

## **Rosiglitazone Decreases C-Reactive Protein to a Greater Extent Relative to Glyburide and Metformin over Four-Years in Spite of Greater Weight Gain: Observations from ADOPT (A Diabetes Outcome Progression Trial)**

Running Title: Changes in CRP in ADOPT

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*Objective:* C-reactive protein (CRP) is closely associated with obesity and cardiovascular disease in both diabetic and non-diabetic populations. In short term, commonly prescribed anti-diabetic agents have different effects on CRP; however, the long-term effects of those agents are unknown.

*Research Design and Methods:* In ADOPT (A Diabetes Outcome Progression Trial), we examined long-term effects of rosiglitazone, glyburide, and metformin on CRP and the relationship between CRP, weight and glycemic variables in 904 subjects over 4 years.

*Results:* Baseline CRP was significantly correlated with HOMA IR, HbA1c, BMI, waist circumference, and waist/hip ratio. CRP reduction was greater in the rosiglitazone group by -47.6% relative to glyburide and -30.5% to metformin at 48 months. Mean weight gain from baseline (at 48 month) was 5.6 kg with rosiglitazone, 1.8 kg with glyburide and -2.8 kg with metformin. The change in CRP from baseline to 12 months was correlated positively with change in BMI in glyburide ( $r=0.18$ ) and metformin ( $r=0.20$ ) groups but not the rosiglitazone ( $r=-0.05$ ,  $p=NS$ ) group. However, there was no longer a significant correlation between change in CRP and change in HOMA IR, HbA1c or waist-hip ratio in any of the three treatment groups.

*Conclusions:* Rosiglitazone treatment was associated with durable reductions in CRP independent of changes in insulin sensitivity, HbA1c, and weight gain. CRP in the glyburide and metformin groups was positively associated with changes in weight, but this was not the case with rosiglitazone.

C-reactive protein (CRP) has been traditionally viewed as one of the acute phase reactants and is a sensitive systemic marker of inflammation and tissue damage. This acute phase inflammatory protein is predominantly secreted in hepatocytes, its release being regulated by interleukin 6 (IL-6) and other inflammatory cytokines (1). Other studies have shown that extra-hepatic sources of CRP production from adipocytes could point to a more systemic generation of CRP in the body after stimulation by inflammatory cytokines and more specifically, by the adipokine, resistin (1).

Both population-based and prospective studies have demonstrated a clear association between CRP and an increased risk of cardiovascular disease and stroke (2). The magnitude of the CRP prediction for future CVD events is similar to other traditional CVD risk factors (cholesterol, hypertension, and smoking status) (2). CRP also may be a mediator of atherosclerosis (1, 3-6). However, there is no available evidence from clinical trials that reduction in CRP directly reduces or prevents further CVD events.

The production of CRP by adipocytes may partially explain why CRP levels are elevated in patients with the metabolic syndrome (1), in whom CVD risk is increased. The strong association between CRP and body adiposity has been observed in both diabetic (7) and non-diabetic subjects (8-11), and was only moderately attenuated by adjustment of insulin sensitivity. This suggests that obesity, insulin resistance and the metabolic syndrome are inter-connected in a proinflammatory state that may be mediated by cytokines and subsequently cause elevated levels of CRP. Elevated CRP concentrations have been shown to predict an increased risk of diabetes (9, 12, 13). Therefore, it may play an active role in the causal relationship between obesity, diabetes and the high risk of

future CVD events. Statins (14) and weight loss (15-17), that can reduce CRP levels and improve other CVD risk factors, also show benefits in reducing CVD events.

