

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

Nils Ekström,¹ Jan Cederholm,² Björn Zethelius,³ Björn Eliasson,¹ Eva Fhärm,⁴ Olov Rolandsson,⁴ Mervete Miftaraj,⁵ Ann-Marie Svensson,⁵ Soffia Gudbjörnsdóttir^{1,5}

To cite: Ekström N, Cederholm J, Zethelius B, *et al*. Aspirin treatment and risk of first incident cardiovascular diseases in patients with type 2 diabetes: an observational study from the Swedish National Diabetes Register. *BMJ Open* 2013;**3**:e002688. doi:10.1136/bmjopen-2013-002688

► Prepublication history and additional material for this paper are available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2013-002688>).

Received 5 February 2013
Revised 12 March 2013
Accepted 13 March 2013

This final article is available for use under the terms of the Creative Commons Attribution Non-Commercial 2.0 Licence; see <http://bmjopen.bmj.com>

For numbered affiliations see end of article.

Correspondence to
Dr Nils Ekström;
nils.ekstrom@gu.se

ABSTRACT

Objectives: To investigate the 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=4608) 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 with 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 beneficial effects on risks of CVD or death. Rather, there was an increased risk of non-fatal/fatal CHD associated with aspirin; HR 1.19 (95% CI 1.01 to 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 to 1.87), p=0.02, and HR 1.28 (95% CI 1.01 to 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 to 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 the benefits and risks associated with aspirin treatment in a large cohort of patients with type 2 diabetes and no previous cardiovascular disease (CVD), 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 CVD.

Strengths and limitations of this study

- 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 and the European Association for the Study of Diabetes do not recommend primary prevention with aspirin, while the American Diabetes Association 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 and epidemiological studies, powered to detect clinically significant effects, are needed. The objective of this study was to investigate

