Antidiabetic Drugs and Heart Failure Risk in Patients With Type 2 Diabetes in the U.K. Primary Care Setting

SHOKO MARU, DSC[1]
GARY G. KOCH, PHD[2]
MONIKA STENDER, DRSCHUM[3]
DOUGLAS CLARK, MBA[3]
LAURA GIBOWSKI, MPH[4]
HANS PETRI, MD, PHD[3]
ALICE D. WHITE, PHD[3]
ROSS J. SIMPSON, JR., MD, PHD[5]

OBJECTIVE — To assess the effects of antidiabetic drugs on the risk of heart failure in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — We conducted a retrospective cohort study with a newly diagnosed diabetes cohort of 25,690 patients registered in the U.K. General Practice Research Database, 1988–1999. We categorized person-time drug exposures to monotherapies in insulin, sulfonylureas (SUs), metformins, and other oral hypoglycemic agents (i.e., acarbose, guar gum) and combination therapy including insulin, combination therapy without insulin, and triple combination therapy with or without insulin. A drug-free time interval served as a reference category. Cox interval-wise (piece-wise) regression analyses were used. The main outcome was incident heart failure.

RESULTS — Among 43,390 drug exposure intervals for 25,690 patients who had a mean follow-up period of 2.5 years, 1,409 patients developed heart failure. Heart failure occurred most frequently in SU monotherapy exposure. After adjusting for duration of diabetes, the timing and order of treatments received, and known risk factors for heart failure, we found no differential effects among type-specific therapies. Patients with any drug use within the first year after diabetes diagnosis had a 4.75-fold higher risk (hazard ratio) for heart failure than those with drug-free status but had no increased risk during subsequent years.

CONCLUSIONS — In conclusion, the use of any pharmacological therapy for type 2 diabetes appears to be associated with an increased risk of heart failure. This risk does not persist beyond the first year after diagnosis of diabetes and does not appear to differ among the types of drug therapy examined. This observation suggests that the severity of diabetes or the preclinical duration of diabetes and the need for drug therapy, and not the therapy itself, is an explanation for heart failure in patients with type 2 diabetes.

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The increased risk of heart failure in patients with type 2 diabetes is not fully explained by the known risk factors of heart failure. Diabetes alone may induce important structural and functional changes in the myocardium that increase the risk of heart failure (1). Furthermore, studies have reported an increased risk of heart failure associated with the use of insulin (2,3) or glitazones (4–6). For example, the Framingham Heart Study (2) reported that the excess risk of congestive heart failure was confined to the insulin-treated diabetic subjects when compared with those treated by diet or orally administrated drugs. In addition, a recent study (3) of type 2 diabetic patients found that insulin use and better glycemic control independently predicted heart failure. On the other hand, the U.K. Prospective Diabetes Study (7,8) reported no increase in cardiovascular events (including heart failure) or death with either insulin or sulfonylurea (SU) use compared with the conventional care group. It remains controversial whether antidiabetic drugs cause an increased risk of heart failure.

Assessing the effects of drugs can be challenging in the context of diseases where it is common for a single patient to receive multiple drugs either simultaneously or over time. In the present study, we attempted to take into account the timing of each therapy initiated and the status of known risk factors for heart failure ascertained at the time each therapy was initiated. Our goal was to estimate the incidence of heart failure in patients newly diagnosed with type 2 diabetes and to assess the effects of antidiabetic drugs on the risk of heart failure.

RESEARCH DESIGN AND METHODS

— Since 1987, >5 million residents in the U.K. have been enrolled with selected general practitioners providing data for research purposes to the General Practice Research Database (GPRD) (9). The information recorded includes characteristics of patients, drugs dispensed, clinical diagnoses, referrals to consultants, hospital admissions, medical histories, and lifestyle information. The details of each prescription, including dose, instructions, and quantity, can be used to derive information on duration of drug exposure (10). The Oxford Medical Information System classification (OX-

From the [1]Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, North Carolina; the [2]Department of Biostatistics, School of Public Health, University of North Carolina, Chapel Hill, North Carolina; [3]Worldwide Epidemiology, GlaxoSmithKline R&D, Greenford, U.K.; [4]Alphametrics, Durham, North Carolina; the [5]Division of Cardiology, School of Medicine, University of North Carolina, Chapel Hill, North Carolina.

