Treatment of Type 2 Diabetes and Outcomes in Patients With Heart Failure: A Nested Case–Control Study From the U.K. General Practice Research Database

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OBJECTIVE — Diabetes and heart failure commonly coexist, and prior studies have suggested better outcomes with metformin than other antidiabetic agents. We designed this study to determine whether this association reflects a beneficial effect of metformin or a harmful effect of other agents.

RESEARCH DESIGN AND METHODS — We performed a case-control study nested within the U.K. General Practice Research Database cohort in which diagnoses were assigned by each patient's primary care physician. Case subjects were patients 35 years or older, newly diagnosed with both heart failure and diabetes after January 1988, and who died prior to October 2007. Control subjects were matched to case subjects based on age, sex, clinic site, calendar year, and duration of follow-up. Analyses were adjusted for comorbidities, A1C, renal function, and BMI.

RESULTS — The duration of concurrent diabetes and heart failure was 2.8 years (SD 2.6) in our 1,633 case subjects and 1,633 control subjects (mean age 78 years, 53% male). Compared with patients who were not exposed to antidiabetic drugs, the current use of metformin monotherapy (adjusted odds ratio 0.65 [0.48–0.87]) or metformin with or without other agents (0.72 [0.59–0.90]) was associated with lower mortality; however, use of other antidiabetic drugs or insulin was not associated with all-cause mortality. Conversely, the use of ACE inhibitors/angiotensin receptor blockers (0.55 [0.45–0.68]) and β-blockers (0.76 [0.61–0.95]) were associated with reduced mortality.

CONCLUSIONS — Our results confirm the benefits of trial-proven anti-failure therapies in patients with diabetes and support the use of metformin-based strategies to lower glucose.

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Diabetes is a common comorbidity in patients with heart failure, but the choice of treatment for type 2 diabetes in individuals with heart failure remains controversial (1). Patients with heart failure have been generally excluded from the trials of glucose-lowering therapies, and the safety of antidiabetic agents in heart failure patients remains unclear (1). In the absence of randomized trial evidence in patients with both diabetes and heart failure (the only placebo-controlled trial conducted in heart failure was small [$n = 224$] and had insufficient clinical events to draw any firm conclusions) (2), one must rely on observational evidence to judge the safety of antidiabetic drugs in patients with concomitant heart failure.

A number of observational studies have reported prognostic differences between various antidiabetic agents when used in patients with concomitant heart failure (3,4). However, all of these studies involved comparisons between patients taking active drug therapy. Without a "no drug" comparison group it is impossible to definitively say whether the observed inter-drug differences were because one of the drug classes was harmful or whether the comparator was beneficial. Moreover, all of these observational studies lacked data on potential confounders such as glycemic control, weight, and other laboratory parameters known to be prognostic in heart failure, raising the possibility that any reported differences between drug classes were actually due to residual confounding.

The U.K. General Practice Research Database (GPRD) is a well-validated cohort with high-quality information on comorbidities and therapy that is often used for studies of benefits and harms related to prescription drugs (5). It was important for our purposes that the GPRD database also contains laboratory data, and the diagnoses are assigned by clinicians (rather than relying on prescription or administrative claims data to define a patient as having diabetes or heart failure). This permits us to include patients who were not exposed to antidiabetic drugs in our analyses. Therefore, we designed this study to examine outcomes in patients with diabetes and heart failure and to determine whether outcomes were associated with antidiabetic drug therapy.

RESEARCH DESIGN AND METHODS

— We conducted a case-control study nested within the prospective U.K. GPRD cohort, which collects data from over 450 general practitioners in the U.K. The database includes information on patient demographics, physio-

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logical and laboratory data (e.g., blood pressure, BMI, renal function, cholesterol), diagnoses, and out-patient prescription medications. Clinical diagnoses are assigned and/or confirmed by each patient's primary care physician and are recorded using the Oxford Medical Information System classification and Read Clinical Terms. Prescription medications are coded according to the GPRD product code (see the online appendix, available at http://care.diabetesjournals.org/cgi/content/full/dc09-2227/DC1). Cardiovascular medication data were examined for the 90 days prior to index date; clinical comorbidities were coded as present if they were diagnosed at any point between entry into the GPRD and the index date. In order to reduce error in the code selection for each diagnosis, code searches were carried out independently by two researchers and the results subsequently were cross-checked by a third.

