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ORIGINAL REPORT

Thiazolidinediones and the risk of incident congestive heart failure among patients with type 2 diabetes mellitus

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ABSTRACT

Background Clinical trials suggest that thiazolidinediones (TZDs) may increase the risk of congestive heart failure (CHF). However, their effect on the risk of incident CHF in unselected populations has not been thoroughly investigated.

Methods Using data from the UK's General Practice Research Database, we conducted a case–control study within a population-based cohort of patients with type 2 diabetes. Cases were identified by a clinical diagnosis of incident CHF and were then classified as possible or probable cases using prescription data. A 90-day drug exposure window was used in the primary analysis, which compared patients prescribed TZDs with those with no prescriptions for anti-diabetic medications.

Results We identified 3405 incident cases (2632 probable and 773 possible) of CHF and 32,042 corresponding controls. TZDs were prescribed in 6.4% of cases and 6.3% of controls. Prescription of TZDs was associated with an increased rate of possible or probable CHF (adjusted rate ratio (RR) = 1.24, 95% CI = 1.01, 1.54 and adjusted RR = 1.24, 95% CI = 0.98, 1.58, respectively). Similar results were obtained when using a 180-day exposure window (RR = 1.38, 95% CI = 1.11, 1.72 and RR = 1.44, 95% CI = 1.12, 1.84, respectively).

Conclusions Given the totality of the evidence from this and previous studies, the probability of an increased risk for CHF with these agents remains high. However, any increase in CHF risk associated with TZDs may be lower than previously reported. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS—congestive heart failure; thiazolidinediones; pioglitazone; rosiglitazone; type 2 diabetes mellitus

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INTRODUCTION

Data from recent clinical trials and meta-analyses suggest that thiazolidinediones (TZDs) may increase the risk of congestive heart failure (CHF).[1–6] The limitations of this evidence were discussed in a Science Advisory from the American Heart Association and American College of Cardiology Foundation.[7] In this Advisory, the authors questioned the purported TZD–CHF association given the apparently contradictory relationship between this association and the effects of TZDs on other cardiovascular outcomes, including no evidence of an association with cardiovascular death[8] and evidence that suggests that they do not impact left ventricular function among patients with diabetes and New York Heart Association class I–II CHF.[9] This seemingly contradictory evidence begs further investigation. In addition, patients seen in routine practice typically have more comorbidities, possibly enhancing the effect of TZDs on the risk of incident, clinically diagnosed CHF. We therefore examined the effect of TZDs on the risk of incident CHF using a case–control study nested within a large, representative, population-based cohort.

METHODS

Data source

The General Practice Research Database (GPRD) is a clinical database that has been used extensively in pharmacoepidemiologic studies, serving as the data source for over 600 peer-reviewed publications,[10] including several studies of type 2 diabetes[11–13] and CHF.[14–16] The GPRD links medical records from over

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400 general practices in the UK, forming a demographically representative sample of 5% of the UK population[17] and containing over 39 million person-years of follow-up data.[18] The GPRD contains detailed information regarding demographic characteristics, clinical diagnoses, and prescriptions issued. In addition, unlike most administrative databases, GPRD data include clinical information such as body mass index (BMI), smoking status, and laboratory test results. The availability of hemoglobin A1c (HbA1c), which serves as a primary parameter of most diabetes treatment guidelines,[19] makes the GPRD particularly well suited for studies of patients with type 2 diabetes. A number of quality assurance protocols have also been implemented in the GPRD, ensuring that these data are valid.[20] Previous studies have examined the validity of diabetes diagnoses. For example, Pringle and colleagues analyzed the GPRD records of four GPRD practices.[21] The investigators found that a diagnosis of type 2 diabetes had a sensitivity of 97% and a specificity of 100%. In addition, the same investigators compared the electronic records with the physical patient charts and found that 82% of all diagnoses and 100% of all prescriptions were captured in the computer records.

Study population

We created a cohort of patients with type 2 diabetes and no previous diagnosis of CHF. The presence of type 2 diabetes was defined as the presence of any of the following three criteria in the patient's electronic medical record: (1) a National Health Service Clinical Term[22,23] or Oxford Medical Information System (OXMIS) code indicating a clinical diagnosis of type 2 diabetes[17]; (2) an HbA1c test result $\geq$7%; or (3) $\geq$2 prescriptions for an anti-diabetic medication. Cohort entry was defined as the latest of the following: the date at which the patient met our criteria for type 2 diabetes, the date at which the medical practice was considered to be "up to standard" based on GPRD data validity criteria, or the patient's registration date at the GPRD practice. If prescriptions of anti-diabetic medications were used to define cohort entry, we used the date of the second prescription as the date of cohort entry. For patients who met these criteria prior to the year 2000, we used 1 January 2000 as the date of cohort entry. We did not consider person-time prior to this date as neither rosiglitazone nor pioglitazone was available prior to 2000.[24] We restricted our cohort to those who met the criteria for cohort entry before 31 December 2005. We excluded all patients with type 1 diabetes and those diagnosed with diabetes at age <30 years as these had a high probability of being type 1. We also excluded all patients with <1 year of follow-up history in the GPRD before cohort entry and those with a previous clinical diagnosis of CHF. Medications were not used to exclude CHF patients as most CHF treatments are not specific to this condition. Due to concerns regarding data validity, patients who were classified as not "acceptable" according to the GPRD as well as those from practices that were not "up to standard" were excluded. Patients were followed until the date of diagnosis of CHF, the date at which they left the medical practice, the date of the last data upload from the practice to the GPRD, or 31 December 2006, whichever came first. Over 90% of included subjects met all three criteria during their time in the GPRD, suggesting that the number of non-diabetics included was minimal.

Case–control selection

From our cohort of patients with type 2 diabetes, we identified all patients with a first clinical diagnosis of CHF. From these patients, two case series were constructed. In the first, we included all patients with a clinical diagnosis of CHF and refer to these as possible cases. We also used a more restricted probable case definition by limiting our analysis to cases with a clinical diagnosis of CHF and either (a) prescriptions for $\geq$2 of following medication classes in the 90 days after CHF diagnosis: digoxin, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), and other anti-hypertensive agents including diuretics; or (b) who died of any cause in the 90 days following CHF diagnosis. For both case series, eligible controls were matched on calendar date, GPRD practice, and birth year (caliper of 3 years), and up to 10 controls per case were randomly selected from each risk set. Index date was defined as the date of CHF diagnosis for each CHF case and as the corresponding calendar date for matched controls.

