The recent discovery of the endocannabinoid system has led to the development of promising treatments for patients with obesity and associated cardiometabolic risk factors. Basic research has demonstrated that the endocannabinoid system plays an integral role in the regulation of food intake, metabolism, and storage. Research with the endocannabinoid receptor antagonist rimonabant has demonstrated statistically significant improvements in body weight, fasting insulin levels, glucose tolerance, high-density lipoprotein cholesterol levels, serum triglyceride levels, and waist circumference, compared with placebo. Rimonabant has also produced statistically significant improvements in inflammatory markers. Research with rimonabant has demonstrated sustained efficacy for as long as 2 years when used in conjunction with a reduced-calorie diet and moderate physical activity. Rimonabant is the first cannabinoid receptor 1 antagonist to be marketed in Europe and the first to file a New Drug Application in the United States. It may provide a novel therapeutic strategy for the treatment of patients with obesity and associated cardiometabolic risk factors.

The Endocannabinoid System

The antiemetic and appetite-inducing effects of Δ⁹ tetrahydrocannabinol, which is the active ingredient in marijuana, have been known for many decades. Despite the long-standing use of this natural compound, its structure was not fully understood until 1964. It was not until the 1990s that receptors for Δ⁹ tetrahydrocannabinol and its endogenous ligands, or endocannabinoids, were identified. The endocannabinoid system is made up of cannabinoid (CB) receptors, endogenous ligands, and enzymes for the synthesis and degradation of the ligands. It is a complex signaling system that appears to have been preserved in all vertebrates.

Endocannabinoid Receptors

Cannabinoid receptor 1 is a G protein-coupled receptor that modulates Ca²⁺ and K⁺ channels in a pertussis toxin-sensitive manner. Cannabinoid receptor 1 is widely distributed throughout the brain in a complex network of interconnected circuits joining parts of the prefrontal cortex, amygdala, and nucleus accumbens with other regions of the limbic system. This network controls the hedonic aspects of such behaviors as food intake, sharing neural connections with the hypothalamus, which influences cravings, satiety signals, and metabolism.

Although CB₁ was initially identified in the brain, subsequent work has identified CB receptors peripherally throughout the body, most notably in adipose tissue and nerve tissue innervating the gastrointestinal tract. Cannabinoid receptor 1 is also found in the adrenal gland, liver, muscle tissue, pituitary gland, testis, and thyroid gland. Another cannabinoid receptor, CB₂, is abundant in immune cells, red blood cells, and keratinocytes. It is also present in the brain.

This continuing medical education supplement is supported by an educational grant from sanofi-aventis US.
Endocannabinoid Activity

Endocannabinoids are endogenous ligands that bind to the cannabinoid receptors. They are metabolites of long-chain polyunsaturated fatty acids. There are two well-described endocannabinoids that stimulate the CB₁ receptor: 2-arachidonoylglycerol (2-AG) and arachidonoylethanolamine (AEA). Arachidonoylethanolamine is also referred to as anandamide, after the Sanskrit word for “internal bliss.” Anandamide has been shown to increase feeding behavior in a number of animal studies, and this effect is thought to be centrally mediated. Levels of central endocannabinoids decline during food deprivation, but increase during ad libitum feeding. Endocannabinoids are also found in the digestive tract, where they modulate gastric emptying, as well as intestinal motility and secretion. In addition, endocannabinoids are involved in adipocyte differentiation.

Endocannabinoids are highly lipophilic and consequently cannot be stored in vesicles, as other neurotransmitters can. They are produced “on demand” and act locally to regulate such important activities as nutrient intake, transport, metabolism, and storage. Once synthesized, anandamide and 2-AG are released from the presynaptic neurons into the synaptic space, where they bind—in a retrograde manner—to CB₁ receptors of the presynaptic neurons. Thus, they essentially function as synaptic retrograde messengers (Figure 1). Once bound to the CB₁ receptors on the presynaptic neurons, the endocannabinoids initiate a sequence of events that leads to a decrease in the release of inhibitory neurotransmitters (e.g., γ-aminobutyric acid [GABA]) from the presynaptic neurons. Normally, the GABA released by presynaptic neurons has an inhibitory effect on postsynaptic neurons.

