Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18 168 people with type 1 diabetes: observational study

Isabelle Steineck,[1] Jan Cederholm,[2] Björn Eliasson,[3] Araz Rawshani,[4] Katarina Eeg-Olofsson,[3] Ann-Marie Svensson,[4] Björn Zethelius,[5,6] Tarik Avdic,[4] Mona Landin-Olsson,[7] Johan Jendle,[8] Soffia Gudbjörnsdóttir[3,4] the Swedish National Diabetes Register

[1]Department of Endocrinology, Aarhus University Hospital, Aarhus Denmark
[2]Department of Public Health and Caring Sciences/Family and Preventive Medicine, Uppsala University, Uppsala, Sweden
[3]Institute of Medicine, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden
[4]National Diabetes Register, Centre of Registers, Gothenburg, Sweden
[5]Department of Public Health and Caring Sciences/Geriatrics, Uppsala University, Uppsala, Sweden
[6]Medical Products Agency, Uppsala, Sweden
[7]Department of Clinical Science, Lund University, Lund, Sweden
[8]Faculty of Health Sciences and Medicine, Örebro University, Örebro, Sweden

Correspondence to: I Steineck
isabelle.steineck@iname.com

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ABSTRACT

OBJECTIVE

To investigate the long term effects of continuous subcutaneous insulin infusion (insulin pump therapy) on cardiovascular diseases and mortality in people with type 1 diabetes.

DESIGN

Observational study.

SETTING

Swedish National Diabetes Register, Sweden 2005-12.

PARTICIPANTS

18 168 people with type 1 diabetes, 2441 using insulin pump therapy and 15 727 using multiple daily insulin injections.

MAIN OUTCOME MEASURES

Cox regression analysis was used to estimate hazard ratios for the outcomes, with stratification of propensity scores including clinical characteristics, risk factors for cardiovascular disease, treatments, and previous diseases.

RESULTS

Follow-up was for a mean of 6.8 years until December 2012, with 114 135 person years. With multiple daily injections as reference, the adjusted hazard ratios for insulin pump treatment were significantly lower: 0.55 (95% confidence interval 0.36 to 0.83) for fatal coronary heart disease, 0.58 (0.40 to 0.85) for fatal cardiovascular disease (coronary heart disease or stroke), and 0.73 (0.58 to 0.92) for all cause mortality. Hazard ratios were lower, but not significantly so, for fatal or non-fatal coronary heart disease and fatal or non-fatal cardiovascular disease. Unadjusted absolute differences were 3.0 events of fatal coronary heart disease per 1000 person years; corresponding figures were 3.3 for fatal cardiovascular disease and 5.7 for all cause mortality. When lower body mass index and previous cardiovascular diseases were excluded, results of subgroup analyses were similar to the results from complete data. A sensitivity analysis of unmeasured confounders in all individuals showed that an unmeasured confounders with hazard ratio of 1.3 would have to be present in >80% of the individuals treated with multiple daily injections versus not presence in those treated with pump therapy to invalidate the significantly lower hazard ratios for fatal cardiovascular disease. Data on patient education and frequency of blood glucose monitoring were missing, which might have influenced the observed association.

CONCLUSION

Among people with type 1 diabetes use of insulin pump therapy is associated with lower cardiovascular mortality than treatment with multiple daily insulin injections.

WHAT IS ALREADY KNOWN ON THIS TOPIC

In patients with diabetes, both hyperglycaemia and hypoglycaemia are risk factors for cardiovascular disease (coronary heart disease or stroke)

Continuous subcutaneous infusion of insulin with a pump could result in fewer episodes of hyperglycaemia and hypoglycaemia than multiple daily injections and provide better glycaemic control

WHAT THIS STUDY ADDS

Treatment of type 1 diabetes with an insulin pump is associated with significantly lower adjusted hazard ratios for fatal coronary heart disease, fatal cardiovascular disease, and all cause mortality, as well as non-significant reduction in hazard ratios for non-fatal or fatal cardiovascular disease

Patient education and frequency of blood glucose monitoring might have influenced the observed association

Introduction

Nobody disputes the fact that type 1 diabetes increases the risk of death from cardiovascular diseases. A recent study from the Swedish National Diabetes Register showed that individuals with type 1 diabetes who have a glycated haemoglobin A1c (HbA_{1c}) concentration of 6.9% (52 mmol/mol or lower have a risk of death from any cause and from cardiovascular causes twice as high as the risk in the general population; the risks are several times higher among patients with higher HbA_{1c} concentrations.[1] The Diabetes Control and Complication Trial and other recent studies have shown that tight glucose control reduces the risk, delays the onset, and slows the progression of complications.[2,3] Other studies have shown that both hyperglycaemia and hypoglycaemia are risk factors for cardiovascular disease.[4]

Continuous subcutaneous insulin infusion involves connection of a catheter on the outside of the body to an insulin pump that is programmed to supply the body's basal needs. The person with the pump administers doses to cover meals and correct blood glucose concentrations. Many pumps these days have a bolus wizard that calculates how much insulin the person needs, taking expected carbohydrate intake, current blood glucose concentrations and previously still active insulin into consideration. Pumps can provide an accurate history of insulin use through their menus. Often

this history can be uploaded and displayed as a graph for purposes of trend analysis.

