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Failure to Continue Lipid-Lowering Drug Use Following the Withdrawal of Cerivastatin

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Abstract

Background: Persistence with lipid-lowering drug use is important in order for patients to gain full treatment benefit. The withdrawal of cerivastatin from the market may have affected persistence due to the fear of serious adverse effects.

Objective: To assess failure of patients to continue lipid-lowering drug use following the withdrawal of cerivastatin.

Methods: A cohort study including 3.5 months follow-up after the withdrawal of cerivastatin in August 2001 was conducted using data from community pharmacies in The Netherlands, covering a population of approximately 600 000 subjects. Patients selected for inclusion in the index group were current users of cerivastatin on August 10, 2001 (the date that cerivastatin was withdrawn from the market). Reference patients were gender, age and pharmacy or region matched patients who were using any HMG-CoA reductase inhibitor other than cerivastatin on the same date. The main outcome measure was discontinuation of lipid-lowering drug use. To assess whether discontinuation had increased in the reference group, discontinuation rates were compared with discontinuation rates in the previous year. Data on these rates in 2000 were obtained from the population-based PHARMO record linkage system.

Results: A total of 31 pharmacies of the research network (response rate 86.1%) provided medication histories of 234 current users of cerivastatin and 431 matched patients using any other HMG-CoA reductase inhibitor. In addition, 352 current users of cerivastatin and 704 matched patients using any other HMG-CoA reductase inhibitor were obtained from the PHARMO database. Overall, 13.7% of subjects in the cerivastatin group (n = 586) and 9.5% in the reference group (n = 1135) discontinued lipid-lowering medication (adjusted odds ratio [OR] 1.44; 95% CI 1.04–2.00). The rate of discontinuation in the reference group was comparable to this rate in the previous year.

Discontinuation was more prevalent in women who had been taking cerivastatin (adjusted OR 1.74; 95% CI 1.09–2.78), those receiving low doses of cerivastatin (adjusted OR 2.45; 95% CI 1.20–4.97), those who received their last cerivastatin prescription from a specialist (adjusted OR 1.92; 95% CI 1.02–3.60)

and those who had recently started using cerivastatin (adjusted OR 2.80; 95% CI 0.98–7.98), although the latter was not statistically significant.
Conclusions: Failure to continue lipid-lowering drug use was higher in patients using cerivastatin than in users of other HMG-CoA reductase inhibitors, especially in women, those using low doses of HMG-CoA reductase inhibitors and recent starters of lipid-lowering medication. The prevention of unwarranted discontinuation of drugs due to market withdrawal should be a joint task of healthcare providers, industry and regulatory bodies.

Background

In August 2001, the lipid-lowering drug cerivastatin was withdrawn from the market after its use was associated with the deaths of 52 patients, due to rhabdomyolysis, in Europe and the US.[1] Therefore, users of cerivastatin had to switch to an alternative lipid-lowering therapy, which may have led to discontinuation of lipid-lowering therapy.

Low persistence significantly reduces the effectiveness of HMG-CoA reductase inhibitors.[2] A recent study showed that discontinuation of HMG-CoA reductase inhibitors shortly after the onset of coronary syndromes tended to increase cardiac risk,[3,4] which also emphasises the importance of persistence with lipid-lowering drugs.

It has also been shown in other cases that regulatory actions can have a profound effect on use and outcomes of drug therapy. Examples include an increase in the occurrence of thrombotic events after a non-dose equivalent switch from simvastatin to fluvastatin due to a change in reimbursement policy,[5] a shift to the prescribing of recently introduced antihistaminergic drugs and to older, sedating antihistaminergic drugs after a change in reimbursement status,[6] unwarranted discontinuation of drug use after the contraceptive pill 'scare',[7,8] and reports of cases of cardiogenic shock due to drug-drug interactions after the withdrawal of the calcium channel antagonist mibefradil.[9]

The aim of this study was to assess the failure of patients to continue lipid-lowering drug use following the withdrawal of cerivastatin from the market.

