

# Direct medical cost of metformin and metformin-glimepiride in type 2 diabetes mellitus patients

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## ARTICLE INFO

### Article history

Received: 25-08-2021  
Revised: 10-03-2022  
Accepted: 18-06-2022

### Keywords

Cost Analysis  
Type 2 DM  
Metformin  
Metformin-Glimepiride

## ABSTRACT

Diabetes mellitus (DM) requires long-term therapy. Selection of the right therapy was very important to provide optimal results at an affordable cost. One of the main standards of oral antidiabetic therapy prescribed for type 2 DM (T2DM) is metformin, either alone or in combination therapy. The purpose of this study was to describe the direct medical costs in type 2 DM patients between metformin and metformin-glimepiride therapy. This research was an observational and descriptive. Demographic and clinical data were taken prospectively from the complete medical records of data patients with the main diagnosis of DM who fulfilled the inclusion criteria in the period January 2019– November 2020 at RSU Nene Mallomo Sidenreng Rappang, South Sulawesi and the two Public Health Centers namely Puskesmas Galur. II and Panjatan II Kulon Progo Yogyakarta. Cost data includes total medical costs from the hospital/ healthcare perspective (cost of drugs, doctor's services and checkups, fees for checking Random Blood Glucose (RBG) and total costs from the Badan Penyelenggara Jaminan Sosial (BPJS)/ payer perspective (INA-CBG's rates) were covered by insurance. The results showed that the average direct medical costs at the hospital and the two Public Health Centers respectively were metformin therapy in IDR (Indonesian Rupiah) namely IDR 120.736 and IDR 9.072,- and metformin-glimepiride therapy of IDR 126.298,- and IDR 18.634,-. It can be concluded that the average direct medical cost of metformin therapy is lower than metformin-glimepiride therapy.

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## 1. Introduction

Type 2 diabetes mellitus (T2DM) is a group of metabolic diseases characterized by hyperglycemia, occurring due to abnormalities in insulin secretion, insulin action, or both (Decroli, 2019). Impaired insulin secretion is a pathophysiology of T2DM. People with T2DM can't increase insulin secretion sufficiently to overcome insulin resistance and have a low disposition index. Over time, hyperglycemia tends to become more severe and more difficult to treat. The progressive nature of T2DM is usually caused by decreased  $\beta$ -cell function (Rodriguez & Saldana, 2019).

In 2015, about 415 million adults had DM, a fourfold increase from 108 million in the 1980s. It is estimated by 2040 this number will be increasing to 642 million (Cho et al., 2018). In Indonesia, the prevalence of Riskesdas 2013 showed that DM patients aged 15 years and over doubled from Riskesdas 2007. The prevalence of Riskesdas 2018 showed that DM patients aged 15 years and over increased by 2% from Riskesdas 2013 (Riskesdas, 2013). The prevalence of DM based on a doctor's diagnosis in the population of all ages is 1.5%, the prevalence in males is 1.2% and in females 1.8%

according to Riskesdas 2018 (Kemenkes RI, 2018). DM is diagnosed based on checking blood glucose levels. The recommended blood glucose test is the enzymatic glucose test on venous plasma. A blood glucose meter can be used to monitor treatment results through a capillary blood glucose test (Davies et al., 2018).

Metformin is recommended as first-line therapy because it is stable hypoglycemic and cholesterol-lowering effects. As an endogenous hormone analog, insulin decreases blood glucose and lipid concentrations by regulating glucose, fat, and protein metabolism, so it can be widely used in medicine for diabetic patients of all ages (Wei & Dou, 2019). Previous studies done by (Dimic et al., 2016) showed that metformin had a thyroid-stimulating hormone lowering effect in patients with T2DM and hypothyroidism. However, the thyroid-stimulating hormone lowering effect of metformin was not dependent on long-term metformin therapy. Sulfonylureas are oral antidiabetic drugs recommended as second-line treatment in patients with T2DM. Sulfonylureas remain the most frequently used antidiabetic drugs prescribed after treatment failure with the first-line drug metformin (Dourous et al., 2018). The combination of metformin and sulfonylurea is one of the combinations used and can achieve a better decrease in HbA1c (0.8-1.5%) than a single drug. Metformin's use is associated with reduced all-cause mortality and reduced cardiovascular mortality (Hemmingen et al., 2014).

