Better Glycemic Control with Insulin Premix 50/50 TID Compared to Insulin Premix 70/30 BID

Premix 50/50 İnsulin ile Premix 70/30 İnsuline Kıyasla Daha İyi Glisemik Kontrol Mümkündür

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Abstract

Objective: Since only a small proportion of diabetics achieve optimal glycemic targets, intensification of treatment with insulin is needed in most of the cases. Application of insulin lispro premix 50/50 TID provides better glycemic control compared to human insulin premix 70/30 and comparable results reported with basal-bolus insulin regimen.

The aim of this study was to determine the effect of insulin lispro premix 50/50 TID (Group 1, n=60) in comparison with insulin aspart premix 70/30 (Group 2, n=62).

Materials and Methods: Type 2 diabetic patients, who were started on insulin treatment for the first time, were screened retrospectively. Change in A1C levels, 4-point self-monitored blood glucose measurements and rate of hypoglycemia within a 3-month period were recorded.

Results: Basal A1C levels were higher (p=0.002) and the rate of improvement was greater in patients of Group 1 than in Group 2 patients (p=0.0006). There was no difference between the patients in achieving target A1C level and in the rate of hypoglycemia. A greater decrease in postprandial blood glucose level was achieved in patients of Group 1 (p<0.0001).

Conclusion: Compared to insulin aspart premix 70/30, insulin lispro premix 50/50 provided better glycemic control without increasing the risk of hypoglycemia. *Turk Jem 2010; 14: 60-5*

Key words: Premix insulins, glycemic control, type 2 diabetes mellitus

Özet

Amaç: Hedef glisemik değerlere ulaşabilmek için diyabet tedavisinin yoğunlaştırılması gereklidir. Premix 50/50 insülin lispro günde 3 kullanıldığında premix 70/30 insan insülininden daha iyi, bazal-bolüs tedavisine eşdeğer sonuçlar vermiştir. Bu çalışmanın amacı Premix 50/50 insülin lisproyu (Grup 1, n=60) premix 70/30 insülin aspart (Grup 2, n=62) ile karşılaştırmaktır.

Gereç ve Yöntemler: Yeni insülin başlanan tip 2 diyabetli hastalar 3 ay boyunca retrospektif olarak taranmıştır ve glisemik kontrol ve hipoglisemi açısından değerlendirilmiştir.

Bulgular: Grup 1'deki hastaların başlangıç A1C düzeyi daha yüksek iken daha fazla düşüş sağlanmıştır (p=0,002). Tokluk kan şekeri kontrolü grup 1'de daha fazla sağlanmıştır (p<0,0001). Hipoglisemi ve hedef A1C düzeylerine ulaşan hasta oranları açısından gruplar arasında fark yoktu.

Sonuç: Premix 50/50 insülinin günde üç kez kullanımı ile premix 70/30 insülinin iki kez kullanımına kıyasla hipoglisemi riskinde artış olmaksızın daha iyi glisemik kontrol sağlanabilmektedir. *Türk Jem 2010; 14: 60-5*

Anahtar kelimeler: Karışım insülinler, glisemik kontrol, tip 2 diabetes mellitus

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Introduction

Type 2 diabetes mellitus is a progressive disease. Irrespective of therapeutic regimen, glycemic control deteriorates with time (1,2). Achieving the optimal glycemic treatment goals reduces long-term microvascular complications and delays the risk of macrovascular disease (3). Achievement and maintenance of tight glycemic control require titration of the therapy by initiating insulin when oral hypoglycemic agents fail to reduce A1C levels to the target. However, only a small proportion of people with type 2 diabetes mellitus actually are able to succeed in treatment goals and the number of patients requiring insulin therapy eventually rise (4-6). The results of a UK Prospective Diabetes Study (UKPDS) substudy and large observational PRESENT study revealed that initiation or early addition of insulin to oral therapy further improved the glycemic control in type 2 diabetic patients (3,7). The optimal insulin regimen in type 2 diabetes mellitus varies among physicians depending on the properties of the patients and guidelines released by diabetes federations. Although the choice of initial insulin regimen varies, biphasic insulins are the most prescribed insulin throughout the world (8).