Insulin pumps can result in fewer episodes of hyperglycaemia and hypoglycaemia than multiple daily injections.[5 6] Some studies have shown that insulin pumps provide better glycaemic control than multiple daily injections.[7] Three meta-analyses of randomised controlled trials investigated the association between treatment with a pump and the occurrence of hyperglycaemia. All three analyses found that insulin pump treatment was associated with improvement in HbA_{1c} compared with multiple daily injections, without a higher rate of hypoglycaemia.[8-10] Fredheim and colleagues found that insulin pump therapy reduced the rate of severe hypoglycaemia by 27% compared with multiple daily injections.[11] Given the importance of glycaemic control,[1-3] and the presumed advantages of insulin pump treatment, it is important to investigate whether use of insulin pumps affects the risk of cardiovascular mortality.

In 2013 in Swedish people with type 1 diabetes, one out of every four women and one out of every five men used insulin pump treatment. Over half of all Swedish children with type 1 diabetes also use insulin pumps.[7] Sceptics argue that subcutaneous infusion of insulin by a pump could increase costs of treatment and cause practical problems for people with diabetes. Because of the scarcity of data, the relative risk for cardiovascular disease of associated with the treatments is unknown.

Sweden offers excellent opportunities for studying individuals with type 1 diabetes. All affected people are treated at negligible personal cost. About 95% of all individuals with type 1 diabetes have been entered in the National Diabetes Register, which includes detailed clinical data from each appointment. The register can be linked via Sweden's unique personal identity number to the cause of death, inpatient, socioeconomic, and other population based registers. Our primary aim was to analyse the effect of insulin pump treatment on cardiovascular mortality.

Methods

Swedish National Diabetes Register

The Swedish National Diabetes Register was initiated in 1996 as a caregiver tool for local quality assurance and to provide feedback as part of diabetes care. Trained doctors and nurses report annually to the register,[12] either online or through clinical record systems; no stringent criteria exist for how often patients visit an outpatient clinic. Information is collected during appointments at hospital outpatient clinics and primary healthcare centres nationwide. Several previous reports have been published concerning trends in risk factor control and risk prediction based on the register,[1 13 14] including a more detailed description of the register and the Swedish healthcare system for patients with diabetes.[15]

Patient involvement

There was no patient involvement in this study. The work within the Swedish National Diabetes Register, as this article, is done in a continuous but informal dialogue with people with diabetes.

Participants

We included 18 168 people with type 1 diabetes entered in the Swedish National Diabetes Register for whom data were available about the use of insulin pump therapy or multiple daily injections. A total of 2441 people were being treated with insulin pump therapy during the study period from baseline to the final year, and 15 727 were treated with multiple daily injections during the whole study period to final year. Type 1 diabetes was epidemiologically defined as all patients who received insulin treatment only (for diabetes mellitus) and were aged under 30 at onset, almost all of whom had been reported by outpatient clinics from about 90 Swedish hospitals. Baseline appointments took place in 2005-07 with follow-up until 31 December 2012. Treatment with insulin pump has been documented in the register since the year 2004. All individuals were recruited from the Swedish National Diabetes Register with no exclusion criteria.

Examinations at baseline and the end of the study

Clinical characteristics at baseline included type of glucose lowering treatment, age, duration of diabetes, sex, HbA1c, systolic blood pressure, diastolic blood pressure, height, weight, waist circumference, physical activity, smoking habits, total cholesterol, high density lipoprotein cholesterol, triglycerides, microalbuminuria, plasma creatinine, use of antihypertensive drugs, lipid lowering drugs and acetylsalicylic acid (aspirin), atrial fibrillation, and histories of cardiovascular disease, heart failure and atrial fibrillation, Furthermore, baseline yearly income (in Swedish kroner), marital status (single, married, divorced, or widowed) and educational level (lower (up to school year 9), intermediate (years 10-12 of upper secondary school), and higher (college/university)) were obtained from the Longitudinal Integration Database for Health Insurance and Labour Market Studies, Statistics Sweden. Body mass index (BMI) was calculated as weight/height2. Waist circumference (cm) was measured at the height of the navel. Physical activity was graded as low (no activity or less than once a week) or higher (twice or more a week). Smoking was defined as one or more cigarettes a day, one pipe a day, or having quit within the past three months. The Swedish standard for recording blood pressure as used by the Swedish National Diabetes Register is the average (mm Hg) of two supine readings (Korotkoff sounds I-V) with a cuff of appropriate size after at least 5 minutes of rest. Analyses of HbA1c were quality assured nationwide by regular calibration with the HPLC Mono-S method and then converted to mmol/mol.[16] Albuminuria was classed as urine albumin excretion >20 µg/min on two out of three consecutive tests (microalbuminuria or macroalbuminuria). A history of cardiovascular disease was defined the same way as for the outcome; ICD-10 (international classification of diseases, 10th revision) code I50 for heart failure; code I48 for atrial fibrillation; C00-C097 for all cancer; codes

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K70-74 for liver disease; and codes F20-29 and F30-39 for mental disorders.

We estimated updated mean HbA_{1c} during the study period using all values from baseline until the year before an event occurred during the study or otherwise from baseline until 31 December 2012. Change in HbA_{1c} during the study period was estimated as the difference between baseline and final measurements, the latter estimated as the value before the year of an event or otherwise the value in 2012. Hypoglycaemic attacks that required a hospital admission, with ICD-10 codes for hypoglycaemia and coma from the hospital discharge register, were entered during the study period from baseline until 31 December 2012.