Based on research, it is known that metformin is one of the drugs most often combined with sulfonylureas in patients newly diagnosed with T2DM between 2000 and 2013. In addition, the use of metformin is increasing every year. In 2000 the use of metformin was 45.1%, increased to 91% in 2013 (Sharma et al. 2016). In single therapy the most frequently prescribed drug was metformin (20%) while in combination therapy the most frequently prescribed was metformin-glimepiride (9.3%) (Rani & Reddy, 2015).

Cost analysis is a way of calculating the amount of unit expenditure (cost) in monetary units (rupiah), in the form of direct costs or indirect costs to achieve goals (Riskesdas, 2013). Cost analysis becomes an even more important deciding factor in clinical practice. A comparative evaluation based on scientific analysis rather than the apparent cost of the therapy helps the decision-makers choose a more cost-effective treatment option, especially for patients makes health services become more efficient and economical (Bootman et al., 2005). The economic burden of DM must be a concern of the implementation of the National Health Insurance/ Jaminan Kesehatan Nasional (JKN) in managing chronic non-infectious disease problems. Estimating the cost of illness with the cost analysis method is an important element in the decision-making process for chronic diseases such as DM (Sutrisno, 2016). In addition, it can help pharmacists compare inputs (costs for pharmaceutical products and services) and outputs (outcomes of treatment). Cost analysis enables pharmacists to make important decisions about formulary determination, disease management, and treatment assessment (Makhinova & Rascati, 2013).

Research by Yuswantina & Dyahariesti (2018) shows that the lowest average direct medical cost is on biguanide oral antidiabetic (ADO) therapy per 1 month, which is IDR 21,285,-. Previous studies were done by Lubis & Suprianto (2018) which state that the lowest average direct medical cost for biguanide combination antidiabetic therapy with complications is IDR 79.254,-. The difference between the two studies previously is in the research conducted by Yuswantina & Dyahariesti (2018) shows that the aim of the study was to find the most cost-effective single or combination ADO drug, while the research of Lubis & Suprianto (2018) shows that the purpose of this study was to determine and evaluate the cost-effective use of ADO in combination with complications and combination without complications in type 2 DM patients, BPJS participants at RSU Haji Medan. whereas this study only describes the direct medical costs in T2DM patients between metformin single therapy and metformin-glimepiride combination therapy, which drug will have the lower medical cost between the two therapies. Based on the above background, a study was conducted with the aim of describing the direct medical costs in T2DM patients between metformin and metformin-glimepiride therapy.

## 2. Materials and Methods

This research design was a descriptive observational method with data collection carried out prospectively. Prior approval of the Ethical Clearance of the study protocol was taken from the Research Ethics Committee of Ahmad Dahlan University (KEP UAD) with letter number 012011080. This study did not use a sampling method so that the research subjects were all affordable populations that met the inclusion and exclusion criteria. The subjects of this study were the medical records of all

DM patients who were undergoing treatment visits at RSU Nene Mallomo Sidenreng Rappang, Galur II, and Panjatan II Public Health Centers Kulon Progo in the period January 2019–December 2020 which met the inclusion criteria. The inclusion criteria in this study were: patients > 25 years who were diagnosed with DM with or without comorbidities, patients with type 2 DM at least 2 months after the diagnosis was made by a doctor, and complete medical records in the form of demographic data and clinical data (patient identity), blood glucose levels, diagnosis, and treatment is given), as well as drug use data. Exclusion criteria were: patients with cancer or infected by human immunodeficiency virus (HIV), incomplete, missing, or unreadable data.

### 2.1. Research Instruments

The instrument in this study was a data collection table. The data used were medical records and details of costs from the finance department.

### 2.2. Research Course

Collecting data on patients with DM and receiving antidiabetic therapy with metformin and metformin-glimepiride. We chose patient data that were included in the research criteria. Counting the number of DM patients at each study site. Collecting patient medical record data according to the inclusion criteria. Then record the required data on the patient data collection sheet. The reason for choosing research locations at the Galur II and Panjatan II Health Centers in Kulon Progo was because the public health centers were the first-level Health facilities (Faskes) which was a non-specialist (primary) individual health service. The two public health centers had the same service characteristics, while RSU Nene Mallomo Sidenreng Rappang was a type C hospital or second level of health facility that can be used as a continuation of the first level of health facilities with referrals. The number of DM patients at RSU Nene Mallomo Sidenreng Rappang was 501 patients in the January 2019–November 2020 range, while at the Galur II and Panjatan II health centers Kulon Progo were 150 patients at the same time.

