fatal/nonfatal					
All	18,646	20 (0.1)	0.3	2.49 (1.00 – 6.20)	0.05
Women	8,341	8 (0.1)	0.3	2·99 (0.68 – 13.2)	0.1
Men	10,305	12 (0.1)	0.3	2.37 (0.73 – 7.71)	0.2
Ventricular ulcer					
All	18,646	93 (0.5)	1.4	1.64 (1.06 – 2.53)	0.02
Women	8,341	41 (0.5)	1.4	2.32 (1.24 – 4.36)	0.009
Men	10,305	52 (0.5)	1.4	1.23 (0.67 – 2.26)	0.4

Abbreviations: CI: confidence interval. Other haemorrhages: respiratory or unspecified.

* Adjusted by stratification with deciles of a propensity score including the covariates age, sex,

diabetes duration, previous hospitalisation, type of hypoglycaemic treatment, HbA1c, smoking, BMI, systolic blood pressure, ratio total-to-HDL cholesterol, albuminuria >20 µg/min, antihypertensive drugs, statins, other lipid lowering drugs, oestrogen, multidose dispensation. Sex (when applicable) and HbA1c were also added as covariates.

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Aspirin treatment and risk of first incident cardiovascular diseases in patients with type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR)

Authors: Nils Ekström[1] (MD, PhD-student), Jan Cederholm[2] (MD, PhD, Associate professor), Björn Zethelius[3] (MD, PhD, Associate professor), Björn Eliasson[1] (MD, PhD, Adjunct professor), Eva Fhärm[4] (MD, PhD) Olov Rolandsson[4] (MD, PhD), Mervete Miftaraj[5] (M.S.), Ann-Marie Svensson[5] (PhD), Soffia Gudbjörnsdottir[1, 5] (MD, PhD, Associate professor)

Affiliations

1 Department of Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden

2 Department of Public Health and Caring Sciences / Family Medicine and Preventive Medicine, Uppsala University, Sweden

3 Department of Public Health and Caring Sciences / Geriatrics, Uppsala University and Medical Products Agency, Uppsala, Sweden

4 Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

5 Centre of Registers in Region Västra Götaland, Gothenburg, Sweden

Corresponding author:

Nils Ekström

Address: Olivedalsgatan 18, 41310 Göteborg, Sweden

E-mail: nils.ekstrom@gu.se

Phone: +46(0)702890121

Word count: body: 3247, abstract: 280

References: 30

Tables and Figures: 5 tables, 1 supplementary table and 1 figure

Abstract

Objectives: ~~To investigate the effects of aspirin for primary prevention of cardiovascular disease (CVD), in patients with type 2 diabetes, in clinical practice.~~ To investigate benefits and risks associated with aspirin treatment in patients with type 2 diabetes and no previous cardiovascular disease (CVD), in clinical practice.

Design: Population-based cohort study between 2005 and 2009, mean follow-up 3.9 years.

Setting: Hospital outpatient clinics and primary care in Sweden.

Participants: Men and women with type 2 diabetes, free from CVD, including atrial fibrillation and congestive heart failure, at baseline, registered in the Swedish National Diabetes Register, with continuous low-dose aspirin treatment (n=4,608) or no aspirin treatment (n=14,038).

Main outcome measures: Risks of CVD, coronary heart disease (CHD), stroke, mortality and bleedings, associated with aspirin compared to no aspirin, were analysed in all patients and in subgroups by gender and estimated cardiovascular risk. Propensity scores were used to adjust for several baseline risk factors and characteristics at Cox regression, and the effect of unknown covariates was evaluated in a sensitivity analysis.

Results: ~~No beneficial effects on cardiovascular outcomes or death were seen with aspirin.~~ There was no association between aspirin use and risks of CVD or death. Rather, there was an increased risk of nonfatal/fatal CHD associated with aspirin; HR 1.19 (95% CI 1.01 – 1.41), p=0.04. The increased risk of cardiovascular outcomes associated with aspirin was seen when analysing women separately; HR 1.41 (95% CI 1.07 – 1.87), p=0.02 and HR 1.28 (95% CI 1.01 – 1.61), p=0.04 for CHD and CVD respectively, but not for men separately. There was a trend towards increased risk of a composite of bleedings associated with aspirin, n=157; HR 1.41 (95% CI 0.99 – 1.99).

Conclusions: ~~The results oppose routine use of aspirin in patients with type 2 diabetes~~

and no previous CVD. The results support the trend towards more restrictive use of aspirin in patients with type 2 diabetes and no previous CVD. More research is needed to explore the differences in aspirin's effects in women and men.

Article summary

Article focus:

To evaluate the effects of primary prevention with long term aspirin treatment in a large cohort of patients with type 2 diabetes and in subgroups by gender and estimated cardiovascular risk. To evaluate benefits and risks associated with aspirin treatment in a large cohort of patients with type 2 diabetes and no previous cardiovascular disease, as well as in subgroups by gender and estimated cardiovascular risk.

Key messages:

No beneficial effects on cardiovascular outcomes or death were seen with aspirin. There were no beneficial effects on cardiovascular outcomes or death associated with aspirin treatment.

The results oppose routine use of aspirin in patients with type 2 diabetes and no previous CVD. The results support the trend towards more restrictive use of aspirin in patients with type 2 diabetes and no previous CVD.

Strengths and limitations:

A large cohort with comprehensive data on patient characteristics, where groups of aspirin users and aspirin non-users were balanced regarding relevant covariates with use of propensity score, was studied.

Despite extensive adjustments for relevant covariates, including balancing the groups

with the use of propensity score, covariates of possible importance could have been missed. Although sensitivity assessment showed that the effect of an unknown covariate had to be of considerable magnitude to affect the study results, the possibility of residual confounding cannot be ruled out.