Glucose lowering agents have different effects on CRP, weight, insulin sensitivity, and glycemic control in the treatment of type 2 diabetes. The thiazolidinediones (TZD) rosiglitazone and pioglitazone, insulin sensitizing oral anti-diabetic agents, have been shown to be effective in reducing CRP in several short-term (6 months or less) studies (18-21). However, it is not clear if the weight gain associated with TZDs could attenuate the effect on CRP reduction over larger periods of time. In short-term studies, metformin moderately decreases CRP (16, 18), increases insulin sensitivity and produces weight loss (16). The longer term relationships between these three commonly used oral antidiabetic agents (TZDs, sulfonylureas, and metformin) with CRP, insulin sensitivity, weight, and glycemic control have not been previously investigated. A Diabetes Outcome Progression Trial (ADOPT) provided the opportunity to evaluate the effects of members of these three classes of oral agents in a randomized, double-blind, controlled trial involving over 4000 patients, treated for a median time of four years (22, 23). This study compared the efficacy and safety of rosiglitazone, glyburide and metformin in newly diagnosed ( $\leq 3$  years) drug-naïve type 2 diabetic patients. We have previously reported the association of CRP, obesity, and insulin resistance in the baseline examination of the ADOPT study (7). We discuss here a sub-group analysis of ADOPT where we examine prospectively the long-term effects of rosiglitazone, glyburide and metformin on CRP reduction and the relationship between CRP, insulin sensitivity, weight and glycemic variables.

## RESEARCH DESIGN AND METHODS

**Subjects and Study Design.** ADOPT randomized 4351 subjects from Europe and North America who were drug naïve and recently diagnosed with type 2 diabetes. The study design of this international, multicenter trial has been previously described (23). A subgroup of 904 subjects from investigative centers in the United States, who had baseline CRP values were included in this analysis. Of those 904 subjects, 304 were randomized to rosiglitazone, 302 to glyburide, and 298 to metformin. A total of 783 subjects had both baseline and at least one on-therapy value for CRP.

Briefly, eligible subjects were 30 to 75 years of age and had a fasting plasma glucose concentration between 7 and 10 mmol/l despite diet and exercise intervention. Eligible subjects were randomized to double-blind treatment with 1:1:1 ratio of the three glucose lowering medications. Initial daily doses were 4 mg of rosiglitazone, 500 mg of metformin, or 2.5 mg of glyburide and the dose was titrated to the maximum effective daily dose (4 mg of rosiglitazone twice daily, 1 g of metformin twice daily, and 7.5 mg of glyburide twice daily). Uptitration of study medication was required at each visit when the fasting plasma glucose level was 7.8 mmol/l or greater, while a reduction in the dose of study medication was permitted if adverse events occurred. The primary outcome was time to monotherapy failure on maximum-tolerated dose of the study medication, defined as a fasting plasma glucose >10 mmol/l (>180 mg/dl) on two successive occasions or by independent adjudication. The study protocol was reviewed and approved by institutional review boards for each center and participants gave written, informed consent before participating in the study.

**Measurements and Assays.** Subjects had anthropometric measurements (weight, height, waist and hip circumference) using standardized procedures across all study

centers. Fasting blood samples were drawn for measurement of metabolic variables including plasma glucose, HbA1c, immunoreactive insulin and CRP. Metabolic assessments were collected at baseline and every 6 months over 4 years of treatment. Anthropometric measurements were collected at baseline and at yearly visits.

All assays were performed at a central laboratory. Plasma glucose was measured using a hexokinase method (Olympus America Inc., Melville, NY). HbA1c was determined using the Biorad Variant Hemoglobin A1c assay (Hercules, CA). Serum immunoreactive insulin was quantified using a double antibody radioimmunoassay (Linco, St. Louis, MO). Highly sensitive CRP was measured by fixed time nephelometry (reporting range: 0.2 mg/L – 10 g/L, CV: <7%; Dade Behring, Deerfield, IL). Insulin sensitivity was estimated with HOMA2 IR using software available at <http://www.dtu.ox.ac.uk/homa>.

**Statistical Methods.** All statistical analyses were performed with SAS version 8.2 (SAS Institute Inc., Cary, NC). All randomized patients who received at least one dose of study medication, had baseline CRP and at least one post-baseline assessment of CRP were included in the analysis. While the greatest reduction in CRP was observed at 6 months, 12 month correlations are presented due to availability of data for all parameters evaluated at this time point.

CRP and HOMA IR values were log-transformed to achieve a normal distribution prior to analysis. Results are presented as median (first quartile, third quartile) at baseline and the percent change from baseline at each follow-up time. Changes in CRP and weight over time were analyzed by a normal errors repeated measures model adjusted for baseline value and gender (24). Partial correlation analyses were performed using the Spearman method; the p-value for differences between groups was determined by the

Wilcoxon test. Other continuous data are presented as mean  $\pm$  SE. A two-sided  $p \leq 0.05$  was considered statistically significant.

