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STUDY TO KNOW THE PREVALENCE OF URINARY TRACT INFECTIONS IN TYPE II DIABETIC PATIENTS TAKING DAPAGLIFLOZIN

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Abstract:

Objective: *In type 2 diabetes, the most common complication is Urinary tract infection. The most common causing factors are glucosuria, treatment with sodium glucose cotransporter 2 inhibitors (SGLT2). Dapagliflozin is a research proved SGLT2 inhibitor with proven controls over glycemia in patients of diabetes mellitus. Dapagliflozin data from several safety trials were checked to prove the asoociation between urinary tract infection and glycosuria.*

Study Design: *A Randomized Control trial.*

Place and Duration: *In the Medicine Departments of Services Hospital Lahore for one year duration from June 2017 to June 2018.*

Methods: *The randomized controlled safety data of 12 placebo-controlled studies were collected to assess the association between glycosuria and UTI in non compliance diabetes mellitus patients (HbA1c N6.5% - 12%). The subjects were given once daily with either dapagliflozin (2.5, 5 or 10 mg) or placebo, either for 12 to 24 weeks or as as monotherapy in addition to insulin, metformin, thiazolidination or sulfonylurea. Clinical diagnosis and incidence of UTI were evaluated.*

Results: *This study consisted of 3050 patients who were given monotherapy or supplementary treatment and received dapagliflozin (31 mg [n = 790], 5 mg [n = 1080] or 10 mg [n = 1180] once a day and 1380 placebo patients were treated. For 10 mg, 5 mg, 2.5 mg and placebo for dapagliflozin, the identified infections were recorded as 5.6%,3.7%, 3.8% and 4.2% respectively. In the urine, the levels of glucose were gradually increased with the dose of dapagliflozin but not the urinary tract infection incidence increases. Most of the identified infections were diseases that were typical for diabetes mellitus patients. Interruption in urine due to UTI was rare: 8 (0.3%) patients managed with dapagliflozin and in 1 (0.1%) cases treated with placebo. The antimicrobial standard therapy were given for detected infections in mild to moderate form.*

Conclusion: *With 5 or 10 mg dapagliflozin on daily for the type 2 diabetes mellitus treatment is associated with a slightly high UTI risk. Most of the time the mild to moderate infection was observed and easily treatable. This study did not show a definite dose association between urinary tract infection and glycosuria.*

Key Words: *Dapagliflozin, Urinary tract infection, type 2 diabetes, glycosuria.*

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INTRODUCTION:

In human urine, the growth of Escherichia coli and its analysis shows very high concentrations of glucose cause low rate when pH of urine was not maintained, although the E. coli growth rate increased when glucose was added into the urine [1]. A retrospective statistical analysis of women with diabetes, the UTI has not association with glycosuria recognized risk factor. Glucosuria is a research class antidiabetic therapy targeting (SGLT2) sodium glucose cotransporter 2, which is particularly interesting due to its association with glucose or reabsorption glucose mediated by the kidney. SGLT2 inhibitors act regardless of insulin secretion or reduce glucose reabsorption action, leading to high urinary glucose elimination with a corresponding decrease in blood glucose levels. Dapagliflozin is a potent selective SGLT2 orally administered inhibitor used for type 2 diabetes treatment. In placebo-controlled clinical trials, Dapagliflozin has been analyzed as a complementary treatment or as monotherapy to other antidiabetic therapies(as a first-line treatment in combination with metformin). Patients receiving dapagliflozin in each study had significantly higher control over glycemia than those receiving placebo and usually well tolerated [2]. The clinical pharmacology data and studies have shown an increase in dose-dependent glycosuria at doses of 2.5, 5 and 10 mg.); Increases were lower with doses of N10 mg, and because the mechanism of action resulted in a higher urinary glucose elimination, dapagliflozin-controlled clinical trials offer the favorable time to assess the association between UTI and glucosuria.

MATERIALS AND METHODS:

The data of 12 placebo-controlled randomized studies (Appendix 1) were collected to determine the association between urinary glucose excretion which is pharmacologically induced and UTI in type II diabetes mellitus patients managed with dapagliflozin. In the attached article " balanitis and Vulvovaginitis in patients managed with dapagliflozin" (Johnsson et al., 2013) (3) details of the methodology of these studies are given. Patients having previous UTI or having risk factor were not included in clinical analysis trials. All studies were held in collaboration with the Good Clinical Practice guidelines and each participant was approved by the institutional review boards and ethical committee. The informed consent in written form was taken from all subjects to partake in their clinical trials.