Exposure assessment

Diabetic medications were classified as TZDs, insulin, metformin, sulfonylureas, or other. Patients not prescribed one of these classes of medications were categorized as unexposed. In our primary analyses, exposure was defined as any prescription for a given medication within 90 days of the index date. The 90-day exposure window was selected a priori because this was felt to be the etiologically pertinent time window. Previous studies have shown that the risk of myocardial infarction with TZDs is greater when evaluating prescriptions within 90 days than when evaluating those within 180 days.[25] However, data from clinical trials suggest

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that the weight gain associated with TZDs occurs early after treatment initiation. In addition, a recent study suggested that the increased risk may only occur after a few months of exposure.[26] For this reason, we conducted sensitivity analyses with 30- and 180-day exposure windows. Medications were then grouped into the following mutually exclusive exposure categories: TZDs (with or without non-TZD oral anti-diabetics), metformin monotherapy, sulfonylurea monotherapy, other oral monotherapy, non-TZD combination oral therapy, any insulin, and unexposed.

Covariates

Covariate data including demographic (e.g., birth year, sex) and clinical characteristics (e.g., smoking status, BMI) were also extracted from the GPRD. BMI and smoking were extracted from the patient file. We categorized smoking status as current, past, or never smoker. Comorbidities and diabetic complications were defined using National Health Service Clinical Terms and OXMIS codes as any clinical diagnosis or referral occurring any time before the exposure assessment period. Laboratory covariates, including HbA1c and total cholesterol, and systolic and diastolic blood pressure were defined using the mean value of test results from the year preceding the exposure window. Finally, we used the time in years between when a patient met our diabetes definition (including time before 2000) and the beginning of the exposure window as a proxy for duration of diabetes.

Statistical analyses

Our time-matched nested case–control study was analyzed using conditional logistic regression, with the estimated odds ratio approximating the rate ratio (RR). Anti-diabetic medications were assessed as described above with unexposed as the reference category since the CHF effects of other anti-diabetic medications remain poorly delineated. The use of this reference category also facilitates comparison of our analyses with those of clinical trials, where patients are typically randomized to TZD or placebo. Three models were created to examine the effect of TZDs on the risk of CHF for each case series: (1) a "crude" model; (2) an adjusted model that included demographic and clinical characteristics, comorbidities, medication prescriptions, diabetic complications, systolic and diastolic blood pressure, total cholesterol, and duration of diabetes; and (3) a fully adjusted model that also included HbA1c. This final model estimates the effect of TZDs independent of any risks of poorly controlled diabetes, an independent risk factor for CHF.[27] These analyses were then repeated with two indicator variables for pioglitazone or rosiglitazone to examine the effects of the individual TZDs. Subjects with missing lifestyle variables and laboratory covariates were excluded from analyses that adjusted for these variables; there were no missing data for diagnoses or prescription data. In sensitivity analyses, we examined the effect of using 30- and 180-day exposure windows. In addition, we investigated whether a history of myocardial infarction prior to the exposure assessment period modified the effect of TZDs on the risk of CHF as patients with a history of myocardial infarction may be at an increased risk due to existing myocardial damage. We also used metformin as our reference category to facilitate comparison of our results with those from the A Diabetes Outcome Progression Trial (ADOPT) trial[5] and used non-TZD oral combination therapy as our reference group to conduct a more "real-world" comparison.

All analyses were conducted using SAS 9.1.3 (SAS Corporation, Cary, NC).

RESULTS

Our final cohort consisted of 63,462 patients with type 2 diabetes and no previous history of CHF (Figure 1). From this cohort, we identified 3405 possible or probable cases of CHF and 32,042 corresponding controls. The cases included 2632 probable cases. Overall, each case had a mean of 9.4 (SD = 1.8) matched controls (median = 10).

Patient characteristics

In both case series, cases were more likely to be male, had a higher BMI, and had more comorbidities than controls (Table 1). Particularly prominent differences include differences in history of coronary artery disease, myocardial infarction, and stroke. Higher proportions of cases were also prescribed cardiovascular medications within 90 days of the beginning of the exposure assessment window, including ACE inhibitors, aspirin, digoxin, nitrates, and other anti-hypertensive agents including diuretics. Compared with controls, cases had a slightly longer duration of diabetes but had similar mean HbA1c levels. In addition, cases were more likely to have had amputations, nephropathy, neuropathy, and retinopathy.

Differences in anti-diabetic medical therapy within 90 days of the index date were also present (Table 2). A higher proportion of cases were prescribed insulin compared with controls, and a lower proportion of cases were unexposed. The proportions of patients receiving metformin or sulfonylureas were similar between groups. The proportion of patients prescribed

