

SPECIAL ARTICLE

Cardiovascular Outcomes after a Change in Prescription Policy for Clopidogrel

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ABSTRACT

BACKGROUND

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Drug-reimbursement policies may have an adverse effect on patient outcomes if they interfere with timely access to efficacious medications for acute medical conditions. Clopidogrel in combination with aspirin is the recommended standard of care for patients receiving coronary stents to prevent thrombosis. We examined the population-level effect of a change by a Canadian provincial government in a pharmacy-benefits program from a prior-authorization policy to a less restrictive, limited-use policy on access to clopidogrel among patients undergoing percutaneous coronary intervention (PCI) with stenting after acute myocardial infarction.

METHODS

We conducted a population-based, retrospective, time-series analysis from April 1, 2000, to March 31, 2005, of all patients 65 years of age or older with acute myocardial infarction who underwent PCI with stenting in Ontario, Canada. The primary outcome was the composite rate of death, recurrent acute myocardial infarction, PCI, and coronary-artery bypass grafting at 1 year, with adjustment for sex and age. The secondary outcome was major bleeding.

RESULTS

The rate of clopidogrel use within 30 days after hospital discharge following myocardial infarction increased from 35% in the prior-authorization period to 88% in the limited-use period. The median time to the first dispensing of a clopidogrel prescription decreased from 9 days in the first period to 0 days in the second period. The 1-year composite cardiovascular outcome significantly decreased from 15% in the prior-authorization group to 11% in the limited-use group ($P=0.02$). Rates of bleeding in the two groups did not change.

CONCLUSIONS

The removal of a prior-authorization program led to improvement in timely access to clopidogrel for coronary stenting and improved cardiovascular outcomes.

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PATIENTS WITH ST-ELEVATION MYOCARDIAL infarction may receive coronary stents as part of acute revascularization with primary percutaneous coronary intervention (PCI), whereas patients with acute coronary syndromes may undergo PCI with stent implantation as part of an early invasive-management strategy.^{1,2} Clopidogrel plus aspirin is recommended to patients receiving either bare-metal stents or drug-eluting stents, given that this dual antiplatelet regimen has been shown to reduce stent thrombosis and, in patients undergoing PCI for non-ST-elevation acute coronary syndromes, to reduce the rate of death from cardiovascular causes, myocardial infarction, or stroke.^{1,3}

Guidelines suggest that all patients should receive clopidogrel before undergoing PCI and continue receiving the drug immediately after the procedure for at least 1 month for bare-metal stents, for 3 months for sirolimus stents, and for 6 months for paclitaxel stents. More recent recommendations are that patients should continue receiving clopidogrel for a minimum of 1 year after the insertion of a drug-eluting stent because of concern about late stent thrombosis.^{1,4}

Just as clinicians may delay their uptake of new evidence, drug policy may also lag behind rapidly evolving clinical evidence. In addition, policymakers need to balance evidence and costs.⁵ Since medication expenditures are one of the fastest-growing costs in the health care system, there is concern that escalating expenses may soon outpace the ability of governments and third-party payers to pay.⁶ Between 1996 and 2001, we found that the costs of cardiovascular medications in Canada nearly doubled.⁷ As such, many medications that are expensive or have benefits limited to specific populations, like clopidogrel, which costs around \$4 (in U.S. dollars) per day, often have restricted reimbursement by payers in order to control unwarranted and excessive use, thereby potentially reducing medication costs to drug insurance programs. The use of a prior-authorization policy, which restricts the use of medications by requiring prior approval from an insurer, has gained popularity in both the United States and Canada as a cost-containment method.⁸

In an attempt to prevent inappropriate use of clopidogrel in Ontario, Canada's largest province, the government payer restricted reimbursement for the drug with a prior-authorization policy in 1998. Although this policy may have been effective

when clopidogrel was used for nonurgent indications such as the secondary prevention of vascular disease, since the appearance of its use in emergency settings, such as PCI for acute myocardial infarction, this policy may have resulted in a barrier to timely use of clopidogrel. The payer changed the clopidogrel policy in September 2003 to one of limited use for certain indications.