Introduction

The great burden of cardiovascular disease (CVD) in patients with type 2 diabetes is well known. In patients with established CVD, long-term aspirin treatment (secondary prevention) has proven beneficial, with cardiovascular risk reductions clearly outbalancing the increased risk of bleedings. (1, 2) Irrespective of diabetes diagnosis, the net benefit of aspirin treatment in patients with no previous CVD (primary prevention) is more controversial, partly because a relatively low incidence of CVD in this population makes the absolute risk reduction small. (3, 4)

Current knowledge of the effects of aspirin treatment for primary prevention in patients with diabetes is to a large extent based on subgroup analyses in trials designed to evaluate its effects in a general population, which increases the risk of bias. (5) Concerns have also been expressed over insufficient power in the available trials. (5) The scarce evidence is reflected in the diverging recommendations from international expert organisations. The European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) do not recommend primary prevention with aspirin, while the American Diabetes Association (ADA) recommend primary prevention in patients with diabetes and high estimated cardiovascular risk. (6, 7)

Altogether, several questions regarding the net benefit of aspirin treatment for primary prevention of CVD in patients with diabetes remain, including the effect of factors such as gender, cardiovascular risk, and dosing. Against this background, further investigation with high quality randomised controlled trials (RCTs) and epidemiological studies, powered to detect clinically significant effects, are needed. The objective of this

study was to investigate benefits and harms associated with aspirin for primary prevention of CVD in a large cohort of patients with type 2 diabetes in clinical practice.

Subjects and methods

The Swedish National Diabetes Register

The Swedish NDR was initiated in 1996 as a tool for local quality assurance in diabetes care. Annual reporting to the NDR is carried out by trained physicians and nurses via the Internet or clinical records databases, during patient visits at hospitals and primary health care centres nationwide. All included patients have agreed by informed consent to register before inclusion. The Regional Ethics Review Board at the University of Gothenburg approved this study. Several reports concerning risk factor control and risk prediction in patients with diabetes have been published previously. (8-13)

Subjects

This observational study included 18,646 patients with type 2 diabetes, aged 30-80 years, and with data available for all analysed variables at baseline in 2006 (Figure 1). ~~Two study groups consisted of 4,608 patients with aspirin treatment at baseline and 14,038 patients with no aspirin treatment.~~ The cohort was divided into two study groups consisting of 4,608 patients with aspirin treatment and 14,038 patients with no aspirin treatment based on aspirin exposure at baseline. Exclusion criteria, measured at baseline, were other anticoagulant drugs except aspirin, cardiac glycosides, organic nitrates, history before baseline of CHD (ICD-10 I20-I25 or PCI or CABG), stroke including cerebral bleeding (I60-I64), heart failure (CHF) (I50), atrial fibrillation (AF) (I48), peripheral vascular disease (PVD), amputation, renal failure (N17-N19), gastric/duodenal/peptic ulcer (K25-K27), ventricular bleeding (K92.0-K92.2), respiratory bleeding (R04), unspecified bleeding (R58), and all forms of cancer (C00-C927), as well as BMI <18 kg/m^2 and plasma creatinine >150 µmol/l. The definition of type 2 diabetes was treatment with diet only, oral hypoglycaemic agents only, or onset age of diabetes

≥40 years and insulin only or combined with oral agents.

Study information was linked from four national registers in Sweden: the National Diabetes Register (NDR), the Prescribed Drug Register, (14) the Cause of Death Register, and the Hospital Discharge Register. (15, 16) Patients had to be registered in the NDR and the Prescribed Drug Register from 1st July 2005 to 30th June 2006 with regard to prescription of aspirin and other drugs. ~~In each patient, baseline was defined as occurring after 12 months of continuous use of aspirin.~~ Only patients, on aspirin treatment, who had filled at least three prescriptions or 19 fills of multi-dose dispensed drugs during this 12-month period were included. Thus, 12 months of continuous ~~aspirin~~ medication ~~at baseline~~ in aspirin-treated patients was ensured at baseline in 2006.

Examination at baseline

Clinical characteristics included at baseline ~~1st July 2005 – 30th June 2006~~ were: Aspirin treatment, age, gender, diabetes duration, previous hospitalisation (for at least three consecutive days within 6 months prior to baseline), type of hypoglycaemic treatment, HbA1c, weight, height, smoking, systolic blood pressure, total cholesterol, HDL cholesterol, cumulative microalbuminuria, use of antihypertensive drugs, statins and other lipid-lowering drugs, multi-dose dispensation. Aspirin treatment was defined as a daily oral intake of 75 mg acetyl salicylic acid per day. BMI (kg/m^2) was calculated as $weight/height^2$. The Swedish standard for blood pressure recording, used in the NDR, is the mean (mmHg) of two readings (Korotkoff 1–5) with a cuff of appropriate size, after at least 5 minutes of rest. A smoker was defined as a patient smoking one or more cigarettes/day, or smoking tobacco using a pipe, or stopped smoking within the past three months.

Laboratory analyses of HbA_{1c} and serum lipids were carried out at local laboratories. HbA1c analyses are quality assured nationwide by regular calibration with the HPLC Mono-S method. HbA1c values were converted to the DCCT standard values. (17)

Albuminuria was defined as cumulative microalbuminuria: urine albumin excretion >20 µg/min in two out of three consecutive tests.

We also estimated 5-year risk (%) for fatal/nonfatal CVD with use of the NDR risk model, based on 12 predictors at baseline, as previously described. (13) All patients were divided in two subgroups based on high or lower risk, 3,688 patients with risk ≥15% and 15,842 patients with risk <15%.