Detection and measurement of safety signals:

Due to an increased risk potential for treatment-induced glycosuria-associated UTI, a comprehensive approach has been used to increase the detection potential of any signal presenting an enhances risk. During the clinical trial program on Dapagliflozin, a hard work was done to record all symptoms, signs and events that suggest UTI. Further to the symptom reports spontaneously indicated by the analysis subjects, the researchers proactively asked the symptoms of UTI (currently experienced or pre-study visit) at each follow-up. This proactive inquiry is performed to check the chances that participants will not notice that various symptoms are familiar. Complementary case report forms were given to provide more explanatory information for the evaluation.

For the first analysis, a wide network was created using an array of Regulatory Activities Medical Glossary (MedDRA) version 13.0 Presumed preferred terms (Annex 2) to capture UI thought, as well as signs and symptoms (eg, Dizuria) [(4)]. These terms are referred to as UTI". When a predetermined and preferred period was reported, the researcher completed a case report questionnaire to fully identify the risk factors and status. Second, in particular studies, 49 predetermined terms used for clinical diagnosis of UTIs. To enhance the diagnostic specificity, the investigators take a urine culture to establish the diagnosis in suspected cases suffering from UTI. The study standard was to continue drug clinically evidence of presumed urosepsis or pyelonephritis in subjects until infection treatment was completed and improvement was achieved clinically.

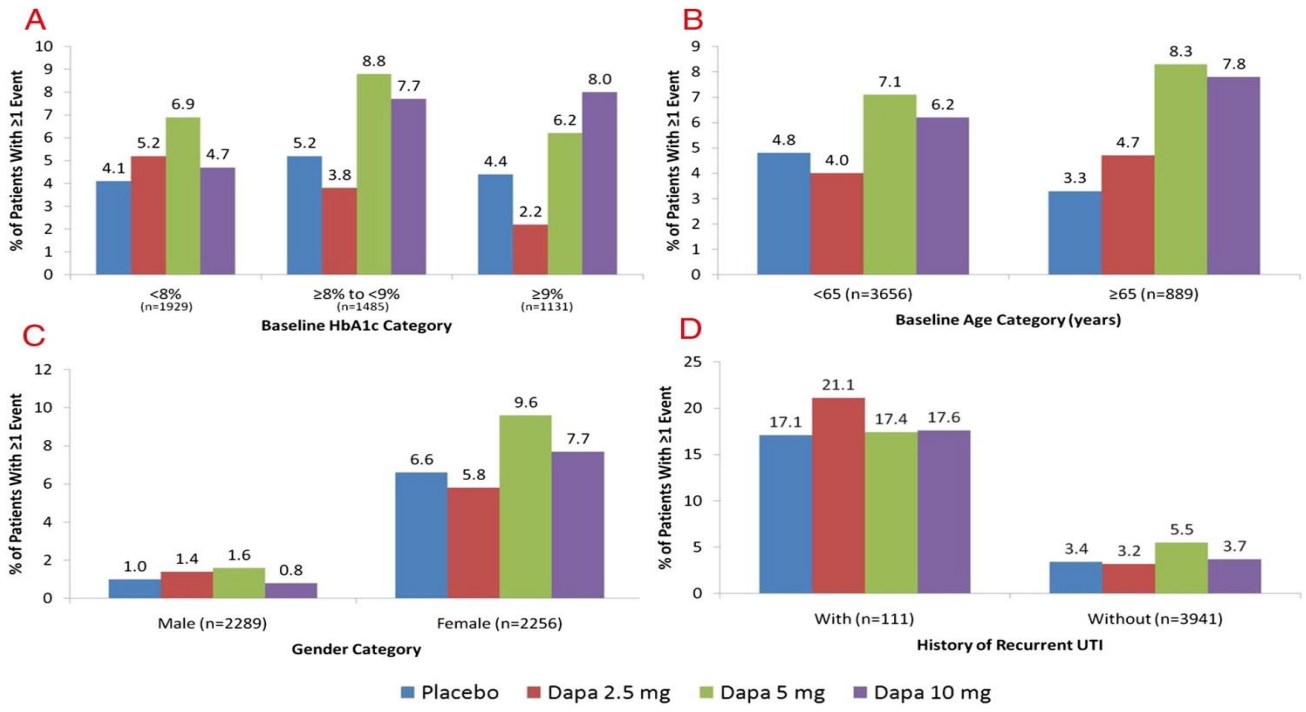
RESULTS:

For this study total subjects were 4545 taken from 12 clinical trials. The groups of treatment consisted of 3050 patients (2.5 mg [n = 790], 5 mg [n = 1080] or 10 mg [n = 1180] once a day and 1380 placebo patients were treated. These analytic groups were balanced generally according to the demographic characteristics of the reference and the characteristics of the disease (Table 1).

Baseline characteristics and demographic data of patients.

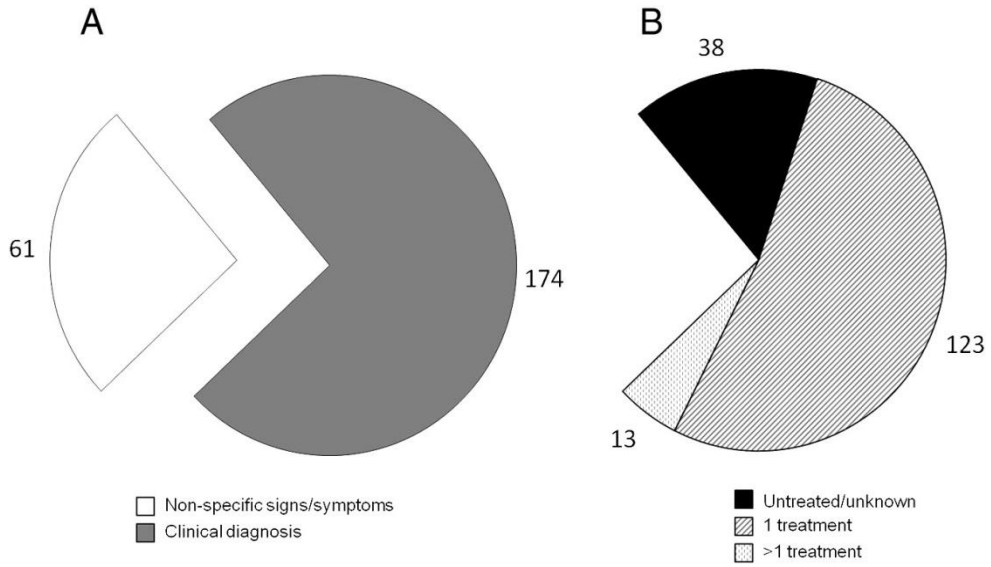
Characteristic	Placebo (n = 1380)	Dapagliflozin 2.5 mg/d (n = 790)	5 mg/d (n = 1080)	10 mg/d (n = 1180)
Age (y), mean (SD)	55.2(9.96)	56.95(11.1)	54.86(9.66)	55.01(9.95)
Sex, n (%)				
Women	668(47.99)	370(48.98)	520(48.20)	605(51.10)
Men	712(50.95)	420(51.62)	560(52.80)	575(49.90)
Weight (kg), mean (SD)	86.96(20.01)	85.86(18.75)	85.20(18.86)	87.90(20.10)
Body mass index, n (%)				
≥25 kg/m^2	1239(88.90)	709(86.20)	990(86.95)	1050(91.07)
≥30 kg/m2	785(56.85)	466(57.50)	650(56.80)	690(57.90)
Diabetes duration (y), mean (SD)	4.9(6.26)	6.4(6.82)	5.3(6.58)	5.9(6.59)
HbA1c (%), mean (SD)	8.3(1.09)	7.9(0.84)	8.5(1.10)	8.2(1.02)

The basal HbA1c was 7.9% to 8.2%. Above 85% of subjects had ≥25 kg / m2 BMI and N55% BM30 kg / m2. Various disease duration (mean 5.3 to 6.5 years) and progression were shown in the selected subjects. In patients treated with dapagliflozin, the average exposure time ranged from 147.92 to 151.05 days. The average time of exposure in patients managed with placebo was 148.34 days.