Methods

Setting and Study Population

Data were obtained from Dutch community pharmacies. Because the use of cerivastatin in The Netherlands was limited, we used two approaches to obtain data on patients using cerivastatin. A total of 36 community pharmacies, each covering a population of approximately 9000 patients, were directly invited to participate in the study. These pharmacies belong to a research network connected to the Faculty of Pharmaceutical Sciences of the Utrecht University. Pharmacy students or the community pharmacists provided the data according to a strict protocol. In addition, data were obtained from the PHARMO database, a record linkage system containing drug dispensing records from community pharmacies and linked hospital discharge records of approximately 300 000 subjects. This database covers a well-defined population of residents of six medium-sized cities in The Netherlands. Clustering of all pharmacies within each city results in medication histories that contain >95% of all prescriptions dispensed to a particular patient.[10] There is no overlap in pharmacies between the research network and pharmacies included in the PHARMO database. The overall source population therefore consisted of approximately 600 000 subjects.

Medication histories were extracted for all patients who were current users of cerivastatin (index group) on August 10, 2001 (index date). On this date, all physicians and pharmacists received the 'Dear Doctor' letter from Bayer Pharmaceuticals stating that cerivastatin had been withdrawn from the market.[11,12] A patient was classified as a current user of cerivastatin if the last prescription for a lipid-lowering drug (s)he had filled before the index date

was for cerivastatin, and the theoretical end date of this prescription was after July 10, 2001. The theoretical end date equals the dispensing date plus the estimated duration of drug use, the latter being calculated by dividing the number of dispensed tablets by the prescribed daily dose. The 30-day gap between July 10 and August 10 was allowed to correct for irregular dispensing.

For each current user of cerivastatin two gender-, age- (±3 years) and pharmacy- or region- (in PHARMO) matched reference patients were randomly selected. The reference patients had to be current users of an HMG-CoA reductase inhibitor other than cerivastatin at the index date (as defined earlier). Index patients were excluded if no reference patients were available. Complete medication histories were available from January 1, 2001 until November 26, 2001 (last day of the study).

To assess whether failure to continue lipid-lowering drug use had increased in the reference group, we compared discontinuation rates in our reference group with those in a second reference group who were current users of HMG-CoA reductase inhibitors in the previous year. For this analysis, data were extracted for the period August 10, 2000 until November 26, 2000 from the PHARMO database.

Definitions

The main study outcome was failure to continue lipid-lowering drug use in patients using cerivastatin at the index date compared with those using any other HMG-CoA reductase inhibitor, and failure to continue lipid-lowering drug use among users of any other HMG-CoA reductase inhibitor at the index date compared with users of HMG-CoA reductase inhibitors on August 10, 2000. Failure to continue lipid-lowering drug use was defined as not filling a prescription for any lipid-lowering drug (HMG-CoA reductase inhibitor or non-HMG-CoA reductase inhibitor) after the index date and before the end of the study period (November 26, 2001). If a patient did not fill a prescription within this period of 3.5 months then it was assumed that lipid-lowering drug therapy had been discontinued.

Secondary analyses included several subgroup analyses, e.g. for gender and for age. The administration of HMG-CoA reductase inhibitors was used as a marker for disease severity. To compare administration of different HMG-CoA reductase inhibitors we expressed the prescribed daily dose as the number of defined daily doses (DDDs; table I). This unit corresponds to the average daily dose of a drug for its main indication in adults, and is recommended by the WHO for drug utilisation studies.[13]

A history of other lipid-lowering drug use in 2001 before the index date was defined as filling at least one prescription in 2001 for any lipid-lowering drug that was different from the drug used at the index date. This prescription had to be filled before the index prescription was filled. If a patient filled prescriptions for two lipid-lowering drugs from different classes on the same day, this was defined as co-prescribing.

In The Netherlands, the estimated duration for a first prescription dispensed for a newly started drug is 14 days. A patient was defined as a starter if the first prescription in 2001 for a lipid-lowering drug had a legend duration of 14 days and there was no history of other lipid-lowering drugs in this year.

No additional medical information on co-morbidity was available. Therefore, the presence of co-morbidity was derived from pharmacy data. The use of insulin or oral antidiabetic therapy indicated the presence of diabetes mellitus. Cardiovascular drug use included the use of antihypertensive agents (β-blockers, diuretics except loop diuretics, angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers, calcium channel antagonists, α-blockers and other antihypertensive agents such as ketanserin and moxonidine), antiplatelet therapy, anticoagulants, nitrates, loop diuretics and antiarrhythmic drugs.