Follow-up, definition of endpoints

All patients were followed from baseline examination until a first incident event or death, or otherwise until censor date 31st December 2009. Mean follow-up was 3.9 years. Nonfatal coronary heart disease (CHD) was defined as nonfatal myocardial infarction (ICD-10 code I21), percutaneous coronary intervention and/or coronary artery bypass grafting, and fatal CHD defined as ICD-10 codes I20-I25. Nonfatal or fatal stroke (nonfatal/fatal cerebral infarction, intracerebral haemorrhage) had ICD-10 codes I61, I63, I64). Cardiovascular disease (CVD) was a composite of CHD or stroke, whichever occurred first. Nonfatal or fatal intracerebral haemorrhage was defined as ICD-10 code I60-I62, ventricular bleeding as ICD-10 K92.0-K92.2, bleeding UNS including respiratory bleeding as ICD-10 R04 or R58. A composite variable, any bleeding, comprised these three bleeding endpoints. Ventricular ulcer was defined as ICD-10 code K25-27. History of atrial fibrillation was defined as ICD-10 code I48, and History of heart failure as ICD-10 code I50. All events were retrieved by data linkage with the Swedish Cause of Death and Hospital Discharge Registers, which is a reliable validated alternative to revised hospital discharge and death certificates. (15, 16)

Statistical methods

Baseline characteristics are presented as means ± 1 SD (standard deviation) or frequencies in Table 1, with crude significance levels of differences in patients with or without aspirin treatment, when analysed using student's t-test or X^2-test.

Propensity scores, in all patients and also in analysed subgroups, were estimated for each patient with logistic regression, (18) including the following variables: age, gender, diabetes duration, previous hospitalisation, baseline HbA1c, BMI, systolic blood pressure, smoking, ratio total-to-HDL cholesterol, cumulative albuminuria, type of hypoglycaemic treatment, statins, other lipid-lowering drugs, antihypertensive drugs, oestrogen, and multi-dose dispensation. Table 1 shows significance levels in the covariate variables between the two groups in all patients, after adjustment by stratification with deciles of the propensity score, when analysed using GLM (general linear modelling).

Cox regression analysis was used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for risk of the outcomes with aspirin compared to no aspirin (Tables 2, 3, 4 and 5). The propensity scores were used for adjustment in all Cox regression analyses, by stratification with deciles of the scores.

The proportional hazards assumption at Cox regression was confirmed with the test of all time-dependent covariates simultaneously introduced. Interactions between aspirin treatment and covariates were analysed with maximum likelihood estimation, and were found to be non-significant for all included covariates.

Unmeasured confounders may affect the results if they are unrelated to or not fully accounted for by measured confounders, or if they affect the decision to prescribe aspirin. Therefore, we performed a sensitivity analysis by quantifying the effects of a hypothetical unmeasured confounder in comparison between patients with or without aspirin treatment, (Supplementary Table 1). (19)

All statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC, USA). A p-value <0.05 at two-sided test was considered statistically significant.

Results

18,646 men and women, aged between 30 and 80 years, with type 2 diabetes, and no previous CVD were included in the study. 4,608 of the patients received low-dose aspirin treatment while 14,038 patients did not receive aspirin treatment, corresponding to 69,743 aspirin person-years, and 102,754 non-aspirin person-years. Table 1 gives clinical characteristics at baseline. In both groups, there were approximately 55% men and 15% smokers. Mean HbA1c was about 7% (53 mmol/mol), mean BMI about 30 kg/m^2, mean systolic blood pressure about 140 mmHg, and mean total cholesterol about 5 mmol/L.

The small p-values for differences in baseline characteristics between the groups were to a large extent a consequence of the large cohort included in the analysis. Nevertheless, there were important differences between the groups. Patients receiving aspirin were older and had longer diabetes duration compared to patients receiving no aspirin. They also more often received glucose-lowering treatment with multiple-drug combinations, lipid lowering and blood pressure lowering treatment, indicating that these patients generally were treated more aggressively and were more likely to receive lipid-lowering treatment for primary prevention as well. However, after adjustment by stratification with a propensity score, the groups were balanced regarding the baseline variables.

Table 2 gives HR with 95% CIs for all endpoints with aspirin treatment compared to no aspirin in the whole sample, adjusted for covariates as given in the table by stratification with a propensity score. As HbA1c and sex remained significantly different between the two groups, these variables were also added as covariates in the Cox regression. Aspirin treatment was associated with a significantly increased risk of nonfatal/fatal CHD; HR 1.19 (95% CI 1.01 – 1.41), p=0.04. Regarding the other analysed endpoints, including nonfatal/fatal CVD, fatal CVD, nonfatal/fatal stroke, fatal stroke, and total

mortality, there were no significant differences between the groups. In a corresponding analysis of subgroups by gender (Table 3), the increased risk of nonfatal/fatal CHD associated with aspirin seen in Table 2 was confirmed in women; HR 1.41 (95% CI 1.07 – 1.87), p=0.02, but not in men; HR 1.09 (95% CI 0.89 – 1.35), p=0.4. Furthermore, there was a significantly increased risk of nonfatal/fatal CVD associated with aspirin treatment in women; HR 1.28 (95% CI 1.01 – 1.61), p=0.04, which was not seen in men; HR 0.98 (95% CI 0.82 – 1.17), p=0.8.

The effects of aspirin on the analysed endpoints were similar in patients at high estimated cardiovascular risk (5-year CVD risk ≥15%) and patients at low estimated cardiovascular risk (5-year CVD risk <15%). No significant difference, regarding risks of the analysed endpoints, were seen between patients receiving aspirin and patients receiving no aspirin in either the group with high cardiovascular risk or the group with low cardiovascular risk when analysed separately (Table 4).