## RESULTS

Of 904 participants, 706 remained at month 12 (239 in rosiglitazone, 220 in glyburide, and 247 in metformin), and 413 at month 48 (153 in rosiglitazone, 112 in glyburide, and 148 in metformin). As reported previously, major reasons for withdrawals were due to reaching monotherapy failure endpoint, adverse events, and consent withdrawal (22).

Baseline anthropometric and metabolic variables are listed in Table 1. Females were more obese, insulin resistant and had markedly greater CRP levels. However, baseline CRP values between the three treatment groups were comparable [geometric mean 3.9 mg/L in the rosiglitazone, 3.8 mg/L glyburide, and 3.7 mg/L metformin groups].

At baseline CRP was positively correlated with BMI ( $r = 0.44$ ), waist circumference ( $r = 0.40$ ), waist/hip ratio ( $r = 0.11$ ) and insulin resistance ( $r = 0.30$ ) (all  $p < 0.001$ ). However, the correlation between CRP and HbA1c ( $r = 0.10$ ,  $p = 0.004$ ) was relatively weaker.

Percent change in CRP over time by treatment group is illustrated in Figure 1A. CRP declined over time in all three treatment groups, with the greatest decrease in the rosiglitazone group, intermediate in the metformin group, and least in the glyburide group. CRP declined by over 40% within 6 months of initiation of rosiglitazone treatment, compared to less than 20% with glyburide and metformin. At month 12, CRP was reduced from baseline by 42% in the rosiglitazone group, 10% in the glyburide group, and 26% in the metformin group. After 12 months, CRP continued to decrease gradually in all treatment groups. After 48 months, the CRP reduction was greater in the rosiglitazone group, 47.6% ( $p < 0.001$ ) relative to the glyburide group and 30.5% ( $p = 0.004$ )

relative to the metformin group. While the absolute changes in CRP were greater in women than in men, the percent changes in CRP over time were comparable between genders (Figures 1B and 1C).

Weight gain was observed in the rosiglitazone and glyburide groups, while weight loss was seen in the metformin group (Figure 2). At month 12, patients treated with rosiglitazone or glyburide gained an average of 3.6 kg and 2.8 kg respectively, while patients treated with metformin lost 2.2 kg. At month 48, patients treated with rosiglitazone had significantly greater weight gain compared to glyburide (3.8 kg,  $p < 0.0001$ ) and metformin (8.5 kg,  $p < 0.0001$ ). Changes from baseline in HbA1c, and HOMA IR by treatment in this subgroup were similar to those in the entire study population (22). As previously reported (22), subjects treated with rosiglitazone demonstrated greater improvement in HOMA IR compared to both glyburide and metformin. Rosiglitazone provided sustained decreases in long-term HbA1c compared to both glyburide and metformin; however, during the first year after commencing treatment, HbA1c reduction was greatest with glyburide and least with rosiglitazone. Changes in waist, hip circumference, and waist/hip ratio in each treatment group observed in this cohort were similar to the entire cohort as well. Subjects treated with rosiglitazone and glyburide had an increase in waist and hip circumference, while a decrease in both waist and hip circumference was observed in subjects with metformin (22). The change in waist/hip ratio between the treatment groups was not different (22).

The relationships between the change in CRP from baseline to one year and the change over the same time interval in anthropometric and metabolic variables are presented in Table 2. CRP showed a weak, positive correlation with BMI in the glyburide and metformin groups and with waist circumference in the glyburide group. With rosiglitazone, CRP was not

correlated with glycemic or anthropometric variables. Of note, the correlation between change in CRP and change in BMI with rosiglitazone treatment trended to be negative, but was not significant ( $r = -0.052$ ,  $p = 0.464$ ).

