Original Article

# Utilization of statins and aspirin among patients with diabetes and hyperlipidemia: Taiwan, 1998−2006[☆]

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## Abstract

*Background*: The proper use of statins and aspirin decrease the risk of coronary heart disease (CHD) among patients with diabetes (DM) and hyperlipidemia. The purpose of this study was to analyze the time trends and determinants of prescribing statins and aspirin among patients with DM and hyperlipidemia in medical practice in Taiwan.
*Methods*: A cohort of 21,667 patients with DM and hyperlipidemia during the period from 1998 to 2006 was identified by using data of ambulatory care claims from Taiwan's National Health Insurance Database. The dataset was categorized into two equal calendar periods: Period 1 (September 1998−June 2002) and Period 2 (July 2002−April 2006). Multivariate logistic regression analyses were used to determine the independent determinants associated with receipt of lipid-lowering agents and aspirin among these patients.
*Results*: There were significant increases in the prescribing of statins (OR 1.78; 95% CI 1.66−1.91) and aspirin (OR 1.47, 95% CI 1.50−1.59) in Period 2 as compared with Period 1. Nevertheless, 30% of patients with coexisting CHD neither received statins nor aspirin. Only 15% to 25% of DM patients with hyperlipidemia and CHD received the combined treatment with aspirin and statin. In multivariate logistic regression, we found that women received aspirin less frequently than men. Old patients (>45 years) with concomitant CHD were more likely to receive statins and aspirin.
*Conclusion*: Despite the increasing trend in the use of statins and aspirin in DM patients with hyperlipidemia in Taiwan, the improvements were at best modest, particularly for secondary prevention. Our data indicate the need for continued efforts to improve the utilization of these drugs in daily practice.
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*Keywords:* aspirin; diabetes; drug utilization; hyperlipidemia; statins

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## 1. Introduction

The burden of coronary heart disease (CHD) in patients with diabetes (DM) is substantial. Patients with DM are associated with a 2- to 4-fold increase in the incidence of CHD and have an elevated risk of premature death compared with people without DM.[1−3] Existing evidence convincingly indicates that DM patients can benefit from treatments of

3-hydroxy-3-methylgluatryl coenzyme A reductase inhibitors (statins) in both primary and secondary prevention of CHD.[4] The role of aspirin therapy in the secondary prevention of cardiovascular events in DM patients is also well established.[5] Furthermore, Hennekens et al.[6] found that there were additive benefits from the combined use of aspirin and a statin in the secondary prevention of CHD, which were not present if either agent were administered alone. Based on this compelling evidence, the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) has strongly recommend the use of statins and aspirin in patients with diabetic dyslipidemia who already have concomitant CHD.[7]

Despite the widespread dissemination of the NCEP ATP III guidelines, it has been suggested that aspirin and statins were underutilized in patients with DM in practice.[8−11] The reasons for statins and aspirin being underutilized in the medical community are unclear. Understanding the time trends and factors associated with the prescription of statins and aspirin among DM patients with hyperlipidemia may help to identify subgroups worth targeting, such that more patients will undergo drug therapies. The objectives of this study were to evaluate the trends and the determinants of prescribing statins and aspirin in patients with DM and hyperlipidemia over a 9-year period from 1998 to 2006 in Taiwan, by using data of ambulatory care claims from Taiwan's National Health Insurance (NHI) program.

## 2. Methods

### 2.1. Study design and data source

Data were obtained from Taiwan's NHI database, which was maintained by the National Health Research Institutes (NHRI) and overseen by the state-run Bureau of NHI for research purposes.[12] The NHI program in Taiwan was started in 1995 and covered 23 million beneficiaries (almost 99.5% of the population) by the end of 2009.[13] The NHI claim datasets provide Taiwan-based information on diseases and prescription details to researchers. With ethical approval from the NHRI, we used data from ambulatory care claims (1998−2006) for the current study. The dataset was a representative sample of the national outpatient insurance claims. The NHRI employed a systemic random sampling method retrieving 1 in 500 records of outpatient visits in the NHI program, together with the related details of medical orders for those patients. The Bureau performed periodic reviews on a random sample of every 50−100 claims in each contracted hospital and clinic for quality assurance, and false diagnostic reports triggered a considerable penalty. The dataset we used in this study included information on patients' age, gender, diagnostic codes, and prescription details over a period of 92 months (September 1998 to April 2006). The dataset was categorized into two equal calendar periods (each spanned 46 months): Period 1 (September 1998−June 2002) and Period 2 (July 2002−April 2006), comparing the trends in drug prescriptions. Each patient's personal identification number was replaced by a dummy number, and the same patient kept the same dummy number in the dataset. All patients had to be older than 20 years to be included in the study. To avoid duplicated information, the data from the same patient were only allowed to be sampled once in the dataset. If a patient was sampled more than one time during the 92-month period, only the outpatient data of the earliest date was counted, and the repeated sample data (about 0.5% of the total information volume) were excluded from the analyses.

