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The Blood Pressure-Lowering Effect and Safety of Chlorogenic Acid from Green Coffee Bean Extract in Essential Hypertension

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Chlorogenic acids (CGA) in green coffee bean extract (GCE) reduce blood pressure in spontaneously hypertensive rats and humans. The authors examined the blood pressure-lowering effect and safety of CGA in patients with mild hypertension through a placebo-controlled, randomized clinical trial. Subjects (n=28) were randomized to receive treatment with CGA (140 mg/day) from GCE or placebo. Blood pressure, pulse rate, body mass index, routine blood test, hematochemistry, urinalysis, and subjective symptoms were recorded throughout the study. In the CGA group, but not the placebo group, blood pressure (systolic and diastolic) decreased significantly during the ingestion period. There was no difference in body mass index and pulse rate between groups, nor were there any apparent side effects. Thus, CGA from GCE is effective in decreasing blood pressure and safe for patients with mild hypertension.

Keywords blood pressure, functional foods, chlorogenic acid, green coffee beans, clinical trial

Introduction

Many functional foods reduce blood pressure (BP) (1,2). Polyphenols are well-known antioxidants that protect body tissues against damage caused by reactive oxygen species. Polyphenols are widely distributed in foods such as tomatoes, apples, chocolate, coffee, and tea (3). Many epidemiologic studies suggest that the consumption of polyphenol-rich foods prevents various kinds of diseases related to oxidative stress. For example, wine and tea might protect against coronary heart disease (4), whereas soy might protect against cancer (5).

Green coffee bean extract (GCE) has a high polyphenol content and is particularly rich in chlorogenic acids (CGA)(6). CGA are a family of esters that are formed by quinic acid and several hydroxycinnamic acids, particularly caffeic, ferulic, and *p*-coumaric acids,

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each of which forms three isomeric CGA by conjugating with the quinic acid hydroxyl group located at the 3, 4, or 5 position (7). The major CGA in GCE are caffeoylquinic (CQA), feruloylquinic, and dicaffeoylquinic (diCQA) acids, in a ratio of 70:19:11. The ratio of CQA isomers is 22:27:51 for 3-CQA, 4-CQA, and 5-CQA, respectively.

Suzuki et al. reported that in spontaneous hypertensive rats (SHR), the ingestion of GCE reduces BP in a dose-dependent manner (8). The single oral administration of 5-CQA, the major component of CGA in GCE, decreases BP in SHR, suggesting that the effect of GCE on BP is at least partially due to 5-CQA (8). The same group subsequently confirmed that both short-term and long-term oral administration of ferulic acid (4-hydroxy-3-methoxycinnamic acid), a metabolite of 5-CQA in humans (9), has hypotensive effects in SHR (10).

The present study used GCE (a natural product) instead of CGA (a chemical compound) to investigate the hypotensive effects in humans. The current authors recently demonstrated that the short-term ingestion of GCE in humans has a hypotensive effect and reported a dose-response relationship from 70 mg to 280 mg CGA per day (11). In the present study, the aim was to examine the hypotensive effect of long-term ingestion of CGA from GCE and its safety in patients with mild hypertension.

Materials and Methods

Forty Japanese patients with mild essential hypertension who were otherwise healthy were enrolled in this study. Mild essential hypertension was defined as systolic BP (SBP) of 140–159 mmHg and/or diastolic BP (DBP) of 90–99 mmHg. The patients were trying to modify their lifestyle through methods such as weight reduction, dietary sodium reduction, physical activity such as brisk walking, and modification of alcohol consumption. The present authors monitored their BP and lifestyle modifications over two months. Exclusion criteria included serious medical problems requiring specific treatment, pregnancy, or possible pregnancy. Of the 40 patients, 28 patients with mild essential hypertension after the two-month monitoring period were selected for analysis. Twelve patients did not meet the BP inclusion criteria. None of the subjects were taking antihypertensive agents.

Materials

The subjects received 125 mL/day fruit and vegetable juice mixed with GCE (0.48 g). The placebo consisted of the fruit and vegetable juice only. The CGA content in GCE determined by high-pressure liquid chromatography was 30.9% (w/w). Based on this value, the CGA consumption in the CGA group was determined to be 140 mg/day. This dose was chosen based on the findings of the authors' previous dose-response study (11).