In this pooled analysis, in 24 weeks a dose-dependent increase in glycosuria was recorded; The initial change in urinary excretion in placebo, 10 mg, 5 mg and 2.5 mg fasting urine was -240.70 mg / dL (SE 36.2), + 1470.51 mg / dL (SE 68.6) + 2150.09 (SE 65.97) and + 2593.93 (SE 65.4), respectively. When long-term data were available for elimination of glucose in urine, levels were consistent with short-term analysis.

Sixty-one of the 63 pre-determined and MedDRA which were preferred terms used to record symptoms, signs and events showing the UTI were reported in 1 patient (Figure 2 in Appendix 2).



The highest proportion of subjects taking 5 and 10 mg dapagliflozin groups shows UTI (7.2% and 6.4%, respectively. In the placebo group and in the 2.5 mg dapagliflozin group shows 4.4% and 4.3%, respectively (Figure 3). In all treatment groups, the infection was mild to moderate. These circumstances more usual in females than in males in all groups. Patients indicating one percent of females in one or more of the groups taking dapagliflozin and events were diagnosed with dysuria symptom, cystitis and UTI (Table 2).

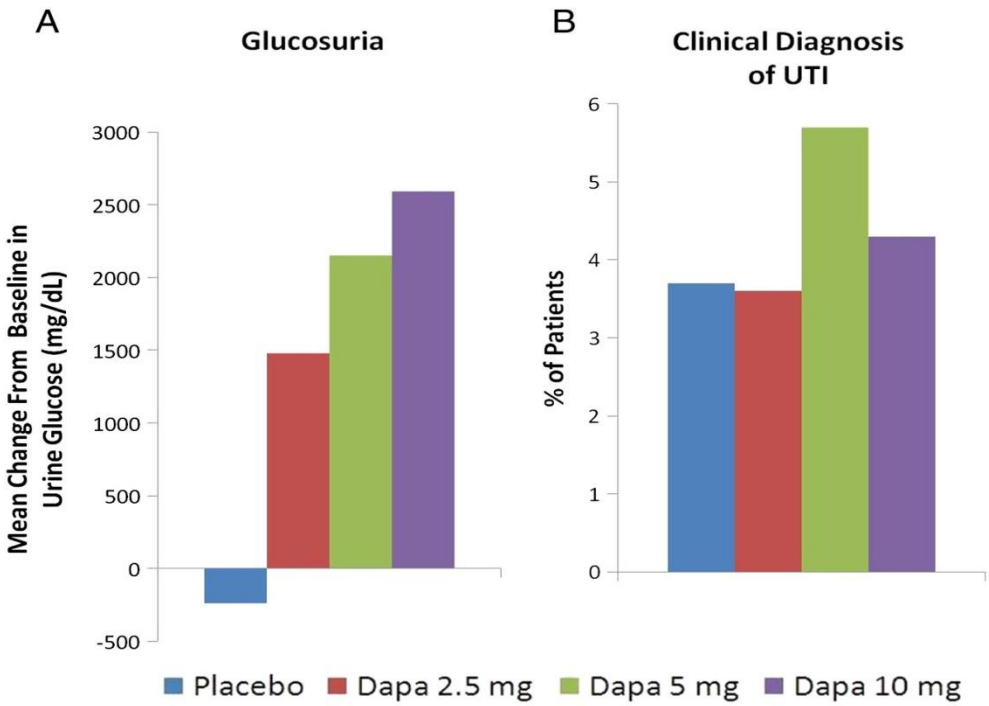
No of patients	Placebo	Dapagliflozin 5 mg/d (n = 1080)	2.5 mg/d (n = 790)	10 mg/d (n = 1180)
Women	**668(47.99)**	**370(48.98)**	**520(48.20)**	**605(51.10)**
Signs, symptoms, and events suggestive of UTI				
UTI	**34(5.1)**	**19(5.1)**	**46(7.9)**	**37(6.3)**
Dysuria	**5((0.8)**	**4(0.9)**	**09(1.6)**	**11(1.9)**
Cystitis	**9(1.4)**	**3(0.6)**	**6(1.1)**	**8(1.3)**
Clinical diagnoses of UTI				
UTI	**34(5.1)**	**20(5.1)**	**46(7.9)**	**38(6.4)**
Cystitis	**9(1.4)**	**3(0.7)**	**8(1.3)**	**8(1.3)**
Men	**712(50.95)**	**420(51.62)**	**560(52.80)**	**575(49.90)**
Signs, symptoms, and events suggestive of UTI				
Dysuria	**3(0.5)**	**3(0.6)**	**7(1.3)**	**12(2.1)**
UTI	**2(0.2)**	**3(0.9)**	**5(0.99)**	**5(0.8)**
Clinical diagnoses of UTI				
UTI	**4(0.5)**	**5(1.1)**	**7(1.2)**	**5(0.8)**