the 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

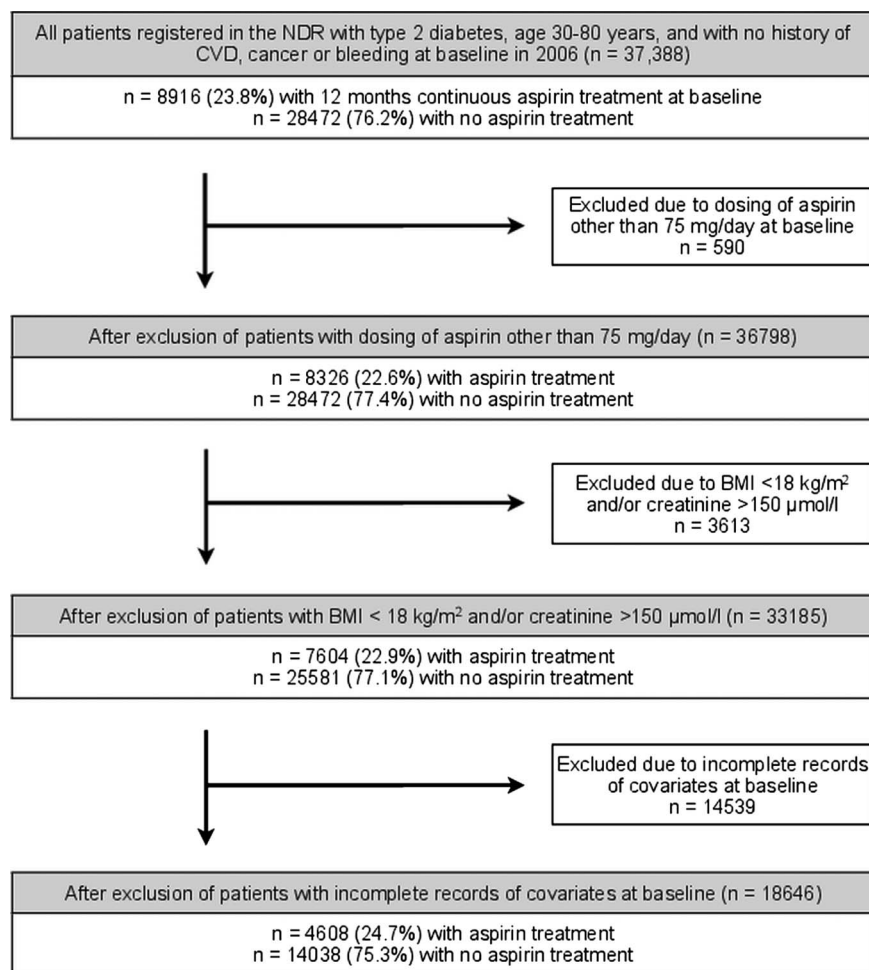
Swedish National Diabetes Register

The Swedish National Diabetes Register (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 healthcare 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

Figure 1 Enrolment of patients.



of 4608 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 coronary heart disease (CHD; International Classification of Diseases (ICD)-10 I20–I25 or percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)), stroke including cerebral bleeding (I60–I64), heart failure (CHF) (I50), atrial fibrillation (AF) (I48), peripheral vascular disease, 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 body mass index (BMI) $<18 \text{ kg/m}^2$ and plasma creatine $>150 \mu\text{mol/l}$. 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 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 1 July 2005 to 30 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 multidose-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, glycated haemoglobin (HbA1c), weight, height, smoking, systolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, cumulative microalbuminuria, use of antihypertensive drugs, statins and other lipid-lowering drugs and multidose 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/height². The Swedish standard for blood pressure recording, used in the NDR, is the mean (mm Hg) of two readings (Korotkoff 1–5) with a cuff of appropriate size, after at least 5 min 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 3 months.

Laboratory analyses of HbA1c and serum lipids were carried out at local laboratories. HbA1c analyses are quality assured nationwide by regular calibration with the high-performance liquid chromatography Mono-S method. HbA1c values were converted to the DCCT standard values.¹⁷ Albuminuria was defined as

cumulative microalbuminuria: urine albumin excretion $>20 \mu\text{g/min}$ in two of three consecutive tests.

We also estimated a 5-year risk (%) for fatal/non-fatal 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, 3688 patients with risk $\geq 15\%$ 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 31 December 2009. Mean follow-up was 3.9 years. Non-fatal CHD was defined as non-fatal myocardial infarction (MI; ICD-10 code I21), PCI and/or CABG and fatal CHD defined as ICD-10 codes I20–I25. Non-fatal or fatal stroke (non-fatal/fatal cerebral infarction, intracerebral haemorrhage) had ICD-10 codes I61, I63, I64. CVD was a composite of CHD or stroke, whichever occurred first. Non-fatal or fatal intracerebral haemorrhage was defined as ICD-10 code I60–I62, ventricular haemorrhage as ICD-10 K92.0–K92.2, other haemorrhage including unspecified and respiratory bleedings as ICD-10 R04 or R58. A composite variable, total haemorrhages, comprised these three bleeding endpoints. Ventricular ulcer was defined as ICD-10 code K25–27. History of AF 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 \pm 1 SD or frequencies in table 1, with crude significance levels of differences in patients with or without aspirin treatment, when analysed using Student t test or χ^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 multidose 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 general linear modelling.

Cox regression analysis was used to estimate HR with 95% CI for risk of the outcomes with aspirin compared with no aspirin (tables 2–5). 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

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

	Aspirin	No aspirin	p Value*	p Value**
Numbers	4608	14038		
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 (mm Hg)	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 inhibitors+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
β Receptor blockers	38.3	21.7	<0.001	0.29
Diuretics	26.6	15.0	<0.001	0.35
α 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.

*Significance using t test or χ^2 test.

**Significance using GLM after adjustment by stratification with a propensity score.

BMI, body mass index; BP, blood pressure; GLM, general linear modelling; HDL, high-density lipoprotein.