Follow-up and definition of endpoints

All individuals were monitored from the baseline examination until death or the first incident or until 31 December 2012. The mean follow-up period was 6.8 years, with a total of 114 135 person years. The major primary endpoints were fatal or non-fatal coronary heart disease, fatal or non-fatal cardiovascular disease, fatal cardiovascular disease, and total mortality. Non-fatal coronary heart disease was defined as non-fatal myocardial infarction (ICD-10 code I21), unstable angina (ICD-10 code I20.0), percutaneous coronary intervention, and/or coronary artery bypass grafting. Fatal coronary heart disease was defined as ICD-10 codes I20-I25. Stroke was defined as fatal or non-fatal cerebral infarction, intracerebral haemorrhage, or unspecified stroke (ICD-10 codes I61, I63, I64). Cardiovascular disease was defined as the composite of coronary heart disease or stroke, whichever came first. A secondary endpoint was mortality from non-cardiovascular disease.

A history of heart failure was defined as ICD-10 code I50, and atrial fibrillation before the study start was defined as ICD-10 code I48. All events were obtained by linking to the Swedish cause of death and hospital discharge registers, a reliable validated alternative to revised hospital discharge and death certificates.[17 18]

Statistical analysis

We applied five imputations using the Markov chain Monte Carlo technique for missing data in the sample of 18 168 individuals, using the SAS MI and MIANALYSE procedures.[19] We recorded baseline clinical features as mean values (SD) or frequencies (%) of each multiple imputed variable in the two treatment groups (insulin pump therapy or multiple daily injections) and calculated significance for crude differences between the two groups with Student's t test or χ^2 test. We used crude Kaplan-Meier curves for all outcomes to compare the two groups with log rank test and for observed hypoglycaemic episodes during study follow-up.

We estimated a propensity score for treatment with pump with logistic regression as the conditional probability of being treated with pump given the baseline characteristics,[20 21] including the covariates age, sex, duration of diabetes, history of cardiovascular disease, heart failure, atrial fibrillation, baseline HbA_{1c}, systolic and diastolic blood pressure, BMI, total and high density lipoprotein cholesterol, triglycerides, cumulative microalbuminuria, creatinine, renal insufficiency, smoking, physical activity, antihypertensive drugs, lipid lowering drugs and aspirin, educational levels, yearly income, marital status and baseline years. We calculated P values for differences between the two treatment groups after adjustment with the propensity score, including all 36 variables, estimated by generalized linear models (link id for continuous data and link logit for dichotomous data). We also computed standardised differences between the two groups; a difference of less than 10% was considered to be satisfactory.[21 22] The distribution of the propensity score stratified in fifths was calculated for the two treatment groups, as well as the number of outcomes by each fifth of the score (appendix table A).

We used Cox regression analysis to estimate hazard ratios with 95% confidence intervals for outcomes comparing insulin pump treatment with multiple daily injections. Covariate adjustment was performed by stratification with fifths of the propensity score.[20 21]

The proportional hazard assumption of the Cox regression analyses was tested by adding an interaction term of the predictor and log time and by analysing Schoenfeld residuals—both were found to be non-significant and satisfied the proportional hazard assumption.[23] Interactions between the two treatment groups and all covariates included in the propensity score were analysed by means of maximum likelihood estimation; no interactions were found between any covariates.

Unmeasured confounders can affect the results if they are unrelated to, or not fully accounted for by, measured confounders or if they affect the decision to use insulin pump treatment and not multiple daily injections (treatment allocation bias). We therefore performed a sensitivity analysis by quantifying the effects of a hypothetical unmeasured confounder when comparing individuals treated with insulin pump therapy and multiple daily injections with an algorithm as presented by Lin and colleagues,[24] yielding progressive changes of the hazard ratios observed for the analysed outcome with presence of an unmeasured covariate of 1.3 or 1.4 and present more frequently in one of the groups (injection) than the other.[25-28]

All statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC). A two sided $P<0.05$ was considered significant.

Results

Table 1 shows baseline crude characteristics of the two groups (insulin pump treatment or multiple daily injections). The group treated with insulin pump therapy was somewhat younger with similar durations of diabetes, slightly lower systolic blood pressure, fewer men, fewer smokers, greater physical activity, less albuminuria, less renal insufficiency, less use of antihypertensive drugs, lipid lowering drugs, and aspirin, less history of cardiovascular disease and heart failure, better educated, and more likely to be married. Standardised differences between the two groups were sufficiently low and clearly below 10% for all

Table 1 | Baseline data for 18 168 individuals with type 1 diabetes followed for seven years until 2012 according to insulin treatment by insulin pump therapy or multiple daily injections (MDIs). Figures are means (1 SD) unless stated otherwise