The clinical diagnoses of the patients were coded by using the International Classification of Disease, ninth revision (ICD-9-CM) post-1995, and the A code (abridged code) prior to 2000. Patients with concurrent diagnoses of diabetes (ICD-9-CM 250.00−250.99 and A181) and hyperlipidemia (ICD-9-CM 272.0−272.4 and A182 and A189) were included in the analyses. The patients were further subdivided into those with or without CHD (ICD-9-CM 410.0−414.95 and A 270 and A279) in the analyses. Drug prescriptions were coded by using the National Drug Codes in the NHI program.[13] The lipid-lowering drugs included in the study were categorized into statins (including atorvastatin, fluvastain, lovastatin, pravastatin, rosuvastatin, and simvastatin) and fibrates (bezafibrate, clofibrate, etofibrate, fenofibrate, and gemfibrozil). Among the statins, only rosuvastatin has been reimbursed since 2005, the others were all reimbursed before 1998. All fibrates listed in the study were available in Taiwan before 1998. Those patients who had received any dose of aspirin (taken orally) were considered aspirin users in the study.

### 2.2. Statistical analysis

Data are expressed as mean (SD) or $n$ (%). Categorical variables were compared by $\chi^2$ test and continuous variables were compared by one-way analysis of variance or Student $t$ test. Univariate analyses were performed to choose potential markers of medication prescriptions (data not shown). Variables with $p < 0.05$ on univariate analysis, including age ($\geq$65 years, 45−64 years vs. <45 years), gender (men vs. women), periods (Period 2 vs. Period 1), CHD (yes vs. no), and total medication costs per visit ($\leq$US\$ 4 vs. >US\$ 4; US\$ 4 being the median value), were entered into multivariate logistic regression models to identify the independent determinants associated with the prescribing of lipid-lowering agents and aspirin among patients with DM and hyperlipidemia. For all regression analyses, adjusted odds ratios and 95% confidence intervals were reported. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). A $p$ value of < 0.05 was considered statistically significant.

## 3. Results

A study cohort of 21,667 patients with concomitant DM and hyperlipidemia during 1998 to 2006 was identified, and the process of patient selection for analysis was displayed in Fig. 1. The characteristics of these patients are summarized in Table 1. Among study participants, 5.5% of patients in Period 1 and 5.2% in Period 2 had CHD, with men exceeding women in acquiring the disease ($p < 0.01$). The time trends and
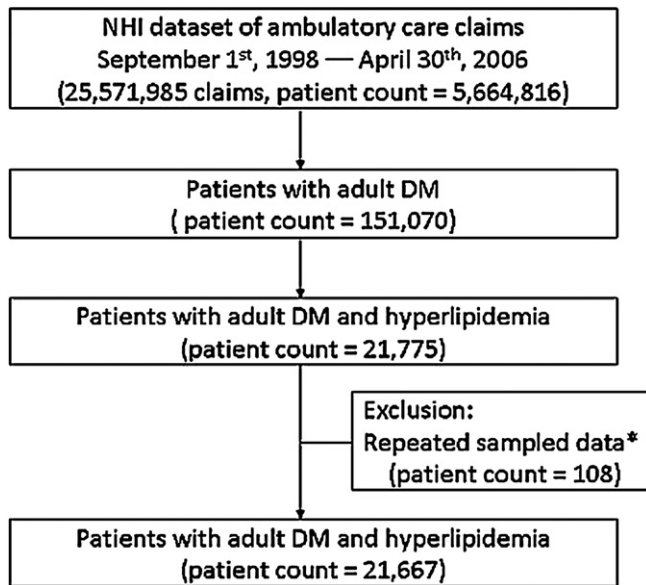
Fig. 1. Study flow diagram of patient selection for the analysis. NHI = National Health Insurance program. *If a patient was sampled more than once during the 92-month study period, only the outpatient data of the earliest date were included, and the repeated sampled data were excluded from the analyses.