## **DISCUSSION**

We have demonstrated for the first time a greater reduction in CRP in newly diagnosed patients with type 2 diabetes treated for four years with rosiglitazone compared to glyburide and metformin. These observations occurred in both men and women and are in line with those from several small, short-term studies in patients with type 2 diabetes treated with rosiglitazone (19-21), troglitazone (18) and pioglitazone (19, 25). Treatment with rosiglitazone or pioglitazone results in a rapid reduction in CRP that occurs as early as two weeks after initiation of treatment (25, 26), well before the full effect of TZDs on glucose lowering, lipid profile changes and weight gain are manifest. This temporal difference in changes in CRP and metabolic markers with rosiglitazone suggests an improvement in adipose tissue metabolism could be a prelude for other, later metabolic changes. Unlike with rosiglitazone, the reduction in CRP in the glyburide and metformin groups was smaller and gradual over time. Previous studies with metformin in subjects with type 2 diabetes (18) and impaired glucose tolerance (16) have made similar observations of a modest reduction in CRP levels.

In previous cross-sectional reports CRP was positively associated with obesity in both diabetic and non-diabetic patients (7-11). The current analysis using change in CRP and BMI from baseline to 12 months shows that rosiglitazone treatment disassociates the relationship between CRP and BMI; in contrast, the relationship is positive in both the glyburide and metformin groups as has been shown in observational studies (7, 8, 10, 11). Subjects treated with rosiglitazone

experienced weight gain over time; however, this increase in weight occurred gradually and was not accompanied with an increase in CRP. This may possibly be due to the increase in subcutaneous adipose tissue and fluid retention that can be attributed to rosiglitazone. The correlation between CRP and waist circumference or WHR followed a similar pattern.

There was a strong positive correlation between CRP and insulin resistance at baseline in all three groups. However, the changes from baseline to one year in these parameters in the rosiglitazone group were not significant. This was quite unexpected, since changes in CRP and insulin resistance over time in the rosiglitazone group would have been predicted to be positively correlated. This observation suggests that rosiglitazone regulates CRP and insulin resistance through different mechanisms, which have not yet been elucidated.

A weak correlation between CRP and HbA1c was observed in the cohort at baseline, in keeping with observations in non-diabetic (27) and elderly type 2 diabetic subjects (28). This probably reflects subclinical microinflammation of the vasculature associated with increased blood glucose. However, in this analysis, improvement in HbA1c after initiation of glucose-lowering therapy did not correlate with the changes in CRP with all three treatments. In keeping with glucose not being an important determinant of CRP, in ADOPT over the duration of the study HbA1c trended upward with both glyburide and metformin, with a slope of 0.24% and 0.14% per year respectively (22), while CRP values trended downward over time in both groups. This observation also suggests that different pharmacological agents affect HbA1c and CRP through different pathways.

Recently, evidence from large population-based and prospective studies provided support that systemic inflammation

biomarkers, such as CRP, may be integrated into the algorithm when calculating the risk of future CVD events (2). Some investigators have challenged the importance of CRP in prediction of CHD (29) using an area under the receiver operating curve (AROC) approach while others have pointed out limitations of the AROC approach (30). Furthermore, there is little data specifically addressing the role of CRP in predicting future CVD events in patients with type 2 diabetes. CRP might possibly be checked periodically along with other CVD risk factors in patients at higher risk of developing cardiovascular disease but probably should not be used at this time in clinical practice to follow the effect of glycemic interventions.

The discrepancy between the possible benefit in surrogate markers (19-21) and even in atherosclerosis (31) and CVD events with TZDs is not well understood. In a recent publication of a rosiglitazone meta-analysis (32), an increased risk of myocardial infarction and CVD deaths was observed in combined small, short-term trials. However, this increased risk in CVD death was not observed in large, long-term trials. While ADOPT (22) had a low rate of CVD events, the interim analysis from the Rosiglitazone Evaluated for Cardiovascular Outcomes Study (RECORD) (33) (vs metformin or sulfonylurea) was based on adjudicated events and showed statistically insignificant increases in myocardial infarction and statistically insignificant decreases in CVD death. In PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE) (34), pioglitazone improved glycemic control and lipoproteins relative to placebo, but these benefits did not translate to expected significant decreases in CVD outcomes as defined for the primary endpoint (although a secondary cardiovascular endpoint was significantly reduced with pioglitazone). C-reactive protein concentration was not assessed in