There was a borderline statistically significant increased risk of nonfatal/fatal total haemorrhages; HR 1.41 (95% CI 0.99 – 1.99), p=0.05 and nonfatal/fatal other haemorrhages; HR 2.49 (95% CI 1.00 – 6.20), p=0.05 in patients treated with aspirin (Table 5). When the sample was broken down by gender the statistical significance for these risk estimates slightly weakened due to wider CIs. HRs for nonfatal/fatal cerebral haemorrhage, fatal cerebral haemorrhage and nonfatal/fatal ventricular haemorrhage with aspirin compared to no aspirin were generally well above one, but the CIs were wide and none of the risk estimates were statistically significant. Aspirin was associated with a significantly increased risk of ventricular ulcer in the whole sample and in women; HR 1.64 (95% CI 1.06 – 2.53), p=0.02 and HR 2.32 (95% CI 1.24 – 4.36), p=0.009 respectively, but not in men; HR 1.23 (95% CI 0.67 – 2.26), p=0.4.

The sensitivity analysis (Supplementary Table 1) gives the quantified effects of a hypothetical confounder in the two groups of all aspirin users or aspirin non-users. To

invalidate our findings in table 2 concerning fatal/nonfatal CVD (i.e., for aspirin to be significantly associated with CVD), a binary confounder with a HR for total CVD of 1.3 would have to be present in at least 40% (absolute) more non-users versus users. Concerning all other outcomes with non-significant aspirin effect in Table 2 (all except fatal/nonfatal CHD), a binary confounder with a HR for these outcomes of 1.3 would have to be present in over 80% more non-users versus users.

Discussion

We found no evidence of beneficial effects ~~of primary prevention with aspirin on cardiovascular outcomes or death in patients with type 2 diabetes.~~ associated with aspirin on cardiovascular outcomes or death in patients with type 2 diabetes and no previous CVD. Rather, there was a significantly increased risk of nonfatal/fatal CHD, although not of stroke, associated with aspirin compared to no aspirin. The increased risk associated with aspirin was seen when analysing women separately, but not for men separately. The risk for adverse events of cerebral or ventricular bleeding did not differ between aspirin or no aspirin, although a significantly increased risk of ventricular ulcer was associated with aspirin, especially in women

Our results indicating a modest increase in risk of nonfatal/fatal CHD associated with aspirin, although merely of tendency significance, are somewhat in contrast with previous findings. Meta-analyses evaluating the effects of primary prevention with aspirin consistently indicate modest reductions in risk of CVD with aspirin, although not statistically significant. (3, 5, 20-22) These finding, however, rely on subgroup analyses within trials designed to evaluate the effects of aspirin in a general population.

Three randomised trials have evaluated the effects of aspirin for primary prevention of CVD exclusively in patients with diabetes, and do not support routine use in these patients. (23-25) The Early Treatment of Diabetic Retinopathy Study (ETDRS) of 3711 patients with diabetes (half of them with previous CVD) showed a non-significant 15%

lower risk of nonfatal or fatal MI with 650 mg of aspirin a day compared to placebo after 5 years. (23) The small Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial of 1276 patients with diabetes (no previous CVD) presented similar results for two primary composite endpoints after median 7 years of follow-up: fatal/nonfatal CVD or amputation above the ankle (HR: 0.98, 95% CI: 0.76 – 1.26), and fatal CVD (HR 1.23, 95% CI: 0.79 – 1.93) comparing the aspirin to the placebo groups. (24) In the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial, among 2539 patients with type 2 diabetes and no CVD at baseline, followed for mean 4 years, aspirin (81–100 mg daily) compared to placebo had no significant effect on the primary composite endpoint of fatal or nonfatal CHD, fatal or nonfatal stroke, and peripheral arterial disease. Only one of several secondary endpoints, fatal CHD and stroke, showed a significantly lower risk with aspirin. (25)

Interestingly, our results indicated a difference in the effect of aspirin between women and men, which also has been shown in previous studies. Women's Health Study (WHS) found a significantly reduced risk of stroke in female diabetes patients receiving aspirin, but no beneficial effect on CHD. (26) Similar results were seen in the ETDRS and in several meta-analyses. (3, 21, 22, 27) Altogether, in the general population, the effect of aspirin on cardiovascular events has been suggested to be similar in women and men, but with a reduced risk of myocardial infarction in men and a reduced risk of stroke in women. (27) However, these differences have been regarded as uncertain, (5) since the findings are strongly affected by the results from one trial (WHS) and because such sex differences have not been found in studies investigating the effect of aspirin for secondary prevention. (3) Our study, in a type 2 diabetes population, suggest somewhat different results as women but not men showed more harmful effects of aspirin on risk for CHD, while both women and men showed a non-significant effect of aspirin on risk for stroke.