	Pump (n=2441)	MDIs (n=15 727)	Standardised difference (%)‡	P value*	P value†
Age (years)	38 (13)	41 (15)	3.4	<0.001	0.18
Onset age (years)	16 (8)	13 (7)	1.8	<0.001	0.7
Duration (years)	25 (12)	26 (15)	2.3	<0.001	0.3
% of men	45.0	57.1	1.2	<0.001	0.6
HbA_{1c} (mmol/mol)	63 (13)	64 (14)	0.4	0.3	0.8
HbA_{1c} (%)	7.9 (1.3)	8.0 (1.3)	0.4	0.3	0.8
Systolic blood pressure (mm Hg)	126 (15)	128 (16)	1.7	<0.001	0.5
Diastolic blood pressure (mm Hg)	73 (8)	73 (9)	0.7	0.2	0.7
% taking antihypertensives	32.0	36.7	1.1	<0.001	0.7
Total cholesterol (mmol/L)	4.7 (0.9)	4.8 (0.9)	2.4	<0.001	0.3
HDL cholesterol (mmol/L)	1.6 (0.5)	1.6 (0.5)	2.8	0.2	0.3
Triglycerides (mmol/L)	1.0 (0.7)	1.1 (0.8)	2.7	<0.001	0.6
% taking lipid drugs	21.0	26.4	0.6	<0.001	0.8
BMI (kg/m^2)	25.3 (3.8)	25.4 (4.1)	0.2	0.061	0.8
% with low physical activity	21.8	24.0	0.4	0.01	0.7
% of smokers	10.5	13.5	2.5	<0.001	0.4
% taking aspirin	15.0	18.8	1.4	<0.001	0.6
Creatinine (μmol/L)§	82 (46)	85 (55)	0.3	0.009	0.5
% with eGFR <60	10.4	11.7	0.2	0.04	0.7
% with cumulative albuminuria	20.7	24.0	2.5	<0.001	0.3
% with previous CVD	5.4	8.0	1.8	<0.001	0.5
% with previous heart failure	0.9	2.3	3.2	<0.001	0.9
% with previous atrial fibrillation	0.6	1.0	0.7	0.05	0.9
% with previous cancer	0.9	1.2	1.2	0.2	0.4
% with previous liver diseases	0.3	0.2	0.3	0.5	0.7
% with previous mental disorders	2.0	1.8	2.6	0.6	0.3
% with low education level	9.8	19.0	3.0	<0.001	0.6
% with medium education level	52.9	53.5	1.9	0.6	0.4
% with high education level	37.3	27.6	3.1	<0.001	0.3
Annual income $\times 10^{-2}$ (SK)	1697 (1184)	1702 (1203)	3.9	0.9	0.10
% single	51.6	51.5	1.8	0.9	0.5
% married	40.3	36.5	2.6	<0.001	0.3
% divorced	7.4	10.3	0.3	<0.001	0.9
% widow	0.7	1.7	1.9	<0.001	0.7
% with baseline year 2005	69.4	66.9	1.7	0.01	0.5
% with baseline year 2006	21.7	21.2	2.0	0.6	0.4
% with baseline year 2007	11.4	9.3	0.4	0.001	0.7

HDL=high density lipoprotein; CVD=cardiovascular disease; eGFR=estimated glomerular filtration rate, according to MDRD (modification of diet in renal disease; SK=Swedish kroner (1k=£0.8, €0.11, $0.12).
*Crude values from Student's *t* test or χ^2 test.
†After adjustment with propensity score including all variables in table, estimated with generalised linear models (SAS Proc Genmod).
‡Value <10% is regarded as sufficient.
§Median (interquartile range) for plasma creatinine: 74 (64-87) μmol/L with pump and 76 (65-90) μmol/L with injections.

covariates. The distribution of the propensity score among the fifths (see appendix table A) shows a satisfactory overlap between the two treatment groups, as well as a sufficient number of outcomes by each fifth of the score. The mean percentage of missing data among all 36 variables was 5%—the highest proportions were for physical activity (32%), total cholesterol (25%), high density lipoprotein cholesterol (22%), triglycerides (21%), creatinine (11%), microalbuminuria (10%), and BMI (9%).

All individuals were monitored for a total of 114 135 person years over a mean follow-up period of 6.8 years. There were 1423 cases of fatal or non-fatal cardiovascular disease during the study period. The incidence rate for cardiovascular disease was 1.1 cases a year or 12.5 cases per 1000 person years.

Figure 1 shows Kaplan-Meier crude survival curves for all outcomes during follow-up, with significant differences at log rank test. Table 2 shows adjusted hazard ratios for the outcomes with insulin pump treatment, with multiple daily injections as the reference group. After adjustment for the propensity score, including all variables presented in table 1, insulin pump treatment was associated with a hazard ratio of 0.81 (0.66 to 1.01) for fatal or non-fatal coronary heart disease, 0.55 (0.36 to 0.83) for fatal coronary heart disease, 0.58 (0.40 to 0.85) for fatal cardiovascular disease, and 0.73 (0.58 to 0.92) for all cause mortality. Non-significantly lower hazard ratios were found for fatal or non-fatal cardiovascular disease. Differences in absolute rates (per 1000 person years) were 4.5 for fatal/non-fatal coronary heart disease, 4.8 for fatal/non-fatal cardiovascular