The ideal insulin treatment must mimic the endogenous physiological insulin profile. The most resembling model is basal-bolus insulin treatment. The results of the above-mentioned studies indicate that compared to basal-bolus insulin treatment, insulin lispro premix 50/50 TID provided similar glycemic profile with better postprandial glycemic control but with worse fasting glycemia than basal-bolus treatment (9). Although there are some studies comparing human insulin premix 70/30 with insulin lispro premix 50/50 revealing better glycemia with the latter, there is no study comparing different premix analog insulins (10).

The aim of this study was to compare the efficacy and safety of insulin lispro premix 50/50 with insulin aspart premix 70/30 in patients with type 2 diabetes mellitus.

Materials and Methods

Subjects

Patients with type 2 diabetes mellitus aged 18-80 years started on insulin treatment due to poor glycemic control because of either inadequacy of oral agents or severe hyperglycemia (defined as fasting blood glucose above 200 mg/dl) on the admission were enrolled. The study population consisted of a total of 122 type 2 diabetic patients who were commenced on insulin treatment for the first time either with insulin lispro premix 50/50 three times daily (n=60) or insulin aspart premix 70/30 two times daily (n=62) at the outpatient clinic of endocrinology of Yeditepe University Hospital. Only those patients who were self monitoring their blood glucose at least 4 times in a week in a scheduled manner and patients whose A1C levels could be obtained at the start and end of the study period were included into the study. Patients who had end-stage diseases such as renal, hepatic or heart failure, active cancer treatment and were on steroid therapy were not included in the study.

Study Design

This was a single-centre, retrospective study conducted at Yeditepe University Hospital from January 2009 to June 2010 in accordance with Good Clinical Practice and the ethical principles of the Declaration of Helsinki. All study documentation was reviewed and approved by the Institutional Review Board.

Data collected from the electronic database of the hospital included demographic characteristics, medical history, physical examination findings, all laboratory measurements either done at Yeditepe University Hospital or other laboratories, if recorded and treatment recommendations in each visit. The patients were followed up in a scheduled manner every three months and the above data were recorded in each visit. At the start of treatment, all patients were strictly educated about the application of insulin, use of insulin delivery devices (insulin pens), proper measurement and recording of blood glucose, awareness and management of hypoglycemia and nutrition. The patients were encouraged to self-measure their blood glucose levels every single day of the week at 7-point (before and 2 hours after each main meal and at bedtime) or 4-point (before each main meal and at bedtime) profile and were asked to report their measurements weekly the day after it was done to either diabetes nurse or doctor. Communication was conducted via a direct phone call to diabetes nurse or, if preferred by the patient, via fax, e-mail, or short visit. At each visit, the patients were asked about compliance with insulin applications, meal planning, any hypoglycemia and its management, and all information gathered was recorded. The insulin dose titrations were done by the nurse or doctor. More than 80% of patients preferred the 4-point profile, but there was no difference in the compliance of patients in the whole group. Those patients with 80% or above measurements obtained were included into the study. The measurements were done by glucometers approved by the Ministry of Health of Turkey. Four different glucometers were used by the patients.

Objectives

The primary objective was to determine whether greater improvements in glycemic control could be achieved with insulin lispro premix 50/50 TID compared to insulin aspart premix 70/30 BID. The secondary objective was to investigate the differences in fasting and postprandial blood glucose measurements, rate of improvement in A1C or blood glucose measurements, initial and mean insulin doses, incidence and rate of hypoglycemia.

Symptomatic hypoglycemia was defined as an event with symptoms consistent with hypoglycemia below 70 mg/dl.

Severe hypoglycemia was the one, in which symptoms consistent with hypoglycemia required the assistance of another person. Nocturnal hypoglycemia was defined as symptoms of hypoglycemia occurring after the last insulin injection and before the morning insulin dose.

Laboratory Measurements

A1C levels were analyzed using turbidimetric inhibition immunological analysis (TINIA) (Tina-quant Hemoglobin A1c Gen.2, COBAS INTEGRA 400/800, Roche Diagnostics GmbH, Mannheim, Germany; normal reference range 4.8-5.9%) at the central laboratory of Yeditepe University Hospital.