We chose a nested case–control design to reduce confounding by indication and to account for time varying changes in patient characteristics and antidiabetic drug exposures. Prior studies have confirmed that the nested case–control design we employed provides unbiased estimates of associations similar to those obtained from traditional cohort time-to-event analyses but with greater efficiency (5,6).

Study sample

Our cohort consisted of all patients older than age 35 with both newly diagnosed type 2 diabetes and newly diagnosed heart failure between January 1988 and October 2007. We excluded patients with a prevalent diagnosis of diabetes or heart failure before 1988 and those with type 1 diabetes, gestational, or drug-induced diabetes. We restricted our cohort to only those patients who had at least 1 year of data prior to their index date. The accuracy of the U.K. GPRD clinical diagnoses of diabetes and heart failure have previously been validated by chart audit (7). All subjects were followed from the date they were diagnosed with diabetes or heart failure until death, termination of their involvement in the GPRD ("transferred out of practice"), or October 31, 2007.

We selected case subjects (patients within the cohort with diabetes and heart failure who had died) and 1:1 matched them to control subjects from our cohort based on age (±5 years), sex, general practice, calendar year, and years of follow-up within the GPRD (Table 1).

To be eligible as a control subject, subjects had to have diabetes and heart failure and be alive on the index date (i.e., the date their matched case died on). We chose all-cause mortality (rather than cardiac or heart failure mortality) as we felt that this would best capture both the safety and the benefits of antidiabetic therapies.

Exposure definitions

For each drug examined, we defined current use as at least one prescription recorded in the 90 days prior to the index date (death for case subjects or analogous date for control subjects). We classified antidiabetic drug exposure into seven mutually exclusive categories: no antidiabetic drug therapy, sulfonylurea monotherapy, metformin monotherapy, thiazolidinedione monotherapy, insulin monotherapy, combination therapy with insulin, and combination oral therapy without insulin.

To evaluate the robustness of our observations, we evaluated "any use" of antidiabetic drugs in a sensitivity analysis (either as monotherapy or in combination with other agents) in the 90 days prior to the index date in our multivariate models. In other sensitivity analyses, we adjusted for duration of diabetes, duration of heart failure, and whether the patient developed diabetes or heart failure first. Finally, we also examined drug use in the 6 months and 12 months prior to the index date.

Statistical analyses

Conditional logistic regression was used to estimate crude and adjusted ORs for the seven drug exposure categories described above. In addition to the matched variables (age, sex, general practice, years of follow-up within the GPRD), we adjusted for numerous potential confounding variables (Table 2). We did not have access to ejection fraction or electrocardiogram data. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC), and statistical significance was accepted at a P value of 0.05. The protocol was approved by the GPRD Independent Scientific Advisory Committee.

RESULTS — Of the 8,404 patients in the U.K. GPRD who were newly diagnosed with both diabetes and heart failure between 1988 and 2007, we were able to match 1,633 patients who died with 1,633 control subjects. The mean time living with both diabetes and heart failure was 2.8 years and was similar in case and control subjects (Table 1). Diabetes was diagnosed first in 54% of case subjects and 41% of control subjects, and the mean time until they were diagnosed with heart failure was 3.9 ± 3.3 and 3.5 ± 2.9 years, respectively. Heart failure was diagnosed first in 44% of case subjects and 58% of control subjects, and the mean time until they were diagnosed with diabetes was 3.1 ± 2.8 and 3.2 ± 2.9 years, respectively. Diabetes and heart failure were diagnosed at the same visit in 2% of case subjects and 1% of control subjects.

Baseline characteristics

The mean age of our study sample was 78 years (SD 8) at the index date, 1,738 were male (53%), and the average time followed within the GPRD was 11 years (SD 4). Case and control subjects were well-matched with respect to age, sex, and time within the GPRD (Table 1). As expected, case subjects (i.e., patients who died) exhibited significantly higher rates of comorbidities and abnormal laboratory values than control subjects, and they were significantly less likely to receive various anti-failure medications (Table 1). In unadjusted analyses, hypotension, elevated serum creatinine, anemia, chronic obstructive pulmonary disease, cancer, dementia, cerebrovascular disease, and prior myocardial infarction were all poor prognostic factors in patients with diabetes and heart failure; on the other hand, elevated BMI was associated with lower mortality risk.