Experimental Protocol

A double-blind, placebo-controlled, randomized clinical trial was conducted. Keycode data are kept only by the controller until the entire trial is completed and the patient data are fixed. This study was approved by the Ethics Committee of the Health Center, Isogo Central & Neurosurgical Hospital, Japan. After written informed consent was obtained, subjects were randomly allocated to either the placebo (n =14) or CGA (n =14) group. The subjects were required to keep a lifestyle case card to evaluate the extent of non-pharmacologic therapy with weight reduction, dietary sodium reduction, physical activity, and modification of alco-

hol consumption. In the analysis of BP and pulse rate, patients were instructed not to eat breakfast and to visit the hospital in the morning. BP and pulse rate were measured in a sitting position after resting for 5 min. This procedure was repeated three times, and the average of the three measurements was taken as the BP and pulse rate for assessment.

After a two-week run-in period, subjects ingested the drink containing 140 mg CGA (CGA group) or the placebo drink (placebo group) daily for 12 weeks. Each of the following measurements was taken throughout the run-in period, during the intake period, and after the intake period: BP, pulse rate, body mass index, routine blood test, hematochemistry, urinalysis, and subjective symptoms. Body mass index was calculated by dividing body weight (kg) by height (m) squared. Blood and urine samples were collected in the morning after an overnight fast. An analysis of subjective symptoms and side effects was performed by a physician based on the questionnaire survey.

Data and Statistical Analysis

All data were expressed as mean ± SE. Differences between the means of the two groups were evaluated by repeated measures two-way analysis of variance (ANOVA). A p value of less than 0.05 was considered to indicate statistical significance. A Mann-Whitney U test was performed for post hoc analysis. Outlier data were defined as data points greater than 1.5 box-lengths either below or above the 25^{th} and 75^{th} percentiles, respectively. Outliers were not involved in the statistical analyses, but are shown in the box plot. Statistical analysis was performed using SPSS 10.0J software for Windows (SPSS, Chicago, Illinois, USA).

Results

Hypotensive Effect

The subjects' characteristics are shown in Table 1. There was no significant difference in baseline characteristics between the two groups. There were also no significant differences between the two groups in the prevalence of patients on non-pharmacologic therapy, such as weight reduction, dietary sodium reduction, physical activity, and modification of alcohol consumption. None of the 28 subjects dropped out of the study, and all received all examinations during the study. Distributions of the BP values are shown in Figure 1, and the changes in BP for the two groups are shown in Figure 2. There was no significant

Table 1
Characteristics of the two groups

	Group	
	Placebo group*	CGA group*
Number of patients (male/female)	14(6/8)	14(5/9)
Age (years)	51 ± 8	52 ± 11
BMI (kg/m^2)	25.0 ± 3.5	23.8 ± 3.3
SBP (mmHg)	147 ± 5	145 ± 6
DBP (mmHg)	90 ± 4	91 ± 2

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.
*Each value represents the mean ± SD.

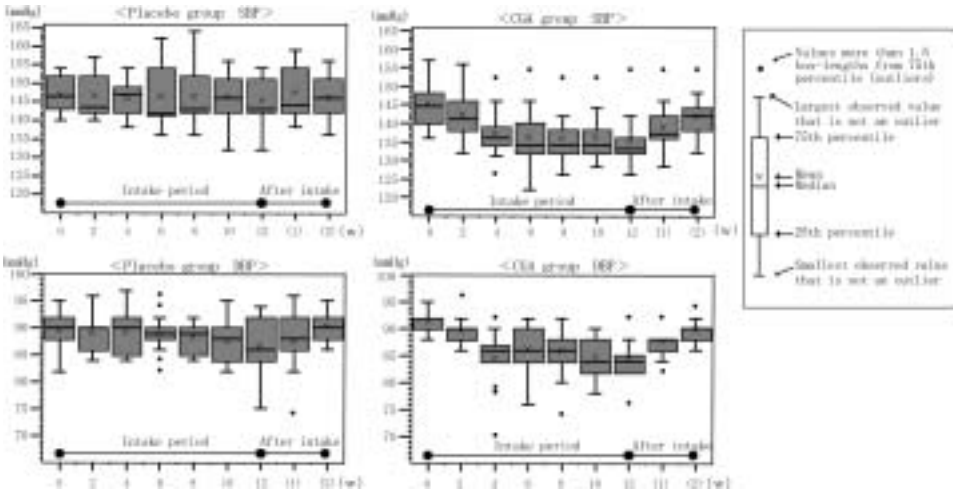

Figure 1. Distributions of blood pressure values.