Address correspondence and reprint requests to Ross J. Simpson, Jr., MD, PhD, Division of Cardiology, University of North Carolina at Chapel Hill, CB no. 7075, 130 Mason Farm Rd., Suite 4128, Chapel Hill, NC 27599-7075. E-mail: rsimpson@med.unc.edu.

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Abbreviations: GPRD, General Practice Research Database; OHA, oral hypoglycemic agent; OXMIS, Oxford Medical Information System; SU, sulfonylurea.

MIS) and Read Clinical Terms (11) are used to enter medical diagnoses, and a coded drug dictionary based on the Prescription Pricing Authority's Dictionary is used for prescription details.

The study cohort consisted of 25,690 type 2 diabetic patients newly diagnosed between 1988 and 1999. Included were patients with OXMIS or Read codes equivalent to ICD-8 diagnostic codes (1): 250.0 (adult-onset diabetes, not otherwise specified), 250.1 (adult-onset diabetes and coma), and 250.2 (adult-onset diabetes complication, not elsewhere classified) and aged 35 years or older at diagnosis to minimize the chance of type 1 diabetes (2). Patients were excluded if *1*) they received exclusive insulin therapy during the first 3 months postdiagnosis to exclude type 1 diabetes; *2*) they had a record of diabetes diagnosis or treatment, including clinic visits within the first 6 months on the database to exclude possible prevalent type 2 diabetes; or *3*) they had a diagnosis of heart failure or pulmonary edema before type 2 diabetes diagnosis.

Outcome definition

The first physician diagnosis of heart failure based on OXMIS and Read codes containing the following terms was defined as incident heart failure: heart failure, cardiac failure, myocardial failure, cardiac dropsy, right ventricular failure, left ventricular failure, impaired left ventricular function, weak heart, low-output syndrome, cardiac asthma, cardiac insufficiency, and myocardial insufficiency. We performed a validation study on a small sample of patients, whereby questionnaires were sent to the general practitioner to confirm the diagnosis of heart failure. In 83.4% of the cases, the heart failure diagnosis was confirmed, which is consistent with findings of other validation studies carried out in GPRD (12,13).

Exposure definition

We estimated the duration of drug exposure based on the quantity prescribed and the daily dosage instructions recorded. The status of combination therapy was determined when more than one estimated duration of drug use overlapped in time. Histories of myocardial infarction, valvular disease, angina pectoris, coronary intervention procedure, and atherosclerotic vascular disease were based on physician diagnosis at the time of type 2 diabetes diagnosis and at the onset of a therapy, if any.

Explanatory variables were categorized as follows:

- Use of antidiabetic drugs: type of drug class; status of monotherapy, combination therapy, or triple therapy; and use in current, any prior, and immediately preceding intervals.
- History of established risk factors of heart failure: myocardial infarction, valvular disease, angina pectoris, coronary interventional procedures (such as coronary stent, coronary artery bypass grafting, or coronary angioplasty), and hypertension (by diagnosis or systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg on at least two occasions during a 1-year period before or after the diagnosis of type 2 diabetes).
- History of atherosclerotic vascular disease: carotid artery stenosis, intermittent claudication, amputation (due to atherosclerotic vascular disease), abdominal aortic aneurysm, aneurysm, or aneurysm repair.
- Presence of risk factors for atherosclerotic vascular disease: age at the onset of a therapy (in 10 years), smoking (never/ever), obesity (BMI ≥30.0 kg/m^2 or obesity-related diagnosis), and lipid anomaly (hypercholesterolemia, dyslipidemia, or hypertriglyceridemia).
- Duration of type 2 diabetes.