Data Analysis

A Kaplan-Meier plot was used to show the association between time after the index date and the

Table I. Defined daily doses for HMG-CoA reductase inhibitors

Statin	Defined daily dose (mg)
Atorvastatin	10
Cerivastatin	0.2
Fluvastatin	40
Pravastatin	20
Simvastatin	15

Table II. Patient characteristics at the index date

	Index group: users of cerivastatin (n = 586)	Reference group: users of any other HMG-CoA reductase inhibitor (n = 1135)
Male gender [no. (%)]	326 (55.6)	625 (55.1)
Mean age in years (SD)	61.0 (10.8)	61.2 (10.7)
HMG-CoA reductase inhibitor prescribed [no. (%)]		
Cerivastatin	586 (100)	
Atorvastatin		323 (28.5)
Fluvastatin		69 (6.1)
Pravastatin		199 (17.5)
Simvastatin		544 (47.9)
Prescribing physician [no. (%)]		
General practitioner	372 (63.5)	902 (79.5)
Specialist	182 (31.1)	192 (16.9)
Unknown	32 (5.5)	41 (3.6)
Prescribed daily dose [no. (%)]		
<1.00 DDD	87 (14.8)	232 (20.4)
1.00–1.99 DDD	229 (43.6)	508 (44.8)
≥2.00 DDD	270 (46.1)	395 (34.8)
Co-prescribing of a fibrate [no. (%)]	11 (1.9)	18 (1.6)
Start with HMG-CoA reductase inhibitor in 2001 [no. (%)]	168 (28.7)	81 (7.1)
History of other lipid-lowering drugs in 2001 [n (%)]	58 (9.9)	29 (2.6)
Co-morbid diabetes mellitus [no. (%)]	116 (19.8)	196 (17.3)
Use of any cardiovascular drug (except lipid-lowering drugs) [no. (%)]	432 (73.7)	869 (76.6)

DDD = defined daily dose; **SD** = standard deviation.

filling of a new prescription for lipid-lowering therapy. We calculated odds ratios (ORs) of failure to persist and the 95% CI at the end of the study period. A multivariate logistic regression model was used to adjust for potential confounders. We performed stratified analyses to study failure to continue lipid-lowering drug use in several subgroups.

Results

A total of 31 pharmacies of the research network (response rate 86.1%) provided medication histories for 234 current users of cerivastatin and 431 matched patients who were using any other HMG-CoA reductase inhibitor. In addition, 352 current users of cerivastatin and 704 matched patients using any other HMG-CoA reductase inhibitor were obtained from the PHARMO database. A small majority of patients was male and the mean age was approximately 60 years (table II). In the reference group, simvastatin was the most frequently prescribed HMG-CoA reductase inhibitor (47.9%). Co-prescribing of a fibrate was rare (1.9% and 1.6% in the index and reference groups, respectively). But despite the recently issued contraindication for the combined use of cerivastatin and gemfibrozil, six patients were using this combination. Among the current users of cerivastatin, more patients had recently started lipid-lowering drug use or had a history of other lipid-lowering drugs compared with current users of any other HMG-CoA reductase inhibitor, and prescribed daily doses tended to be higher. The prevalence of diabetes mellitus and the use of cardiovascular co-medication were comparable in both groups.

Figure 1 shows the time to a new prescription for any lipid-lowering drug after the index date. In the reference group, half of the patients had refilled a prescription for a lipid-lowering drug after approximately 45 days, which is half of the estimated duration of a prescription for chronic medication in The Netherlands. In contrast, 50% of the current users of cerivastatin had refilled a prescription for a new lipid-lowering drug within 15 days. Among patients using cerivastatin, 291 (57.5%) filled a new pre-

scription for a lipid-lowering drug before the theoretical end date of the cerivastatin prescription at the index date, compared with 337 patients (32.8%) in the reference group (OR 2.77, 95% CI 2.22–3.45). Although the 'Dear Doctor' letter stated that patients could take the remaining tablets of cerivastatin, many patients chose to almost immediately fill a new prescription for another lipid-lowering drug.