Statistics

Statistical data were analyzed by SPSS® 15.0 for Windows®. Descriptive statistics were provided for each variable including demographic, laboratory and self-monitored blood glucose measurements. Variables were not normally distributed as tested by the Kolmogorov-Smirnov test. Nonparametric tests were used. Results are shown as median (minimum-maximum). Comparisons between groups were done using the Mann-Whitney U test and Wilcoxon matched-pairs test as appropriate. For categorical variables χ^2-based tests were used. The Spearman test was used for correlation analysis. For repeated measurements of blood glucose, the Friedman test was used. Statistical significance considered at $p < 0.05$.

Results

Demographic Data

Demographic characteristics of the study subjects are presented in Table 1. The patients in Group 1 were younger (p=0.005) and with shorter disease period (p=0.04) than the patients in Group 2. Fifty three percent of patients in Group 1 and 68% of patients in Group 2 were younger than 65 years. Elderly patients above the age of 70 years were equally distributed among the groups and constituted less than 10% of the study population. Eleven percent of patients in Group 1 and 20% in Group 2 had newly diagnosed diabetes.

Change in A1C level

Glycemic parameters are listed in Table 2. Median basal A1C level was found to be higher in Group 1 compared to Group 2 (p=0.002). There was no difference in the final A1C level between the groups (Figure 2), but the rate of improvement was greater in Group 1. The net decrease in A1C was 1.4% (-1.5% - 5.8%) in Group 1 and 0.7% (-1.0% - 4.2%) in Group 2 (p=0.0006) (Figure 3).

Target A1C

There was no difference in the number of patients achieving target A1C level (p=0,519). Thirty one percent (n=19) of patients in Group 1 and 25% (n=15) in Group 2 achieved the target A1C level of below 6.5%.

Blood Glucose Levels

Basal fasting blood glucose (FBG) levels were similar and improved during the study in both groups. The final mean FBG level was found to be significantly lower in patients using insulin aspart premix 70/30 compared to those using insulin lispro premix 50/50 (p=0,008).

Actual 2-h postprandial blood glucose measurements could not be obtained but instead, pre-meal blood glucose was measured and will be cited as PPG elsewhere in the text. The cumulative PPG was found to be significantly lower in the patients of Group 1 compared to group 2 patients (p<0.0001 (Figure 4). Four-point blood glucose measurements revealed better results in pre-lunch (p=0.007) and pre-supper (p=0.03) blood glucose values in favor of patients in Group 1. There was no statistically significant difference in midnight blood glucose measurements between the groups. Four-point measurements are shown in Figure 1.

Total Daily Insulin Dose

The total daily insulin dose administered was higher in both basal (p<0.0001) and at the end point (p=0.01) in patients using insulin lispro premix 50/50 compared to patients using insulin aspart premix 70/30 (Table 2). There was no statistically significant difference in the total daily dose of insulin during the study period "within the groups. Insulin therapy was initiated as three equal doses of the calculated total daily insulin,

Table 1. Baseline characteristics of the treatment groups

	Insulin Lispro Premix 50/50	Insulin Aspart Premix 70/30	p-value
Gender (F/M)	28/32	28/34	0.886
Age (years)*	60 (24-84)	65 (39-90)	0.005
Duration of diabetes (years)*	8.0 (0-36)	9.5 (0-37)	0.04
BMI (kg/m^2)*	30 (27-36)	29 (26-36)	0.814
Complications (%)			
Any microvascular	10	12	0,871
Any macrovascular	5	6	0.869
Co-existing disease (%)			
Hypertension	40	58	0.201
Hyperlipidemia	68	76	0.334

Table 2. Major findings of the study groups

	Insulin Lispro Premix 50/50	Insulin Aspart Premix 70/30	p-value
Change in A1C (%)			
Basal A1C	8.9±1.7	7.9±1.2	0.002
Last A1C	7.3±1.0	7.1±0.9	ns
Δ A1C	1.61±1.47	0.87±0.93	0.0006
Change in FBG (mg/dl)			
Basal FBG	193.4±66.7	167.8±53.0	ns
Last FBG	138.1±24.8	129.0±27.9	0.008
Δ FBG	30.3±45.9	59.5±64.6	0.005
Total daily insulin dose (U/day)			
Basal dose	60.9±23.2	42.4±16.6	<0.0001
Last dose	59.8±28.3	47.1±21.9	0.002
Mean dose	59.0±22.3	44.9±16.6	0.0003
Hypoglycemia (event/patient)			
Cumulative	0.91±0.86	1.53±1.59	ns
Nocturnal	0.26±0.48	0.43±0.69	ns

which was administered before each meal in Group 1, and 2/3 of the dose before breakfast and 1/3 of the dose before supper in Group 2. But at the end point, about 40% of the total daily dose was used in the evening and other doses relatively decreased compared to the basal doses in Group 1, while the ratio remained almost constant in Group 2.