In the placebo group, cystitis and UTI noted in 1% of females. In 1% of males, UTI and Dysuria were reported in one or more of the groups taking dapagliflozin. Urinary cultures were taken in 40% to 51% of subjects with dapagliflozin and with placebo in 50% of patients who were supposed to be having UTI. In all treatment groups, the cultures taken were positive in 2/3rd of cases; Most common organisms identified in type 2 diabetes mellitus patients (eg, Klebsiella pneumoniae, Proteus and E. coli).

To understand the UTI possible risk factors, the prevalence rates were HbA1c categories (% b8, ≥8 to b9 and% ≥9), age (b8; b65 and ≥65 years old), gender, and history of recurrent infection (Figure 1). More events suggestive of UTI have been recorded in patients aged ≥65 years against younger patients managed with dapagliflozin; In all groups taking treatment, more cases of UTI were noted in females than in males. The ratio of UTI events was also determined in subjects who completed the treatment and who continued their trials during the long-term treatment period of trial 102 weeks (dapagliflozin n = 2160, placebo n). = 694). The proportion of patients in long-term analysis with events supposed of the UTI was higher slightly than the short time management. In the short time period treatment, the rates were 4.5% in the placebo group and 4.1% to 7.5% in the dapagliflozin groups. An analysis of the onset time of the first event suggesting the UTI showed that patients given dapaglilozin 5 or 10 mg had a higher risk of an initial event compared to those receiving placebo or 2.5 mg starting at about 2 months after the treatment initiation. (Appendix 4 Figure). In all groups of treatment during the combined periods of treatment, initial events noted initially during trials; after 24 weeks in the first 24 weeks, the first event was occur. From the aforementioned 49 terms, the preferred MedDRAs associated with specific UTI clinical diagnose in the TI1 patient were reported to be 9 (Figure 2 in Appendix 2). 230 total patients, UTI: 56 for placebo, 35 for dapagliflozin. The frequency of the detected infection was evaluated for statistical importance for both the subgroups and the total pooled population classified with the HbA1c reference (Table 3).

	Dapagliflozin 2.5 mg/d (n = 790)	5 mg/d (n = 1080)	10 mg/d (n = 1180)	Placebo
Total pooled population No. patients with events (%)	28(3.5)	63(5.4)	50(4.2)	50(3.5)
P value vs placebo	0.8299	0.0199	0.4795	
Baseline HbA1c category, no. patients with event (%)				
b8%	14(3.8)	22(5.4)	15(3.0)	18(3.2)
P value vs placebo	0.5793	0.789	0.9749	
≥8% and b9%	10(3.7)	25(6.5)	19(5.2)	16(3.9)
P value vs placebo	0.8719	0.815	0.3837	
≥9%	4(2.3)	16(4.8)	13(4.8)	15(4.1)
P value vs placebo	0.4269	0.7439	0.6589	

The UTI frequency was higher significantly for subjects managed with 5 mg dapagliflozin in the total selectees compared to placebo; No other comparison was statistically significant. In general, the UTI clinical diagnosis was more common in patients given with dapagliflozin than in group of placebo. In all treatment groups, rates for women were higher than men. Clinically diagnosed ICU treatment was given by the patient's physician. The management was not according to trial protocols and was given according to the physician's preference and management protocols. Treatment was documented in 78% of 174 patients treated with dapagliflozin documented with a clinical diagnosis of UTI. Many of these subjects were treated with a standard antimicrobial therapy (Figure 2).