## 3. Data analysis

The cost analysis at the research sites of the Galur II and Panjatan II Health Centers in Kulon Progo was carried out based on the payer perspective, namely BPJS. This is done because the puskesmas is a First Level Health Facility and patients registered as BPJS participants get free medical facilities. The tariff used at the Galur II and Panjatan II Health Centers in Kulon Progo is the capitation rate, which is the monthly payment made by BPJS Kesehatan to the first-level health facilities based on the number of registered participants (including the type and number of medical services provided) (BPJS Kesehatan, 2015). The price of the drug used was the price of the drug in the e-catalog, while the cost analysis at RSU Nene Mallomo Sidenreng Rappang was carried out using a cost analysis based on a healthcare perspective (hospital).

The data were analyzed and the research results were processed which included the characteristics of the research subjects analyzed by looking at the number (percentage) of each group of patient characteristics. The calculation of the average direct medical cost is carried out by measuring costs, namely, each cost was first described by its components (healthcare perspective: medicine costs, Doctor's Examinations and Consultation Fee, Administration Cost Examination Fees of RBG; payer perspective (drug cost: only metformin and metformin- glimepiride); Indonesian-Case Based Groups/ INA-CBG's rates).

## 4. Results and discussion

The results of data collection at RSU Nene Mallomo Sidenreng Rappang fulfilled the inclusion criteria, 14 patients (46.67%) were on metformin and 16 patients (53.33%) were on metformin-glimepiride. While at the Galur II and Panjatan II Health Center Kulon Progo fulfilled the inclusion criteria, 15 patients (25%) were on metformin and 45 patients (75%) were on metformin-glimepiride.

### 4.1. Subject Demographics of Research

Subjects were obtained from the medical records of all DM patients who were undergoing treatment visits and fulfilled the inclusion and exclusion criteria. The description of the characteristics of the research subjects includes age, gender, complications that occur, and the patient's comorbidities. The demographic characteristics of Type 2 DM patients can be seen in Table I.

The demographic description of the sex characteristics was mostly female at RSU Nene Mallomo Sidenreng Rappang as many as 23 patients (76.67%) and 45 patients (75%) at the Galur II and Panjatan II Public Health Centers in Kulon Progo. This is supported by research by Mildawati et al. (2019) which stated that females experienced more DM events, namely 59 patients (71.1%). In line with research conducted by Nugroho & Musdalifah (2020) stated that females were more at risk of developing DM than as many as 69 patients (62.2%). Research conducted by Usman et al. (2020) stated that female suffering from DM was 44 patients (69.8%). This is due to unhealthy food patterns such as frequently consuming fatty foods and containing high glucose. According to research, the incidence of T2DM in females is higher than in males, and females have a higher risk of diabetes because females are more likely to increase their body mass index (Lee et al., 2020).

In terms of age characteristics, patients in the elderly category ( $\geq 46$  years) suffer from DM more. The percentage gain from the Nene Mallomo General Hospital and the two health centers, namely the Galur II Health Center and the Panjatan II Health Center Kulon Progo, respectively, were 70% and 93.33%. Based on research Mildawati et al. (2019) show that the age with the most DM was in the elderly category ( $\geq 46$  years) as many as 38 patients (45.8%). This research is in line with Desi et al. (2018) show that the majority of 43 patients (71.67%) were 46 years old. Study by Isnaini & Ratnasari (2018) obtained in the age group 46 years as many as 44 patients (83%). Aging can cause a decrease in insulin sensitivity and a decrease in the body's glucose metabolic function (Setiyorini & Wulandari, 2017), which mostly occurs in DM patients with the most age being  $>46$  years according to research (Lee et al., 2020). Increasing age causes changes in carbohydrate metabolism and changes in insulin release which are influenced by glucose in the blood and inhibits the release of glucose into cells because it is influenced by insulin (Isnaini & Ratnasari, 2018). It can be concluded that most of the patients suffering from T2DM are 46 years old or in the elderly category. Early elderly age is the preelderly age, where function and integration begin to decline, the ability to mobilize and activity has begun to decrease so that several diseases appear that cause health status to decline (Hestiana, 2017). Previous studies done by Setyorogo & Trisnawati (2013) there is a significant relationship in the age group over 46 years which is more at risk of suffering from T2DM.