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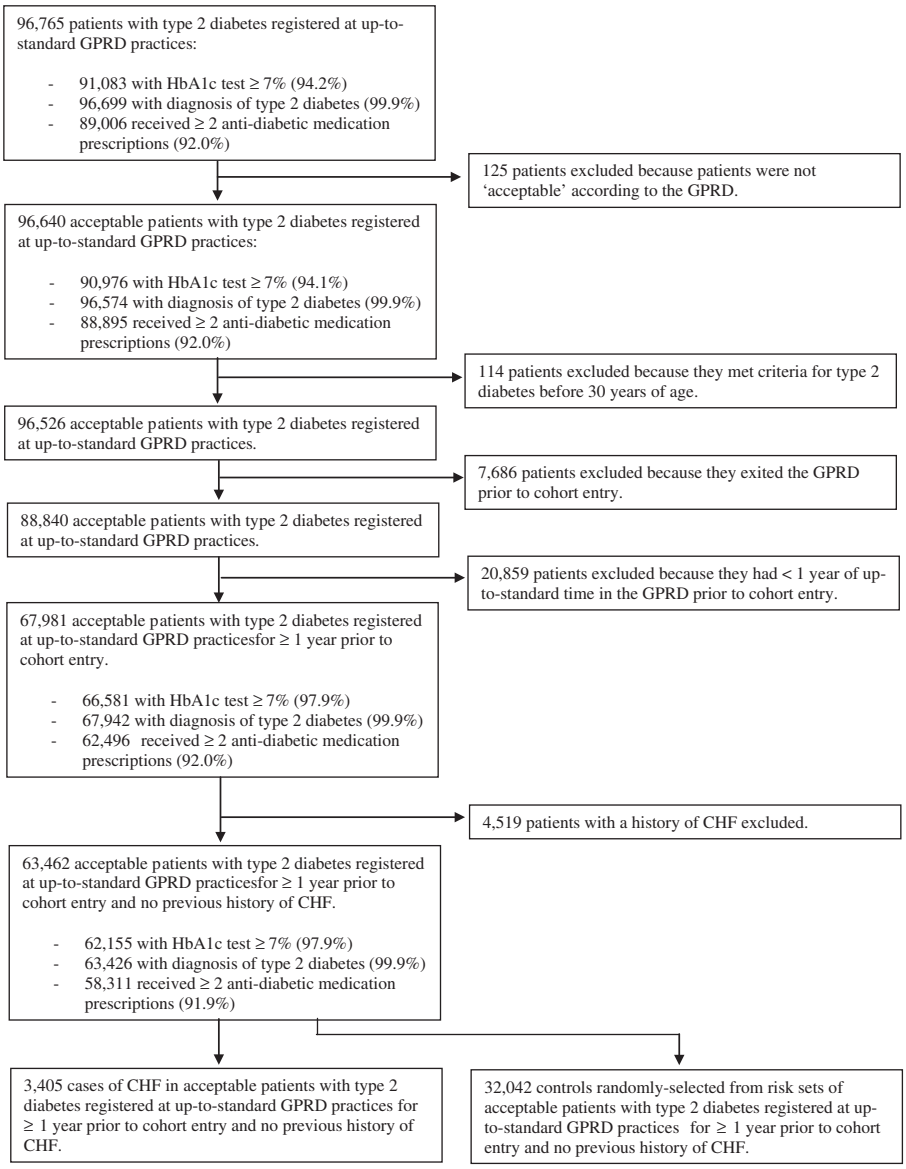

Figure 1. Flow diagram describing construction of nested case–control study database of patients with type 2 diabetes mellitus identified in the General Practice Research Database

TZDs was low in both cases and controls. A total of 14 cases and 102 controls received TZD monotherapy within 90 days of the index date, 13 cases and 63 controls received a TZD and insulin (with or without other oral agents), and 191 cases and 1838 controls received a TZD with another oral agent. Patterns of medical therapy within 30 days of the index date are presented in Online Appendix 1, and those within 180 days are presented in Table 3.

Effect of thiazolidinediones on congestive heart failure

We found an association between TZD prescriptions within 90 days of the index date and an increased rate of incident CHF compared with patients who were unexposed to anti-diabetic medical therapy (adjusted RR = 1.24, 95% CI = 1.01, 1.54) (Table 4). This result was similar in patients prescribed pioglitazone (adjusted RR = 1.29, 95% CI = 0.91, 1.83) and in those prescribed rosiglitazone (adjusted RR = 1.23, 95% CI = 0.97, 1.55), although these estimates are accompanied by wide 95% CIs. Similar results were also obtained when our analyses were restricted to probable CHF cases. In addition, there was no evidence that a history of myocardial infarction modified the effect of TZDs on the rate of CHF (RR for interaction:

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Table 1. Baseline demographic and clinical characteristics of congestive heart failure cases and matched controls*