The resultant net effect of endocannabinoids is to increase activity (i.e., disinhibition) of the postsynaptic neurons. Anandamide is subsequently rapidly inactivated by fatty acid amide hydrolase (FAAH), and 2-AG is degraded by monoacylglycerol lipase. Thus, the regulation of the signaling actions of endocannabinoids is tightly controlled by their synthesis, release, reuptake, and ultimate degradation (Figure 1).

Endocannabinoids have been shown to play a key role in promoting weight gain in obese patients. When endocannabinoid concentrations in adipose tissue biopsies were compared from lean postmenopausal women (n=20) and obese postmenopausal women (n=20) following weight loss, levels of anandamide and 2-AG were increased 35% and 52%, respectively.
in the obese women.\textsuperscript{6} However, levels of CB\textsubscript{1} and FAAH were not affected by the weight loss, suggesting that dysregulation of the endocannabinoid system in patients with obesity is primary, rather than secondary, to the obese state.\textsuperscript{6}

\textbf{Cannabinoid Receptor 1 Antagonists}

Because of the recently understood role of the endocannabinoid system in promoting human obesity, CB\textsubscript{1} antagonists have been developed to block the effects of endocannabinoids.\textsuperscript{7,8} These CB\textsubscript{1} antagonists have been tested extensively, and the data have demonstrated a therapeutic benefit for this class of medications in treating patients with multiple cardiometabolic risk factors associated with visceral adiposity.\textsuperscript{7,8} Cannabinoid receptor 1 antagonists have been shown to have multiple central and peripheral effects in laboratory animals.\textsuperscript{7} The activation of CB\textsubscript{1} receptors in the hypothalamus mediates food-deprived hunger, whereas CB\textsubscript{1} agonism in the nucleus accumbens shell mediates the hedonically driven motivation to consume highly palatable foods, such as fats and sweets.\textsuperscript{7} One clinical implication for inhibiting the central effects of endocannabinoids with CB\textsubscript{1} antagonists is decreased food consumption, particularly the cravings that may be associated with obesity.

In terms of peripheral effects, CB\textsubscript{1} receptors regulate the synthesis of adiponectin—a cytokine that is inversely associated with cardiovascular risk factors—in white adipose tissue.\textsuperscript{5,9} Cannabinoid receptor 1 antagonism in adipocytes leads to increased adiponectin production and decreased lipogenesis. Clinically, these effects translate into an improvement in dyslipidemia, a decrease in insulin resistance, and a decrease in cardiometabolic risk.\textsuperscript{8,9}

The blockade of CB\textsubscript{1} in muscle tissue results in increased glucose uptake and decreased insulin resistance.\textsuperscript{17} In the liver, CB\textsubscript{1} blockade has the effect of decreasing the production of the lipogenic transcription factor SREBP-1c (sterol regulatory element binding protein 1c), which, in turn, decreases the synthesis of its targets, acetyl coenzyme-A carboxylase and fatty acid synthase. This change results in decreased de novo fatty acid synthesis.\textsuperscript{10,11} Cannabinoid receptor 1 has been shown to mediate the degradation of FAAH in the liver.\textsuperscript{10,11} Cannabinoid receptor 1 antagonists can reverse this effect, blocking the pathway to hepatic lipogenesis.\textsuperscript{10,11} Thus, CB\textsubscript{1} antagonists may ultimately lead to reversal of hepatic steatosis, resulting in an improvement in dyslipidemia and insulin resistance.

In summary, endocannabinoid receptor antagonism works through a variety of different mechanisms. Endocannabinoid receptor antagonists have been shown to decrease food intake, increase adiponectin, decrease lipid accumulation, improve glucose tolerance, and reduce fatty acid synthesis. Figure 2 presents mechanisms and clinical implications regarding the central and peripheral effects of CB\textsubscript{1} blockade.