Statistical analysis

We categorized person-time drug exposures according to seven groups: monotherapies in insulin, SUs, metformins, and other oral hypoglycemic agents (OHAs; i.e., acarbose, guar gum) and combination therapy including insulin, combination therapy without insulin, and triple combination therapy with or without insulin. A drug-free time interval served as a reference category.

We used a drug exposure interval as a unit of observation, i.e., 43,390 intervals of exposure apply to the applicable sequences of treatments for 25,690 patients. An interval was defined as the duration from the onset of a drug exposure to the onset of the next drug exposure or until censored or heart failure. Thus, if a patient were drug-free throughout the observation period, only one interval was applicable for this patient. If a patient were prescribed with SU monotherapy at the time of type 2 diabetes diagnosis and switched to a combination therapy of SUs and metformins and stayed with that combination therapy until a heart failure occurred or until censored, this patient was considered to have contributed two intervals in total.

To adjust for possible differences in the risk of heart failure across different intervals, we defined interval 1 as the reference, and assessed interval 2 or higher, interval 3 or higher, interval 4 or higher, and interval 5 or higher to address risks associated with later treatments. All time-dependent variables were reascertained at the onset of each of the following intervals: type-specific drug use (7 categories), duration of type 2 diabetes (10 categories), age (in 10 years), and histories of myocardial infarction, valvular disease, angina pectoris, coronary interventional procedures, and atherosclerotic vascular disease. The following variables were ascertained at the time of type 2 diabetes diagnosis and remained fixed throughout the observation period: sex, smoking habits, hypertension, and obesity. Duration of type 2 diabetes was computed as the time from type 2 diabetes diagnosis to the onset of each interval (the time each therapy was initiated) and was categorized into the following 10 groups (in days): <180, 180–360, 361–540, 541–720, 721–900, 901–1,080, 1,081–1,440, 1,441–1,800, 1,801–2,520, and >2,520.

We analyzed the entire follow-up period as well as its separate components for the cumulative time of the first, second, and beyond the second year after type 2 diabetes diagnosis. In the "first year" risk set, a duration of type 2 diabetes of 0.5–1.0 year, the "second year" risk set 1.5–2.0 years, and the "beyond second year" risk set 2.5–3.0, 3.0–4.0, 4.0–5.0, 5.0–7.0, and >7 years were included in the corresponding model.

Cox interval-wise (piece-wise) regression analyses (14) were used to assess the effects of risk indicators for heart failure. First, we built model 1, which assessed the effects of seven type-specific drugs. After examining the β-coefficients of the variables of type-specific drug use, we built model 2, which assessed the effect of any drug use (versus drug-free), while adjusting for the same set of covariates as in model 1. Then, goodness-of-fit of model 2 relative to model 1 was assessed by comparing the difference in the log-likelihood

Table 1—*Characteristics of 43,390 drug exposure contributions (intervals*) at the onset of each drug exposure*

	Drug-free	SU monotherapy	Metformin monotherapy	Insulin monotherapy
n	21,245 (49.0)	11,350 (26.2)	4,579 (10.6)	861 (2.0)
Follow-up time (days)	568 ± 641 (323)	642 ± 620 (445)	552 ± 570 (359)	662 ± 615 (467)
Men†	11,516 (54.2)	5,953 (52.5)	2,206 (48.2)	404 (46.9)
Age at the onset of interval (years)	63 ± 12.5	64 ± 12.0	59 ± 11.4	58 ± 12.7
Having ever smoked†	6,595 (31.0)	3,397 (29.9)	1,544 (33.7)	303 (35.2)
BMI ≥30 kg/m^2 or obesity diagnosis†	5,702 (26.8)	2,422 (21.3)	2,197 (48.0)	160 (18.6)
History				
Edema	2,197 (10.3)	1,219 (10.7)	620 (13.5)	116 (13.5)
Myocardial infarction	1,203 (5.7)	667 (5.9)	216 (4.7)	44 (5.1)
Valvular heart disease	137 (0.6)	84 (0.7)	26 (0.6)	6 (0.7)
Angina pectoris	2,280 (10.7)	1,278 (11.3)	502 (11.0)	101 (11.7)
Coronary interventional procedures	277 (1.3)	176 (1.6)	68 (1.5)	23 (2.7)
Hypertension†	7,090 (33.4)	3,791 (33.4)	1,786 (39.0)	241 (28.0)
Athrosclerotic vascular disease	643 (3.0)	432 (3.8)	122 (2.7)	31 (3.6)
Renal insufficiency	68 (0.3)	47 (0.4)	21 (0.5)	6 (0.7)
Interval where a given therapy was prescribed*				
1	21,245 (100)	3,365 (29.7)	983 (21.5)	2 (0.2)
2	0	7,147 (63.0)	2,979 (65.1)	148 (17.2)
3	0	333 (2.9)	300 (6.6)	192 (22.3)
4	0	457 (4.0)	292 (6.4)	257 (29.9)
5	0	24 (0.2)	15 (0.3)	156 (18.1)
6	0	24 (0.2)	8 (0.2)	72 (8.4)
7	0	0 (0)	1 (0.0)	27 (3.1)
8	0	0 (0)	1 (0.0)	7 (0.8)