Characteristic†	Possible and probable case analysis††		Probable case analysis††	
	Cases ($n = 3405$)	Controls ($n = 32,042$)	Cases ($n = 2632$)	Controls ($n = 24,903$)
Demographic				
Male, *n* (%)	1934 (56.8)	16,541 (51.6)	1502 (57.1)	12,827 (51.5)
Age [years] (Mean ± SD)	73.2 ± 9.6	72.3 ± 9.0	73.0 ± 9.5	72.2 ± 9.0
Lifestyle variables				
Body mass index [kg/m^2]				
Mean ± SD	29.8 ± 6.4	28.7 ± 5.6	29.9 ± 6.5	28.7 ± 5.6
Missing, *n* (%)	177 (5.2)	1033 (3.2)	133 (5.0)	768 (3.1)
Smoking, *n* (%)				
Current	391 (11.5)	3660 (11.4)	297 (11.2)	2819 (11.3)
Previous	1445 (42.4)	11,621 (36.2)	1116 (42.4)	9070 (36.4)
Never	1529 (44.9)	16,472 (51.4)	1189 (45.2)	12,793 (51.3)
Missing	40 (1.1)	289 (0.01)	30 (1.1)	221 (0.9)
Comorbidities, *n* (%)				
Atrial fibrillation	518 (15.2)	2043 (6.4)	439 (16.7)	1594 (6.4)
Cerebrovascular disease	748 (22.0)	4626 (14.4)	571 (21.7)	3567 (14.3)
COPD	335 (9.8)	1517 (4.7)	260 (9.9)	1160 (4.7)
Coronary artery disease	1657 (48.7)	8617 (26.9)	1283 (48.8)	6642 (26.7)
Dyslipidemia	909 (26.7)	8286 (25.9)	696 (26.4)	6550 (26.3)
Hypertension	2193 (64.4)	19,517 (60.9)	1764 (67.0)	15,274 (61.3)
Myocardial infarction	709 (20.8)	2934 (9.2)	565 (21.5)	2271 (9.1)
Peripheral vascular disease	364 (10.7)	1733 (5.4)	281 (10.7)	1332 (5.4)
Previous CABG	294 (8.6)	1186 (3.7)	233 (8.9)	914 (3.7)
Previous coronary angiogram	390 (11.5)	1676 (5.2)	308 (11.7)	1323 (5.3)
Previous PCI	139 (4.1)	672 (2.1)	104 (4.0)	535 (2.2)
Renal failure	218 (6.4)	915 (2.9)	140 (5.3)	708 (2.8)
Rheumatoid arthritis	533 (15.7)	4358 (13.6)	395 (15.0)	3364 (13.5)
Stroke	262 (7.7)	1559 (4.9)	203 (7.7)	1197 (4.8)
Unstable angina	194 (5.7)	813 (2.5)	150 (5.7)	627 (2.5)
Diabetic history				
Duration of diabetes [years]				
Mean ± SD	9.6 ± 7.7	8.2 ± 7.3	9.8 ± 7.8	8.2 ± 7.3
Median (IQR)	8.2 (3.7, 13.7)	6.4 (2.8, 11.7)	8.4 (3.8, 14.0)	6.3 (2.8, 11.7)
Complications, *n* (%)				
Amputations	102 (3.0)	355 (1.1)	80 (3.0)	274 (1.1)
Nephropathy	75 (2.2)	370 (1.2)	56 (2.1)	284 (1.1)
Neuropathy	381 (11.2)	2311 (7.2)	294 (11.2)	1770 (7.1)
Retinopathy	755 (22.2)	5142 (16.1)	596 (22.6)	4038 (16.2)
Medication use, *n* (%)				
ACE inhibitors	1564 (45.9)	12,209 (38.1)	1348 (51.2)	9614 (38.6)
ARBs	376 (11.0)	3012 (9.4)	326 (12.4)	2421 (9.7)
Aspirin	1637 (48.1)	12,334 (38.5)	1300 (49.4)	9659 (38.8)
Beta-blockers	911 (26.8)	7507 (23.4)	710 (27.0)	5865 (23.6)
Calcium channel blockers	1274 (37.4)	9394 (29.3)	1006 (38.2)	7343 (29.5)
COX-2 inhibitors	83 (2.4)	624 (2.0)	65 (2.5)	487 (2.0)
Digoxin	374 (11.0)	1325 (4.1)	338 (12.8)	1030 (4.1)
Diuretics or other anti-hypertensive agents	1880 (55.2)	11,324 (35.3)	1568 (59.6)	8854 (35.6)
Nitrates	869 (25.5)	3478 (10.9)	706 (26.8)	2697 (10.8)
Non-aspirin antiplatelets	244 (7.2)	1268 (4.0)	194 (7.4)	983 (4.0)
Non-statin lipid therapies	97 (2.9)	769 (2.4)	79 (3.0)	620 (2.5)
Other NSAIDS	425 (12.5)	4000 (12.5)	335 (12.7)	3080 (12.4)
Statins	1483 (43.6)	13,117 (40.9)	1182 (44.9)	10,444 (41.9)
Warfarin	373 (11.0)	1221 (3.8)	312 (11.9)	958 (3.9)
Diabetic medications, *n* (%)				
Insulin	922 (27.1)	5331 (16.6)	757 (28.8)	4169 (16.7)
Metformin	1450 (42.6)	14,351 (44.8)	1175 (44.6)	11,258 (45.2)
Sulfonylureas	1415 (41.6)	13,517 (42.2)	1068 (40.6)	10,490 (42.1)
TZDs	218 (6.4)	2003 (6.3)	180 (6.8)	1596 (6.4)
Pioglitazone	60 (1.8)	516 (1.6)	52 (2.0)	409 (1.6)
Rosiglitazone	159 (4.7)	1495 (4.7)	129 (4.9)	1195 (4.8)
Other oral anti-diabetics	77 (2.3)	689 (2.2)	56 (2.1)	565 (2.3)

(*Continues*)

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Table 1. (Continued)

Characteristic[†]	Possible and probable case analysis[††]		Probable case analysis[††]	
	Cases ($n = 3405$)	Controls ($n = 32,042$)	Cases ($n = 2632$)	Controls ($n = 24,903$)
Laboratory tests				
HbA1c				
Test in previous year, *n* (%)	2789 (81.9)	26,504 (82.7)	2193 (83.3)	20,666 (83.0)
Mean HbA1c [%] (Mean ± SD)	7.9 ± 1.5	7.7 ± 1.4	7.9 ± 1.5	7.7 ± 1.4
HbA1c ≤ 7%, *n* (%)	806 (23.7)	8288 (25.9)	618 (23.5)	6451 (25.9)
7 < HbA1c ≤ 8, *n* (%)	883 (25.9)	8995 (28.1)	688 (26.1)	7056 (28.3)
8 < HbA1c ≤ 9, *n* (%)	554 (16.3)	4811 (15.0)	440 (16.7)	3711 (14.9)
9 < HbA1c ≤ 10, *n* (%)	277 (8.1)	2392 (7.5)	221 (8.4)	1865 (7.5)
HbA1c >10, *n* (%)	269 (7.9)	2018 (6.3)	226 (8.6)	1583 (6.4)
Missing, *n* (%)	616 (18.1)	5538 (17.3)	439 (16.7)	4237 (17.0)
Mean total cholesterol [mmol/L][‡]				
Reading in previous year, *n* (%)	2352 (69.1)	22,722 (70.9)	1861 (70.7)	17,837 (71.6)
Mean ± SD	4.8 ± 1.0	4.9 ± 1.0	4.8 ± 1.0	4.9 ± 1.0
Median (IQR)	4.7 (4.1, 5.5)	4.8 (4.2, 5.6)	4.7 (4.0, 5.4)	4.8 (4.2, 5.6)
Systolic blood pressure				
Reading in previous year, *n* (%)	3036 (89.2)	29,030 (90.6)	2374 (90.2)	22,653 (91.0)
Mean systolic blood pressure [mmHg][‡]				
Mean ± SD	146.0 ± 18.6	146.0 ± 16.6	146.3 ± 18.5	145.9 ± 16.6
Median (IQR)	145.0 (134.0, 157.2)	145.0 (135.0, 156.0)	145.3 (134.5, 157.3)	145.0 (135.0, 156.0)
Diastolic blood pressure				
Reading in previous year, *n* (%)	3034 (89.1)	29,018 (90.6)	2373 (90.2)	22,645 (90.9)
Mean diastolic blood pressure [mmHg][‡]				
Mean ± SD	78.0 ± 9.1	78.7 ± 8.6	78.0 ± 9.2	78.7 ± 8.6
Median (IQR)	78.0 (71.5, 83.5)	79.0 (73.0, 84.0)	78.0 (71.3, 83.5)	79.0 (73.0, 84.0)

ACE, angiotensin converting enzyme; ARBs, angiotensin II receptor blockers; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disorder; COX, cyclooxygenase; HbA1c, hemoglobin A1c; IQR, inter-quartile range; NSAIDs, non-steroidal anti-inflammatory drug; PCI, percutaneous coronary intervention; SD, standard deviation; TZDs, thiazolidinediones.