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

Table 2 HRs for outcomes with aspirin treatment compared with 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	HR* (95% CI)	p Value
Non-fatal/fatal CVD	18646	1003 (5.4)	15.3	1.08 (0.93 to 1.24)	0.3
Fatal CVD	18646	205 (1.1)	3.1	0.84 (0.61 to 1.14)	0.3
Non-fatal/fatal CHD	18646	698 (3.7)	10.6	1.19 (1.01 to 1.41)	0.041
Fatal CHD	18646	176 (0.9)	2.6	0.78 (0.56 to 1.10)	0.2
Non-fatal/fatal stroke	18646	338 (1.8)	5.1	0.91 (0.71 to 1.16)	0.5
Fatal stroke	18646	33 (0.2)	0.5	1.24 (0.60 to 2.57)	0.3
Total mortality	18646	655 (3.5)	9.8	0.88 (0.74 to 1.06)	0.2

*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 and previous hospitalisation. Sex and HbA1c were also added as covariates.

BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein.

Table 3 HRs for outcomes with aspirin treatment compared with 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	HR* (95% CI)	p Value
Non-fatal/fatal CVD					
Women	8341	349 (4.2)	11.8	1.28 (1.01 to 1.61)	0.04
Men	10305	654 (6.4)	18.2	0.98 (0.82 to 1.17)	0.8
Fatal CVD					
Women	8341	65 (0.8)	2.2	1.22 (0.73 to 2.06)	0.6
Men	10305	140 (1.4)	3.8	0.70 (0.48 to 1.04)	0.08
Non-fatal/fatal CHD					
Women	8341	231 (2.8)	7.8	1.41 (1.07 to 1.87)	0.02
Men	10305	467 (4.5)	12.9	1.09 (0.89 to 1.35)	0.4
Fatal CHD					
Women	8341	54 (0.7)	1.8	1.09 (0.61 to 1.93)	0.7
Men	10305	122 (1.2)	3.3	0.69 (0.45 to 1.05)	0.08
Non-fatal/fatal stroke					
Women	8341	128 (1.5)	4.3	1.02 (0.68 to 1.52)	0.9
Men	10305	210 (2.0)	5.8	0.85 (0.62 to 1.16)	0.3
Fatal stroke					
Women	8341	12 (0.1)	0.4	1.71 (0.51 to 5.69)	0.7
Men	10305	21 (0.2)	0.6	1.02 (0.41 to 2.55)	0.9
Total mortality					
Women	8341	249 (3.0)	8.3	1.07 (0.81 to 1.40)	0.6
Men	10305	406 (3.9)	11.1	0.81 (0.64 to 1.02)	0.07

*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 and multidose dispensation. HbA1c was also added as covariate. BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein.

Table 4 HRs for outcomes with aspirin treatment compared with 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	HR*(95% CI)	p Value
Non-fatal/fatal CVD					
5-year CVD risk <15%	15296	593 (3.9)	10.8	1.07 (0.88 to 1.30)	0.5
5-year CVD risk ≥15%	3350	410 (12.2)	34.9	1.09 (0.88 to 1.35)	0.4
Fatal CVD					
5-year CVD risk <15%	15296	89 (0.6)	1.6	0.83 (0.51 to 1.36)	0.5
5-year CVD risk ≥15%	3350	116 (3.5)	9.9	0.86 (0.57 to 1.28)	0.5
Non-fatal/fatal CHD					
5-year CVD risk <15%	15296	409 (2.7)	7.5	1.21 (0.96 to 1.51)	0.1
5-year CVD risk ≥15%	3350	289 (8.6)	25.2	1.18 (0.92 to 1.51)	0.2
Fatal CHD					
5-year CVD risk <15%	15296	74 (0.5)	1.3	0.73 (0.42 to 1.28)	0.3
5-year CVD risk ≥15%	3350	102 (3.0)	8.7	0.85 (0.55 to 1.30)	0.5
Non-fatal/fatal stroke					
5-year CVD risk <15%	15296	200 (1.3)	3.6	0.83 (0.59 to 1.17)	0.3
5-year CVD risk ≥15%	3350	138 (4.1)	11.8	1.03 (0.71 to 1.50)	0.9
Fatal stroke					
5-year CVD risk <15%	15296	15 (0.1)	0.3	1.45 (0.49 to 4.31)	0.5
5-year CVD risk ≥15%	3350	18 (0.5)	1.5	1.09 (0.40 to 2.95)	0.8
Total mortality					
5-year CVD risk <15%	15296	370 (2.4)	6.7	0.94 (0.74 to 1.20)	0.6
5-year CVD risk ≥15%	3350	285 (8.5)	24.3	0.88 (0.68 to 1.14)	0.3