\textbf{Rimonabant in Obesity (RIO) Clinical Trials}

Selective CB\textsubscript{1} antagonists have potential to be effective in the treatment of patients with multiple cardiometabolic risk factors, including visceral adiposity and insulin resistance. The first selective CB\textsubscript{1} antagonist to be developed—rimonabant—has been examined extensively in a series of registration clinical trials titled the Rimonabant In Obesity (RIO) trials.\textsuperscript{12-15} In these clinical trials, the effect of treatment with rimonabant (5 mg/d or 20 mg/d) on cardiometabolic disorders associated with visceral adiposity and insulin resistance have been examined.
The RIO-North America study (N=3045) and RIO-Europe study (N=1508) examined the effects of rimonabant on weight-stable patients with a body mass index (BMI) greater than or equal to 30, or a BMI greater than 27 with treated or untreated dyslipidemia or hypertension. The RIO-Lipids study (N=1036) examined the effects of rimonabant on overweight or obese patients with dyslipidemia. The RIO-Diabetes study (N=1047) examined the effects of rimonabant on patients with type 2 diabetes mellitus (T2DM) who had been treated with either sulfonylurea or metformin. The Table presents an overview of the RIO trials.

The study design for each RIO trial included a patient screening period of 2 weeks that was followed by a 4-week single-blind placebo run-in period. During the run-in period, every patient was placed on a mildly hypocaloric diet (ie, energy deficit of approximately 600 kcal/d in relation to the calculated daily intake to maintain body weight). The average weight loss during the run-in period for the four RIO trials was approximately 2 kg. After the run-in period, individuals were randomly assigned to one of three treatment arms: placebo, 5 mg of rimonabant per day, or 20 mg of rimonabant per day. Stratification into each treatment arm was based on the amount of weight loss during the run-in period. Patients were stratified based on whether their weight loss was less than 2 kg or greater than 2 kg during the run-in period.

The treatment period lasted 1 year for all RIO trials except RIO-North America. At the conclusion of year 1 in RIO-North America, there was an additional randomization for a second year of treatment. Patients who received rimonabant in year 1 were randomly assigned to continue receiving their original dose of rimonabant (5 mg/d or 20 mg/d) during year 2 of the study or to receive placebo during that time. The goal of this approach was to examine the effects on patients after discontinuation of treatment with rimonabant. The design of the RIO trials is presented in Figure 3.

### Effect of Rimonabant on Body Weight and Body Composition

Patients’ weight loss after 1 year of treatment was remarkably similar across all four RIO trials. The weight loss in the placebo arms of the trials ranged from 1.5 kg to 1.8 kg based on a last-observation-carried-forward analysis. The weight loss in the treatment arms receiving 5 mg of rimonabant per day was not significantly different from that in placebo arms (P<.001). However, a significant weight loss was associated with the rimonabant treatment groups receiving 20 mg/d compared with those receiving placebo. Based on a last-observation-carried-forward analysis, the average weight loss after 1 year of treatment with 20 mg of rimonabant per day was between 6.3 kg and 6.9 kg for patients without T2DM. Patients with T2DM who received 20 mg of rimonabant per day for 1 year lost an average of 5.3 kg.

In the RIO-North America trial, patients who remained on rimonabant therapy after year 1 continued to respond to treatment by losing additional weight during year 2 of the trial. In the last-observation-carried-forward analysis at the end of year 2, the average weight loss for patients who continued taking 20 mg rimonabant per day for both years (n=256) was 7.4 kg. Alternatively, patients who were randomly assigned from the arm receiving 20 mg/d arm to placebo (n=225) regained their weight by the end of year 2, gradually returning to values seen in the placebo arm of the study.

In the four RIO trials, there was a placebo-subtracted decrease in waist circumference ranging from 3.3 cm (Rio-Diabetes) to 4.7 cm (Rio-Lipids). Waist circumference is an excellent surrogate marker for visceral adiposity. Predictably, the decrease in waist circumference was most significant in those individuals receiving 20 mg of rimonabant per day, compared with those receiving placebo (P<.001). After the second randomization in RIO-North America, the results for patients’ waist circumference mirrored those seen with their weight. The benefits of rimonabant, 20 mg/d, were lost during year 2 in those patients who were randomly switched from rimonabant to placebo versus those patients who were randomly assigned to continue treatment with rimonabant. In patients who con-