In line with previous findings in the general population, (3) we found a non-significant

effect of aspirin on CVD outcomes in patients with higher baseline cardiovascular risk estimated by a risk model. However, the finding in the general population of a weak risk-reducing effect of aspirin in patients at lower baseline cardiovascular risk (3) was not verified in our patients with type 2 diabetes. Furthermore, previous studies have suggested factors associated with increased cardiovascular risks to be associated with increased risks of bleedings as well, (3, 28) and a recently published meta-analysis showed that the benefits of primary prevention with aspirin in a general population was independent of baseline cardiovascular risk. (29)

As in several previous studies on patients with diabetes, (21, 24, 25) the present study showed no increased risk of major cerebral- or ventricular haemorrhages associated with aspirin treatment, while a recent meta-analysis concluded that primary prevention with aspirin in the general population caused equal amounts of major bleedings as it prevented major cardiovascular events. (29) A large observational study found an increased risk of major bleedings associated with long-term aspirin treatment in a general population, but not in the subgroup of patients with diabetes. (28) Why patients with diabetes seem to react differently to aspirin is not fully understood, but several mechanisms including an accelerated platelet turn over has been suggested as contributing factors. (30) However, in the present study, there was a significantly increased risk of ventricular ulcer and borderline significantly increased risks of other haemorrhages and total haemorrhages associated with aspirin treatment. When broken down by gender, the increased risk of ventricular ulcer associated with aspirin treatment was confirmed in women but not in men.

The large sample size of 18,646 patients with type 2 diabetes is an apparent strength of the present survey. Data are collected from the NDR database with a currently estimated coverage of more than 90% of all patients in hospital outpatient clinics and almost 80% of all patients in primary care in Sweden, suggesting it to be highly

representative of clinical practice. The use of propensity score for adjustments enabled us to balance the two groups regarding numerous important covariates. However, despite extensive adjustments for reasonably relevant covariates, including balancing the groups for previous hospitalisation as a marker for important co-morbidities, ~~other covariates of possible importance could have been missed.~~ the possibility of residual confounding due to unknown and unmeasured covariates cannot be ruled out. According to the conducted sensitivity analysis such unmeasured confounding associated with the outcomes, independently of all known and relevant covariates included in our propensity score and independently of treatment, would have to be of reasonable magnitude (over 80% more present in aspirin non-users than in aspirin users for almost all outcomes) to invalidate the findings.

In this study, patients with no recorded diagnosis of CVD from previous hospital visits at baseline were considered to be free from CVD. A small portion of these patients may have had a mild CVD not requiring any hospital visits. If so, some patients treated with aspirin for secondary prevention may have been included in this study, which would result in an overestimation of the benefits of aspirin.

In conclusion, ~~the present study shows no beneficial effects of aspirin for primary prevention in patients with diabetes and no previous CVD, and opposes routine use of aspirin in these patients, also underlined by the increased risk of ventricular ulcer with aspirin. When analysed by gender, the results indicated even harmful effects associated with aspirin use in women, although not verified in men. More research is needed to explore and better understand the differences in aspirin's effects in women and men.~~ the present study shows no association between aspirin use and risks of CVD or mortality in patients with diabetes and no previous CVD, and supports the trend towards a more restrictive use of aspirin in these patients, also underlined by the increased risk of ventricular ulcer associated with aspirin. When analysed by gender, the results indicated more unfavourable benefit-risk ratios associated with aspirin treatment in women, but more research is needed to explore and better understand the differences in aspirin's effects in women and men.

Author contributions: NE, JC, BZ, BE, EF, OR, MM, AMS, and SG contributed to the conception and design. JC, MM, and AMS contributed to the acquisition of data. JC and NE performed the statistical analyses. NE, JC, BZ, BE, EF, OR, MM, AMS, and SG contributed to the analysis and interpretation of data. NE, JC, and BZ contributed to drafting the article. NE, JC, BZ, BE, OR, MM, AMS, and SG contributed to revising the article critically for important intellectual content and final approval of the version to be submitted.

Acknowledgements

We thank all regional NDR coordinators, contributing nurses, physicians, and patients. The patient organisation Swedish Diabetes Association, and the Swedish Society of Diabetology support the NDR. The Swedish Association of Local Authorities and Regions funds the NDR.

We also thank Linus Schiöler for assistance in statistical sensitivity analysis.

Funding

The Region Västra Götaland and the Swedish Association of Local Authorities and Regions fund the National Diabetes Register (NDR). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Conflicts of interest

The authors declared no conflicts of interest.

Disclaimer

Results and views of the presented study represent the authors and are not necessarily any official views of the Swedish Medical Products Agency where one author is employed (BZ).

Table 1. Baseline characteristics in 18,646 patients with type 2 diabetes, aged 30-80 years.

	Aspirin	No Aspirin	P value [1]	P value [2]
Numbers	4,608	14,038		
Age, years	65.2±8.3	61.4±9.8	<0.001	0.85
Diabetes duration, years	8.1±6.5	6.6±6.0	<0.001	0.11
HbA1c, % (mmol/mol)	7.1±1.1 (54)	7.0±1.2 (53)	0.03	0.035
Systolic BP, mmHg	142±16	139±16	<0.001	0.41
BMI, kg/m^2	29.8±5.0	29.6±5.3	0.02	0.68
Total cholesterol, mmol/l	4.80±0.92	5.06±0.97	<0.001	-
HDL cholesterol, mmol/l	1.36±0.40	1.38±0.41	0.003	-
Ratio total:HDL cholesterol	3.77±1.16	3.93±1.27	<0.001	0.07
Male gender	56.1	55.0	0.2	0.005
Smoking	15.0	15.5	0.3	0.60
Albuminuria >20 µg/min	24.2	18.5	<0.001	0.90
Previous hospitalisation	4.5	4.4	0.8	0.68
Hypoglycaemic treatment				
Oral agents only	46.2	44.5	0.004	0.51
Oral agents and insulin	20.1	12.3	<0.001	0.72
Insulin only	12.6	14.0	0.02	0.44
ACE inhibitors	32.8	18.8	<0.001	0.70
ACE inhibitors + diuretics	5.3	2.6	<0.001	0.56
ACE inhib + Ca antagonists	0.04	0.02	0.4	0.04
AT2 antagonists	15.2	9.9	<0.001	0.91
AT2 antagonists + diuretics	9.8	5.2	<0.001	0.40
Ca antagonists	26.3	14.2	<0.001	0.23
Beta receptor blockers	38.3	21.7	<0.001	0.29
Diuretics	26.6	15.0	<0.001	0.35
Alpha receptor blockers	1.5	0.7	<0.001	0.68
Statins	55.7	29.1	<0.001	0.19
Other lipid lowering drugs	2.5	1.6	<0.001	0.39
Oestrogen	5.2	5.4	0.6	0.42

Multidose dispensation	1.1	0.8	0.07	0.35

Means ± SD and frequencies (%) are given. [1] Significance using t-test or X^2 test. [2] Significance using GLM after adjustment by stratification with a propensity score.