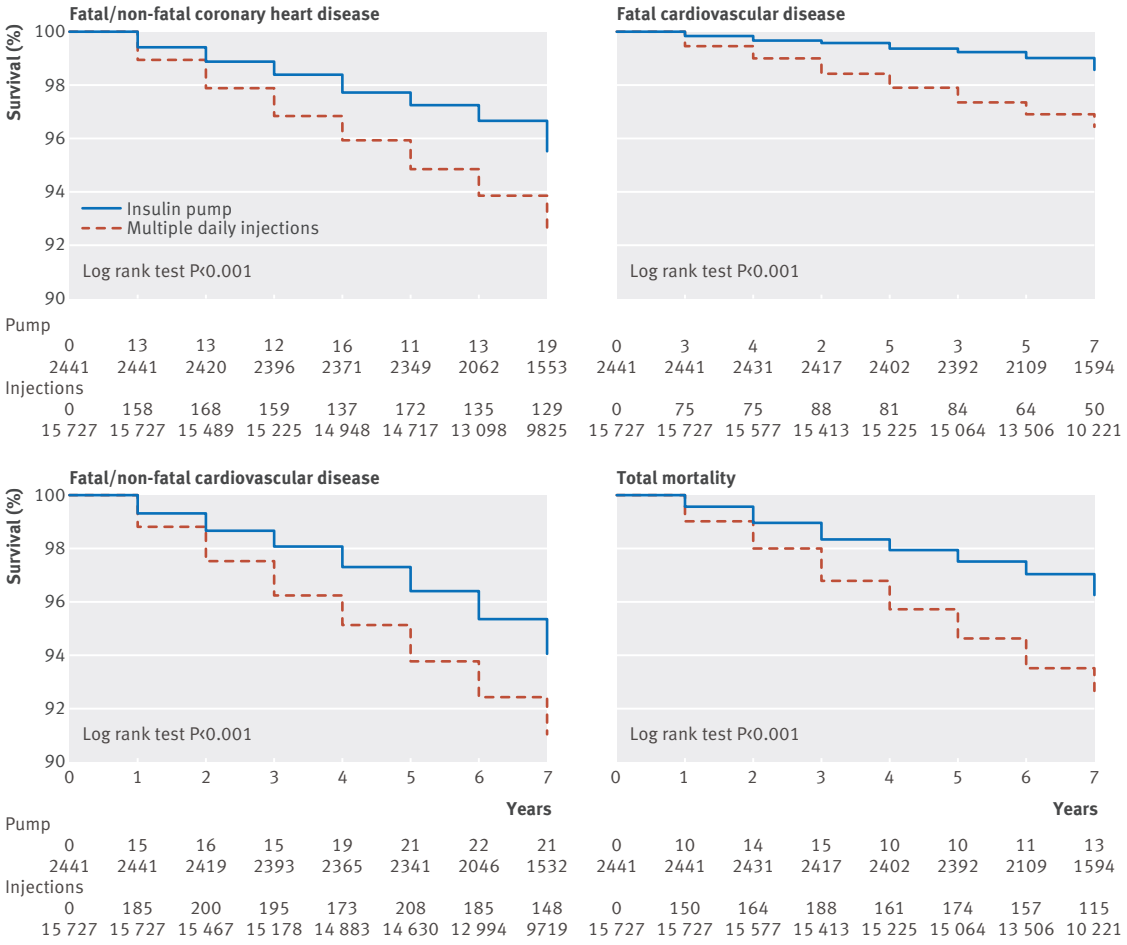

Fig 1 | **Kaplan-Meier crude survival curves in 18 168 individuals with type 1 diabetes according to treatment with insulin pump therapy or multiple daily injections. No of cases and individuals at risk are given in each group**

disease, 3.3 for fatal cardiovascular disease, and 5.7 for total mortality.

We performed a sensitivity analysis with a hypothetical unmeasured confounder. Table 3 shows, for example, how a binary confounder with a hazard ratio of 1.3 or 1.4 would change the hazard ratio of 0.58 (95% confidence interval 0.40 to 0.85) for fatal cardiovascular disease, depending on its prevalence in the group. If no patient treated with insulin pump therapy is exposed to the confounder (prevalence of 0.0), with a hazard ratio of 1.3, the difference between groups would not be significant (0.72, 0.50 to 1.05), assuming that 80% were exposed in the insulin pump group. The corresponding figure for a confounder with a hazard ratio of 1.4 would be 60% (0.72, 0.50 to 1.05).

Complementary analyses

We carried out a subgroup analysis consisting of 16 427 individuals with BMI ≥18 and no history of cardiovascular disease, heart failure, or atrial fibrillation (see appendix table B).

The same pattern of results was seen as in all individuals, with borderline significant hazard ratios of 0.77 (P=0.046) for fatal or non-fatal coronary heart disease. Hazard ratios were significant for fatal coronary heart disease 0.39 (P=0.007), fatal cardiovascular disease (0.48, P=0.01), and total mortality (0.75, P=0.04). The hazard ratios for the other endpoints were not significant.

Another subgroup analysis of the 10 282 patients with complete data for all variables in table 1 also showed similar results to the results for all patients (tables C and D in appendix). Differences between the pump therapy and injection groups for all variables after adjustment with a propensity score were not significant—standardised differences were sufficient and clearly below 10%. Pump therapy was associated with a significantly lowered hazard ratio of between 26% and 44% for fatal/non-fatal coronary heart disease, fatal coronary heart disease, fatal cardiovascular disease, and all cause mortality.

Analyses during study period

Kaplan-Meier analysis disclosed significantly fewer (P=0.034) hypoglycaemic incidents with insulin pump therapy compared with multiple daily injections in patients with three or more incidents during seven years of follow-up (fig 2). There were no significant differences (P=0.9) in patients with one or two incidents during follow-up. The number of patients admitted to hospital for hypoglycaemic incidents during the study period was 148 in those treated with pump therapy and

Table 2 | Hazard ratio (95% confidence intervals) for various outcomes with insulin pump treatment compared with multiple daily injections (MDIs) in 18 168 people with type 1 diabetes followed for mean of 6.8 years from 2005 to 2012