*Cases and controls were matched for practice, age (±3 years), and calendar date.

[†]Comorbidities and diabetic complications are based on any previous diagnosis in the GPRD prior to the exposure period (i.e., 90 days before the index date). Non-diabetic medication data are for prescriptions within 90 days of the exposure period, anti-diabetic medication data are for prescriptions within 90 days of the index date, and laboratory test data are for the year prior to the exposure assessment period. Age and duration of diabetes were defined at the beginning of the exposure assessment period.

[††]The possible and probable case analysis includes all cases with a clinical diagnosis of congestive heart failure. The probable case analysis was restricted to cases with a clinical diagnosis of congestive heart failure and either (a) prescriptions for ≥2 of following medication classes in the 90 days after CHF diagnosis: digoxin, ACE inhibitors/ARBs, and diuretics or other anti-hypertensive agents; or (b) who died in the 90 days following CHF diagnosis.

[‡]Among those with a test in the previous year.

Table 2. Patterns of diabetic therapy within 90 days of the index date among patients with type 2 diabetes who were diagnosed with congestive heart failure and their matched controls*

Mutually exclusive treatment category, n (%)[†]	Possible and probable case analysis[††]		Probable case analysis[††]	
	Cases ($n = 3405$)	Controls ($n = 32,042$)	Cases ($n = 2632$)	Controls ($n = 24,903$)
TZDs	205 (6.0)	1940 (6.1)	167 (6.3)	1547 (6.2)
Any insulin	922 (27.1)	5331 (16.6)	757 (28.8)	4169 (16.7)
Non-TZD oral combination therapy	660 (19.4)	6500 (20.3)	512 (19.5)	5070 (20.4)
Sulfonylurea monotherapy	585 (17.2)	5648 (17.6)	418 (15.9)	4356 (17.5)
Metformin monotherapy	410 (12.0)	5233 (16.3)	330 (12.5)	4110 (16.5)
Other oral monotherapy	7 (0.2)	78 (0.2)	3 (0.1)	63 (0.3)
Unexposed	616 (18.1)	7312 (22.8)	445 (16.9)	5588 (22.4)

TZDs, thiazolidinediones.

*Cases and controls were matched for practice, age (±3 years), and calendar date.

[†]Anti-diabetic medication data are for prescriptions within 90 days of the index date. The TZD treatment category includes TZD prescriptions with and without prescriptions for non-TZD oral agents.

[††]The possible and probable case analysis includes all cases with a clinical diagnosis of congestive heart failure. The probable case analysis was restricted to cases with a clinical diagnosis of congestive heart failure and either (a) prescriptions for ≥2 of following medication classes in the 90 days after CHF diagnosis: digoxin, ACE inhibitors/ARBs, and diuretics or other anti-hypertensive agents; or (b) who died in the 90 days following CHF diagnosis.

1.20, 95% CI = 0.77, 1.87). Compared with metformin monotherapy, TZD therapy was associated with an increased rate of CHF (RR = 1.24, 95% CI = 1.01, 1.52). Compared with non-TZD oral combination therapy, TZD had a RR of 1.04 (95% CI = 0.85, 1.26).

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Table 3. Patterns of diabetic therapy within 180 days of the index date among patients with type 2 diabetes who were diagnosed with congestive heart failure and their matched controls*

Mutually exclusive treatment category, n (%)†	Possible and probable case analysis††		Probable case analysis††	
	Cases ($n = 3405$)	Controls ($n = 32,042$)	Cases ($n = 2632$)	Controls ($n = 24,903$)
TZDs	219 (6.4)	2038 (6.4)	178 (6.8)	1626 (6.5)
Any insulin	988 (29)	5640 (17.6)	809 (30.7)	4400 (17.7)
Non-TZD oral combination therapy	724 (21.3)	6910 (21.6)	563 (21.4)	5389 (21.6)
Sulfonylurea monotherapy	558 (16.4)	5663 (17.7)	395 (15.0)	4357 (17.5)
Metformin monotherapy	404 (11.9)	5221 (16.3)	325 (12.3)	4096 (16.4)
Other oral monotherapy	5 (0.1)	69 (0.2)	1 (0)	55 (0.2)
Unexposed	507 (14.9)	6501 (20.3)	361 (13.7)	4980 (20)

TZDs, thiazolidinediones.
*Cases and controls were matched for practice, age (±3 years), and calendar date.
†Anti-diabetic medication data are for prescriptions within 180 days of the index date. The TZD treatment category includes TZD prescriptions with and without prescriptions for non-TZD oral agents.
††The possible and probable case analysis includes all cases with a clinical diagnosis of congestive heart failure. The probable case analysis was restricted to cases with a clinical diagnosis of congestive heart failure and either (a) prescriptions for ≥2 of following medication classes in the 90 days after CHF diagnosis: digoxin, ACE inhibitors/ARBs, and diuretics or other anti-hypertensive agents; or (b) who died in the 90 days following CHF diagnosis.