Table 2. Hazard ratios for outcomes with aspirin treatment compared to no aspirin treatment at Cox regression, in 18,646 patients with type 2 diabetes followed for 4 years.

	Patients N	Events N (%)	Events / 1000 person-years	Hazard ratio* (95% CI)	P value
Nonfatal/fatal CVD	18,646	1003 (5.4)	15.3	1.08 (0.93 – 1.24)	0.3
Fatal CVD	18,646	205 (1.1)	3.1	0.84 (0.61 – 1.14)	0.3
Nonfatal/fatal CHD	18,646	698 (3.7)	10.6	1.19 (1.01 – 1.41)	0.041
Fatal CHD	18,646	176 (0.9)	2.6	0.78 (0.56 – 1.10)	0.2
Nonfatal/fatal stroke	18,646	338 (1.8)	5.1	0.91 (0.71 – 1.16)	0.5
Fatal stroke	18,646	33 (0.2)	0.5	1.24 (0.60 – 2.57)	0.3
Total mortality	18,646	655 (3.5)	9.8	0.88 (0.74 – 1.06)	0.2

Abbreviations: CHD: coronary heart disease. CVD: cardiovascular disease. CI: confidence interval.

* Adjusted by stratification with deciles of a propensity score including the covariates age, sex, diabetes duration, type of hypoglycaemic treatment, HbA1c, smoking, BMI, systolic blood pressure, ratio total-to-HDL cholesterol, albuminuria >20 µg/min, antihypertensive drugs, statins, other lipid lowering drugs, oestrogen, multidose dispensation, previous hospitalisation. Sex and HbA1c were also added as covariates.

Table 3. Hazard ratios for outcomes with aspirin treatment compared to no aspirin treatment at Cox regression, by gender in 18,646 patients with type 2 diabetes followed for 4 years.

	Patients N	Events N (%)	Events / 1000 person-years	Hazard ratio* (95% CI)	P value
Nonfatal/fatal CVD					
Women	8341	349 (4.2)	11.8	1.28 (1.01 – 1.61)	0.04
Men	10305	654 (6.4)	18.2	0.98 (0.82 – 1.17)	0.8
Fatal CVD					
Women	8341	65 (0.8)	2.2	1.22 (0.73 – 2.06)	0.6
Men	10305	140 (1.4)	3.8	0.70 (0.48 – 1.04)	0.08
Nonfatal/fatal CHD					
Women	8341	231 (2.8)	7.8	1.41 (1.07 – 1.87)	0.02
Men	10305	467 (4.5)	12.9	1.09 (0.89 – 1.35)	0.4
Fatal CHD					
Women	8341	54 (0.7)	1.8	1.09 (0.61 – 1.93)	0.7
Men	10305	122 (1.2)	3.3	0.69 (0.45 – 1.05)	0.08
Nonfatal/fatal stroke					
Women	8341	128 (1.5)	4.3	1.02 (0.68 – 1.52)	0.9
Men	10305	210 (2.0)	5.8	0.85 (0.62 – 1.16)	0.3
Fatal stroke					
Women	8341	12 (0.1)	0.4	1.71 (0.51 – 5.69)	0.7
Men	10305	21 (0.2)	0.6	1.02 (0.41 – 2.55)	0.9
Total mortality					
Women	8341	249 (3.0)	8.3	1.07 (0.81 – 1.40)	0.6
Men	10305	406 (3.9)	11.1	0.81 (0.64 – 1.02)	0.07

Abbreviations: CHD: coronary heart disease. CVD: cardiovascular disease. CI: confidence interval.

* Adjusted by stratification with deciles of a propensity score including the covariates age, diabetes duration, previous hospitalisation, type of hypoglycaemic treatment, HbA1c, smoking, BMI, systolic blood pressure, ratio total-to-HDL cholesterol, albuminuria >20 µg/min, antihypertensive drugs, statins, other lipid lowering drugs, oestrogen, multidose dispensation. HbA1c was also added as covariate.

Table 4. Hazard ratios for outcomes with aspirin treatment compared to no aspirin treatment at Cox regression, by level of 5-year CVD risk, in 18,646 patients with type 2 diabetes followed for 4 years.