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**Table: Rimonabant in Obesity (RIO) Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>N</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIO-North America</td>
<td>Obese or overweight with or without comorbidities (excluding T2DM)</td>
<td>3045</td>
<td>1 + 1 y, Rerandomized</td>
</tr>
<tr>
<td>RIO-Europe</td>
<td>Obese or overweight with or without comorbidities (excluding T2DM)</td>
<td>1508</td>
<td>2 y</td>
</tr>
<tr>
<td>RIO-Lipids</td>
<td>Obese or overweight with untreated dyslipidemia (excluding T2DM)</td>
<td>1036</td>
<td>1 y</td>
</tr>
<tr>
<td>RIO-Diabetes</td>
<td>Obese or overweight with T2DM</td>
<td>1047</td>
<td>1 y</td>
</tr>
</tbody>
</table>

**Abbreviation:** T2DM, type 2 diabetes mellitus.
continued to take 20 mg of rimonabant per day for 2 years, the decrease in waist circumference was 7.6 cm based on the last-observation-carried-forward analysis. This compared with a decrease in waist circumference of 3.8 cm in patients randomized from rimonabant to placebo ($P < 0.001$).12

### Effect of Rimonabant on High-Density Lipoprotein Cholesterol and Triglycerides

The four RIO trials also assessed the effect of rimonabant on patients' serum high-density lipoprotein cholesterol (HDL-C) and serum triglyceride levels.12-15 The baseline serum HDL-C value in the RIO-Lipids study14 was 43 mg/dL, slightly lower than the baseline HDL-C values in the other RIO studies (48-49 mg/dL).12,13,15 This difference was due to the fact that patients with dyslipidemia were included in the RIO-Lipids study by design. In patients treated with 20 mg of rimonabant per day in each trial, there was a statistically significant increase in serum HDL-C compared with subjects receiving placebo ($P < 0.001$). This increase ranged from 12.6% (RIO-North America) to 22.3% (RIO-Europe).12-15 Although the increases seen in HDL-C were statistically significant, it is prudent to note that the clinical significance of raising HDL-C levels in patients remains unproven.18

In addition to the observed increase in HDL-C, there was also a statistically significant decrease in serum triglyceride concentrations in patients taking 20 mg of rimonabant per day versus placebo in each of the four RIO trials ($P < 0.001$).12-15 The most robust decreases in triglycerides (−12.6%) were seen in the RIO-Lipids study,14 in which baseline triglyceride values were the highest. In the RIO-North America trial,12 along with the continued increase in HDL-C during the second year, there was also stabilization in the decline of triglyceride concentrations.

Based on an analysis of covariance of the serum HDL-C levels and the serum triglyceride concentrations, approximately half of the effect of rimonabant on lipids could be attributed to factors independent of weight loss.12-14 Thus, the effect of rimonabant on lipid parameters is only partially attributable to weight loss. It is well documented that elevations in triglyceride concentrations are associated with increased cardiovascular risks that are independent of major traditional risk factors.19

### Effect of Rimonabant on Glycemic End Points

Most of the morbidity and mortality associated with cardiometabolic risk arises from the disorders associated with insulin resistance and T2DM.20 Consequently, the glycemic end points in the RIO trials are of particular interest.

The patients in the RIO-Lipids trial14 underwent an oral glucose-tolerance test. It included a 75-g glucose challenge, and blood samples were
drawn and analyzed for glucose and insulin areas under the curve (AUC) over a 2-hour period. A statistically significant reduction in glucose AUC was seen with the 20-mg daily dose of rimonabant versus placebo at the end of 1 year (P < .001). The analysis of the insulin AUC yielded a similar result, with a statistically significant reduction observed with the 20-mg daily dose of rimonabant compared with placebo (P < .001). In addition, fasting insulin levels showed statistically significant declines in each of the RIO trials.

The RIO-Diabetes trial enrolled 1047 overweight or obese individuals with T2DM who were receiving monotherapy with either metformin or sulfonylurea (approximately two thirds and one third, respectively, of the patients in the study). In addition, the patients’ serum hemoglobin A1c (HbA1c) levels had to be between 6.5% and 10% to be included in the study. The baseline HbA1c values were similar across treatment groups, ranging from 7.2% to 7.3%. These individuals were then randomly assigned to one of three arms: placebo (n = 348); rimonabant 5 mg/d (n = 358); or rimonabant 20 mg/d (n = 339).