In the characteristics of patients with other comorbidities, at Nene Mallomo Hospital Sidenreng Rappang showed that osteoarthritis and respiratory disorders were higher by 20% and at Galur II Health Center and Panjatan II Health Center Kulon Progo showed that myalgia disease was higher by 5%. Characteristics of DM patients with complications, the results of this study showed that there were more patients without complications than patients with complications, namely 60% and 56.67% at Nene Mallomo Hospital Sidenreng Rappang and both Public Health Centers of Galur II and Panjatan II Kulon Progo respectively. This research is in line with research conducted by Setiyorini & Wulandari (2017) at RSD Mardi Waluyo Blitar state that most of the elderly suffering from T2DM did not have complications of 83 people (83%) compared to those who had fewer complications, namely 17%. The incidence of complications has a minimal percentage that can be caused by many factors, such as adherence to medication use, exercise, diet, and regularity of blood glucose control (Desi et al., 2018).

The characteristics of DM with complications at RSU Nene Mallomo Sidenreng Rappang were heart failure as many as 6 patients (20%), while at Galur II and Panjatan II Kulon Progo Public Health Centers the most was hypertension with 16 patients (26.67%). Previous studies done by Lie et al. (2016) states that 40% of DM patients have a history of cardiovascular disease and as many as 48% of patients have hypertension. Macrovascular and microvascular complications in diabetes occur mainly due to prolonged exposure to hyperglycemia with risk factors such as arterial hypertension, dyslipidemia and genetic predisposition (Paneni et al., 2013). Several studies have shown that the number of cardiovascular events and mortality from cardiovascular disease in DM patients is quite high, where DM patients have a 2-3 times higher risk of developing cardiovascular disease (Taylor et al., 2013; Soedamah-Muthu et al., 2006). T2DM patients have a high risk of developing atherosclerosis which contributes to an increased risk of cardiovascular disease (Paneni et al., 2013; ADA, 2015). In research by Pambudi et al. (2019) patients with the most complications are T2DM mellitus patients with hypertension complications with a total of 78.3%, following by hyperlipidemia complications as many as 16.22% and stroke complications only 5.4%. This research is in accordance with research of (Yulianti et al., 2014) states that 1,5-3 times more complications of hypertension are found in DM patients than other diseases. Hypertension can make pancreatic beta cells insensitive to insulin, causing insulin resistance (Mihardja, 2009).

**Table 1.** Patient Demographic Characteristics of Nene Mallomo Hospital Sidenreng Rappang, Galur II and Panjatan II Public Health Centers Kulon Progo

Characteristics	RSU Nene Mallomo		Characteristics	Puskesmas Galur II & Panjatan II	
	Total n=30	Percentage (%)		Total n=60	Percentage (%)
<b>Gender</b>					
Male	7	23.33	Male	15	25
Female	23	76.67	Female	45	75
<b>Age Group</b>					
Adult (26- 45 Years)	9	30	Adult (26- 45 Years)	4	6.67
Elderly (≥ 46 Years)	21	70	Elderly (≥ 46 Years)	56	93.33
<b>Comorbidities</b>					
without comorbidities	14	46.67	without comorbidities	49	81.67
with comorbidities	16	53.33	with comorbidities	11	18.33
Osteoarthritis	6	20	Dyspepsia	2	3.33
Tuberculosis	2	6.67	Gastritis	1	1.67
Bronchopeumonia	6	20	Vertigo	1	1.67
Vertigo	1	3.33	Myalgia	3	5
GERD	1	3.33	Myalgia + urticaria	1	1.67
			Neuropathy	2	3.33
			Neuropathy + Retinopathy	1	1.67
<b>Complicated Complications</b>					
Without Complicated Complications	18	60	Without Complicated Disease	34	56.67
With Complicated Complicated	12	40	With Complicated Disease	26	43.33
Heart Failure	6	20	Hypertension	16	26.67
Dyslipidemia	5	16.67	Dyslipidemia	4	6.67
Coronary Artery Disease	1	3.33	Hypertension+ Dyslipidemia	6	10

#### 4.2. Average of Direct Medical Cost

The components of direct medical costs used at RSU Nene Mallomo Sidenreng Rappang include the total cost of drugs and average drug costs, doctor's examination and consultation fees, administrative costs and examination fees of RBG, while the direct medical cost components at the Galur II and Panjatan II Health Centers in Kulon Progo include total and average drug costs. The direct medical costs of metformin and metformin-glimepiride therapy can be seen in Table 2.