Data are means ± SD, *n* (%), or means ± SD (median). *A drug exposure interval was used as a unit of observation, i.e. 43,390 intervals of exposure to the applicable sequences of treatments for 25,690 patients. An interval was defined as the duration from the onset of a drug exposure to the onset of a next drug exposure or until censored. †These variables were ascertained only at the time of diabetes diagnosis and remained fixed throughout the observation period.

ratio statistics relative to the difference in the degrees of freedom of the two models.

Further, we assessed whether knowing the drug exposure in any prior interval or immediately preceding an interval influences heart failure risk in addition to knowing the drug exposure in the current interval. We also examined whether myocardial infarction, valvular disease, angina pectoris, coronary interventional procedures, and atherosclerotic vascular disease occurring in the immediately preceding interval would further explain the risk of heart failure beyond those occurring at any time before the current interval. The possibily multiple intervals from the same patient were managed as essentially independent risk sets, since only intervals up to the time of the first heart failure or up to the end of follow-up were included in the analyses, and there was no subsequent consideration of recurrent heart failure events.

Only the drug-free periods observed during the first interval were managed as "drug-free" in our analyses, as these are most likely to approximate a diet and exercise therapy. The total person-years, number of patients, and number of intervals that were not counted due to the ignored drug-free period beyond the first interval were 1,118 person-years, 6,977 patients, and 7,835 intervals (1.6% of the total person-years of exposure). No heart failure occurred in the ignored drug-free periods. The criterion for statistical significance was $P < 0.05$ (two sided). All statistical analyses were performed using SAS 8.01 (SAS Institute, Cary, NC).

RESULTS — Among the 25,690 patients with 43,390 drug exposure intervals during 67,787 person-years, the mean follow-up period was 2.5 years, and 1,409 patients developed heart failure (732 men and 677 women).

Among all pharmacological therapies, SU monotherapy was most frequently prescribed ($n = 11,350$), followed by metformin monotherapy ($n = 4,579$) and OHA combination therapy ($n = 4,107$) (Table 1). Smoking was less common for patients with drug-free and SU monotherapy. Obesity was most prevalent in metformin. Hypertension was most prevalent in metformin monotherapy and other OHA combination and triple therapies. A total of 21,245 (82.7%) subjects were drug-free in the first interval. Among those who initiated pharmacotherapy immediately after type 2 diabetes diagnosis (17.3%), SU monotherapy followed by metformin was prescribed most frequently in the first interval. SU, metformin, and OHA combination therapies were prescribed most frequently in the second interval. OHA combination therapy was most common in the third interval. Insulin (as a monotherapy or in combinations) and triple therapy were relatively more common in the fourth and later intervals.