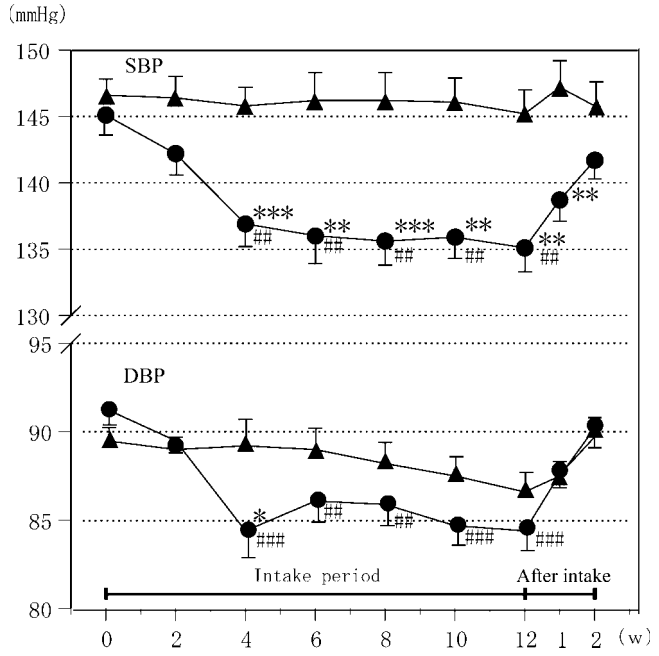

Figure 2. Change in BP: ▲, placebo group; ●, CGA group. Each value represents the mean ± SE (n=14). *p<0.05, **p<0.01, ***p<0.001 vs placebo group. #p<0.05, ##p<0.01, ###p<0.001 vs baseline value.

change in BP in the placebo group. In the CGA group, BP values decreased from 145 ± 1 / 91 ± 1 mm Hg at baseline to 142 ± 2 / 90 ± 1 mm Hg at 2 weeks, 137 ± 2 / 84 ± 2 mm Hg at 4 weeks, and 135 ± 2 / 84 ± 1 mm Hg at 12 weeks (SBP p <0.001, DBP p<0.05). SBP and DBP were significantly reduced in the CGA group compared to the placebo group.

Table 2
Change in pulse rate and body mass index

		Intake period (w)							After intake (w)	
	Group	0	2	4	6	8	10	12	1	2
Pulse rate (beats/min)	Placebo group	78 ± 2	78 ± 2	78 ± 2	77 ± 2	77 ± 2	77 ± 2	78 ± 2	78 ± 2	78 ± 2
	CGA group	76 ± 1	74 ± 1	74 ± 1	74 ± 1	73 ± 1	73 ± 1	72 ± 1	74 ± 1	75 ± 1
BMI (kg/m^2)	Placebo group	25.0 ± 0.9		25.0 ± 1.0		25.0 ± 1.0		25.0 ± 1.0		25.0 ± 1.0
	CGA group	23.8 ± 0.9		23.7 ± 0.9		23.8 ± 0.8		23.9 ± 0.8		23.8 ± 0.8

Each value represents the mean ± SE (n = 14).

Changes in pulse rate and body mass index are shown in Table 2. There was no significant difference between the two groups in these measures.

Safety

There were no serious side effects in either group, and all subjects completed the study. Long-term ingestion of CGA produced no changes in the serum biochemical variables (see Table 3). There was no significant change in serum iron, magnesium, copper, zinc, or vitamin B1 in the two groups (see Figure 3). A physician judged the general clinical safety with regard to side effects.