PROACTIVE. Several possibilities for the discrepancy between the lack of positive effects on CVD and the beneficial effects on surrogate markers include chance due to low power and short duration of many studies; alternatively surrogates such as CRP or measures of atherosclerosis may not be informative for TZDs, as was the case with the HDL-raising medication torcetrapib (35, 36). Another possibility is that TZDs may have other effects which are not understood and could potentially counter balance the effects of reducing inflammation. Any benefits of CRP reduction by TZDs may only be adequately evaluated in a long-term study for CVD outcomes in which variables such as glucose and lipids are well controlled on therapy. Thus, at this time we believe the long-term effect of TZDs should be viewed largely for their improvement in adipose tissue metabolism, modulation of endocrine functionality of adipocytes and durability of glycemic control, and therefore, partially reducing the long-term burden for atherogenesis in patients with type 2 diabetes. In conclusion, we have reported the long-term differential effects of three commonly used anti-diabetic oral agents on the systemic inflammatory biomarker CRP in recently diagnosed type 2 diabetic subjects. Treatment with rosiglitazone was associated with a rapid and durable reduction in CRP independent of changes in insulin sensitivity, HbA1c, and weight gain. Treatment with glyburide and metformin was associated with a moderate and gradual reduction in CRP and was partly associated with changes in weight, but independent of glycemic control and insulin sensitivity. The possible value of CRP reduction by glucose lowering therapy for future CVD events needs to be considered with other CVD risk factors in patients with type 2 diabetes. This issue needs to be evaluated in larger, longer term clinical trials with adequate sample and adjudication of cardiovascular events.

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## **FIGURE LEGENDS**

Figure 1: Percent (A-C) changes from baseline in CRP in different treatment groups. Data are change  $\pm$  SE. Rosiglitazone is in blue, metformin green and glyburide red. Data are shown for the whole cohort (A), females (B) and males (C) over time in different treatment groups.

Figure 2: Change from baseline in weight in different treatment groups. Rosiglitazone is in blue, metformin green and glyburide red.

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Table 1: Metabolic and Anthropometric Variables in North American Subjects with CRP Value at Baseline<sup>2</sup>

Parameter	Male (N=467)	Female (N=437)	Total (N=904)
CRP <sup>1</sup> (mg/L)			
Median, (Q1, Q3)	2.5, (1.3, 5.1)	6.2, (2.9, 10.2)***	4.0, (1.9, 8.4)
HOMA IR <sup>1</sup> (%)			
Median, (Q1, Q3)	3.1, (2.2, 4.5)	3.8, (2.5, 5.3)***	3.5, (2.3, 5.0)
HbA1c (%)			
Mean ± SD	7.5 ± 0.99	7.4 ± 0.94	7.5 ± 0.97
Age (years)			
Mean ± SD	55.9 ± 10.16	54.5 ± 10.67**	55.2 ± 10.42
Weight (kg)			
Mean ± SD	100.7 ± 20.7	93.3 ± 20.9***	97.1 ± 21.1
BMI (kg/m <sup>2</sup> )			
Mean ± SD	32.1 ± 5.96	35.2 ± 7.59***	33.6 ± 6.97
Waist Circumference (cm), n	467	436	903
Mean ± SD	109.0 ± 15.34	105.8 ± 16.17**	107.4 ± 15.82
Waist/ Hip Ratio			
Mean ± SD	0.97 ± 0.061	0.90 ± 0.079***	0.94 ± 0.080

1. Data were log-transformed and expressed as median and 25<sup>th</sup> and 75<sup>th</sup> quartiles

2. Data from subjects who had baseline CRP value

Wilcoxon test indicated significant differences between male and female (\*P<0.05, \*\*P<0.01, \*\*\*P<0.0001)

Abbreviations: HOMA IR = homeostasis model, insulin resistance; WC = waist circumference; WHR = waist to hip ratio; CRP = C-reactive protein; BMI = body mass index

Table 2: Correlations of Changes from Baseline to 12 months in CRP with Like Changes in Metabolic and Anthropometric Parameters

	Treatment Group			
	Rosiglitazone	Glyburide	Metformin	Total
HOMA IR	-0.035 p=0.631	0.082 p=0.285	0.0053 p=0.940	0.090 p=0.031
HbA1c	0.089 p=0.210	0.048 p=0.513	0.052 p=0.454	0.046 p=0.255
BMI	-0.052 p=0.464	0.176 p=0.016	0.201 p=0.003	0.055 p=0.178
WC	-0.002 p=0.972	0.236 p=0.001	0.124 p=0.071	0.090 p=0.024
WHR	0.052 p=0.460	0.017 p=0.813	0.008 p=0.898	0.032 p=0.423