Some policies for restricting access to drugs, such as reference-based pricing, have not been clearly demonstrated to adversely affect health outcomes, whereas others, such as those limiting the number of medications for Medicaid patients, have been associated with increased hospitalizations.⁹⁻¹² The effect of a prior-authorization program on clinical outcomes at the population level has received limited scrutiny, particularly for cardiovascular medications. This study evaluated the population-level effect on cardiovascular outcomes of a change from a prior-authorization policy to a limited-use policy for clopidogrel.

METHODS

DESIGN AND DATA SOURCES

We conducted a retrospective, population-based, time-series analysis using linked health care databases in Ontario, Canada. During the period from April 1, 2000, to March 31, 2005, Ontario had a population of about 12.3 million, of whom approximately 1.5 million were 65 years of age or older. This elderly population has universal access to acute hospital care, physicians' services, and prescription medications covered under the Ontario Drug Benefit (ODB) provincial formulary. We examined the ODB computerized prescription records, which contain information on outpatient prescriptions dispensed for all elderly residents of Ontario. Residents may fill prescriptions at any pharmacy within Ontario and have a minimum copayment of \$2 (in Canadian dollars) per prescription or a yearly deductible of \$100, then \$6.11 per prescription for higher-income seniors. Hospitalization records obtained from the discharge abstract database of the Canadian Institute for Health Information (CIHI) include demographic characteristics, coexisting illnesses, in-hospital procedures, and mortality. We obtained vital-status information from the Ontario Registered Persons Database. The registry database of the Cardiac Care Network (CCN) of Ontario, which captures data for patients who are awaiting an invasive cardiac

procedure, was used to identify the placement of coronary stenting during PCI.¹³ Information from these databases was linked together with the use of encrypted identifiers for patients.

The study was approved by the ethics review board of Sunnybrook Health Sciences Centre, Toronto. The study was designed and written by the authors.

IDENTIFICATION OF PATIENTS

We identified all patients who were hospitalized with acute myocardial infarction and were discharged between April 1, 2000, and March 31, 2005, using code 410/I21 of the *International Classification of Diseases, 9th Revision and 10th Revision* (ICD-9 and ICD-10) as the most responsible diagnosis and exclusion criteria that have been described previously.¹⁴ We then determined that these patients had undergone percutaneous transluminal coronary angioplasty using Canadian Classification of Procedures (CCP)/Canadian Classification of Interventions (CCI) codes 4802, 4803, 4809, 1IJ50, and 1IJ57 and had undergone coronary stenting using the codes for stenting from the CCN database or CCI codes 1IJ50GQO and 1IJ57GQO from the CIHI database. Codes that were used in the ICD-9 were revised for the ICD-10, and the CCP was replaced by the CCI as of April 1, 2002, before the change in the policy regarding clopidogrel.

STUDY INTERVENTION

The study intervention was a change in reimbursement policies for clopidogrel, which occurred in September 2003. The government payer restricted its reimbursement from the ODB plan with a prior-authorization policy (starting when clopidogrel first entered the Canadian market in October 1998), which required that physicians submit a letter justifying the need for the use of the drug on a per-patient basis. Reports from the ODB program indicated that in April 2002 through March 2003, about 90% of clopidogrel claims were approved after clinical review in the prior-authorization process. To improve system efficiency, the payer changed the policy from prior authorization to limited use in September 2003. The limited-use policy eased the prior-authorization restriction, allowing for the use of clopidogrel for approved indications according to prespecified prescribing codes, including those for acute coronary syndromes and PCI, which facilitated more timely access to clopidogrel for these indications.

OUTCOMES

We divided the 5-year study period into monthly intervals, for a total of 60 consecutive data points. For each monthly period, we identified the rate of clopidogrel use within 30 days after hospital discharge for patients with acute myocardial infarction receiving stents. The date of the clopidogrel use was defined as the date of the first prescription after discharge following myocardial infarction. The primary outcome was the composite rate of readmission for myocardial infarction, death, repeat PCI, and coronary-artery bypass grafting (CABG) performed within 1 year after discharge, as measured with the use of ICD-9 and ICD-10 and CCP/CCI codes. Two secondary outcomes were rates of death from any cause and major bleeding (defined as bleeding requiring hospitalization) at 1 year.