Cardiovascular therapy

Six hundred and four (18%) subjects received both an ACE inhibitor/angiotensin receptor blocker (ARB) and a β-blocker; 271 (12%) of those with atherosclerotic disease (i.e., prior myocardial infarction, revascularization, angina, cerebrovascular, or peripheral vascular disease) received an ACE inhibitor/ARB, a β-blocker, a statin, and aspirin. The use of ACE inhibitors, ARBs, β-blockers, aspirin, digoxin, and statins were all independently associated with reduced mortality risk in patients with concomitant heart disease and diabetes (Table 2).

Diabetes therapy

A substantial minority of patients were not exposed to antidiabetic drugs in the 90 days prior to the index date (n = 1,306

Table 1—*Characteristics of case patients and matched control patients*

	Control subjects (n = 1,633)	Case subjects (n = 1,633)	Crude OR (95% CI)
At time of index date:			
Years in GPRD (mean, SD)	11.2 ± 4.0	11.3 ± 3.9	Matching variable
Time living with both diabetes and HF (mean, SD)	2.9 ± 2.6	2.7 ± 2.6	0.96 (0.93–0.98)
Mean age ± SD	77.8 ± 7.8	78.2 ± 8.0	Matching variable
Male, n (%)	869 (53.2)	869 (53.2)	Matching variable
Lab/physical exam values at the time HF and diabetes concomitant diagnoses made:			
Systolic BP <120 mmHg	184 (11.3)	250 (15.3)	1.43 (1.16–1.75)
BMI ≤25	286 (17.5)	372 (22.8)	reference
25–29.9	554 (33.9)	544 (33.3)	0.76 (0.63–0.93)
≥30	605 (37.1)	460 (28.2)	0.56 (0.46–0.69)
Hemoglobin ≤120 g/l	271 (16.6)	351 (21.5)	1.75 (1.45–2.12)
Serum creatinine, μmol/l			reference
≤132	1,182 (72.4)	1,001 (61.3)	
133–221	248 (15.2)	270 (16.5)	1.30 (1.07–1.58)
≥222	26 (1.6)	48 (2.9)	2.20 (1.35–3.60)
A1C <6	226 (13.8)	247 (15.1)	reference
6–6.9	530 (32.5)	453 (27.7)	0.74 (0.59–0.92)
7–7.9	370 (22.7)	292 (17.9)	0.67 (0.52–0.86)
≥8	320 (19.6)	304 (18.6)	0.84 (0.66–1.08)
Comorbidities:			
Hypertension	929 (56.9)	857 (52.5)	0.82 (0.71–0.95)
Prior myocardial infarct or coronary revascularization	497 (30.4)	625 (38.3)	1.44 (1.23–1.67)
Valvular heart disease	157 (9.6)	189 (11.6)	1.25 (0.99–1.58)
Angina	679 (41.6)	672 (41.2)	0.98 (0.85–1.13)
Atrial fibrillation	588 (36.0)	589 (36.1)	1.00 (0.87–1.16)
Dyslipidemia	332 (20.3)	287 (17.6)	0.80 (0.65–0.97)
Chronic obstructive lung disease	276 (16.9)	366 (22.4)	1.44 (1.20–1.72)
Cerebrovascular disease	381 (23.3)	488 (29.9)	1.43 (1.21–1.67)
Current smoker	185 (11.3)	202 (12.4)	1.11 (0.88–1.40)
Peripheral vascular disease	260 (15.9)	245 (15.0)	0.93 (0.77–1.13)
Cancer	128 (7.8)	259 (15.9)	2.21 (1.76–2.78)
Dementia	45 (2.8)	69 (4.2)	1.57 (1.07–2.31)
Peptic ulcer disease	147 (9.0)	169 (10.4)	1.17 (0.93–1.49)
Medications within 90 days of index date:			
ACE inhibitor	994 (60.9)	778 (47.6)	0.57 (0.49–0.65)
ARB	214 (13.1)	116 (7.1)	0.47 (0.36–0.61)
Aspirin	878 (53.8)	685 (42.0)	0.61 (0.53–0.70)
Digoxin	539 (33.0)	463 (28.4)	0.80 (0.69–0.93)
β-blocker	442 (27.1)	313 (19.2)	0.61 (0.52–0.73)
Statin	760 (46.5)	571 (35.0)	0.47 (0.39–0.56)
Spironolactone	194 (11.9)	263 (16.1)	1.44 (1.17–1.77)