Hypoglycemia

There was no difference between the groups regarding hypoglycemic events. Sixty-five percent of patients in Group 1 and 66.6% in Group 2 had at least one hypoglycemic episode. Only 20% of patients in Group 1 had more than one hypoglycemic episode, while it was 45% in Group 2 (p=0.001). Hypoglycemia was mostly recorded to be related to incompliance with life style. None of the patients had severe hypoglycemia. Elderly patients were prone to hypoglycemia in Group 1; 70% of patients having hypoglycemia were above the age of 70 years. There was no age distribution in Group 2. Although it was not statistically significant, the mean hypoglycemic episode in patients of Group 1 was less than in patients of Group 2 (Figure 5). A median of 1,0 (0,0-2,0) hypoglycemic episode/patient was observed in Group 1 compared to 1.0 (0.0-6.0) hypoglycemic episode/patient in Group 2. There was no difference between the groups regarding nocturnal hypoglycemia. Hypoglycemic episodes did not correlate with A1C level or mean insulin dose.

Correlations

Delta A1C correlated negatively with the age of the patients (p<0.0001, r=-0.316) and positively with the mean insulin dose administered (p=0.01, r=0.235). There was a correlation between delta FBG and the total daily insulin dose administered (p=0.015, r=0.221). There was no correlation between hypoglycemic events and the total daily insulin dose administered. In addition, duration of diabetes did not correlate with either A1C or blood glucose measurements.

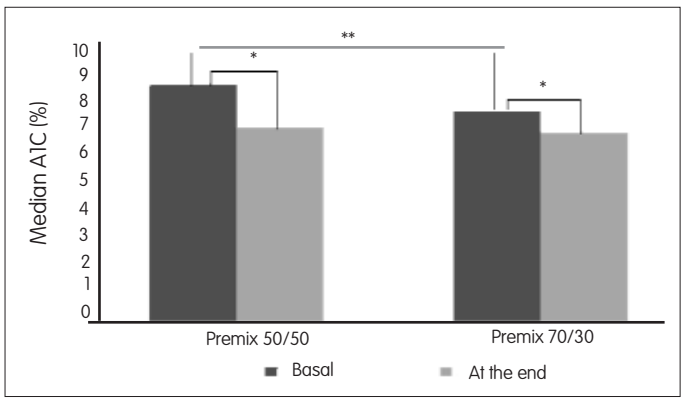

Figure 1. Mean A1C levels at baseline and change during study period in patients with type 2 diabetes mellitus either treated with premix 50/50 insulin lispro TID or premix 70/30 insulin aspart BID. *p<0.001, **p<0.002

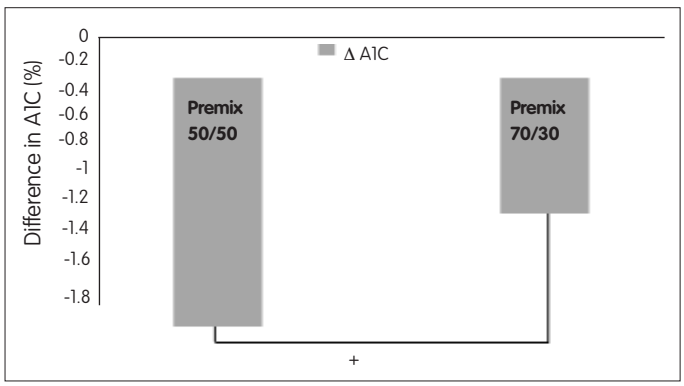

Figure 2. Change in mean A1C from baseline during study period in patients with type 2 diabetes mellitus either treated with premix 50/50 insulin lispro TID or premix 70/30 insulin aspart BID. †p=0.0006