Discussion

Possible Mechanism

Lifestyle modification is recommended as a basic treatment for mild hypertension. Dietary modification through the use of functional foods is included as part of this non-pharmacologic approach. The present study evaluated the hypotensive effect of 12-week administration of CGA. This study appears to be the first to demonstrate a depressor effect of CGA from GCE following long-term ingestion in patients with mild hypertension. The present results are consistent with those of a previous study of short-term GCE ingestion in rats (8,10) and humans (11).

Ambulatory blood pressure monitoring (ABPM) provides information about BP during daily activity and sleep. The present authors incorporated no data on ABPM—a limitation that needs to be considered in future studies.

The hypotensive effect of CGA might involve nitric oxide (NO)-mediated vasodilation, as suggested by Suzuki et al. (8). The role of reactive oxygen species in hypertension is attracting considerable attention (12). Patients with uncontrolled hypertension have elevated levels of hydrogen peroxide and superoxide anions (13). Superoxide anions deplete NO bioavailability in endothelial tissue by reacting with NO to produce peroxynitrite ($ONOO^-$)(14). Many investigators have proposed that NO deficiency is a cause of hypertension (e.g., 14). Calver et al. suggested that NO-mediated dilation is reduced in hypertensive patients (15). CGA intake might improve NO bioavailability in hypertensive patients because ferulic acid, a metabolite of 5-CQA (9), scavenges superoxide (16) and exhibits hypotensive effects in SHR (10).

Safety

CGA are well-known polyphenols with anti-oxidative properties (3) and have long been considered to be protective factors against cancer (17). Therefore, their consumption might have potential health benefits. The Japanese consume approximately 1 g/day polyphenols from their diet (18), whereas Americans consume 1.1 g/day (19). In the present study, subjects ingested 140 mg of CGA from GCE daily for 12 weeks. Based on the average intake of polyphenols per day, the dose of CGA in the present study is likely to be within safety limits. Indeed, green coffee beans are commonly used as a supplement in processed foods and beverages in Japan, and people commonly ingest this ingredient in their daily diet. This study confirmed the dietary safety of CGA for patients with mild

Table 3
Change in serum biochemical variables

		Placebo group				CGA group			
		Baseline	4 weeks	12 weeks	After intake	Baseline	4 weeks	12 weeks	After intake
WBC	(/mm^3)	5429 ± 278	5254 ± 260	5854 ± 271	5615 ± 309	5436 ± 440	6393 ± 516	5771 ± 323	6464 ± 485
RBC	(×10000/mm^3)	456 ± 11	449 ± 11	438 ± 12	446 ± 41	452 ± 12	445 ± 12	445 ± 11	453 ± 9
Hb	(g/dl)	14 ± 1	14 ± 1	13 ± 1	14 ± 0.5	14 ± 0.5	14 ± 0.4	14 ± 0.4	14 ± 0.3
Ht	(%)	42 ± 1	41 ± 1	40 ± 2	41 ± 1	42 ± 1	42 ± 1	41 ± 1	42 ± 1
Platelet	(×10000/mm^3)	23 ± 1	24 ± 1	26 ± 1	25 ± 1	24 ± 2	26 ± 2	27 ± 2	26 ± 2
NEUT	(%)	56 ± 3	53 ± 3	59 ± 3	54 ± 3	53 ± 3	56 ± 3	50 ± 3	55 ± 4
EOSINO	(%)	3 ± 1	2 ± 0.3	2 ± 0.2	3 ± 0.5	3 ± 1	3 ± 1	3 ± 0.3	3 ± 1
BASO	(%)	1 ± 0.1	1 ± 0.1	1 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.6 ± 0.1
LYMPH	(%)	34 ± 3	39 ± 3	33 ± 3	38 ± 3	38 ± 2	35 ± 2	40 ± 3	36 ± 3
MONO	(%)	5 ± 1	5 ± 0.4	5 ± 0.4	5 ± 0.5	6 ± 0.4	5 ± 0.4	6 ± 0.3	5 ± 1
Total protein	(g/dl)	7.1 ± 0.1	7.4 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	7.4 ± 0.1	7.4 ± 0.1	7.4 ± 0.1	7.4 ± 0.1
Albumin	(g/dl)	4.3 ± 0.1	4.4 ± 0.1	4.4 ± 0.1	4.4 ± 0.1	4.6 ± 0.1	4.5 ± 0.1	4.5 ± 0.1	4.6 ± 0.1
AST	(IU/l)	25 ± 3	23 ± 2	25 ± 5	21 ± 2	21 ± 2	21 ± 2	22 ± 2	20 ± 2
ALT	(IU/l)	33 ± 8	25 ± 4	26 ± 6	23 ± 4	22 ± 3	21 ± 3	24 ± 3	21 ± 2
ALP	(IU/l)	301 ± 62	219 ± 33	243 ± 38	238 ± 39	175 ± 20	181 ± 24	183 ± 23	181 ± 24
γ GTP	(IU/l)	66 ± 24	53 ± 20	54 ± 23	51 ± 21	23 ± 4	23 ± 5	22 ± 4	25 ± 5
LDH	(IU/l)	327 ± 25	309 ± 31	291 ± 28	303 ± 30	318 ± 24	310 ± 24	323 ± 37	304 ± 23