Data are frequency (%) unless otherwise indicated. For lab/physical exam values, data was missing on systolic blood pressure (BP) for 43 patients, BMI for 445 patients, hemoglobin for 906 patients, creatinine for 491 patients, and A1C for 523 patients. HF, heart failure.

[40%]). We presumed these patients were controlled with diet and lifestyle as 1,102 (84%) had not received any antidiabetic drugs in the 12 months preceding their index date (we did not examine medication use more than 12 months prior to the index date). Sulfonylurea monotherapy was the most common antidiabetic drug regimen among case and control subjects (n = 753 [23%]), followed by combination oral therapies without insulin (n = 470 [14%]), and metformin monotherapy (n = 376, [12%]).

All-cause mortality

In unadjusted analyses, when compared with patients not exposed to antidiabetic therapy, current users of sulfonylurea monotherapy, metformin monotherapy, or combination therapy all exhibited lower mortality risk (Table 2). However, only current use of metformin monotherapy was associated with lower mortality risk after adjustment for covariates (Table 2) (adjusted OR 0.65 [0.48–0.87]). The association between current metformin monotherapy and lower mortality was maintained even if duration of diabetes and duration of heart failure were included in the Table 2 multivariate

Table 2—*Use of antidiabetic drugs and risk of mortality*

	Control subjects $n = 1,633$	Case subjects $n = 1,633$	Unadjusted OR (95% CI)	Adjusted OR (95%CI)
Diabetes treatment in the 90 days prior to index date:				
No antidiabetic drugs	573 (35)	733 (45)	Reference category	
Sulphonylurea monotherapy	391 (24)	362 (22)	0.73 (0.61–0.88)	0.84 (0.67–1.06)
Metformin monotherapy	221 (14)	155 (9)	0.54 (0.42–0.68)	0.65 (0.48–0.87)
Thiazolidinedione monotherapy	4 (0.2)	5 (0.3)	0.93 (0.24–3.53)	1.08 (0.23–5.07)
Insulin monotherapy	89 (5)	141 (9)	1.19 (0.88–1.60)	1.24 (0.85–1.80)
Combination therapy with insulin	76 (5)	46 (3)	0.47 (0.32–0.70)	0.72 (0.44–1.17)
Combination oral therapy without insulin	279 (17)	191 (12)	0.52 (0.42–0.65)	0.74 (0.56–0.99)
Any use of diabetic drugs in the 90 days prior to index date (as monotherapy or as part of combination therapy):				
Any sulphonylurea	674 (41)	566 (35)	0.75 (0.65–0.87)	0.90 (0.75–1.08)
Any metformin	529 (32)	349 (21)	0.55 (0.46–0.65)	0.72 (0.59–0.90)
Any thiazolidinedione	59 (4)	40 (2)	0.64 (0.42–0.99)	0.92 (0.54–1.55)
Any insulin	165 (10)	187 (11)	1.16 (0.92–1.45)	1.11 (0.83–1.50)
Covariates included in the multivariate models:				
Age (adjusted OR per year)				1.08 (1.03–1.13)
Systolic BP (adjusted OR for <120 mmHg)				1.89 (1.48–2.40)
Diastolic BP (adjusted OR for ≥90 mmHg)				0.96 (0.71–1.31)
BMI (adjusted OR for ≥30)				0.67 (0.52–0.86)
Hemoglobin (adjusted OR for <120 g/l)				1.76 (1.41–2.19)
Hemoglobin A1C (adjusted OR for ≥8)				1.06 (0.77–1.46)
GFR (adjusted OR for <30 ml $\cdot$ min^{-1} $\cdot$ kg^{-1})				2.04 (1.44–2.88)
Hypertension				1.05 (0.87–1.26)
Prior myocardial infarct or coronary revascularization				1.83 (1.49–2.25)
Valvular heart disease				1.22 (0.91–1.63)
Angina				1.02 (0.84–1.24)
Atrial fibrillation				1.08 (0.87–1.34)
Dyslipidemia				0.95 (0.73–1.22)
Chronic obstructive lung disease				1.17 (0.93–1.48)
Cerebrovascular disease				1.56 (1.27–1.90)
Smoker (current or former)				0.84 (0.69–1.04)
Peripheral vascular disease				1.01 (0.79–1.28)
Cancer				1.94 (1.47–2.55)
Dementia				1.25 (0.77–2.01)
Peptic ulcer disease				1.01 (0.75–1.36)
Medication use within 90 days of index date:				
ACE inhibitor/ARB				0.55 (0.45–0.68)
Aspirin				0.66 (0.55–0.80)
Digoxin				0.74 (0.59–0.93)
β-blocker				0.76 (0.61–0.95)
Statin				0.59 (0.46–0.75)
Spironolactone				1.20 (0.93–1.55)