STATISTICAL ANALYSIS

Descriptive statistics were used to portray the characteristics of the patients during the prior-authorization period and the limited-use period. We used two methods to examine patterns in the prescription rates of clopidogrel within 30 days after discharge following myocardial infarction and in the 1-year rates of the combined cardiovascular outcome with adjustment for age and sex. We first compared data from the prior-authorization period with those from the limited-use period using traditional chi-square analysis. However, given the limitations of this method with time-dependent data, we also conducted an interrupted time-series analysis using interventional autoregressive integrated moving average models with a step function.¹⁵⁻¹⁷

Time-series analysis consisted of several techniques for modeling autocorrelation in temporally sequenced data and is well suited to address secular trends and evaluate interventions.¹⁵⁻¹⁷ We tested for a shift in the rate of the composite outcome in September 2003 by including an indicator variable in the time-series model that took the value 0 before September 2003 and 1 thereafter. The autocorrelation, partial-autocorrelation, and inverse-autocorrelation functions were assessed for model appropriateness and seasonality. Stationarity (in which statistical properties are all constant over time) was assessed with the use of autocorrelation functions and the augmented Dickey-Fuller test.¹⁸ The presence of white noise was evaluated by examining the autocorrelations at various lags with the Ljung-Box chi-square statis-

tic¹⁹ (for further details, see the Supplementary Appendix, available with the full text of this article at www.nejm.org). Subgroup analyses using logistic regression compared the composite outcome according to the policy period for differing baseline characteristics (statin use and stent type) that may influence outcomes with adjustment for age and sex. All P values were two-sided. Data were analyzed with the use of SAS software, version 9.1 (SAS Institute).

RESULTS

PATIENTS

Of 49,340 patients who were hospitalized with a myocardial infarction during the study period, we identified 6161 who received a PCI with coronary stenting during their hospitalization. There were some differences in baseline characteristics between patients in the prior-authorization period and those in the limited-use period. In particular, during the limited-use period, patients had lower rates of aspirin use and higher rates of statin use (Table 1). Overall, within 7 days after discharge following myocardial infarction, 71% of patients were dispensed a statin, 75% a beta-blocker, 73% an angiotensin-converting-enzyme (ACE) inhibitor or angiotensin-receptor blocker, and 31% aspirin within the ODB program. Since aspirin is also available over the counter in Ontario, the true rate of aspirin use was probably significantly higher. Statin use increased from 63% in the prior-authorization period to 80% in the limited-use period ($P<0.001$). Drug-eluting stents comprised approximately 40% of stent use in the cohort beginning in the prior-authorization period.¹³

In the limited-use period, 64% of patients filled a clopidogrel prescription immediately after the time of discharge, as compared with only 11% of patients during the prior-authorization period. The rate of clopidogrel use within 30 days after discharge following myocardial infarction increased from 35% in the prior-authorization period to 88% in the limited-use period ($P<0.001$). Among patients who received clopidogrel within 1 year after discharge, the median time to the first dispensing of clopidogrel after hospital discharge decreased from a median of 9 days in the prior-authorization period to a median of 0 days in the limited-use period. Among patients who received clopidogrel within 30 days after discharge following myocardial infarction, the use of clopidogrel between 9 months and 12 months

increased by 120% between the two study periods. The rate of the 1-year composite cardiovascular outcome decreased significantly, from 15% in the prior-authorization period to 11% in the limited-use period, with the use of the standard chi-square test ($P<0.001$) (Table 2) and time-series analysis ($P=0.02$) (Fig. 1). Secondary analyses showed a nonsignificant reduction in the rate of death, from 5% in the prior-authorization period to 4% in the limited-use period ($P=0.42$). Rates of bleeding requiring hospitalization at 1 year were unchanged between the prior-authorization period and the limited-use period (Fig. 1).

A subgroup analysis conducted with only patients who were prescribed statins within 7 days after discharge following myocardial infarction in both the prior-authorization period and the limited-use period confirmed a significant reduction in the 1-year composite outcome, from 14% to 10%, with the use of chi-square analysis ($P<0.001$). A subgroup analysis conducted with only patients receiving a bare-metal stent in both the prior-authorization period and the limited-use period confirmed a significant reduction in the 1-year composite outcome, from 15% to 11%, with the use of chi-square analysis ($P<0.001$).