differences in prescribing statins, fibrates, and aspirin among the study patients with or without CHD between the two periods are shown in Fig. 2. There were significant increases in prescribed statins and aspirin in Period 2 as compared with that in Period 1 ($p < 0.01$ for all comparisons). Nevertheless, it is noteworthy that 30% of all patients with CHD did not receive a statin or aspirin. The prescribing of fibrates decreased significantly from Period 1 to Period 2, among patients both with and without CHD. The proportions of patients who received both aspirin and a statin during the two study periods are shown in Fig. 3. Only 15% to 25% of DM patients with hyperlipidemia and CHD received combined treatment with aspirin and statin. Moreover, the combined use

Table 1
Characteristics of 21,667 patients with diabetes and hyperlipidemia in Taiwan, 1998−2006.

| Periods | Period 1 ($n = 6202$) (September 1, 1998−June 30, 2002) | | Period 2 ($n = 15,465$) (July 1, 2002−April 30, 2006) | |
|---|---|---|---|---|
| | CHD | CHD | CHD | CHD |
| | (−) | (+) | (−) | (+) |
| Number of patients | 5862 | 340 | 14,659 | 806 |
| Women (%) | 3178 (54%) | 157 (46%) | 7792 (53%) | 358 (44%) |
| Age (y) | 59.2 (11.9) | 62.5 (11.0) | 60.0 (11.8) | 64.0 (10.7) |
| Age groups | | | | |
| 20−44 y | 689 (12%) | 21 (6%) | 1397 (9%) | 30 (4%) |
| 45−64 y | 3086 (53%) | 167 (49%) | 7882 (54%) | 381 (47%) |
| ≥65 y | 2087 (35%) | 152 (45%) | 5380 (37%) | 395 (49%) |
| Total numbers of prescriptions | 35,738 | 2,356 | 93,099 | 5,877 |

Data are expressed as mean (SD) or $n$ (%).
CHD = coronary heart disease.

of statin and aspirin for primary prevention was uncommon in the study cohort, where <10% of patients with DM and hyperlipidemia received both agents.

In the multivariate logistic regression models (Table 2), the percentage of patients with DM and hyperlipidemia who received statins and aspirin increased significantly from Period 1 to Period 2 (all $p < 0.0001$), while the percentage of DM patients who received fibrates decreased by 20% in the latter period. Old patients (>45 years old) with coexisting CHD were more likely to have statins and aspirin prescribed to them. In addition, men had a higher probability of receiving fibrates and aspirin compared to women. Of note, the prescribing of lipid-lowering drugs (both statins and fibrates) was significantly associated with more costly prescriptions. However, the receipt of aspirin was highly associated with lower-cost prescriptions (Table 2).

## 4. Discussion

We found that during the 9-year study period, the prescribing of statins among ambulatory patients with DM and CHD increased from 30% to 40%, and the use of aspirin increased from 40% to 50% (Fig. 2). The magnitude of rise in the use of aspirin and statins was modest, particularly for secondary prevention. For context, however, it is important to understand that underutilization of statins and aspirin in patients with DM in Taiwan was not a country-specific issue.[9−11] For example, Bolka et al[10] estimated the prevalence of regular aspirin use among adults with diagnosed DM in the United States and found that aspirin was used by 37% of those with DM and CHD and by 13% of those with one or more CHD risk factors. Additionally, Berthold et al[11] assessed statin prescription in 51,640 patients with DM in a German registry. They reported that <40% of patients with DM and established atherosclerotic disease received statins for secondary prevention, and only 18% of patients were put on statins for primary prevention. The causes of undertreatment with aspirin and statins among people with DM remain unclear. Multiple reasons may account for the widespread underutilization of these drugs. Exploring the factors associated with aspirin and statin use might help identify patients who will be more or less inclined to receive the medications.