	No with events (%)	Events/1000 person years	Hazard ratio* (95% CI)	P value
Major endpoints				
Fatal/non-fatal coronary heart disease:				
MDIs	15 727/1058 (6.7)	10.7	1.0	0.05
Pump	2441/97 (4.0)	6.2	0.81 (0.66 to1.01)	
Fatal/non-fatal cardiovascular disease:				
MDIs	15 727/1294 (8.2)	13.1	1.0	0.2
Pump	2441/129 (5.3)	8.3	0.88 (0.73 to1.06)	
Fatal cardiovascular disease:				
MDIs	15 727/517 (3.3)	5.1	1.0	0.005
Pump	2441/29 (1.2)	1.8	0.58 (0.40 to 0.85)	
Total mortality:				
MDIs	15 727/1109 (7.1)	11.0	1.0	0.007
Pump	2441/83 (3.4)	5.3	0.73 (0.58 to 0.92)	
Secondary endpoints				
Fatal coronary heart disease:				
MDIs	15 727/453 (2.9)	4.5	1.0	0.004
Pump	2441/24 (1.0)	1.5	0.55 (0.36 to 0.83)	
Fatal stroke:				
MDIs	15 727/79 (0.5)	0.8	1.0	0.4
Pump	2441/5 (0.2)	0.3	0.67 (0.27 to 1.67)	
Non-cardiovascular disease mortality:				
MDIs	15 722/592 (3.8)	5.9	1.0	0.3
Pump	2441/54 (2.2)	3.4	0.86 (0.64 to 1.13)	

*Adjustment by stratification with fifths of propensity score including covariates of age, sex, diabetes duration, histories of cardiovascular disease, heart failure, atrial fibrillation, cancer, liver disease, mental disorders, education levels, and baseline values of HbA_{1c}, systolic and diastolic blood pressure, current smoking, physical activity, BMI, total and high density lipoprotein cholesterol, triglycerides, albuminuria, creatinine, renal insufficiency, antihypertensive drugs, lipid lowering drugs, aspirin, income, educational level, marital status and baseline year.

967 in those treated with injections, and the number of hypoglycaemic incidents was 206 and 1366, respectively (table F in appendix).

Analyses of updated mean HbA_{1c}, as well as difference between baseline and final HbA_{1c}, during the study period did not show significant differences between the treatments. Updated mean HbA_{1c} was 64 mmol/mol (8%) in all those treated with pump therapy and 64 mmol/mol (8%) in all those treated with injections, and the mean decrease from baseline to final HbA_{1c} was 2.1 mmol/mol in both groups. Similarly, there was no difference in HbA_{1c} during the study period when patients were subdivided by combinations of fifths of baseline HbA_{1c}, as well as baseline BMI, to exclude differences because of these baseline values (appendix table E).

Discussion

Principal findings

This is the first large study from a population based setting that documents the relation between insulin pump treatment and cardiovascular mortality. We studied individuals with type 1diabetes during a mean follow-up period of 6.8 years. Among 2441 of those treated with insulin pump therapy and 15727 treated with multiple daily injections, insulin pump treatment was associated with a reduction of 45% for fatal coronary heart disease, 42% for fatal cardiovascular disease, and 27% for all cause mortality. We evaluated the patient who used insulin pump therapy and do not know if the observed effect is attributable to continuous infusion of insulin or that some, if not all, of the effect is attributable to intensified glucose monitoring, increased motivation to control blood glucose, or a better knowledge about having diabetes type 1.

Comparison with other studies

The reduced number of severe hypoglycaemic episodes could explain why insulin pump treatment is associated with a reduced cardiovascular mortality. Such episodes can trigger cardiac arrhythmias and coronary plaque rupture.[29 30] Administration of insulin by continuous infusion has been reported to reduce the frequency of severe hypoglycaemia compared with administration of insulin by multiple daily injections.[31 32] There are indications that episodes of hypoglycaemia occur together with cardiac arrhythmia.[33 34] Stahn and colleagues used continuous glucose measurements and continuous electrocardiograms for five days to monitor 30 people with type 2 diabetes and previous cardiovascular disease,. They found a 10-fold increase in ventricular arrhythmias (mean 1.0 *v* 0.1) during hypoglycaemic episodes. The corresponding figure for ventricular couplets was 7.6 (41.7 *v* 5.5).[35]

Logically, having an insulin pump could result in a more stable blood glucose concentration than multiple daily injections.[6 36] Often the history recorded by the pumps can be uploaded and displayed as a graph for purposes of trend analysis.[37]

Mechanisms for results

There is a rationale for insulin pump treatment resulting in more stable blood glucose concentrations than multiple daily injections. Hypoglycaemia is a risk factor for cardiovascular events, particularly among high risk individuals.[38 39] We have recently found evidence that Swedish patients with type 1 diabetes and previous severe episodes of hypoglycaemia have an increased risk of mortality after a cardiovascular event.[4] The Diabetes Control and Complication Trial of type 1 diabetes, however, found no significant association between frequent severe hypoglycaemic episodes and increased cardiovascular mortality among individuals in the intensive treatment group.[40] The EURODIAB Prospective Complications Study of 2181 people with type 1 diabetes who were monitored for seven years also reported no association between baseline hypoglycaemia and the risk of cardiovascular disease.[41] A retrospective analysis of a large cohort of people with type 1 diabetes treated with insulin pump therapy, however, pointed to a higher prevalence of cardiovascular disease in those with a history of repeated hypoglycaemic episodes.[42]

Another mechanism worth consideration is that treatment with insulin pump might lead to a lower frequency and duration of hyperglycaemia, corresponding to reduced long term occurrence of microvascular and cardiovascular complications. The Diabetes Control and Complication Trial has shown that good glycaemic control for six years with follow-up for 11 years can significantly decrease the risk of any cardiovascular