	Patients N	Events N (%)	Events / 1000 person-years	Hazard ratio* (95% CI)	P value
Nonfatal/fatal CVD					
5-y CVD risk <15%	15,296	593 (3.9)	10.8	1.07 (0.88 – 1.30)	0.5
5-y CVD risk ≥15%	3,350	410 (12.2)	34.9	1.09 (0.88 – 1.35)	0.4
Fatal CVD					
5-y CVD risk <15%	15,296	89 (0.6)	1.6	0.83 (0.51 – 1.36)	0.5
5-y CVD risk ≥15%	3,350	116 (3.5)	9.9	0.86 (0.57 – 1.28)	0.5
Nonfatal/fatal CHD					
5-y CVD risk <15%	15,296	409 (2.7)	7.5	1.21 (0.96 – 1.51)	0.1
5-y CVD risk ≥15%	3,350	289 (8.6)	25.2	1.18 (0.92 – 1.51)	0.2
Fatal CHD					
5-y CVD risk <15%	15,296	74 (0.5)	1.3	0.73 (0.42 – 1.28)	0.3
5-y CVD risk ≥15%	3,350	102 (3.0)	8.7	0.85 (0.55 – 1.30)	0.5
Nonfatal/fatal stroke					
5-y CVD risk <15%	15,296	200 (1.3)	3.6	0.83 (0.59 – 1.17)	0.3
5-y CVD risk ≥15%	3,350	138 (4.1)	11.8	1.03 (0.71 – 1.50)	0.9
Fatal stroke					
5-y CVD risk <15%	15,296	15 (0.1)	0.3	1.45 (0.49 – 4.31)	0.5
5-y CVD risk ≥15%	3,350	18 (0.5)	1.5	1.09 (0.40 – 2.95)	0.8
Total mortality					
5-y CVD risk <15%	15,296	370 (2.4)	6.7	0.94 (0.74 – 1.20)	0.6
5-y CVD risk ≥15%	3,350	285 (8.5)	24.3	0.88 (0.68 – 1.14)	0.3

Abbreviations: CHD: coronary heart disease. CVD: cardiovascular disease. CI: confidence interval.

* Adjusted by stratification with deciles of a propensity score including the covariates age, sex, diabetes duration, previous hospitalisation, type of hypoglycaemic treatment, HbA1c, smoking, BMI, systolic blood pressure, ratio total-to-HDL cholesterol, albuminuria >20 µg/min, antihypertensive drugs, statins, other lipid lowering drugs, oestrogen, multidose dispensation. Sex and HbA1c were also added as covariates.

Table 5 Hazard ratios for haemorrhages or ventricular ulcer with aspirin treatment compared to no aspirin treatment at Cox regression, in 18,646 patients with type 2 diabetes followed for 4 years.

	Patients N	Events N (%)	Events / 1000 person-years	Hazard ratio* (95% CI)	P Value
Total haemorrhages, fatal/nonfatal					
All	18,646	157 (0.8)	2.4	1.41 (0.99 – 1.99)	0.05
Women	8,341	71 (0.9)	2.4	1.32 (0.79 – 2.21)	0.3
Men	10,305	86 (0.8)	2.3	1.53 (0.95 – 2.45)	0.08
Cerebral haemorrhage, fatal/nonfatal					
All	18,646	59 (0.3)	0.9	1.26 (0.70 – 2.25)	0.4
Women	8,341	23 (0.3)	0.8	1.42 (0.57 – 3.58)	0.6
Men	10,305	36 (0.3)	1.0	1.13 (0.54 – 2.38)	0.7
Cerebral haemorrhage, fatal					
All	18,646	14 (0.1)	0.2	1.60 (0.51 – 6.05)	0.4
Women	8,341	3 (0.04)	0.1	1.26 (0.11 – 14.3)	0.9
Men	10,305	11 (0.1)	0.3	1.68 (0.46 – 6.15)	0.4
Ventricular haemorrhage, fatal/nonfatal					
All	18,646	79 (0.4)	1.2	1.27 (0.77 – 2.09)	0.4
Women	8,341	40 (0.5)	1.3	1.05 (0.52 – 2.13)	0.9
Men	10,305	39 (0.4)	1.1	1.69 (0.83 – 3.42)	0.1
Other haemorrhages, fatal/nonfatal					
All	18,646	20 (0.1)	0.3	2.49 (1.00 – 6.20)	0.05
Women	8,341	8 (0.1)	0.3	2·99 (0.68 – 13.2)	0.1
Men	10,305	12 (0.1)	0.3	2.37 (0.73 – 7.71)	0.2
Ventricular ulcer					
All	18,646	93 (0.5)	1.4	1.64 (1.06 – 2.53)	0.02
Women	8,341	41 (0.5)	1.4	2.32 (1.24 – 4.36)	0.009
Men	10,305	52 (0.5)	1.4	1.23 (0.67 – 2.26)	0.4

Abbreviations: CI: confidence interval. Other haemorrhages: respiratory or unspecified.

* Adjusted by stratification with deciles of a propensity score including the covariates age, sex,

diabetes duration, previous hospitalisation, type of hypoglycaemic treatment, HbA1c, smoking, BMI, systolic blood pressure, ratio total-to-HDL cholesterol, albuminuria >20 µg/min, antihypertensive drugs, statins, other lipid lowering drugs, oestrogen, multidose dispensation. Sex (when applicable) and HbA1c were also added as covariates.