We identified that women with DM and hyperlipidemia received aspirin less frequently than men (Table 2). The decreased aspirin prescription in women could partially be attributed to the gender difference in absolute numbers of patients who needed aspirin for secondary prevention, since men were associated with a higher prevalence of CHD compared with women (Table 1). In addition, the role of aspirin for primary prevention of CHD in women is controversial.[14] Levin suggested that it would appear reasonable to avoid prescribing aspirin as a primary preventive measure for CHD in women unless their global risk for the disease was very high.[15] Apparently, there are many practitioners who subscribe to this recommendation.

On the other hand, we found a significantly lower rate of statins prescribed for men than for women (Table 2). The
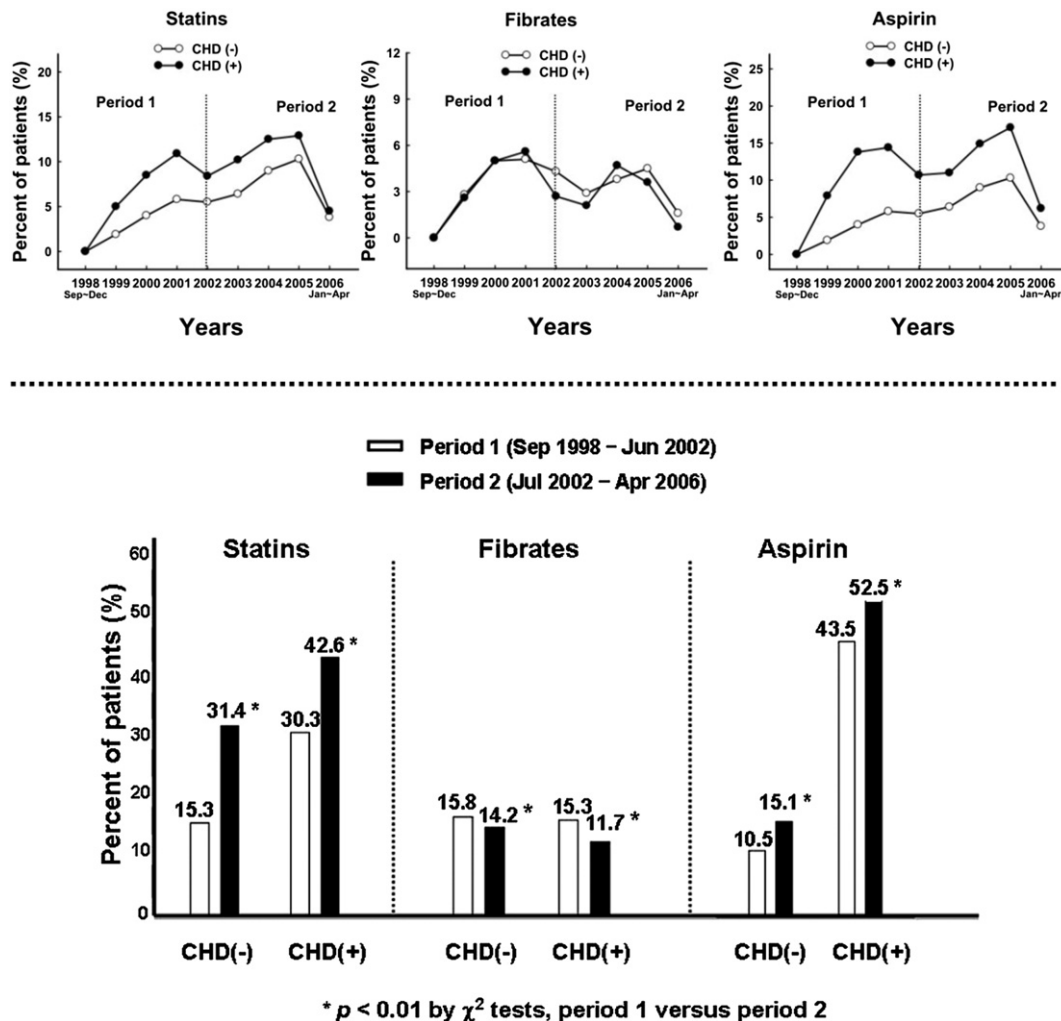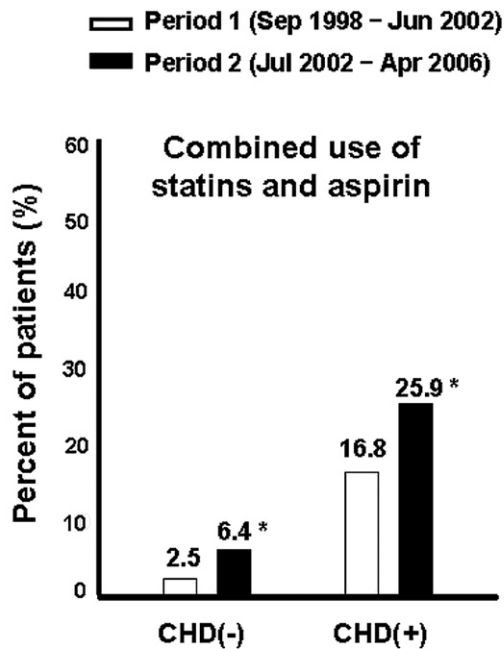
Fig. 2. The temporal changes in the prescribing of statins, fibrates, and aspirin among patients with or without coronary heart disease (CHD) in Taiwan between 1998 and 2006. Upper panel: trends in treatments over time by study years. Lower pannel: Trends in treatments over time by study periods. Period 1: September 1, 1998−June 30, 2002; Period 2: July 1, 2002−April 30, 2006.