DISCUSSION

In this population-based study, we showed that a change from a prior-authorization policy to a limited-use policy for reimbursement for clopidogrel was associated with a substantial increase in prescriptions for clopidogrel filled by survivors of acute myocardial infarction who underwent PCI with stenting. We also showed that the increase in the number of clopidogrel prescriptions corresponded to a decrease in adverse cardiovascular events at 1 year. These findings suggest that a policy change that increased timely access to an acutely required medication may have had a significant influence on prescribing patterns and outcomes for patients. The corollary is that a policy that restricts access to a drug for an urgent indication may unintentionally lead to adverse outcomes for patients.

The likelihood of a true causal association is strengthened by the striking temporal inverse correlation between the increased use of clopidogrel and the decreased event rate, the biologic plausibility around this observation, and its consistency with current evidence about the type of benefits in clinical outcomes that are expected with clopi-

Table 1. Baseline Characteristics of the Patients Undergoing Stenting after Myocardial Infarction.*			
Variable	Prior-Authorization Period (N=3428)	Limited-Use Period (N=2733)	P Value†
Male sex (%)	61	59	0.09
Age			<0.001
Mean (yr)	73.1±5.8	73.7±5.9	
Age group (%)			<0.001
65–75 yr	67	63	
≥76 yr	33	37	
Quintile of income level (%)			0.07
1 (lowest)	20	18	
2	22	20	
3	19	21	
4	19	20	
5 (highest)	20	21	
Coexisting illness (%)			
Congestive heart failure	12	10	0.09
Cerebrovascular disease	2	1	<0.001
Diabetes mellitus	17	13	<0.001
Cancer	1	1	0.84
Renal failure			
Acute	2	2	0.14
Chronic	3	4	0.03
Cardiac dysrhythmia	13	9	<0.001
Hypertension	33	28	<0.001
Chronic obstructive pulmonary disease	6	5	0.09
Clopidogrel use			
Time to first use (days)‡			<0.001
Mean	37	6	
Median	9	0	
Interquartile range	1–39	0–1	
Use at discharge (%)	11	64	<0.001
Use within 30 days after discharge (%)	35	88	<0.001
Use at 9 to 12 mo after discharge (%)§	32	71	<0.001
Use within 90 days after discharge (%)	40	91	<0.001
Medication use within 7 days after discharge (%)			
ACE inhibitor	68	70	0.13
Angiotensin-receptor blocker	3	5	<0.001
Aspirin	40	20	<0.001
Beta-blocker	75	76	0.40
Statin	63	80	<0.001

* Plus–minus values are means ±SD. The policy regarding prescriptions for clopidogrel was changed from prior authorization to limited use for certain indications in September 2003. ACE denotes angiotensin-converting enzyme.

† P values are for the comparison between the prior-authorization policy and the limited-use policy.

‡ Values are for patients for whom clopidogrel was prescribed within 1 year after hospital discharge following acute myocardial infarction.

§ Values are for patients for whom clopidogrel was prescribed within 30 days after hospital discharge following acute myocardial infarction.

Table 2. Cardiovascular Outcomes before and after a Change in the Prior-Authorization Policy.*

Outcome	Prior-Authorization Period (N=3428)	Limited-Use Period (N=2733)	P Value†
	<i>percent</i>		
Readmission for acute myocardial infarction after hospital discharge			
Within 30 days	1	1	0.38
Within 365 days	5	3	<0.001
Death after hospital discharge			
Within 30 days	1	1	0.74
Within 365 days	5	4	0.42
PCI after hospital discharge			
Within 30 days	1	1	0.90
Within 365 days	7	5	<0.001
CABG after hospital discharge			
Within 30 days	0	0	0.75
Within 365 days	2	1	<0.001
Readmission for acute myocardial infarction, death, PCI, or CABG after hospital discharge			
Within 30 days	3	2	0.59
Within 365 days	15	11	<0.001

* The policy regarding prescriptions for clopidogrel was changed from prior authorization to limited use for certain indications in September 2003. CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

† P values are for the comparison between the prior-authorization policy and the limited-use policy and were calculated with the use of the chi-square statistic.