After 1 year of the RIO-Diabetes trial, the patients in the placebo arm had a slight (0.1%) increase in HbA1c. The patients in the arm receiving 20 mg of rimonabant per day, however, had a decline (0.6%) in HbA1c (P < .001). An analysis of covariance revealed that the observed reduction in HbA1c was only partially dependent on weight loss; 57% of the reduction in HbA1c was weight-independent. The placebo-subtracted decline in HbA1c after 1 year of treatment with 20 mg of rimonabant per day was 0.7%.

**Effect of Rimonabant on Blood Pressure**

Blood pressure, another important cardiometabolic risk factor, was also evaluated in the RIO trials. In the RIO-Lipids study, participants taking 20 mg of rimonabant per day (n = 346) had a statistically significant decrease in both systolic blood pressure (P = .015) and diastolic blood pressure (P = .002) versus placebo. The subgroup of individuals with elevated blood pressure (≥140/90 mm Hg) had an even greater decrease in both systolic blood pressure (∼13.1 mm Hg) and diastolic blood pressure (∼6.3 mm Hg). This decrease represented a significant reduction compared with individuals in the placebo arm who had similar elevations in blood pressure (P = .038 systolic, P = .022 diastolic).

**Effect of Rimonabant on C-Reactive Protein and Adiponectin**

In the RIO-Lipids trial, levels of C-reactive protein (CRP) and adiponectin were analyzed at the end of 1 year. C-reactive protein is a marker for inflammation and is associated with increased cardiovascular risk. Adiponectin is an adipose-tissue specific factor that improves insulin sensitivity and inhibits vascular inflammation. Levels of adiponectin are reduced in individuals who are obese and in insulin-resistant condition.

In patients taking 20 mg of rimonabant per day in the RIO-Lipids trial, CRP levels showed statistically significant declines versus CRP levels in those receiving placebo (P = .02), suggesting a modest improvement in inflammation among these patients. Adiponectin levels showed statistically significant increases in the group receiving 20 mg of rimonabant per day (P < .001), suggesting an improvement in insulin sensitivity. These findings were determined to be partially weight-independent, compatible with rimonabant’s other observed salutary effects on multiple cardiometabolic factors.

**Summary of Rimonabant Efficacy**

Figure 4 provides a summary of the efficacy of rimonabant based on the RIO trials. Rimonabant demonstrated efficacy in more than 6600 individuals, with clear improvement in body weight, HDL-C levels, triglyceride concentrations, and waist circumference. Furthermore, rimonabant achieved statistically significant improvements in multiple glycemic end points and biomarkers associated with an overall reduction in cardiometabolic risk. This efficacy was sustained for as long as 2 years.

**Rimonabant Safety Profile**

The most common treatment-emergent adverse events associated with rimonabant in the RIO trials were upper respiratory tract infection and nausea. Most adverse events were mild to moderate in severity. The rate of serious adverse events seen in patients taking 20 mg of rimonabant per day ranged from 4% to 8.7% in the RIO trials, compared with a range of 2.3% to 7.5% among control subjects. The frequency of participants who dropped out of a RIO trial because of an adverse event ranged from 12.8% to 15% for patients receiving 20 mg of rimonabant per day, compared with a range of 5.5% to 9.2% among patients in the placebo groups. Figure 5 presents the incidence of adverse events observed in at least 5% of any treatment group in the RIO trials.

Participants in the groups receiving 20 mg of rimonabant per day discontinued study participation because of adverse events more frequently than did patients receiving placebo. The most commonly occurring adverse events leading to study discontinuation were anxiety, depressive disorders, dizziness, mood alterations with depressive symptoms, and nausea. These adverse events...
appeared to be dose-related, because patients taking 20 mg of rimonabant per day had a higher frequency of such events than did patients taking 5 mg of rimonabant per day. In addition, depressive disorders were reported in 3.2% of patients in the groups receiving 20 mg of rimonabant per day, compared with 1.6% of patients in the placebo arms.22,23 Depressive episodes were usually mild or moderate and resulted in recovery in all cases after corrective treatment or discontinuation of rimonabant.23

During the year of treatment with rimonabant in the RIO-Europe study,13 there were no changes in rates of self-reported depression or anxiety among patients. In year 2 of the RIO-North America study,12 overall rates of adverse events, study withdrawals, and adverse event-related study withdrawals were lower than they were during the first year of study participation, with no differences being noted in overall rates between treatment groups.