Heart failure occurred most frequently in SU monotherapy intervals (4.7%), followed by drug-free (2.9%) and metformin monotherapy (2.8%). Table 2 shows the incidence rates of heart failure by varying cumulative time since type 2 diabetes diagnosis. In the entire period, heart failure incidence was the highest in SU monotherapy (26.6 per 1,000), fol-

Table 1—*Continued*

Other monotherapies	OHA combination therapy	Insulin combination therapy	Triple therapy	Total
242 (0.6)	4,107 (9.5)	456 (1.1)	550 (1.3)	43,390 (100)
318 ± 380 (146)	499 ± 534 (300)	165 ± 299 (31)	199 ± 303 (57)	571 ± 616 (349)
122 (50.4)	1,947 (47.4)	216 (47.4)	238 (43.3)	22,602 (52.1)
60 ± 10.3	61 ± 11.3	57 ± 12.5	59 ± 10.8	62 ± 12.3
84 (34.7)	1,355 (33.0)	172 (37.7)	195 (35.5)	13,645 (31.5)
89 (36.8)	1,469 (35.8)	102 (22.4)	187 (34.0)	12,328 (28.4)
29 (12.0)	493 (12.0)	55 (12.1)	64 (11.6)	4,793 (11.1)
10 (4.1)	227 (5.5)	27 (5.9)	30 (5.5)	2,424 (5.6)
1 (0.4)	27 (0.7)	2 (0.4)	2 (0.4)	285 (0.7)
41 (16.9)	475 (11.6)	51 (11.2)	63 (11.5)	4,791 (11.0)
6 (2.5)	71 (1.7)	7 (1.5)	10 (1.8)	638 (1.5)
83 (34.3)	1,611 (39.2)	148 (32.5)	225 (40.9)	14,975 (34.5)
7 (2.9)	155 (3.8)	17 (3.7)	18 (3.3)	1,425 (3.3)
1 (0.4)	26 (0.6)	3 (0.7)	4 (0.7)	176 (0.4)
40 (16.5)	54 (1.3)	1 (0.2)	0 (0)	25,690 (59.2)
150 (62.0)	1,245 (30.3)	75 (16.5)	8 (1.5)	11,752 (27.1)
22 (9.1)	2,559 (62.3)	171 (37.5)	162 (29.5)	3,739 (8.6)
23 (9.5)	108 (2.6)	91 (20.0)	316 (57.5)	1,544 (3.6)
4 (1.7)	139 (3.4)	75 (16.5)	37 (6.7)	450 (1.0)
2 (0.8)	0 (0)	27 (5.9)	27 (4.9)	160 (0.4)
0 (0)	2 (0.1)	16 (3.5)	0 (0)	46 (0.1)
1 (0.4)	0 (0)	0 (0)	0 (0)	9 (0.0)

lowed by insulin combination therapy (24.3 per 1,000). The heart failure incidence in the drug-free period substantially increased as time elapsed (6.8, 14.7, and 34.4 per 1,000).

In all age-groups, women showed a lower incidence rate than men. The heart failure incidence rates per 1,000 person-years and 95% CIs in men aged 35–44, 45–54, 55–64, 65–74, and ≥75 years were 2.38 (95% CI 1.03–4.70), 6.21 (4.58–8.24), 13.09 (11.09–15.35), 28.86 (25.59–32.43), and 50.48 (44.32–57.26), respectively. In women in the same age-groups, they were 0.87 (0.10–3.15), 4.74 (3.00–7.11), 10.4 (8.36–12.78), 24.75 (21.58–28.25), and 48.45 (43.46–53.86), respectively.