*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 and multidose dispensation. Sex and HbA1c were also added as covariates. BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein.

Table 5 HRs for haemorrhages or ventricular ulcer with aspirin treatment compared with 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	HR* (95% CI)	p Value
Total haemorrhages, fatal/non-fatal					
All	18646	157 (0.8)	2.4	1.41 (0.99 to 1.99)	0.05
Women	8341	71 (0.9)	2.4	1.32 (0.79 to 2.21)	0.3
Men	10305	86 (0.8)	2.3	1.53 (0.95 to 2.45)	0.08
Cerebral haemorrhage, fatal/non-fatal					
All	18646	59 (0.3)	0.9	1.26 (0.70 to 2.25)	0.4
Women	8341	23 (0.3)	0.8	1.42 (0.57 to 3.58)	0.6
Men	10305	36 (0.3)	1.0	1.13 (0.54 to 2.38)	0.7
Cerebral haemorrhage, fatal					
All	18646	14 (0.1)	0.2	1.60 (0.51 to 6.05)	0.4
Women	8341	3 (0.04)	0.1	1.26 (0.11 to 14.3)	0.9
Men	10305	11 (0.1)	0.3	1.68 (0.46 to 6.15)	0.4
Ventricular haemorrhage, fatal/non-fatal					
All	18646	79 (0.4)	1.2	1.27 (0.77 to 2.09)	0.4
Women	8341	40 (0.5)	1.3	1.05 (0.52 to 2.13)	0.9
Men	10305	39 (0.4)	1.1	1.69 (0.83 to 3.42)	0.1
Other haemorrhages, fatal/non-fatal					
All	18646	20 (0.1)	0.3	2.49 (1.00 to 6.20)	0.05
Women	8341	8 (0.1)	0.3	2.99 (0.68 to 13.2)	0.1
Men	10305	12 (0.1)	0.3	2.37 (0.73 to 7.71)	0.2
Ventricular ulcer					
All	18646	93 (0.5)	1.4	1.64 (1.06 to 2.53)	0.02
Women	8341	41 (0.5)	1.4	2.32 (1.24 to 4.36)	0.009
Men	10305	52 (0.5)	1.4	1.23 (0.67 to 2.26)	0.4

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, glycated haemoglobin (HbA1c), smoking, body mass index, systolic blood pressure, ratio total-to-high-density lipoprotein cholesterol, albuminuria >20 µg/min, antihypertensive drugs, statins, other lipid lowering drugs, oestrogen and multidose dispensation. Sex (when applicable) and HbA1c were also added as covariates.

quantifying the effects of a hypothetical unmeasured confounder in comparison between patients with or without aspirin treatment (see online supplementary table S1).¹⁹