Data are *n* (%) unless otherwise indicated. BP, blood pressure.

model (0.63 [0.47–0.86]); even if glomerular filtration rate was included in the model as a continuous rather than categorical variable (0.68 [0.49–0.93]); and even if we adjusted for whether or not diabetes was diagnosed first (0.65 [0.48–0.88]). We did not find any association between current use of other antidiabetic therapies (including insulin) and all-cause mortality, although few subjects were current users of thiazolidinedione monotherapy resulting in risk estimates with very wide CIs.

When we examined the outcomes for "any use" of drugs, whether or not they were dispensed in combination or as monotherapy, again only metformin (adjusted OR 0.72 [0.59–0.90], $P = 0.003$) was significantly associated with all-cause mortality. No association was observed for any of the other antidiabetic drug categories ($P > 0.2$ for all comparisons) (Table 2). When we examined longer-term use of metformin monotherapy (i.e., those patients prescribed metformin monotherapy within the last 6 months and the last 12 months before the index date), the number of individuals available for analysis was fewer (since fewer patients were on monotherapy for 6 or 12

months than for 90 days). Thus, while the point estimates of risk were nearly identical (adjusted OR 0.76 for 6 months and 0.80 for 12 months), the 95% CIs were wider (0.56–1.03 for 6 months and 0.59–1.09 for 12 months).

CONCLUSIONS — We have demonstrated that, compared with those individuals not exposed to antidiabetic drugs, metformin use is associated with a lower mortality risk than other antidiabetic therapies even after adjustment for other potential prognostic factors including glycemic control, renal function, BMI, and blood pressure. This is consistent with prior studies demonstrating that in patients with heart failure, metformin users were at lower mortality risk than users of other antidiabetic therapies (3,4). By including heart failure patients with diabetes who were not exposed to antidiabetic drugs (a subgroup previously demonstrated to have better glycemic control and less of a burden of macrovascular complications than those treated with antidiabetic therapy in the U.K.) (8), we have advanced the evidence base as our results suggest that the apparent benefit of metformin over other antidiabetic agents is due to reduced mortality risk with metformin rather than harm with the other agents. While residual confounding by indication is always a possibility in an observational study, at the very least our results suggest that the use of metformin in outpatients with heart failure and diabetes is not harmful.

While the 40% prevalence of patients not exposed to antidiabetic drugs in our study sample may seem high, it is not inconsistent with prior studies of individuals with type 2 diabetes in U.K. general practice. For example, a cross-sectional study of 253,618 patients from 42 U.K. general practices documented that 31% of all patients with type 2 diabetes (median age 59 years) were being treated with diet and lifestyle rather than medications (8). As our study subjects were nearly two decades older and had a condition (heart failure) that has a poor prognosis and usually necessitates treatment with multiple drugs, it is not unreasonable to speculate that clinicians may have been reluctant to contribute further to the polypharmacy in these patients by adding glucose-lowering agents. In addition, some may question the apparent low frequency of concomitant heart failure and diabetes in the U.K. GPRD. However, the 8,404 individuals we identified with both conditions newly diagnosed between 1988 and 2007 is consistent with another recent analysis from the U.K. GPRD that reported 6,900 incident cases of heart failure in U.K. GPRD enrollees with diabetes between 1990 and 2005 (9).