Table 3 is our final model (model 2), where the seven type-specific drugs used in model 1 are collapsed into the "any drug use" category. Any drug use showed a 4.75-fold increased risk (hazard ratio [HR]) of heart failure compared with no drug use in the first year, and the effect was attenuated in subsequent years. Baseline smoking, time-dependent age, and histories of myocardial infarction, valvular disease, angina pectoris, coronary interventional procedure, and atherosclerotic vascular disease were positively associated with an increased risk of heart failure for the entire period. The effect of baseline smoking increased over time. In model 1, the HRs and 95% CIs of type-specific drug exposure (versus drug-free) in the first year and entire period were as follows: insulin monotherapy HR 2.87 (95% CI 0.62–13.36) and 1.17 (0.70–1.95), respectively; SU monotherapy 4.73 (3.53–6.34) and 1.53 (1.30–1.79), respectively; metformin monotherapy 4.69 (3.09–7.12) and 1.58 (1.26–1.98), respectively; and other OHA monotherapies 12.46 (4.48–34.65) and 1.63 (0.60–4.42), respectively. Insulin combination therapy 7.43 (0.91–60.60) and 2.13 (0.82–5.50), respectively; OHA combination therapy 3.69 (1.77–7.67) and 1.52 (1.11–2.08), respectively; and triple combination therapy 0 (no events) and 0.51 (0.12–2.12), respectively. The risk parameters of all the factors except drug exposures in model 1 were similar to those in model 2. The difference in the log-likelihood ratio statistics between the two models relative to the difference in degrees of freedom was compared within all three risk set periods, but none of the comparisons were statistically significant. Hence, we considered that the seven type-specific drugs (model 1) did not further contribute to what was already explained by any drug use (model 2).

Any prior or immediately preceding drug exposure did not show an additional predictive ability beyond the current drug exposure. This may be because current exposures were highly correlated with any prior and immediately preceding exposures to respective drug categories. Time-dependent variables such as age or medical histories in the immediately preceding interval did not further explain heart failure risk beyond those reascertained at the onset of the current interval.

When we conducted a per-patient analysis and assessed the effect of ever use of insulin using the same dataset, the HR and 95% CI of insulin use was 1.60 (1.29–1.99), adjusted for age, sex, obesity, hypertension, smoking, and histories of myocardial infarction, valvular disease, angina pectoris, coronary interventional procedure, and atherosclerotic vascular disease at the time of type 2 diabetes diagnosis. Similarly, a marked discrepancy

Table 2—*Incidence rates of heart failure per 1,000 person-years by time since diabetes diagnosis and by drug exposure*

	First year (≤1 year)			Second year (1< ~ ≤2 years)			Beyond second year (>2 years)			Total (entire period)		
	Heart failure events	Person-years at risk	Incidence rates	Heart failure events	Person-years at risk	Incidence rates	Heart failure events	Person-years at risk	Incidence rates	Heart failure events	Person-years at risk	Incidence rates
Drug-free	90	13,221.5	6.8	120	8,153	14.7	400	11,636.9	34.4	610	33,011.4	18.5
Insulin monotherapy	2	140.6	14.2	2	264.3	7.6	18	1,155.3	15.6	22	1,560.2	14.1
SU monotherapy	188	5,749	32.7	99	4,834.9	20.5	244	9,388.4	26.0	531	1,9972.3	26.6
Metformin monotherapy	38	1,843.1	20.6	27	1,693.5	15.9	65	3,379.1	19.2	130	6,915.7	18.8
Other OHA monotherapy	4	63.1	63.4	0	54.7	0.0	0	93.2	0.0	4	211	19.0
Insulin combination therapy	1	27.9	35.8	0	33.7	0.0	4	144.2	27.7	5	205.8	24.3
OHA combination therapy	11	697.9	15.8	19	1,018.8	18.6	75	3,894.1	19.3	105	5,610.8	18.7
Triple combination therapy (with or without insulin)	0	17.1	0.0	0	37.2	0.0	2	245.8	8.1	2	300.1	6.7
Total	334	21,760.2	15.3	267	16,090.1	16.6	808	29,937	27.0	1409	67,787.3	20.8

was observed when any drug use was examined at a per-patient level. For example, our results showed a positive association between any drug use and heart failure risk especially during the first year after type 2 diabetes diagnosis (Table 3). However, when we assessed the effect of ever using any drug at any time (n = 14,821) versus never using any drug (drug-free the whole period, n = 10,869) by per-patient analysis, the HR of any drug use was 0.87 (95% CI 0.78–0.96), adjusted for age, smoking, histories of myocardial infarction, valvular disease, angina pectoris, coronary interventional procedure, and atherosclerotic vascular disease at the time of type 2 diabetes diagnosis.