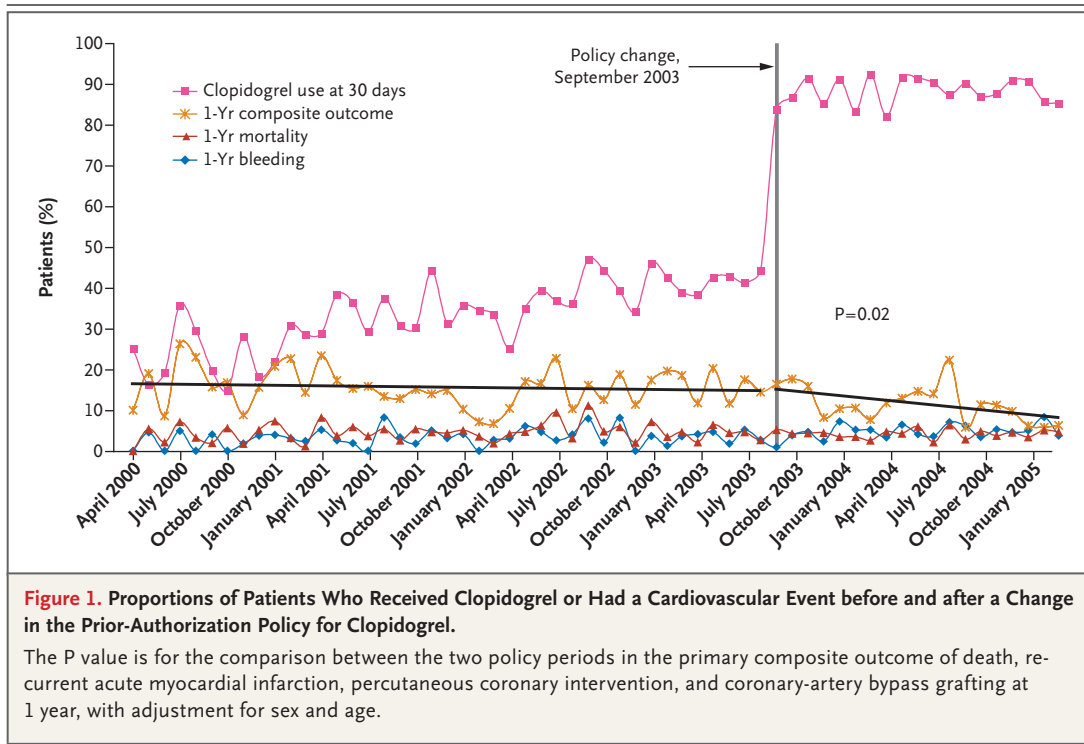
dogrel in this setting. Although the United States does not have a universal drug-benefits plan similar to that in Ontario, our study conditions in the prior-authorization period may be similar to the effects of patients undergoing PCI with stenting without a drug plan in the United States or with prior-authorization policies or high copayments that may lead some patients to forgo the use of clopidogrel in a similar clinical setting.

Although prior-authorization programs may be useful for controlling costs or limiting the use of drugs whose effectiveness has been questioned, such restrictions have the potential to reduce patients' access to beneficial medications in a timely manner, especially when the requisite paperwork is extensive, approvals are delayed, and the medication is needed acutely. In a study by Ackman et al.²⁰ involving 112 patients who received coronary stents, the investigators found a 4-day delay in the filling of clopidogrel prescriptions under a prior-authorization program; when the system was subsequently changed to an authorized-prescriber list, there was no delay. The study showed that 6 of 45 patients in the prior-authorization

period required repeat revascularizations, with two procedures in patients who either delayed filling or did not fill their clopidogrel prescriptions. We similarly saw a significant decrease in the time that patients took to fill their clopidogrel prescriptions, from a median of 9 days to 0 days, after a similar policy change, a factor that potentially contributed to the decreased rate in adverse cardiovascular outcomes after the restrictive policy was liberalized.

During the prior-authorization period, we found low rates of clopidogrel prescription through the expected medication supply channel of the ODB program. We were not able to ascertain whether certain patients elected to pay for the medication directly, were given samples, or had a private drug plan that covered the medication. However, if any patients obtained clopidogrel through other means, resulting in a higher-than-measured use of clopidogrel in the initial prior-authorization period, the actual difference in outcomes between policy periods may have been even greater than what we found.