Although the mechanism of action for metformin is not completely understood, it improves insulin sensitivity. This has important implications because insulin resistance is a negative prognostic factor in patients with heart failure and is associated with more advanced symptoms (10,11). Attention is now focusing on insulin resistance as a potential novel target for therapy in patients with heart failure (12,13), and randomized trials are needed to definitively establish whether insulin-sensitizing agents (such as metformin) reduce morbidity and mortality in patients with heart failure and insulin resistance (with or without overt diabetes).

While we did not find a significant association between baseline or follow-up A1C levels and mortality in our study subjects, we did adjust for this marker of glycemic control in our analyses given the conflicting literature on this topic (14–16). While the issue of optimal glycemic targets in all patients with type 2 diabetes (not just those with heart failure) remains a topic of great debate (17), our case-control design does not permit us to analyze this relationship.

Our demonstration of reduced mortality risk in diabetic heart failure patients who are current users of ACE inhibitors and β-blockers confirms that these antifailure agents proven efficacious in trials are effective when deployed in usual clinical practice in diabetic individuals (18,19). Nevertheless, only 18% of our study patients were receiving both an ACE inhibitor/ARB and a β-blocker, and only 12% of those with heart failure, diabetes, and overt atherosclerotic disease were receiving ACE inhibitor/ARB, β-blocker, statin, and aspirin. The underuse of proven efficacious therapies in patients with diabetes is a common theme in health services research and does result in adverse patient outcomes (20).

Although our study was conducted using data collected prospectively within the U.K. GPRD (and thus is free from recall bias), there are some limitations. We relied on physician diagnoses or documentation of heart failure, comorbidities, and risk factors, and we do not have independent confirmation of diagnoses or data on left ventricular ejection fraction. However, previous studies have validated the accuracy of these diagnoses in the GPRD (7). Moreover, the fact that median survival with both diabetes and heart failure in our cohort was only 2.8 years suggests that the patients likely did have heart failure. While there may be a selection bias in the choice of antidiabetic agents (e.g., "lower-risk" patients being selected for metformin treatment), we have adjusted for clinical and medication covariates associated with mortality in our analyses, and we used those diabetic individuals not exposed to antidiabetic drugs (who are presumably the lowest risk group) as the referent category in our multivariate analyses. While duration of diabetes may be associated with current antidiabetic therapy (e.g. metformin being used in patients earlier in their course of diabetes), we did adjust for duration of both diabetes and heart failure in our sensitivity analyses and the associations we reported were preserved. A recent analysis from a single U.S. center with detailed information on ejection fraction, Brain Natriuretic Peptide (BNP), and functional capacity also found that users of metformin exhibited better outcomes than users of other antidiabetic therapies, although there were too few events to achieve statistical significance after adjustment (adjusted HR 0.63, 95% CI 0.21–1.89) (4). Our analysis focused on current drug therapies taken by patients at their index date and although it provides reassurance that there is no short-term adverse effect with starting metformin in patients with heart failure, it does not inform debates about the long-term effects of these therapies or the impact of switching between drug classes. However, our study design removed the potential for immortal time bias to distort our results, ensured that underascertainment of early events related to drug exposures did not occur, and effectively dealt with attrition of susceptibles and other patient–related factors associated with poor adherence to antidiabetic treatment that can impact analyses using longer time frames to define drug exposure. Finally, this is an observational study and, as such, the potential for unmeasured confounders to have impacted our findings is always present.

In conclusion, while metformin has similar or superior effects on glycemic control, fasting lipids, and weight as other antidiabetic agents (21), data on clinical outcomes with the use of different antidiabetic agents are sparse and inconclusive

(22), especially in patients with heart failure. Our findings are consistent with observational studies conducted in the U.S. and Canada demonstrating that heart failure patients using metformin (compared with users of other antidiabetic agents) have better outcomes (3). However, our study extends this evidence base by illustrating that metformin users exhibited lower mortality risk than a group of age- or sex-matched diabetic individuals not exposed to antidiabetic drugs, and this benefit was independent of glycemic control, BMI, and other prognostic factors not available in previous studies. Until randomized trial evidence becomes available, we believe our study and the extant published literature (3) support the use of metformin-based strategies for glucose lowering in patients with diabetes and heart failure.

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