mean patient age in our study was around 60 years (Table 1), indicating that many of the women we examined were post-menopausal. In the Framingham Offspring Study, Schaefer et al.[16] demonstrated that women over the age of 50 surpassed men in terms of the percentage of low-density lipoprotein (LDL) cholesterol $\geq 160$ mg/dL. The decrease in plasma estrogen after menopause may play a significant role in the reduction of LDLs clearance and subsequent increase in LDL-cholesterol.[16] Kolovou et al[17] examined lipid profiles in 1385 dyslipidemia patients who did not receive lipid-lowering agents. Their investigation found that hypertriglyceridemia was more prevalent in men than women. Therefore, when lipid profile was checked, men were more likely to receive fibrates and women were more likely to receive statins for their lipid problems, as is seen in the present study.

An analysis made by Hennekens et al[6] revealed that, as compared to statin monotherapy, an add-on aspirin therapy further reduced the relative risk of CHD by 24% for secondary prevention, while statin therapy provided an additional 13% risk reduction as compared to aspirin monotherapy. The

combination of aspirin and statins appears to confer greater clinical benefits than either agent alone in term of secondary prevention of CHD. However, we noticed that only 25% of the patients with DM and CHD received such a treatment (Fig. 3). It seems that this practice is not common in actual clinical settings in Taiwan. Chang et al[18] observed that there was a significant increase in the prevalence of DM in Taiwan over the years, from 5.3% in 1993 to 1996 to 9.1% in 2005 to 2008. Considering the escalating disease burden of DM, we support calls for a wider and more expansive use of aspirin and statins in patients with DM.[19]

Osterberg and Blaschke[20] have described that the health care system may create barriers to medication utilization by limiting access to prohibitively expensive drugs. Chou et al[21] reported that the favorable trends towards higher levels of drug utilization for patients with DM in Taiwan have been slowed after the implementation of the NHI's Global Budget Program in 2002. In that program, the NHI negotiated an individual expenditure cap with hospitals to control the growth of health spending. Initially, we hypothesized that the total expenditure

Fig. 3. The temporal changes in the concomitant prescribing of statins and aspirin among patients with or without coronary heart disease (CHD) in Taiwan between 1998 and 2006. Period 1: September 1, 1998–June 30, 2002; Period 2: July 1, 2002–April 30, 2006.