Overall, 80 patients (13.7%) in the cerivastatin group and 108 patients (9.5%) in the reference group failed to continue lipid-lowering medication. In the PHARMO database, we identified 10 477 current users of any HMG-CoA reductase inhibitor on August 10, 2000. Of these patients, 925 (8.8%) discontinued lipid-lowering medication. Compared with this reference group, the current users of any HMG-CoA reductase inhibitor except cerivastatin in 2001 had a similar rate of failure to continue lipid-lowering therapy (OR 1.08, 95% CI 0.88–1.34). Thus, the withdrawal of cerivastatin from the market did not lead to an excess discontinuation of lipid-lowering drugs among users of any other HMG-CoA reductase inhibitor.

The adjusted risk of discontinuation among users of cerivastatin compared with users of any other HMG-CoA reductase inhibitor was 1.44 (95% CI 1.04–2.00; table III). Among men, discontinuation rates were similar in users of cerivastatin and users of any other HMG-CoA reductase inhibitor (adjusted OR 1.20; 95% CI 0.76–1.91). In women, however, discontinuation rates were higher in users of cerivastatin (adjusted OR 1.74; 95% CI 1.09–2.78).

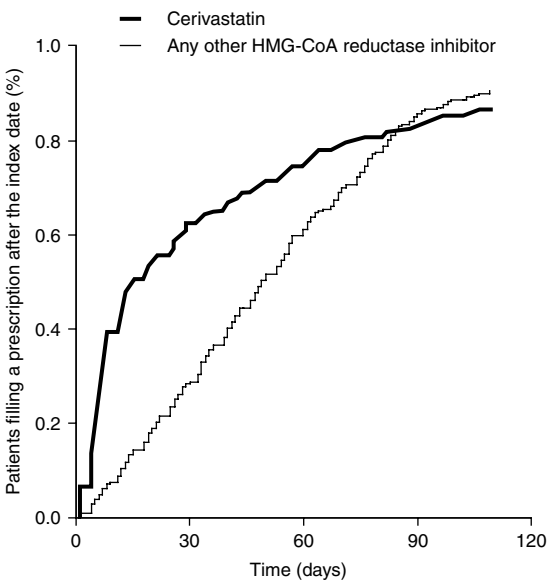

Fig. 1. Time to new prescription after the index date.

Failure to continue lipid-lowering drug use in users of cerivastatin compared with users of any other HMG-CoA reductase inhibitor was also more pronounced in those receiving the lowest doses, i.e. <1.00 DDDs/day (adjusted OR 2.45; 95% CI 1.20–4.97), in patients who started lipid-lowering drug use in 2001 (adjusted OR 2.80; 95% CI 0.98–7.98), and if the prescribing physician was a specialist (adjusted OR 1.92; 95% CI 1.02–3.60). A history of other lipid-lowering drug use in 2001 did not influence the discontinuation rate (data not shown). Discontinuation of cerivastatin tended to be higher in younger patients (adjusted OR 1.64; 95% CI 1.02–2.64 for patients <60 years old vs 1.30; 95% CI 1.30; 0.82–2.05 in for patients ≥60) and lower in patients with diabetes mellitus.

Of the 506 patients who used cerivastatin and continued lipid-lowering drug use, 174 (34.4%) switched to atorvastatin, 168 (33.2%) to pravastatin, 136 (26.9%) to simvastatin, 19 (3.8%) to fluvastatin and 9 (1.8%) to non-HMG-CoA reductase inhibitor lipid-lowering drugs. Although simvastatin was the most frequently prescribed drug among the prevalent users in our control group, atorvastatin and pravastatin were the drugs of first choice after switching.

Many patients (n = 208; 41.1%) switched to relatively higher doses (expressed in DDDs), in 172 patients (34.0%) the relative dose did not change, and 126 patients (24.9%) received a relatively lower dose.