CONCLUSIONS — The types and courses of treatment we found in this primary care setting were consistent with the typical type 2 diabetes management pattern starting with diet and exercise, followed by oral monotherapy, and then combination or insulin therapy.

Overall, type 2 diabetic women showed a lower heart failure incidence rate than men in all age-groups, which has also been described for the general population in GPRD (13). The overall heart failure incidence among type 2 diabetic patients (20.8 per 1,000 per year) was lower than that of type 2 diabetic patients in the hospital discharge data from Kaiser Permanente Northwest (30.33 per 1,000 per year) (3) but higher than that of diabetic patients in the Framingham Study (7.6 in men and 11.4 in women per 1,000 per year) (15) and that of the general population in GPRD (4.2 per 1,000 per year) (13). As our study population consisted of outpatients with newly diagnosed type 2 diabetes, our estimates were expected to be lower than Kaiser estimates.

We performed analyses for drug intervals to account for drug switch and the timing of drug exposure in order to allow the drug-free period to be a control group. We found no evidence indicating that type-specific drug exposures explain the subsequent risk of heart failure beyond knowing the status of any drug use. Although insulin is typically reserved for patients with severe, refractory, and long-standing type 2 diabetes, we did not observe an increased risk of heart failure for patients while receiving insulin.

We observed discrepancies between the results from the interval-wise (piece-

Table 3—*HRs and 95% CIs of risk indicators of heart failure by time since diabetes diagnosis and by drug exposure (model 2)*

	First year (≤1 year)	Second year (1< ~ ≤2 years)	Beyond second year (>2 years)	Total (entire period)
Any drug use (versus drug-free)*	**4.75 (3.57–6.33)**	1.21 (0.82–1.78)	0.89 (0.70–1.14)	**1.54 (1.31–1.80)**
Men	**1.31 (1.04–1.64)**	0.99 (0.77–1.27)	1.06 (0.92–1.22)	1.10 (0.99–1.23)
Baseline ever smoked (versus never smoked)	0.86 (0.66–1.12)	**1.33 (1.01–1.74)**	**1.45 (1.24–1.70)**	**1.27 (1.12–1.43)**
Baseline hypertension	1.07 (0.85–1.35)	0.98 (0.76–1.27)	0.94 (0.81–1.08)	0.97 (0.87–1.08)
Baseline obesity status	0.82 (0.60–1.11)	0.74 (0.53–1.04)	1.29 (1.09–1.53)	1.06 (0.93–1.22)
Age in 10 years*	**2.07 (1.85–2.31)**	**1.99 (1.75–2.25)**	**2.19 (2.03–2.36)**	**2.12 (2.00–2.24)**
History of myocardial infarction*	**2.96 (2.15–4.09)**	**2.82 (1.98–4.03)**	**2.24 (1.80–2.80)**	**2.51 (2.14–2.96)**
History of valvular disease*	1.56 (0.58–4.20)	**3.63 (1.70–7.74)**	**2.30 (1.41–3.75)**	**2.36 (1.61–3.44)**
History of angina pectoris*	1.28 (0.95–1.72)	**1.48 (1.08–2.03)**	**1.68 (1.39–2.02)**	**1.52 (1.32–1.76)**
History of coronary interventional procedure*	1.57 (0.87–2.84)	1.38 (0.70–2.72)	1.49 (0.95–2.35)	**1.52 (1.10–2.09)**
History of atherosclerotic vascular disease*	**1.82 (1.23–2.71)**	**1.80 (1.15–2.80)**	1.14 (0.82–1.57)	**1.45 (1.16–1.80)**
Interval 2 or higher*	0.90 (0.69–1.17)	1.18 (0.79–1.75)	0.84 (0.65–1.09)	0.96 (0.81–1.14
Interval 3 or higher*	0.63 (0.29–1.36)	1.44 (0.86–2.40)	1.11 (0.84–1.48)	1.14 (0.90–1.44)
Interval 4 or higher*	1.72 (0.44–6.66)	0.33 (0.08–1.43)	1.15 (0.74–1.79)	1.02 (0.69–1.52)
Interval 5 or higher*	3.14 (0.32–30.43)	3.94 (0.55–28.21)	0.84 (0.40–1.74)	1.05 (0.55–2.01)
Duration of diabetes				
0.5–1.0 year (vs. 0–0.5 years)*	1.16 (0.65–2.05)	—	—	—
1.5–2.0 years (vs. 0.1–1.5 years)*	—	1.02 (0.40–2.58)	—	—
2.5–3.0 years (vs. 0.2–2.5 years)*	—	—	0.93 (0.60–1.44)	—
3.0–4.0 years (vs. 0.2–2.5 years)*	—	—	0.92 (0.63–1.34)	—
4.0–5.0 years (vs. 0.2–2.5 years)*	—	—	0.92 (0.57–1.49)	—
5.0–7.0 years (vs. 0.2–2.5 years)*	—	—	0.59 (0.30–1.15)	—
>7 years (vs. 0.2–2.5 years)*	—	—	0.96 (0.24–3.89)	—
>1 year (vs. 0–0.5 years)*	—	—	—	0.86 (0.67–1.11)
>2 years (vs. 0–0.5 years)*	—	—	—	0.89 (0.71–1.12)