(Continued)

Table 3
(continued)

		Placebo group				CGA group			
		Baseline	4 weeks	12 weeks	After intake	Baseline	4 weeks	12 weeks	After intake
Bood urea nitrogen	(mg/dl)	16 ± 1	14 ± 1	14 ± 1	14 ± 1	13 ± 1	13 ± 1	12 ± 1	13 ± 1
Creatinine	(mg/dl)	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.04	0.7 ± 0.03	0.7 ± 0.04	0.7 ± 0.04
Na	(mEq/l)	142 ± 0.5	141 ± 1	141 ± 0.5	141 ± 1	143 ± 0.5	142 ± 0.6	142 ± 0.3	141 ± 0.5
Cl	(mEq/l)	103 ± 1	103 ± 1	103 ± 1	103 ± 1	103 ± 0.5	103 ± 1	103 ± 0.5	103 ± 1
K	(mEq/l)	4.2 ± 0.1	4.3 ± 0.1	4.4 ± 0.1	4.4 ± 0.1	3.8 ± 0.1	4.2 ± 0.1	4.1 ± 0.1	4.3 ± 0.1
Ca	(mg/dl)	9.2 ± 0.1	9.2 ± 0.1	9.1 ± 0.1	9.2 ± 0.1	9.4 ± 0.1	9.4 ± 0.1	9.3 ± 0.1	9.2 ± 0.4
P	(mg/dl)	3.9 ± 0.2	3.6 ± 0.2	3.3 ± 0.2	3.5 ± 0.1	3.4 ± 0.2	3.6 ± 0.2	3.3 ± 0.1	3.5 ± 0.2
Cholesterol	(mg/dl)	193 ± 11	208 ± 10	205 ± 12	206 ± 12	194 ± 10	197 ± 8	191 ± 9	194 ± 8
LDL–Cholesterol	(mg/dl)	96 ± 9	112 ± 10	110 ± 10	113 ± 11	108 ± 7	109 ± 6	111 ± 7	114 ± 7
HDL–Cholesterol	(mg/dl)	61 ± 6	70 ± 7	67 ± 7	70 ± 7	55 ± 4	57 ± 5	56 ± 5	59 ± 5
Triglyceride	(mg/dl)	137 ± 25	109 ± 23	133 ± 46	122 ± 40	140 ± 19	132 ± 20	144 ± 27	133 ± 21
Uric acid	(mg/dl)	4.7 ± 0.5	4.7 ± 0.5	4.2 ± 0.4	4.4 ± 0.4	5.2 ± 0.5	5.5 ± 0.4	5.7 ± 0.5	5.3 ± 0.5
Blood sugar	(mg/dl)	109 ± 8	99 ± 5	110 ± 11	103 ± 7	89 ± 2	91 ± 3	90 ± 5	97 ± 2

Each value represents the mean ± SE (n = 14).