Discussion

Failure to continue lipid-lowering drug use was increased in patients who had been using cerivastatin at the time of withdrawal of this lipid-lowering drug. The impact of the withdrawal of cerivastatin, however, did not seem to affect users of any other HMG-CoA reductase inhibitor with regard to discontinuation. Discontinuation of cerivastatin was more prevalent in women, those receiving low doses of HMG-CoA reductase inhibitor therapy, those

Table III. Number (%) of patients discontinuing lipid-lowering medication and risk of discontinuation of lipid-lowering medication in users of cerivastatin compared with users of any other HMG-CoA reductase inhibitor in different strata

	Index group: users of cerivastatin (n = 586)	Reference group: users of any other HMG-CoA reductase inhibitor (n = 1135)	Crude OR (95% CI)	Adjusted OR[a]
Overall	80 (13.6)	108 (9.5)	1.50 (1.10–2.04)	1.44 (1.04–2.00)
Sex				
Men	37 (11.3)	58 (9.3)	1.25 (0.81–1.94)	1.20 (0.76–1.91)
Women	43 (16.5)	50 (9.8)	1.82 (1.18–2.83)	1.74 (1.09–2.78)
Age categories				
<60 years	39 (14.9)	51 (10.1)	1.56 (1.00–2.43)	1.64 (1.02–2.64)
≥60 years	41 (12.6)	57 (9.0)	1.46 (0.95–2.23)	1.30 (0.82–2.05)
Prescribed daily dose				
<1.00 DDD	19 (21.8)	24 (10.3)	2.42 (1.25–4.69)	2.45 (1.20–4.97)
1.00–1.99 DDD	27 (11.8)	46 (9.1)	1.34 (0.81–2.22)	1.28 (0.76–2.14)
≥2.00 DDD	34 (12.6)	38 (9.6)	1.35 (0.83–2.21)	1.45 (0.84–2.51)
Prescribing physician				
General practitioner	44 (11.8)	81 (9.0)	1.36 (0.92–2.00)	1.34 (0.90–2.00)
Specialist	32 (17.6)	21 (10.9)	1.74 (0.96–3.14)	1.92 (1.02–3.60)
Start with HMG-CoA reductase inhibitor				
Before 2001	56 (13.4)	103 (9.8)	1.43 (1.01–2.02)	1.35 (0.95–1.92)
In 2001	24 (14.3)	5 (6.2)	2.53 (0.93–6.90)	2.80 (0.98–7.98)
Co-morbid diabetes mellitus				
No	64 (13.6)	88 (9.4)	1.52 (1.08–2.15)	1.50 (1.04–2.15)
Yes	16 (13.8)	20 (10.2)	1.41 (0.70–2.84)	1.25 (0.59–2.63)
Use of any cardiovascular drug (except lipid-lowering drugs)				
No	23 (14.9)	26 (9.8)	1.62 (0.89–2.95)	1.56 (0.80–3.02)
Yes	57 (13.2)	82 (9.4)	1.46 (1.02–2.09)	1.40 (0.96–2.05)

a Adjusted for all other variables except age and gender.

DDD = defined daily dose; **OR** = odds ratio.

who had recently started using lipid-lowering medication, and those who received their last prescription from a specialist.

This study reflects the impact of the withdrawal of a drug in daily medical practice. To study this impact, we retrieved recent medication dispensing histories from community pharmacies. In The Netherlands, patients usually visit the same pharmacy,[14] and the risk of losing patients during follow-up was therefore minimal. Some of the pharmacists we invited to participate belong to a research network connected to the Faculty of Pharmaceutical Sciences. Pharmaceutical care is usually well developed in these pharmacies, and discontinuation rates of drug use may be relatively low in these pharmacies, possibly affecting the generalisibility of our data to other populations. However, discontinuation rates were similar in the PHARMO database, which is considered representative for the general Dutch population.[10] The 1-year discontinuation rates for HMG-CoA reductase inhibitors reported in literature are higher than those presented in the present study,[15,16] but these rates were measured over a longer period than our observation period of 3.5 months.

In The Netherlands, chronic medication is usually dispensed for 90 days, and we chose a follow-up period long enough to cover this period. Some patients, however, may have filled a prescription for a lipid-lowering drug after the end of our study or may have filled it at a different pharmacy. Hence, discontinuation rates may decline over a longer period or may have been overestimated in the present study, but we expect this to be the same for both users of cerivastatin and users of any other HMG-CoA reductase inhibitor, yielding the same relative risks.

Another limitation of this study is the relatively small number of patients due to the limited use of cerivastatin in The Netherlands.

Previous studies on persistence of lipid-lowering drug use observed that younger patients have the lowest persistence.[16,17] In this study, persistence with lipid-lowering drugs was also lower in younger patients compared with older patients, and the relative risk of discontinuation for users of cerivastatin compared with users of any other HMG-CoA reductase inhibitor tended to be higher in younger patients.