Table 4. Effect of thiazolidinediones within 90 days of the index date on the risk of incident congestive heart failure among patients with type 2 diabetes*

Exposure category	Crude**		Adjusted model A†,‡		Adjusted model B†,‡‡	
	RR	95% CI	RR	95% CI	RR	95% CI
Possible and probable case analysis††						
TZDs	1.36	1.14, 1.61	1.22	0.99, 1.51	1.24	1.01, 1.54
Pioglitazone	1.40	1.03, 1.90	1.26	0.89, 1.79	1.29	0.91, 1.83
Rosiglitazone	1.33	1.10, 1.62	1.21	0.96, 1.52	1.23	0.97, 1.55
Any insulin	2.22	1.98, 2.48	1.52	1.29, 1.79	1.54	1.30, 1.84
Non-TZD oral combination therapy	1.26	1.12, 1.42	1.18	1.01, 1.37	1.20	1.03, 1.40
Sulfonylurea monotherapy	1.22	1.08, 1.38	1.15	0.98, 1.35	1.16	0.99, 1.37
Metformin monotherapy	0.97	0.85, 1.11	1.00	0.84, 1.17	1.01	0.85, 1.19
Other oral monotherapy	1.14	0.52, 2.49	1.06	0.43, 2.59	1.06	0.43, 2.58
Unexposed	1.00	Reference	1.00	Reference	1.00	Reference
Probable case analysis††						
TZDs	1.46	1.20, 1.78	1.24	0.98, 1.56	1.24	0.98, 1.58
Pioglitazone	1.59	1.14, 2.22	1.26	0.86, 1.86	1.28	0.87, 1.89
Rosiglitazone	1.40	1.13, 1.75	1.23	0.96, 1.59	1.23	0.95, 1.60
Any insulin	2.46	2.17, 2.80	1.57	1.30, 1.89	1.56	1.28, 1.90
Non-TZD oral combination therapy	1.33	1.16, 1.52	1.15	0.96, 1.37	1.15	0.96, 1.38
Sulfonylurea monotherapy	1.19	1.03, 1.37	1.09	0.91, 1.32	1.10	0.91, 1.33
Metformin monotherapy	1.06	0.91, 1.23	1.00	0.83, 1.21	1.01	0.84, 1.22
Other oral monotherapy	0.63	0.20, 2.02	0.77	0.22, 2.63	0.76	0.22, 2.60
Unexposed	1.00	Reference	1.00	Reference	1.00	Reference

CI, confidence interval; HbA1c, hemoglobin A1c; RR, rate ratio; TZDs, thiazolidinediones.
*Cases and controls were matched for practice, age (±3 years), and calendar date.
**Two separate crude models were run for each case series. The first included the above exposure categories with TZDs included as a medication class. The second included the above exposure categories with pioglitazone and rosiglitazone.
†Comorbidities and diabetic complications are based on any previous diagnosis in the GPRD prior to the exposure period (i.e., 90 days before the index date). Non-diabetic medication data are for prescriptions within 90 days of the exposure period, anti-diabetic medication data are for prescriptions within 90 days of the index date, and laboratory test data are for the year prior to the exposure assessment period. Age and duration of diabetes were defined at the beginning of the exposure assessment period.
††The possible and probable case analysis includes all cases with a clinical diagnosis of congestive heart failure. The probable case analysis was restricted to cases with a clinical diagnosis of congestive heart failure and either (a) prescriptions for ≥2 of following medication classes in the 90 days after CHF diagnosis: digoxin, ACE inhibitors/ARBs, and diuretics or other anti-hypertensive agents; or (b) who died in the 90 days following CHF diagnosis.
‡Model A: Adjusted for age, sex, smoking, BMI, clinical diagnoses (atrial fibrillation, cerebrovascular disease, chronic obstructive pulmonary disease, coronary artery disease, dyslipidemia, hypertension, peripheral vascular disease, previous cardiac angiogram, previous coronary artery bypass graft surgery, previous myocardial infarction, previous percutaneous coronary intervention, previous stroke, rheumatoid arthritis, renal failure, and unstable angina), medication prescriptions (angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), aspirin, beta-blockers, calcium channel blockers, cyclooxygenase (COX) 2 inhibitors, digoxin, diuretics and other anti-hypertension therapies, nitrates, and statins), mean systolic blood pressure, mean diastolic blood pressure, mean total cholesterol, previous complications of diabetes (blindness, nephropathy, neuropathy, and retinopathy), and duration of diabetes (<5 years, ≥5 years and <10 years, and ≥10 years). Patients with missing smoking, BMI, mean systolic blood pressure, mean diastolic blood pressure, or mean total cholesterol were excluded from this analysis.
‡‡Model B: Adjusted for Model A variables and HbA1c. Patients with missing HbA1c were excluded from this analysis.

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Table 5. Effect of thiazolidinediones within 180 days of the index date on the risk of incident congestive heart failure among patients with type 2 diabetes*

Exposure category	Crude**		Adjusted model A[†,‡]		Adjusted model B[†,‡‡]	
	RR	95% CI	RR	95% CI	RR	95% CI
Possible and probable case analysis[††]:						
TZDs	1.51	1.27, 1.79	1.35	1.09, 1.67	1.38	1.11, 1.72
Pioglitazone	1.48	1.09, 2.00	1.22	0.86, 1.74	1.26	0.88, 1.80
Rosiglitazone	1.49	1.23, 1.80	1.38	1.10, 1.73	1.40	1.11, 1.78
Any insulin	2.44	2.17, 2.74	1.68	1.41, 2.01	1.70	1.41, 2.06
Non-TZD oral combination therapy	1.41	1.25, 1.59	1.30	1.11, 1.53	1.33	1.12, 1.57
Sulfonylurea monotherapy	1.25	1.10, 1.42	1.23	1.03, 1.45	1.24	1.04, 1.48
Metformin monotherapy	1.04	0.91, 1.20	1.03	0.87, 1.23	1.05	0.88, 1.25
Other oral monotherapy	1.00	0.40, 2.49	0.88	0.31, 2.56	0.89	0.31, 2.57
Unexposed	1.00	Reference	1.00	Reference	1.00	Reference
Probable case analysis[††]:						
TZDs	1.65	1.36, 2.01	1.43	1.12, 1.81	1.44	1.12, 1.84
Pioglitazone	1.69	1.21, 2.36	1.27	0.86, 1.90	1.29	0.86, 1.93
Rosiglitazone	1.61	1.29, 1.99	1.47	1.13, 1.90	1.47	1.13, 1.92
Any insulin	2.76	2.41, 3.16	1.77	1.45, 2.17	1.76	1.42, 2.18
Non-TZD oral combination therapy	1.51	1.31, 1.74	1.32	1.10, 1.59	1.33	1.10, 1.61
Sulfonylurea monotherapy	1.23	1.06, 1.43	1.13	0.93, 1.39	1.14	0.93, 1.40
Metformin monotherapy	1.16	0.99, 1.35	1.09	0.89, 1.33	1.09	0.89, 1.34
Other oral monotherapy	0.26	0.04, 1.92	0.32	0.04, 2.45	0.32	0.04, 2.45
Unexposed	1.00	Reference	1.00	Reference	1.00	Reference

CI, confidence interval; HbA1c, hemoglobin A1c; RR, rate ratio; TZDs, thiazolidinediones.