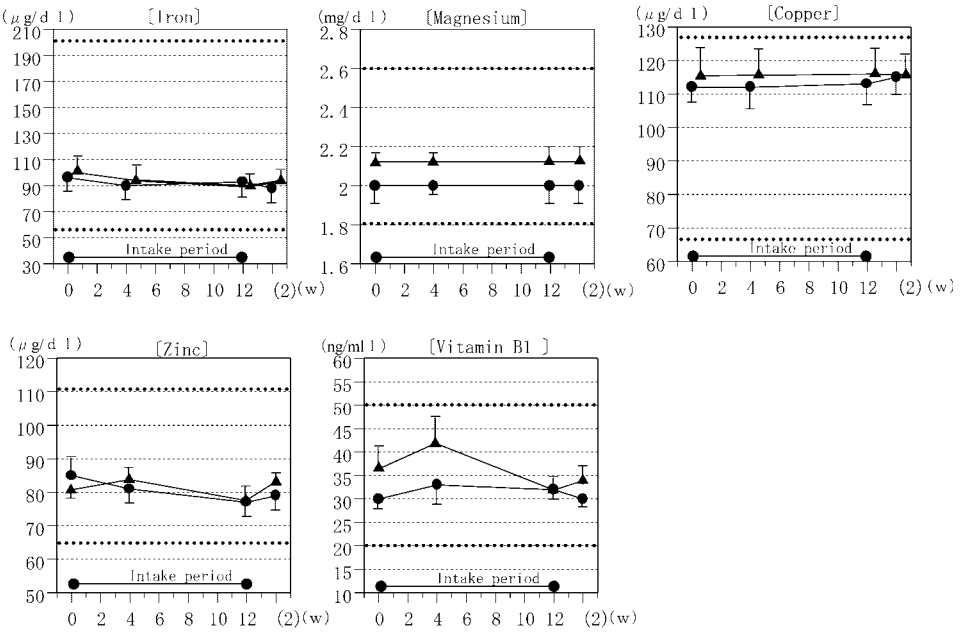

Figure 3. Changes in serum mineral: ▲, placebo group; ●, CGA group. Each value represents the mean ± SE (n=14).

hypertension. No rebound phenomena of BP was observed during the two-week period following CGA ingestion, and there were no apparent side effects. The ingestion of CGA is reported to decrease serum minerals in rats due to its metal-binding phenolic structure (20, 21). There was no change, however, in serum iron, magnesium, copper, zinc, or vitamin B1 in the present study.

Olthof et al. reported that CGA might be partly responsible for elevated homocysteine concentrations, a risk factor for cardiovascular disease, in coffee drinkers (22). In their experiments, they used 2 g CGA/day, an amount approximately 14 times higher than that in the present study. Also, the time interval of their experiment was 1 week, while ours lasted for 12 weeks. The acute ingestion of higher levels of CGA over the short term might be responsible for the potential risk for cardiovascular disease in humans.

Difference between GCE and Roast Coffee

Coffee beverages are a main source of CGA (3). CGA are also called roasted coffee extract, as CGA are usually extracted from roasted coffee beans. Many studies focus on the association between BP and coffee consumption (23–25). The role of coffee in the development of hypertension is controversial: not only is coffee drinking linked to both elevated and reduced BP, but it is also reported to have no effect on BP at all (23–25). Corti et al. (26) suggested that the inconsistencies might be partially attributed to methodologic differences and the failure to control for confounding variables, including baseline BP, smoking habit, sex differences, dietary and alcohol intake, stress, and obesity, as well as inaccurate determinations of daily coffee and caffeine intake. The present study demonstrated the hypotensive effects of GCE, which is manufactured without the roasting process. The differences in the hypotensive effects of the present and previous studies

might also be due to differences in the coffee roasting methods. Clifford (27) reported that CGA might undergo severe structural changes, such as hydrolysis or polymerization, when heated to a high level. These changes might lead to a significantly different product/activity profile. Typical compositional changes in coffee beans during roasting include the degradation of trigonelline, loss of proteins, loss of carbohydrates, formation of melanoidin, and degradation of CGA (7). It is possible that some components of coffee beans that might affect BP are generated or lost, resulting in the loss of hypotensive effects from roasted coffee extract.

The present study is remarkable in terms of focusing on the biologically active materials in green coffee rather than roasted coffee. Thus, the profound effects of these materials could be more easily clarified as they were not altered by the degradation or formation of any material in the coffee beans nor by any structural changes during roasting. In conclusion, the data in the present study demonstrated the hypotensive effect and dietary safety of CGA from GCE in patients with mild hypertension.

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