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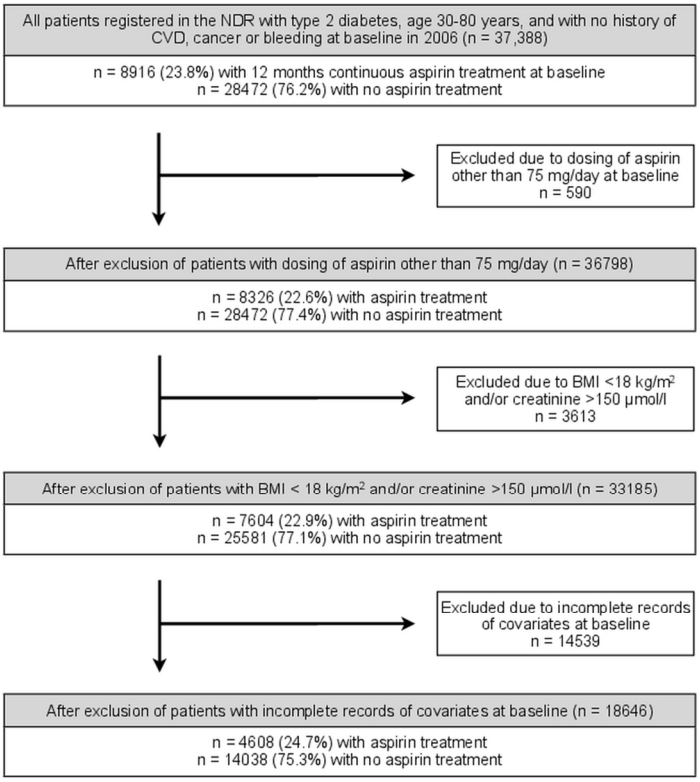
Supplementary Table 1. Quantified effects of hypothetical unmeasured and/or unknown confounders in the cohort with aspirin users or aspirin non-users.
We assigned a hypothetical binary confounder a hazard ratio (HR), for all outcomes listed below, of 1.3 and assessed the HR associated with aspirin treatment given different prevalence of this confounder in the two groups. Numbers in the tables are HR with 95% confidence intervals after adjustment for a binary confounder. Bold is statistically significant.

			P (confounder)(*) for aspirin users		
			0.0	0.2	0.4
Fatal CHD	P (confounder)(*)	0.0	0.78 (0.56-1.10)		
	for aspirin non-users	0.2	0.83 (0.59-1.17)	0.78 (0.56-1.10)	
		0.4	0.87 (0.63-1.23)	0.83 (0.59-1.17)	0.78 (0.56-1.10)
		0.6	0.92 (0.66-1.30)	0.87 (0.63-1.23)	0.83 (0.59-1.17)
		0.8	0.97 (0.69-1.36)	0.92 (0.66-1.30)	0.87 (0.63-1.23)
Fatal/nonfatal CHD	P (confounder)	0.0	**1.19 (1.01-1.41)**		
	for aspirin non-users	0.2	**1.26 (1.07-1.49)**	**1.19 (1.01-1.41)**	
		0.4	**1.33 (1.13-1.58)**	**1.26 (1.07-1.49)**	**1.19 (1.01-1.41)**
		0.6	**1.40 (1.19-1.66)**	**1.33 (1.13-1.58)**	**1.26 (1.07-1.49)**
		0.8	**1.48 (1.25-1.75)**	**1.40 (1.19-1.66)**	**1.33 (1.13-1.58)**
Fatal stroke	P (confounder)	0.0	1.24 (0.60-2.57)		
	for aspirin non-users	0.2	1.31 (0.64-2.72)	1.24 (0.60-2.57)	
		0.4	1.39 (0.67-2.88)	1.31 (0.64-2.72)	1.24 (0.60-2.57)
		0.6	1.46 (0.71-3.03)	1.39 (0.67-2.88)	1.31 (0.64-2.72)
		0.8	1.54 (0.74-3.19)	1.46 (0.71-3.03)	1.39 (0.67-2.88)
Fatal/nonfatal stroke	P (confounder)	0.0	0.91 (0.71-1.16)		
	for aspirin non-users	0.2	0.96 (0.75-1.23)	0.91 (0.71-1.16)	
		0.4	1.02 (0.80-1.30)	0.96 (0.75-1.23)	0.91 (0.71-1.16)
		0.6	1.07 (0.84-1.37)	1.02 (0.80-1.30)	0.96 (0.75-1.23)
		0.8	1.13 (0.88-1.44)	1.07 (0.84-1.37)	1.02 (0.80-1.30)
Fatal CVD	P (confounder)	0.0	0.84 (0.61-1.14)		
	for aspirin non-users	0.2	0.89 (0.65-1.21)	0.84 (0.61-1.14)	
		0.4	0.94 (0.68-1.28)	0.89 (0.65-1.21)	0.84 (0.61-1.14)
		0.6	0.99 (0.72-1.35)	0.94 (0.68-1.28)	0.89 (0.65-1.21)
		0.8	1.04 (0.76-1.41)	0.99 (0.72-1.35)	0.94 (0.68-1.28)
Fatal/nonfatal CVD	P (confounder)	0.0	1.08 (0.93-1.24)		
	for aspirin non-users	0.2	1.14 (0.98-1.31)	1.08 (0.93-1.24)	
		0.4	**1.21 (1.04-1.39)**	1.14 (0.98-1.31)	1.08 (0.93-1.24)
		0.6	**1.27 (1.09-1.46)**	**1.21 (1.04-1.39)**	1.14 (0.98-1.31)
		0.8	**1.34 (1.15-1.54)**	**1.27 (1.09-1.46)**	**1.21 (1.04-1.39)**
Total mortality	P (confounder)	0.0	0.88 (0.74-1.06)		
	for aspirin non-users	0.2	0.93 (0.78-1.12)	0.88 (0.74-1.06)	
		0.4	0.99 (0.83-1.19)	0.93 (0.78-1.12)	0.88 (0.74-1.06)
		0.6	1.04 (0.87-1.25)	0.99 (0.83-1.19)	0.93 (0.78-1.12)
		0.8	1.09 (0.92-1.31)	1.04 (0.87-1.25)	0.99 (0.83-1.19)

* P (confounder) is the probability of the confounder being present.

Figure 1. Enrollment of patients



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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	2, 4, 5-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2, 5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	2, 5-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6, 7
Bias	9	Describe any efforts to address potential sources of bias	7, 8, 13
Study size	10	Explain how the study size was arrived at	5, 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7, 8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5, 6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, 9, 15
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	17-20
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, 10, 17-20
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.