*Cases and controls were matched for practice, age (±3 years), and calendar date.

**Two separate crude models were run for each case series. The first included the above exposure categories with TZDs included as a medication class. The second included the above exposure categories with pioglitazone and rosiglitazone.

[†]Comorbidities and diabetic complications are based on any previous diagnosis in the GPRD prior to the exposure period (i.e., 90 days before the index date). Non-diabetic medication data are for prescriptions within 90 days of the exposure period, anti-diabetic medication data are for prescriptions within 180 days of the index date, and laboratory test data are for the year prior to the exposure assessment period. Age and duration of diabetes were defined at the beginning of the exposure assessment period.

[††]The possible and probable case analysis includes all cases with a clinical diagnosis of congestive heart failure. The probable case analysis was restricted to cases with a clinical diagnosis of congestive heart failure and either (a) prescriptions for ≥2 of following medication classes in the 90 days after CHF diagnosis: digoxin, ACE inhibitors/ARBs, and diuretics or other anti-hypertensive agents; or (b) who died in the 90 days following CHF diagnosis.

[‡]Model A: Adjusted for age, sex, smoking, BMI, clinical diagnoses (atrial fibrillation, cerebrovascular disease, chronic obstructive pulmonary disease, coronary artery disease, dyslipidemia, hypertension, peripheral vascular disease, previous cardiac angiogram, previous coronary artery bypass graft surgery, previous myocardial infarction, previous percutaneous coronary intervention, previous stroke, rheumatoid arthritis, renal failure, and unstable angina), medication prescriptions (angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), aspirin, beta-blockers, calcium channel blockers, cyclooxygenase (COX) 2 inhibitors, digoxin, diuretics and other anti-hypertension therapies, nitrates, and statins), mean systolic blood pressure, mean diastolic blood pressure, mean total cholesterol, previous complications of diabetes (blindness, nephropathy, neuropathy, and retinopathy), and duration of diabetes (<5 years, ≥5 years and <10 years, and ≥10 years). Patients with missing smoking, BMI, mean systolic blood pressure, mean diastolic blood pressure, or mean total cholesterol were excluded from this analysis.

[‡‡]Model B: Adjusted for Model A variables and HbA1c. Patients with missing HbA1c were excluded from this analysis.

When examining prescriptions within 180 days of the index date, we found an association between TZD prescription and the risk of CHF that was comparable with that obtained in our primary analyses (possible cases: RR = 1.38, 95% CI 1.11, 1.72; probable cases: RR = 1.44, 95% CI = 1.12, 1.84) (Table 5). Similar results were obtained for rosiglitazone and pioglitazone. TZDs had an increased risk compared with metformin monotherapy (RR = 1.32, 95% CI = 1.07, 1.62) but a similar risk compared with non-TZD oral combination therapy (RR = 1.04, 95% CI = 0.86, 1.26).

Sensitivity analyses using a 30-day exposure window (Online Appendix 2) did not identify an association between TZDs and the rate of CHF (RR = 1.06, 95% CI = 0.86, 1.31).

DISCUSSION

We found that prescription of TZDs within 90 days of the index date was associated with a 24% increased rate of incident CHF. Results for pioglitazone and rosiglitazone appear to be similar; however, a lack of precision in our TZD-specific estimates prevents us from conclusively ruling out no effect or a small but clinically important increase in CHF for the individual TZDs. We also found no modifying role for previous myocardial infarction. Analysis of TZD prescriptions within 180 days of the index date revealed a clear increased risk of incident CHF. Treatment effects were consistent in both our 90- and 180-day analyses, but the latter were accompanied by greater precision due

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to an increased number of exposed cases. We investigated only incident CHF cases, and our results support the FDA's decision to include a "black box" warning for incident CHF for pioglitazone and rosiglitazone.[28,29] This revised labeling also includes warning of CHF exacerbations for these agents, a population and research question not addressed in this study. Although rosiglitazone has been removed from the European market and its availability in the USA has been greatly restricted due to an increased risk of myocardial infarction, pioglitazone remains available and continues to be used. Given the potential effects of CHF on survival and quality of life, the continued post-marketing surveillance of these effects is warranted.

The effect of TZDs on the risk of CHF has been examined in a number of clinical trials and meta-analyses.[1–6] Using patient-level data from 19 trials, Lincoff and colleagues found that pioglitazone was associated with an increased rate of CHF compared with active or placebo control (hazard ratio (HR) = 1.41, 95% CI = 1.14, 1.76).[4] Singh and colleagues conducted a meta-analysis of four randomized control trials with at least 12 months of follow-up and found that rosiglitazone was associated with a substantial increase in the risk of CHF compared with placebo or active comparator (relative risk = 2.09, 95% CI = 1.52, 2.88).[3]

The results of the present study are most comparable with those of the ADOPT trial.[5] The ADOPT trial, which used patients randomized to metformin as one of their comparison groups, reported a similar estimate as that reported in the sensitivity analysis of the present study. However, with our much larger sample size, our estimate is accompanied by more precise corresponding confidence limits. We found a smaller association between TZDs and CHF than reported in previous trials.[1,2,6] The differences in results between our study and these previous ones are likely due to differences in study design, method of treatment allocation, study population, study drug, comparison group, outcome definitions, and duration of exposure and follow-up. None of the patients included in our study would have been eligible for DREAM,[2] and only a small proportion of the patients in the present study would have been eligible for PROactive[1] or RECORD.[6] RECORD, for example, was conducted in patients aged 40 to 75 years with type 2 diabetes, a BMI > 25 kg/m^2, and receiving maximally tolerated dosages of metformin or a sulfonylurea. In addition, included patients were required to have a baseline HbA1c between 7.0% and 9.0%. In contrast, the present study was conducted in a sample of patients with type 2 diabetes from the general population. Furthermore, patients who participate in trials are intrinsically different from those found in everyday clinical practice,[30] underscoring the difficulties in extrapolating from clinical trial results to routine clinical decision-making. However, as with any observational study, selection, information, and confounding biases may also be at play. In addition, our 30-day analyses are likely affected by channeling bias and should be interpreted with caution.