Abbreviations: HOMA IR = homeostasis model, insulin resistance; WC = waist circumference; WHR = waist to hip ratio; CRP = C-reactive protein; BMI = body mass index

Figure 1

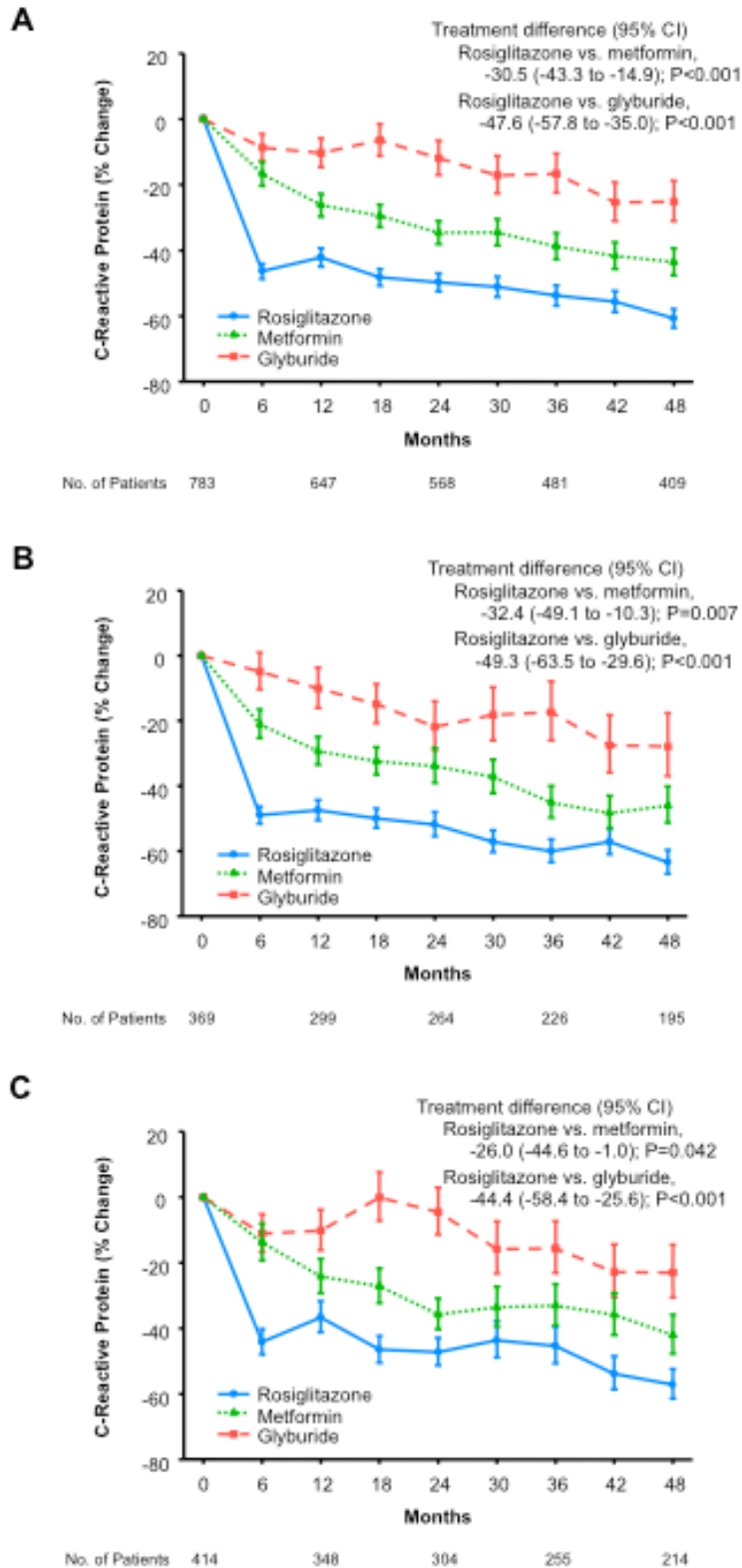


Figure 2