Table 3 | Quantified effects of hypothetical unmeasured and/or unknown confounders in cohort of people with type 1 diabetes treated with insulin pump therapy or multiple daily injections (MDIs). Hypothetical binary confounder was assigned hazard ratio of 1.3 or 1.4 for all outcomes listed below. Hazard ratios associated with insulin pump treatment were given different prevalences of this confounder between two groups. Figures are hazard ratios (95% confidence intervals) after adjustment for binary confounder

	Confounder with hazard ratio 1.3		Confounder with hazard ratio 1.4	
	Prevalence of confounder in pump group		Prevalence of confounder in pump group	
	0.0	0.2	0.0	0.2
Fatal/non-fatal coronary heart disease				
Prevalence of confounder in MDI group:				
0.0	0.81 (0.66 to 1.01)	0.76 (0.62 to 0.95)	0.81 (0.66 to 1.01)	0.75 (0.61 to 0.94)
0.2	0.86 (0.70 to 1.07)	0.81 (0.66 to 1.01)	0.87 (0.71 to 1.09)	0.81 (0.66 to 1.01)
Fatal/non-fatal cardiovascular disease				
Prevalence of confounder in MDI group:				
0.0	0.88 (0.73 to 1.06)	0.83 (0.69 to 1.00)	0.88 (0.73 to 1.06)	0.81 (0.67 to 0.98)
0.2	0.93 (0.77 to 1.12)	0.88 (0.73 to 1.06)	0.95 (0.79 to 1.14)	0.88 (0.73 to 1.06)
Fatal cardiovascular disease				
Prevalence of confounder in MDI group:				
0.0	0.58 (0.40 to 0.85)	0.55 (0.38 to 0.80)	0.58 (0.40 to 0.85)	0.54 (0.37 to 0.79)
0.2	0.61 (0.42 to 0.90)	0.58 (0.40 to 0.85)	0.63 (0.43 to 0.92)	0.58 (0.40 to 0.85)
0.4	0.65 (0.45 to 0.95)	0.61 (0.42 to 0.90)	0.67 (0.46 to 0.98)	0.63 (0.43 to 0.92)
0.6	0.68 (0.47 to 1.00)	0.65 (0.45 to 0.95)	0.72 (0.50 to 1.05)	0.67 (0.46 to 0.98)
0.8	0.72 (0.50 to 1.05)	0.68 (0.47 to 1.00)	0.77 (0.53 to 1.12)	0.72 (0.50 to 1.05)
Total mortality				
Prevalence of confounder in MDI group:				
0.0	0.73 (0.58 to 0.92)	0.69 (0.55 to 0.87)	0.73 (0.58 to 0.92)	0.68 (0.54 to 0.85)
0.2	0.77 (0.61 to 0.97)	0.73 (0.58 to 0.92)	0.79 (0.63 to 0.99)	0.73 (0.58 to 0.92)
0.4	0.82 (0.65 to 1.03)	0.77 (0.61 to 0.97)	0.85 (0.67 to 1.07)	0.79 (0.63 to 0.99)
0.6	0.86 (0.68 to 1.08)	0.82 (0.65 to 1.03)	0.90 (0.72 to 1.14)	0.85 (0.67 to 1.07)

disease event by 42% and the risk of non-fatal myocardial infarction, stroke, or death from cardiovascular disease by 57%.[2] At the group level, it is clear that sensor-augmented pump therapy provides better metabolic control than multiple daily injections in adults with type 1 diabetes. A study in the United States and Canada randomised 329 adults with type 1 diabetes to insulin with sensor-augmented pump therapy or multiple daily injections. After one year, HbA_{1c} had been reduced by 1.0% from baseline among those who had been randomised to sensor-augmented pump therapy. The corresponding figure for injections was 0.4%, with a significant difference.[43] A review of the literature in 2010 found some evidence that insulin pump therapy without continuous glucose monitoring could be better than multiple daily injections for glycaemic control in people with type 1 diabetes, with adjustment for baseline HbA_{1c}.[7] This study gave no information on sensor use, but it was uncommon in Sweden during the period.

Strengths of the study

This study included a large number of participants. Each individual with type 1 diabetes who was entered as being treated with insulin pump therapy or multiple daily injections was reported to the Swedish National Diabetes Register by local units. Nobody was excluded from the study during follow-up, and we have valid information for almost every Swede who has been diagnosed with type 1 diabetes,[12] as well as information regarding the occurrence of cardiovascular disease and death outcomes using established national registers.[17 18] The propensity score allowed for balancing 36 covariates between the insulin pump and multiple daily injection groups, including strong cardiovascular risk factors and important social data—there were only non-significant differences and small standardised differences for all covariates. The stratification into fifths of the score for adjustment at the Cox regressions permitted use of all available patients in the study. Score stratification with fifths is sometimes regarded as causing less residual confounding than not using fifths.[20 21] Subgroup analyses allowed for further verification of the study results in patients with no previous cardiovascular disease or other serious concomitant disease; the marker was low BMI. The analysis of a somewhat smaller sample with complete data and no imputation confirmed our results, which indicated that missing data were random.

We observed clinical practice in Sweden at the time of the study. There were no strict guidelines for switching from multiple daily injections to insulin pump therapy. Among possible reasons for a physician to recommend that an individual with type 1 diabetes switch treatment are unsatisfactory glycaemic control with high HbA_{1c}, large variations in blood glucose concentrations, or the need to improve quality of life by administering insulin more flexibly. In Sweden treatment by pump and multiple daily injections is covered by healthcare providers, there are no additional costs for the patient.