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

RESULTS

In total, 18 646 men and women, aged between 30 and 80 years, with type 2 diabetes, and no previous CVD were included in the study. Four thousand six hundred and eight 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/m², mean systolic blood pressure about 140 mm Hg 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 with 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 with 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 non-fatal/fatal CHD; HR 1.19 (95% CI 1.01 to 1.41), p=0.04. Regarding the other

analysed endpoints, including non-fatal/fatal CVD, fatal CVD, non-fatal/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 non-fatal/fatal CHD associated with aspirin seen in table 2 was confirmed in women; HR 1.41 (95% CI 1.07 to 1.87), $p=0.02$, but not in men; HR 1.09 (95% CI 0.89 to 1.35), $p=0.4$. Furthermore, there was a significantly increased risk of non-fatal/fatal CVD associated with aspirin treatment in women; HR 1.28 (95% CI 1.01 to 1.61), $p=0.04$, which was not seen in men; HR 0.98 (95% CI 0.82 to 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 $\geq 15\%$) 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 non-fatal/fatal total haemorrhages; HR 1.41 (95% CI 0.99 to 1.99), $p=0.05$, and non-fatal/fatal other haemorrhages; HR 2.49 (95% CI 1.00 to 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 non-fatal/fatal cerebral haemorrhage, fatal cerebral haemorrhage and non-fatal/fatal ventricular haemorrhage with aspirin compared with 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 to 2.53), $p=0.02$ and HR 2.32 (95% CI 1.24 to 4.36), $p=0.009$, respectively, but not in men; HR 1.23 (95% CI 0.67 to 2.26), $p=0.4$.

The sensitivity analysis (see online supplementary table S1) 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/non-fatal CVD (ie, for aspirin to be significantly associated with CVD), a binary confounder with an 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/non-fatal CHD), a binary confounder with an 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

non-fatal/fatal CHD, although not of stroke, associated with aspirin compared with 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 non-fatal/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 the risk of CVD with aspirin, although not statistically significant.^{3 5 20–22} These findings, 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 non-fatal or fatal MI with 650 mg of aspirin a day compared with placebo after 5 years.²³ The small Prevention of Progression of Arterial Disease and Diabetes 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/non-fatal CVD or amputation above the ankle (HR 0.98, 95% CI 0.76 to 1.26), and fatal CVD (HR 1.23, 95% CI 0.79 to 1.93) comparing the aspirin to the placebo groups.²⁴ In the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial, among 2539 patients with type 2 diabetes and no CVD at baseline, followed for mean 4 years, aspirin (81–100 mg daily) compared with placebo had no significant effect on the primary composite endpoint of fatal or non-fatal CHD, fatal or non-fatal stroke and peripheral arterial disease. Only one of the 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 MI 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, suggests 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 the 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 risk³ 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 comorbidities, 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 beneficial effects on 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 affiliations

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

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

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

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

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

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.

Contributors NE, JC, BZ, BE, EF, OR, MM, A-MS 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, A-MS 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, A-MS and SG contributed to revising the article critically for important intellectual content and final approval of the version to be submitted.

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 and decision to publish or preparation of the manuscript.

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).

Competing interests None.

Ethics approval The Regional Ethics Review Board at the University of Gothenburg approved this study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death,

- myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81–106.
2. Antiplatelet Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71–86.
3. Baigent C, Blackwell L, Collins R, *et al.* Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849–60.
4. Siller-Matula JM. Hemorrhagic complications associated with aspirin: an underestimated hazard in clinical practice? *JAMA* 2012;307:2318–20.
5. Pignone M, Alberts MJ, Colwell JA, *et al.* Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. *Diabetes Care* 2010;33:1395–402.
6. Perk J, De Backer G, Gohlke H, *et al.* European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (Version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by Representatives of Nine Societies and by Invited Experts). *Int J Behav Med* 2012;19:40–88.
7. American Diabetes Association. Executive summary: standards of medical care in diabetes—2013. *Diabetes Care* 2013;36(Suppl 1):S4–10.
8. Cederholm J, Zethelius B, Nilsson PM, *et al.* Effect of tight control of HbA1c and blood pressure on cardiovascular diseases in type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR). *Diabetes Res Clin Pract* [Research Support, Non-US Gov't]. 2009;86:74–81.
9. Eeg-Olofsson K, Cederholm J, Nilsson PM, *et al.* New aspects of HbA1c as a risk factor for cardiovascular diseases in type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR). *J Intern Med* [Research Support, Non-U.S. Gov't]. 2010;268:471–82.
10. Gudbjornsdottir S, Eliasson B, Eeg-Olofsson K, *et al.* Additive effects of glycaemia and dyslipidaemia on risk of cardiovascular diseases in type 2 diabetes: an observational study from the Swedish National Diabetes Register. *Diabetologia* [Research Support, Non-US Gov't] 2011;54:2544–51.
11. Cederholm J, Gudbjornsdottir S, Eliasson B, *et al.* Blood pressure and risk of cardiovascular diseases in type 2 diabetes: further findings from the Swedish National Diabetes Register (NDR-BP II). *J Hypertens* 2012;30:2020–30.
12. Eliasson B, Cederholm J, Eeg-Olofsson K, *et al.* Clinical usefulness of different lipid measures for prediction of coronary heart disease in type 2 diabetes: a report from the Swedish National Diabetes Register. *Diabetes Care* [Research Support, Non-U.S. Gov't] 2011;34:2095–100.
13. Zethelius B, Eliasson B, Eeg-Olofsson K, *et al.* A new model for 5-year risk of cardiovascular disease in type 2 diabetes, from the Swedish National Diabetes Register (NDR). *Diabetes Res Clin Pract* 2011;93:276–84.
14. Wettermark B, Hammar N, Forel CM, *et al.* The new Swedish Prescribed Drug Register—opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007;16:726–35.
15. Merlo J, Lindblad U, Pessah-Rasmussen H, *et al.* Comparison of different procedures to identify probable cases of myocardial infarction and stroke in two Swedish prospective cohort studies using local and national routine registers. *Eur J Epidemiol* [Comparative Study Research Support, Non-U.S. Gov't] 2000;16:235–43.
16. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, *et al.* Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* [Comparative Study Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.] 1994;90:583–612.
17. Hoelzel W, Weykamp C, Jeppsson JO, *et al.* IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. *Clin Chem* [Comparative Study Multicenter Study Research Support, Non-US Gov't] 2004;50:166–74.
18. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* [Comparative Study] 1998;17:2265–81.
19. Lin DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics* 1998;54:948–63.
20. Calvin AD, Aggarwal NR, Murad MH, *et al.* Aspirin for the primary prevention of cardiovascular events: a systematic review and meta-analysis comparing patients with and without diabetes. *Diabetes Care* 2009;32:2300–6.
21. De Berardis G, Sacco M, Strippoli GF, *et al.* Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. *BMJ* [Meta-Analysis Review] 2009;339:b4531.
22. Zhang C, Sun A, Zhang P, *et al.* Aspirin for primary prevention of cardiovascular events in patients with diabetes: a meta-analysis. *Diabetes Res Clin Pract* 2010;87:211–18.
23. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. ETDRS Investigators. *JAMA* 1992;268:1292–300.
24. Belch J, MacCuish A, Campbell I, *et al.* The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008;337:a1840.
25. Ogawa H, Nakayama M, Morimoto T, *et al.* Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2008;300:2134–41.
26. Ridker PM, Cook NR, Lee IM, *et al.* A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005;352:1293–304.
27. Berger JS, Roncaglioni MC, Avanzini F, *et al.* Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA* 2006;295:306–13.
28. De Berardis G, Lucisano G, D'Ettore A, *et al.* Association of aspirin use with major bleeding in patients with and without diabetes. *JAMA* 2012;307:2286–94.
29. Berger JS, Lala A, Krantz MJ, *et al.* Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease: a meta-analysis of randomized trials. *Am Heart J* 2011;162:115–24 e2.
30. Pulcinelli FM, Biasucci LM, Riondino S, *et al.* COX-1 sensitivity and thromboxane A2 production in type 1 and type 2 diabetic patients under chronic aspirin treatment. *Eur Heart J* 2009;30:1279–86.