In our study, the rates of clopidogrel use of



about 90% within 30 days after discharge following myocardial infarction in the limited-use period are consistent with those reported in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines) initiative involving patients with non-ST-elevation acute coronary syndromes who underwent PCI.²¹ During the study period, the use of secondary-prevention medications was above or close to Canadian quality-indicator benchmarks.²² Statin use exceeded the 70% benchmark, whereas the use of ACE inhibitors and beta-blockers was about 10% lower than the 85% benchmarks. The rate of aspirin use within 7 days after hospital discharge was low, at about 30%, which was consistent with our results reported previously.^{23,24} In Ontario, the over-the-counter cost of aspirin may be lower than the copayment levied through the government prescription plan. However, it is possible that not all patients purchased aspirin without a prescription to take with clopidogrel. Some reports suggest that patients may not understand the need for dual antiplatelet therapy after PCI and may forgo aspirin therapy while taking clopidogrel.⁴ If some patients did not use aspirin in ad-

dition to clopidogrel in the limited-use period, they would have been more likely to have had adverse cardiovascular events related to thrombosis, making it more difficult to find a difference between the two study periods.^{25,26}

Although drug-eluting stents were introduced in Canada in 2002, the rate of their use among all stents in Ontario became consistent at 40% late in the prior-authorization period, a factor that potentially confounds our results.¹³ However, the subgroup analysis confirmed our overall findings even when we accounted for the effect of drug-eluting stents. In addition, the use of drug-eluting stents has a modest effect on reducing target-vessel revascularization and has not been shown in clinical trials to reduce reinfarction. Since we found decreased rates of both PCI and reinfarction, the introduction of drug-eluting stents would not fully explain our findings.¹³ Moreover, late stent thrombosis has been recognized as a serious complication of drug-eluting stents.²⁷ Although during the limited-use period the increased use of drug-eluting stents had the potential to be associated with higher rates of cardiovascular events, we observed lower event rates during this period.

Previous studies have assessed the effect of

prior-authorization programs. However, most of these studies have focused on medications for chronic or nonurgent conditions, often without an assessment of clinical outcomes.²⁸⁻³² Our study's focus on an acute condition, in which timely medication access is crucial, may have uncovered an area in which a prior-authorization program is not a suitable cost-containment method. In this study, the policy was changed to one of restricting clopidogrel use in line with accepted indications and criteria (in the limited-use period), and this change seemed to facilitate timely access to clopidogrel. Other alternatives to prior-authorization policies that may be suitable for urgently needed medications include online computerized adjudication, prescribing according to approved criteria, and the use of authorized prescribers. Another method would be to allow reimbursement of certain medications with an urgent indication for a limited duration of time, during which application for more prolonged coverage could be processed. Although there is nothing intuitively wrong with seeking to base reimbursement decisions on approved guidelines or other evidence-based criteria, the necessary time lag involved with the adjudication of applications for drug use can be detrimental to the outcomes of patients in circumstances in which the treatment is needed urgently.²⁸⁻³²

Some limitations of our study should be noted. Our study was observational rather than a clinical trial. However, it is very rare that clinical trials of various drug policies are conducted, and the large sample size of this population-based study enhances the generalizability of our results. Since the study was limited to patients who were 65 years of age or older, our findings may not apply to younger patients. Although we did not assess

for adherence rates for clopidogrel use, there is no reason that adherence should have been influenced by the change in policy.

A liberalization of a drug-reimbursement policy that allowed more timely access to clopidogrel for accepted urgent indications provided the opportunity to study the potential effect of drug-benefit policies on clinical outcomes. Specifically, the abolishment of a prior-authorization policy was followed by more widespread and earlier use of clopidogrel for recommended urgent indications — in this instance, the treatment of patients with acute myocardial infarction undergoing PCI with stenting. In turn, this increased use appeared to be associated with better clinical outcomes. Although clopidogrel is an expensive medication for a drug formulary, a limitation of access to the drug under a prior-authorization policy in patients after PCI with stenting was associated with an increased rate of cardiac events. The process of limiting access to cardiac medications that are acutely required may merit reconsideration.

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