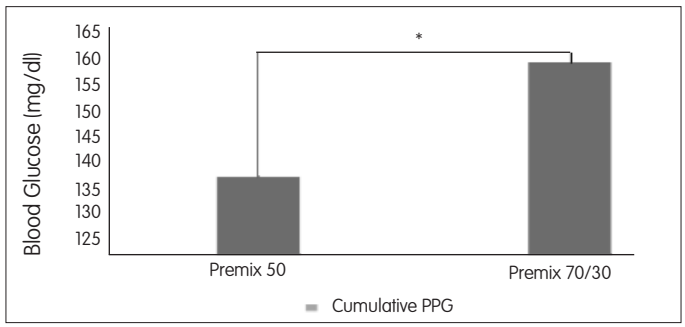

Figure 3. Mean cumulative postprandial blood glucose levels in patients with type 2 diabetes mellitus either treated with premix 50/50 insulin lispro TID or premix 70/30 insulin aspart BID. *p<0.0001

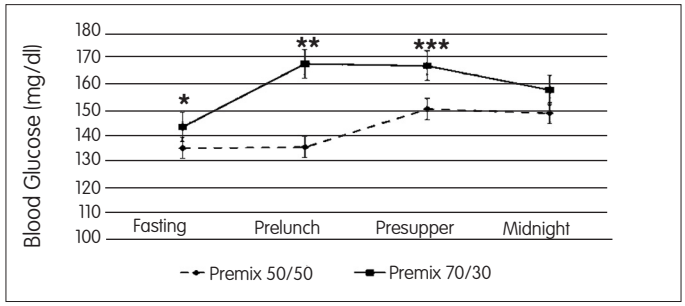

Figure 4. Mean 4-point self-monitored blood glucose profiles in patients with type 2 diabetes mellitus at the end of the study period either treated with premix 50/50 insulin lispro TID or premix 70/30 insulin aspart BID. *p=0.008, **p<0.001, ***p=0.03

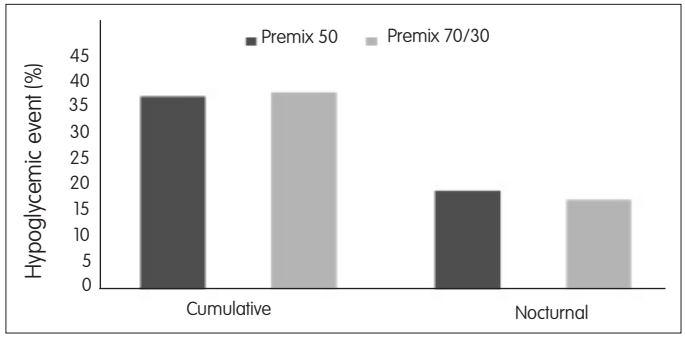

Figure 5. Ratio of patients with hypoglycemic episodes in patients with type 2 diabetes mellitus either treated with premix 50/50 insulin lispro TID or premix 70/30 insulin aspart BID. There was no statistically significant difference

Multiple regression analysis revealed that only the basal A1C and the latest dose of insulin had an effect on ΔA1C.

Discussion

This study demonstrated that treatment with insulin lispro premix 50/50 injected three times daily resulted in significantly better glycemic control compared to insulin aspart premix 70/30 injected two times daily without an increased risk of hypoglycemia.

In modern treatment algorithms for diabetes, insulin is located in the early phases of treatment periods even at the beginning. The ideal insulin regimen should include the agent that best mimics human physiology, can be practically applied and personalized. The gold standard treatment that best fits these rules is basal-bolus insulin regimen. Premixed insulins are a good alternative with their best practicality but lack in mimicking physiology. Application of premixed insulins three times daily was discovered to meet this deficit instead of standard application of two times daily. Insulin lispro premix 50/50 is a well-studied and a good model for three times daily applications. When compared with the gold standard basal-bolus insulin regimen, application of prandial insulin lispro premix 50/50 resulted in similar A1C decrease within 24 weeks of treatment period in a group of diabetic patients. Although fasting blood glucose levels and percentage of patients achieving target A1C levels were in favor of basal-bolus treatment, there was no difference in ability of improving postprandial blood glucose levels and similar risk of hypoglycemia was observed (9). Although noninferiority was not demonstrated, findings provide enough data to make it a good alternative to basal-bolus insulin regimen.