The effect of gender on discontinuation reported in literature is inconsistent. Most studies reported no difference in discontinuation rates between men and women,[16-18] whereas one study reported higher discontinuation rates in women.[15] We observed no difference in users of any other HMG-CoA reductase inhibitor; however, in those patients using cerivastatin women discontinued more frequently. Two other variables related to failure to continue lipid-lowering therapy were low doses of lipid-lowering therapy and the recent start with lipid-lowering medication. These factors have not been studied before.

Over-treatment of hypercholesterolaemia has been reported in daily medical practice,[19] and may also explain discontinuation of lipid-lowering drug treatment in this study. According to the Dutch guidelines on the management of hypercholesterolaemia,[20] which are similar to the joint recommendations of the European Society of Cardiology, the European Atherosclerosis Society and the European Society of Hypertension,[21] women, younger patients and those with lower serum total cholesterol and higher high density lipoprotein cholesterol levels are less frequently eligible for pharmacological treatment of hypercholesterolaemia. The withdrawal of a drug from the market may have been a good opportunity to reassess drug use, and drugs may be more frequently discontinued in those who are less in need for pharmacological treatment. This could be the case in our study since women and those receiving the lowest doses of HMG-CoA reductase inhibitors indeed discontinued cerivastatin more often. To test this hypothesis, however, more information would be needed.

Regulatory actions in general can have a profound effect on use and outcomes of drug therapy. In New Zealand, change of reimbursement status of HMG-CoA reductase inhibitors led to a general switch from the use of simvastatin to fluvastatin.[5] Patients received insufficient doses of this less potent HMG-CoA reductase inhibitor and predictably their serum lipid levels rose subsequently. More importantly, this paralleled a significant increase in the frequency of thrombotic events. Unintended discontinuation of lipid-lowering medication should also be avoided. Patients who discontinue their HMG-CoA reductase inhibitor therapy no longer benefit from the effects of these agents. Data from the West of Scotland Coronary Prevention Study (WOSCOPS) showed that compliance significantly affects the effectiveness of HMG-CoA reductase inhibitors.[2] Recently, the Platelet Receptor Inhibition in Ischemic Syndrome (PRISM) study observed that discontinuation of HMG-CoA reductase inhibitors after the onset of acute coronary symptoms tended to nullify their beneficial effects.[3,4] The risk of death and nonfatal MI even tended to be higher in patients who discontinued HMG-CoA reductase inhibitor therapy compared with patients who did not receive HMG-CoA reductase inhibitors during the entire study period.

In addition to medical care, pharmaceutical care could and should be an important tool to prevent patients from discontinuing medication.[22] In other areas of cardiovascular medicine, pharmaceutical care has led to improved compliance with drug therapy,[23] and even to fewer hospital admissions.[23,24] Another approach is to develop an intervention to guide changing in prescribing. A study on the replacement of short-acting nifedipine with alternative medications following a warning of the US FDA about the safety of short-acting nifedipine showed a beneficial effect of such an intervention.[25] A recent study revealed that patient unawareness of the withdrawal of cerivastatin 2 weeks after the withdrawal was high in a public hospital outpatient pharmacy setting.[26] Over half of the patients using cerivastatin and gemfibrozil concomitantly (19 of 35) had no awareness of the news that there had been a problem with cerivastatin alone or in combination with gemfibrozil. These two studies support our opinion that regulatory actions should be accompanied by a clear guide to action in daily clinical practice.

In conclusion, after the withdrawal of cerivastatin most of the patients who were on cerivastatin therapy switched to other lipid-lowering drugs before they ran out of tablets. However, discontinuation of lipid-lowering drug therapy was higher in these patients than in users of other HMG-CoA reductase inhibitors, especially in women, those using low doses of cerivastatin and those who had recently started cerivastatin medication. Pharmacists and physicians should try to prevent unintended discontinuation of drugs, especially in those who benefit most from the effects of the drugs. To avoid 'adverse effects' of regulatory actions in general, healthcare providers should be supported by a guide to action in daily clinical practice. The prevention of unwarranted discontinuation of drugs due to market withdrawal should be a joint task of healthcare providers, industry and regulatory bodies.

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