Data are HR (95% CI). *Time-dependent variables ascertained at the onset of each interval. Bold: 95% CIs did not include 1.

wise) analyses and from the per-patient analysis. These examples illustrate the complexity of assessing drug effects at the patient level when drug switching is common and support the benefit of accounting for the timing and sequence of treatment received. In a previous study, where duration of type 2 diabetes, follow-up values of HbA_{1c}, and the indicators of atherogenic traits were adjusted in the analyses (3), an odds ratio of 1.66 (95% CI 1.26–2.20) for insulin use on heart failure risk was reported. However, those adjusted variables were not necessarily reascertained at the onset of each drug exposure (i.e., insulin), and the timing of each drug received was not clear, which makes it difficult to attribute the observed risk to insulin.

Confounding by indication (16) is a major concern when studying the effects of medications using nonexperimental designs (17,18). By using interval-wise (piece-wise) analyses, we sought to reduce confounding by indication by considering multiple drug exposures within an individual, i.e., accounting for the timing of each exposure and reascertaining the risk factors for heart failure at the onset of each drug exposure, thus reflecting some of the prognostic characteristics associated with a given therapeutic choice.

Potential limitations of the present study are as follows. The relatively short duration of average follow-up and the shorter duration of the drug exposure intervals may have limited our ability to detect important drug effects. However, our mean drug exposure interval exceeds 120 days (Table 1), and it seems likely that most heart failure diagnoses can be made in this time frame. We relied on physician-diagnosed heart failure for our case ascertainment. It has been suggested that the lack of agreement on a definition of heart failure and the lack of a gold standard to confirm the diagnosis have both resulted in considerable heterogeneity in the diagnosis of heart failure in clinical trials (19) and epidemiological studies (1). However, we do not think that this limitation greatly influenced our results since we observed the heart failure incidence rates that were consistent with previous studies, and known risk indicators for heart failure were found to be of importance in our analyses as well. Furthermore, we had limited information on some factors of interest. HbA_{1c} (2.5%), blood lipid anomaly (10%), renal insufficiency (0.3%), left ventricular hypertrophy (0.07%), and hypoglycemia (0.007%) appear underregistered in our dataset. Weight and height data, used to compute BMI, were available in 65% of patients. Rosiglitazone and pioglitazone were introduced in the U.S. in 1999 and in the U.K. in 2000 (20). We were unable to study the effects of glitazones because the observation period in our data predated the introduction of glitazones into the European market.

In conclusion, use of any pharmacological therapy for type 2 diabetes appears to be associated with an increased risk of heart failure. This risk does not persist beyond the first year after diagnosis of diabetes and does not appear to differ among the types of drug therapy examined. This observation suggests that the severity of diabetes or the preclinical du-

ration of the diabetes and the need for drug therapy, and not the therapy itself, is an explanation for heart failure in many patients with type 2 diabetes.

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