Insulin lispro premix 50/50 injected three times daily was also compared with human insulin premix 70/30injected two times daily. Regarding mean, fasting and postprandial blood glucose levels, insulin lispro premix 50/50 provided better improvement. The decrease from baseline in A1C was significantly greater with insulin lispro premix 50/50 than with human insulin premix 70/30. There was no significant difference between the treatments regarding incidence of hypoglycemia (10).

Our study is first in comparing two different analog insulin regimens. Although the percentage of patients achieving target A1C level of below 6.5% was found to be similar between the treatment groups, insulin lispro premix 50/50 injected three times daily provided better glycemic control with an about 1.5% decrease in A1C levels compared to 0.54% decrease in insulin aspart premix 70/30 injected two times daily. This difference was found to be because of improvement in postprandial blood glucose levels since there was no difference in fasting glycemia between the treatment groups. Postprandial blood glucose control is sometimes more important than fasting glycemia since it was found to be strictly related to macrovascular complications and accepted as an independent cardiovascular risk factor irrespective of fasting blood glucose levels (11). Monnier et al. demonstrated that a true fasting state is 3 only three hours a day in a healthy person and the rest is either postprandial or postabsorbtive state (12). For this reason, any medication that is better in controlling postprandial glycemia will provide better prevention of cardiovascular risk in diabetics. However, postprandial blood glucose levels were above the goals in 31 % of diabetic patients who had normal fasting blood glucose levels (11). Ninety nine percent of patients with an A1C level of above 7% had postprandial blood glucose level of above 200 mg/dl (13). It was obviously shown in the DECODE Study that the control of postprandial glycemic state decreases the risk of cardiovascular disease (11). The results of this study show that insulin lispro premix 50/50 provide better postprandial glycemic control than insulin aspart premix 70/30. Similar results were also demonstrated in the study comparing it with human insulin premix 70/30. Insulin lispro premix 50/50 also provided similar postprandial glycemic control in comparison with basal-bolus insulin regimen. Although not in the scope of the goals of this study, this beneficial effect may provide improvement in cardiovascular risk in diabetics.

One of the main concerns in intensification of insulin regimen is the risk of hypoglycemia. It may deteriorate the health condition in diabetics and sometimes may increase the risk for mortality especially in critically ill patients and hide the benefits of the decrease in A1C levels (14). However, none of the studies showed an increased risk of hypoglycemia with insulin lispro premix 50/50 either compared to premix insulin 70/30 aspart or human insulin or basal-bolus insulin regimens. Thus, application of insulin lispro premix 50/50 three times daily for type 2 diabetic patients seems to be safe.

Another aspect to be considered in insulin treatment is the total dose of insulin required to control glycemia. An increased risk of side effects including increase in body weight and risk of cancer parallel to increase in the daily dose of insulin is reported in studies (15,16). All patients in both groups in this study were started on insulin treatment with a dose of 0.5-0.6 units/kilogram body weight/day. But patients in insulin lispro premix 50/50 required significantly more insulin doses than patients in insulin aspart premix 70/30 group. On the other hand, the total daily insulin dose used during the study did not change compared to the basal doses in both groups. Unfortunately, body weight changes were not recorded properly, so that statistical analysis could not be possible. There were no reported side effects related to insulin treatment in any of the groups. There was no difference in the compliance of patients in the whole group considering use of medications or self-monitoring of blood glucose.

Potential limitations of the current study include the retrospective design and low number of patients. Comparison groups were not homogenous due to the retrospective manner.

Patients were older and had longer duration of diabetes in the group of insulin aspart premix 70/30. The mean A1C levels at the start of insulin treatment was higher in the group of insulin lispro premix 50/50. This may create a bias in the comparison since relatively serious patients were included in this arm. Also the study design does not allow differentiating whether the decrease in A1C level was caused by the injection of insulin three times daily or the use of the molecule itself.

It will be interesting to add a third premix 70/30 injection at lunchtime, which will probably result in a lower mean blood glucose level. However, it cannot be certain that the risk of hypoglycemia will not increase due to higher doses of neutral protamin lispro part of insulin.

In conclusion, insulin lispro premix 50/50 provides better glycemic control without increasing the risk of hypoglycemia in type 2 diabetic patients compared to insulin aspart premix 70/30. Further prospective studies with larger number of patients are needed to better clarify the role of this kind of applications.

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