The effect of TZDs on the risk of CHF has also been examined in a number of observational studies.[31–36] However, early observational studies[31–33] had methodological limitations, including confounding by indication,[31] the use of inappropriate comparators,[32,33] and inappropriate study designs,[33] whereas more recent studies[34–37] are more informative. Of the recent studies, one involving pioglitazone was inconclusive (HR = 1.28, 95% CI = 0.85, 1.92)[34] whereas two others found an increased risk of hospitalization for CHF.[35,36] However, these studies included patients with prevalent CHF cases, which complicates the interpretation of the risk of TZDs. Nonetheless, our results are consistent with those of previous observational studies.[34–37]

Our study has a number of strengths. First, our study involved a representative population-based sample of subjects with type 2 diabetes in the UK. Consequently, our results are more generalizable than those obtained from randomized controlled trials conducted in highly selected patient populations. In addition, unlike previous observational studies,[35,36] our study involved a broader spectrum of patients and focused on the risk of incident CHF. Second, our population-based sample contained a large number of CHF cases, overcoming a major limitation of most TZD trials to date (>6 times the number of CHF cases than in the largest completed trial).[1] Finally, our study involved data extracted from the GPRD and thus included clinical data such as HbA1c that are typically missing from administrative databases. The availability of HbA1c is particularly important when studying patients with diabetes as the severity of disease is often viewed as a source of important residual confounding. In the present study, adjustment for HbA1c did not affect our treatment estimates. The consistency of these results is reassuring; they demonstrate that the results of the present study are robust and suggest that studies that do not include adjustment for glycemic control may have less residual confounding than originally believed.

Our study also has potential limitations. First, our study is observational in nature and, as mentioned previously, may therefore be affected by biases inherent to this design, including confounding by indication and other unmeasured variables. To minimize the potential effects of confounding, we matched

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on age, practice, and calendar date. We also adjusted for a number of potential confounders, the effects of which are illustrated by the attenuation of treatment effects between crude and adjusted models (particularly among insulin users). In addition, we conducted a number of sensitivity analyses, including analyses with and without adjustment for HbA1c, that produced similar results to those of our primary analyses, suggesting our results are robust. TZDs (both pioglitazone and rosiglitazone) have never been approved for CHF patients,[38] and it is therefore possible that physicians are appropriately prescribing TZDs to patients who are deemed to have a low risk of CHF. Thus, if anything, the potential confounding by indication present in this study may result in an underestimation of the true CHF risk of TZDs, but the observed risk may represent that of subjects prescribed these agents in actual clinical practice.

Our results may be affected by misclassification bias, particularly at the level of outcome assessment. Our probable case definition did not include the use of beta-blockers such as metoprolol as the evidence for their benefit only began to become available during the study period and their uptake in clinical practice, where they were historically seen as contraindicated, was very limited. Furthermore, our probable case definition relied on medication use and outcomes that are not specific to CHF and thus did not completely rule out misclassification. However, our analysis restricted to probable cases of CHF revealed similar results to our more inclusive analysis, suggesting that any outcome misclassification bias is likely minimal. Exposure misclassification may also occur, particularly when medication data are derived from prescriptions issued rather than prescriptions filled.[17] Such exposure misclassification, if present, would likely be non-differential leading to a dilution of effect. Misclassification of exposure can also occur due to patient non-adherence. Misclassification of diabetes status is possible, although >90% of patients met all three criteria during their time in the GPRD, suggesting that the number of non-diabetics included in the present study is minimal. While the exclusion of patients with diabetes would reduce prevalence estimates, it is unlikely to bias the estimated rate ratios for the TZD–CHF relationship.

In addition, there are some possible limitations regarding the timing of covariate assessment. Covariate assessment occurred prior to exposure assessment but, in many cases, occurred after the initiation of anti-diabetic medical therapy. It is also possible that BMI was assessed after the initiation of anti-diabetic therapies, including TZDs.

Finally, there were low rates of prescription of TZDs during much of our study period, which limited our ability to accurately estimate clinically meaningful differences, particularly in TZD-specific analyses. Nonetheless, our study sample was sufficiently large to rule out larger increases in CHF such as those reported elsewhere,[2] and our 180-day analyses produced more precise estimates.

CONCLUSIONS

Our study examined the effect of TZD prescription on the risk of incident CHF among patients with type 2 diabetes in a large, population-based cohort. We found that prescription of TZDs in the last 90 days was associated with a 24% increased rate of CHF in this population. Similar results were obtained when a 180-day exposure window was used. Given the totality of the evidence from this and previous studies, the probability of an increased risk for CHF with TZDs remains high, but any increase in CHF risk associated with their use is likely lower than previously reported.

AUTHORS' CONTRIBUTIONS

K. B. F. and J. M. B. conceived of the study idea, and all authors contributed to the design of the study. K. B. F. conducted the statistical analyses and drafted the manuscript. S. S. contributed to the acquisition of data. All authors were involved in revising the article for important intellectual content, interpreting the data, and approving the final version to be published.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- The effect of thiazolidinediones on the risk of incident congestive heart failure in unselected populations has not been thoroughly investigated.
- We found an association between prescription of thiazolidinediones and a 24% increased rate of congestive heart failure.
- Given the totality of the evidence from this and previous studies, the probability of an increased risk for congestive heart failure with thiazolidinediones remains high. However, any increase in congestive heart failure risk associated with thiazolidinediones may be lower than previously reported.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Online Appendix 1. Patterns of diabetic therapy within 30 days of the index date among patients with type 2 diabetes who were diagnosed with congestive heart failure and their matched controls.

Online Appendix 2. Effect of thiazolidinediones on the risk of incident congestive heart failure among patients with type 2 diabetes with exposure assessed using 30-day exposure window.

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