Our analysis of the effect of a hypothetical unmeasured confounder showed that this effector would have to be large (hazard ratios of 1.3-1.4) and with a prevalence of 80% or more in the injection group but no presence in the insulin pump group to eliminate the

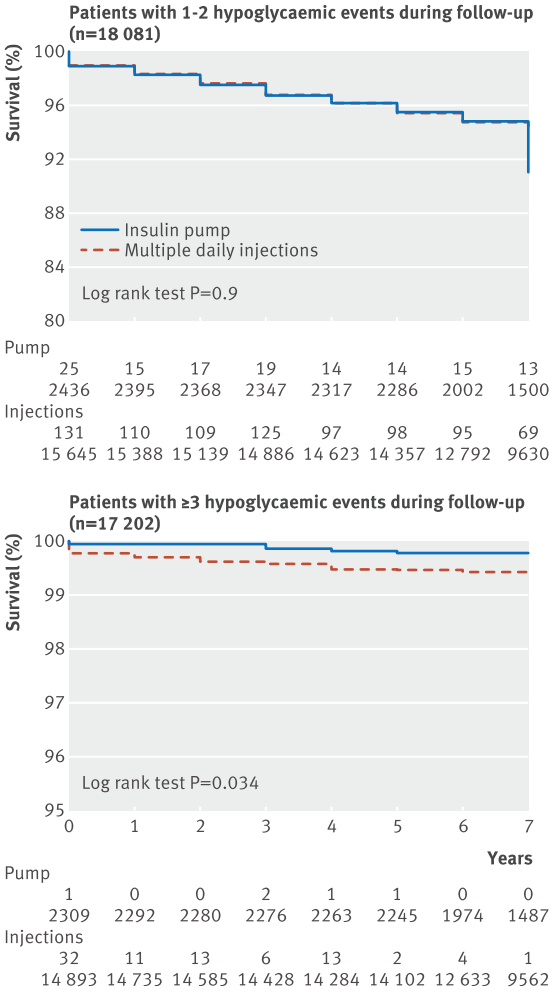

Fig 2 | Kaplan-Meier survival curves for first incident hypoglycaemic events in patients with type 1 diabetes during seven years of follow-up. No of cases and individuals at risk are given for each group

significant findings for risk of fatal coronary heart disease and cardiovascular disease (table 3).[25-28] In light of these simulations, and that we are not aware of any strong unmeasured risk factor for coronary heart disease that is likely to be severely unbalanced between those using pump and injections, we believe we have documented a true effect. Obviously we need more data before we can state without reasonable doubt that pump use results in a lower risk of coronary heart disease or cardiovascular disease.

Limitations of the study

One limitation of the study was that we had no information on duration of insulin pump treatment before study baseline, although our aim was to analyse outcomes from baseline during a long term follow-up period. If the mechanism for the preventive effect of insulin pump treatment on cardiovascular mortality is through a reduced frequency of lethal arrhythmia, we would expect adjustment for the duration of insulin pump treatment to have little or no effect on our hazard ratios. If instead the mechanism is through events with an induction latency time of a year or more, such as plaque formation, adjustment for duration of insulin pump treatment would give even stronger associations than we found. We adjusted the hazard ratio between insulin pump treatment and cardiovascular mortality for baseline values of HbA_{1c}. As some patients had used insulin pumps for some time at baseline, this means that the adjustment might eliminate some of the effect. That is, if this source of error did not exist, we would have estimated the protective effect of insulin pump treatment on cardiovascular mortality to be larger than we now found. We did not adjust for HbA_{1c} after baseline as that would be adjusting for a possible mediating factor. Separate analyses of updated mean HbA_{1c} during the study, or the change between baseline and final HbA_{1c}, however, showed no significant differences between the treatment groups.

Mediating factors, to one extent or another, for the effect of insulin pump treatment on cardiovascular mortality might be increased frequency of glucose monitoring, as well as more appropriate actions at various blood glucose concentrations. Changing from multiple daily injections to insulin pump treatment is accompanied by education about insulin pump treatment, which could be useful in reducing the number of episodes of hypoglycaemia and hyperglycaemia. Moreover, having a pump with the opportunities it offers to fine tune the administration of insulin might itself be an instructive factor. Thus, some of the effect of pump therapy on risk of cardiovascular disease could have been achieved by intensified training of the individual about the disease[44] to improve blood glucose monitoring and achieve a better balance between insulin administration, food intake, and physical activity.

Conclusions

This nationwide observational study of individuals with type 1 diabetes shows that treatment with an insulin pump was associated with a considerable reduction in risk of fatal coronary heart disease, fatal cardiovascular disease, and all cause mortality. Whether the results reflect the physiological consequences of insulin pump treatment, the clinical management that pump users receive, or the educational aspects of having the pump remains elusive.

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Contributors: IS, JC, and SG researched the data; IS and JC performed the statistical analyses; IS, JC, and SG wrote the article, contributed to the discussion, and reviewed and edited the article. BE, AR, KE-O, A-MS, BZ, TA, ML-O, and JJ contributed to the discussion and reviewed and edited the article. SG is guarantor.

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outside the submitted work; ML-O lectures about diabetology and has been paid by different pharmaceutical companies.

Ethical approval: The study was approved by the regional ethical review board at the University of Gothenburg. All individuals with diabetes give their informed consent before being entered.

Data sharing: No additional data available, but data from this study are available on request.

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Appendix: Supplementary tables A-F [posted as supplied by author]