Pyelonephritis was a rare condition in each treatment group with a similar frequency: 2 (0.2%) in the 2.5 mg dapagliflozin group and 1 (0.1%) in the 5 mg dapagliflozin group. 1 (0.1%) in the placebo-treated group managed with 10 mg. Only one case with a serious adverse effect was from the placebo group. 2 patients in the 2.5 mg dapagliflozin group consummate UTI events defined as serious adverse events by the researcher: 1 with UTI and 1 with malacoplakia vesicae. A severe adverse event was reported in a 10 mg group of Dapagliflozin (not previously specified, preferred MedDRA term). Dapagliflozin was not stopped and the patient completed duration of analysis. Due to specific UTI diagnoses, very few patients discontinued treatment: in the dapagliflozin groups 8 (0.3%) patients and in the placebo group1 (0.1%) patients. Among patients managed with dapagliflozin, in the 2.5 mg group of Dapagliflozin 2 patients were stopped given treatment due to pyelonephritis, 2 mg, 3 in the 10 mg group and 2 in the 5 mg group were suspended due to a UTI; Cystitis was suspended due to 2.5 mg. One patient in the placebo group was discontinued due to pyelonephritis. The proportion of patients' history of recurrent UTI was small relatively in all treatment groups (2.0 to 2.8%).

During the period of analysis, patients with a history of UTI were diagnosed more (3.2.1% - 21.1%) than those without recurrent infection history (3.3% - 5.6%). There was no evidence of recurrence of placebo and dapagliflozin in subjects with a recurrent infection history. During trials, UTI recurrence events was recorded in 7.7% of patients treated with placebo in 15.3% to 19.6% of patients treated with dapagliflozin. In trials up to 2 years, a UTI recurrence has been noted in 23.01% of patients managed with dapagliflozin and in placebo-managed patients in 13.5%. The recurrent infections prevalence during trials does not seem to depend on the dose.

DISCUSSION:

A hard effort has been done to determine accurately the UTI risk linked with dapagliflozin treatment by a double approach with proactive questioning and spontaneous reporting of subjects. It was supposed that proactive inquiry would help to detect the incidents reporting suggesting of UTI, and would encourage people to report any relevant incident, reminding them that they were paying attention to the symptoms discussed in clinical visits. Proactive interrogation help patients to disclose any treatment given in-spite of the analysis [5]. The UTI Clinical detection was done in analysis with urine culture collection, opinion of consultant physician. In clinical practice, due to the widespread treatment of UTI in symptomatic condition without taking culture; depending purely on the results of culture reports in these analyses will result in minimum diagnosis of infection. On the other hand, asymptomatic pyuria or bacteriuria cases are biased unless the urinalysis has been routinely performed to all selectees without considering the absence or presence of signs and symptoms [6]. The approach according to the protocol

for quantification and detection of a signal for the increase in UTI reflected practice of clinical medicine and was taken optimal and realistic method for measuring UTI risk. There is a debated and claimed association between UTI and glucosuria. In our 3rd phase of clinical trials, aggregated data shows minimum rise in the UTI incidence in subjects managed with 5 or 10 mg dapagliflozin compared to those managed with placebo [(7)]. However, the infection incidence in all treatment groups was relatively low (b6%). In general, the first UTI events took place initially in early analysis. The UTI clinical diagnosis was much usual in females than in males [(8)]. The reported pathogens are common types in patients of type 2 diabetes mellitus, most of which are mild to moderate and according to protocol antimicrobial management it resolved. Glucosuria that reduces blood sugar levels. In this combined 12 clinical trials safety analysis; with dapagliflozin increased glucose excretion was supposed to rise. However, as shown in Figure 3, a familiar dose-dependent association with the UTI incidence is not shown. Although data proves that for the UTI development glucosuria is an enhancing risk factor, it should be done to detect possible contributing factors [(9)]. For example, recurrent UTI history in patients, including those managed with placebo, accomplished greater UTI rates that demonstrated a tendency to infection without glycosuria during trials

CONCLUSION:

This common 12 clinical trials security analysis shows; if dapagliflozin 5 or 10 mg once a day given for type 2 diabetes treatment shows minimum risk of UTI, but there is no proof of rise in pyelonephritis incidence. These infections were typically common in Type 2 Diabetes patients. Usually discontinuation and relapse were rare. Infections are usually mild to moderate, clinically treateble and it is not linked with obstacle.

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