The overall discontinuation rates in the RIO trials—not only those

Figure 5. Incidence of adverse events occurring in at least 5% of any treatment group after 1 year of treatment with 20 mg of rimonabant per day or placebo in the four Rimonabant in Obesity (RIO) trials: (a) RIO-North America (N=3045); (b) RIO-Europe (N=1508); (c) RIO-Lipids (N=1036); and (d) RIO-Diabetes (N=1047). Adverse events shown for RIO-North America and RIO-Europe are all events reported. Adverse events shown for RIO-Lipids and RIO-Diabetes are those considered treatment emergent. (Source: Henness S, Robinson DM, Lyseng-Williamson KA. Rimonabant [drug profile]. Drugs. 2006;66:2109-2119.)
related to adverse events—were consistent with those seen in many other weight-management studies.\textsuperscript{24} There were no significant differences between the groups receiving 20 mg of rimonabant per day and the groups receiving placebo with respect to the overall discontinuation rate. More patients in the placebo groups than in the rimonabant groups chose to discontinue participation in the studies. It is speculative as to whether their discontinuation was because they were not satisfied with their weight loss. The discontinuation rates were somewhat higher in the two general overweight/obesity trials—RIO-North America (49.1% placebo, 45.9% rimonabant) and RIO-Europe (41.6% placebo, 39.4% rimonabant)—compared with the studies in which patients were specifically enrolled because of dyslipidemia (37.6% placebo, 36.3% rimonabant) or T2DM (33.6% placebo, 32.4% rimonabant).\textsuperscript{12-15} These results suggest that discontinuation rates are lower in those clinical trials in which the burden of disease is higher.

Clinical trials for the weight loss agents orlistat and sibutramine present an opportunity to examine the patient dropout rates in obesity trials conducted for drugs other than rimonabant. Dropout rates in clinical trials with orlistat and sibutramine have been high, attributable in part to the high incidence of adverse events seen with these medications. A review that evaluated 11 orlistat weight loss studies (four of which were 2-year trials) and five sibutramine studies (three weight loss and two weight maintenance trials) showed that orlistat attrition rates averaged 33\%, while sibutramine attrition rates averaged 43\%.\textsuperscript{25}

**Rimonabant Safety Summary**

In summary, the most frequently reported adverse events associated with rimonabant use in the RIO trials involved the nervous system, being neurologic or psychiatric.\textsuperscript{22} The neurologic and psychiatric adverse events occurred without new or increased long-term risks or changes in patients’ electrocardiogram values or other vital signs. These and most other adverse events tended to happen early during the course of treatment and were mild or moderate in intensity. The incidence of both depression-related adverse events and anxiety was increased, but the overall incidence of adverse events remained low in the RIO trials.\textsuperscript{22}

**Comment**

In an effort to manage the increasing prevalence of obesity and associated cardiometabolic risk factors, a number of clinical trials have examined treatment based on the endocannabinoid system. Such treatment has shown great promise. Basic research has demonstrated that the endocannabinoid system plays an integral role in the regulation of food intake, metabolism, and storage. In particular, research with rimonabant, a first-in-class CB\textsubscript{1} antagonist, indicates that such agents show promise for the treatment of patients with obesity and associated cardiometabolic risk factors.

The effects of rimonabant have been evaluated in more than 6600 overweight and obese patients with multiple cardiometabolic risk factors, including dyslipidemia and T2DM. Treatment with 20 mg of rimonabant per day produced statistically significant improvements in body weight, serum HDL-C levels, serum triglyceride levels, and waist circumference, compared with placebo. In addition, rimonabant at a dose of 20 mg/d achieved statistically significant improvements in fasting insulin levels, glucose tolerance, and glycemic control. Finally, 20 mg of rimonabant per day also produced statistically significant decreases in CRP and increases in adiponectin—important indicators of reduced inflammation and improved insulin sensitivity in patients.

In each of these end points, rimonabant demonstrated sustained efficacy for as long as 2 years when used in conjunction with a reduced-calorie diet and moderate physical activity. Thus, the evidence indicates that rimonabant may provide a novel strategy for the treatment of patients with obesity and associated cardiometabolic risk factors.

**References**


JAOA • Supplement 2 • Vol 107 • No 4 • April 2007 • 519

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