The strengths of this study include the nationwide representative sample, the large sample size, and the detailed prescription data. Nevertheless, several factors would have biased our results. First, our dataset did not allow us to follow up the same patient, and the nature of the dataset might lead to an overestimation of the use of statins and aspirin, particularly among those "high-risk" patients. If a patient visited the NHI clinics more frequently than others, the individual would have an increased likelihood of being sampled in the study dataset. To minimize this potential problem, we employed a per-patient-per-visit strategy in data analysis. The cross-sectional nature of the data could also result in an underestimate of the frequency of concomitant treatment with aspirin and statin because both drugs might not be prescribed during the same outpatient visit for an individual patient. However, the rates of aspirin use for primary prevention observed in the study were similar to that in the US,[9] and the rates of statin use were close to those reported by other studies.[10,11] It seemed to us that the magnitude of the above-mentioned overestimation or underestimation might not be substantial. Second, the datasets we used did not have the patient lipid profile data. We used "the diagnosis of hyperlipidemia" as a proxy of "high serum levels of lipids" in the study. We acknowledge that coding hyperlipidemia was not an indicator of prescribing lipid-lowering agents in the NHI program. The prescription rates of statins and fibrates might be underestimated accordingly. Nonetheless, the time trends and the prescribing patterns remained valid in the study because the proxy was used consistently throughout the study periods. The use of aspirin could also be underestimated because aspirin can be obtained without a prescription. However, aspirin prescriptions are eligible for reimbursement in Taiwan, the probability of obtaining over-the-counter aspirin was likely to be low in the study. Finally, the diffusion patterns of new drugs on the health care market will certainly exert effects on the uses of these drugs.[22] However, the impact of drug diffusion on aspirin and statin utilizations in DM are beyond the scope of our study. Anyway, the drugs involved in our study, except rosuvastatin, were all available in Taiwan before 1998. Additionally, we did not have

by patients for drugs in one visit might be an important factor causing medication underuse. The prescribing physicians conceivably would not prescribe expensive medications such as statins to the patients already taking other high-cost medications. Our data show that the uses of statins and fibrates were associated with high total costs of drugs. Conversely, the prescriptions of aspirin were associated with low total costs of drugs (Table 2). When these medications were prescribed, it appeared that the total costs of medications were not a major consideration to the prescribing physicians. Overall, the significance of these findings remains uncertain.

Table 2
Variables associated with the prescribing of statins, fibrates, and aspirin among patients with diabetes and hyperlipidemia in Taiwan, 1998–2006.

| | Statins | Fibrates | Aspirin |
|---|---|---|---|
| Period | | | |
| Period 2 vs. Period 1 | 1.80 (1.68–1.93)*** | 0.78 (0.72–0.84)*** | 1.47 (1.35–1.59)*** |
| Age | | | |
| 20–44 y | Reference | Reference | Reference |
| 45–64 y | 1.25 (1.13–1.39)*** | 0.69 (0.62–0.77)*** | 2.00 (1.69–2.37)*** |
| ≥65 y | 1.26 (1.31–1.41)*** | 0.47 (0.42–0.54)*** | 2.43 (2.05–2.88)*** |
| Gender | | | |
| Men vs. women | 0.81 (0.77–0.86)*** | 1.25 (1.16–1.35)*** | 1.19 (1.11–1.28)*** |
| CHD | | | |
| CHD vs. Non-CHD | 1.24 (1.12–1.38)*** | 0.73 (0.61–0.86)** | 3.60 (3.27–3.97)*** |
| Total medication costs per visit | | | |
| ≤US\$ 4 vs. >US\$ 4 | 30.31 (26.34–34.88)*** | 10.26 (9.10–11.58)*** | 0.004 (0.003–0.007)*** |

Data presented are adjusted odds ratios (95% confidence intervals), which were adjusted for all other variables listed in Table 2. **$p < 0.01$; ***$p < 0.0001$.
CHD = coronary heart disease.

information to differentiate the differences in practice patterns among different regions of the country. We did not have the patient admissions records, although the diagnosis of CHD might actually be more accurate using claims of hospitalization. These are limitations of our study.

In conclusion, we found that more than 50% of patients with DM and hyperlipidemia did not receive statin treatments in the current study. Only 15% to 25% of the study patients with concomitant CHD received the combined treatment of aspirin and statin for secondary prevention. We found that men, patients younger than 45, and those without CHD were less likely to receive statin therapy, and women were less likely to receive aspirin. Given the increasingly prevalence of DM in Taiwan, high priority should be given to improving the use of aspirin and statins among patients with DM, especially among those with concomitant CHD.

## Acknowledgments

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