The results of processing direct medical costs obtained from data from the financial division of hospitals and health centers, in Table II it can be seen that the average of direct medical costs at RSU Nene Mallomo Sidenreng Rappang on the used of metformin and metformin-glimepiride therapy were IDR. 120.736,- and IDR. 126.298,-. Meanwhile, the average direct medical costs at the Puskesmas Galur II and Panjatan II Kulon Progo on the used of metformin and metformin-glimepiride therapy were IDR. 9.072,- and IDR. 18.634,-, respectively. The cost that is most often measured is direct medical costs, which are inputs to provide therapy that is used directly (Andayani T.M., 2013). Doctor's examination and consultation fees, administration fees and laboratory fees were the same at Nene Mallomo Hospital Sidenreng Rappang. Direct medical costs at the Galur II and Panjatan II Health Centers in Kulon Progo only cover drug costs because the total cost from BPJS used a payer perspective (INA-CBG's tariff) which was a package rate that includes all components of hospital resources used in both medical and nonmedical services (Depkes RI, 2014).

**Table 2.** Direct Medical Costs for Metformin and Metformin-Glimepirid Therapy at Nene Mallomo Hospital Sidenreng Rappang and Galur II and Panjatan II Health Centers in Kulon Progo

Cost Components (IDR/ Rupiah)	RSU Nene Mallomo		Galur II & Panjatan II Health Centers	
	Metformin n=14	Metformin- Glimepiride n=16	Metformin n=15	Metformin- Glimepiride n=45
<b>Medicine cost</b>				
- Total	108.300	212.764	136.089	838.539
- Average	7.736	13.298	9.072	18.634
<b>Doctor's Examination and Consultation Fee</b>				
- Total	210.000	240.000	0	0
- Average	15.000	15.000	0	0
<b>Administration Cost</b>				
- Total	238.000	272.000	0	0
- Average	17.000	17.000	0	0
<b>Examination Fees of RBG</b>				
- Total	1.134.000	1.296.000	0	0
- Average	81.000	81.000	0	0
<b>Average of Direct Medical Cost</b>	<b>120.736</b>	<b>126.298</b>	<b>9.072</b>	<b>18.634</b>
<b>P value Mann Whitney Test</b>	<b>0.317</b>		<b>0.317</b>	

Table II described the comparison of the p value of the direct medical cost variable between the Nene Mallomo General Hospital and the Galur II and Panjatan II health centers statistically using the Mann Whitney Test. The difference was considered significant if the p value  $\leq 0,05$ . From the statistical analysis above, it can be seen that there was no significant difference between the average cost of ADO with a p value of 0.317 ( $>0.05$ ). Metformin didn't have a statistical difference in cost with metformin-glimepiride in this study. The results of this study indicate that the average direct medical cost didn't have a significant difference, but the average direct medical cost of using metformin single therapy is lower than the use of metformin-glimepiride combination therapy. The patient's ADO drug costs had a slight difference between metformin therapy and metformin-glimepiride therapy, so it can be concluded that the size of the medical costs is directly influenced by the number of ADO drugs received by the patient. This causes a small cost difference between one drug (metformin) and another (metformin-glimepiride) because the drugs received by patients receiving metformin therapy and patients receiving metformin-glimepiride therapy are the same amount of drug each month. According to (Hastuti et al., 2022) state that the price obtained from the pharmacy unit was influenced by the number of drugs used and medical devices (alkes) intended for patients.

Research conducted by (Romadhoni, 2018) show that the difference in the average total direct medical costs of each treatment is most likely due to the presence of nonantidiabetic drugs consumed by patients to treat patients comorbidities. Differences in nonantidiabetic drugs consumed by patients can affect other costs, many patients who use metformin suffer from other comorbidities so that it can affect the total direct medical costs of the patient. Likewise for glimepiride, the most influential cost component is the cost of drugs other than DM. This is different from the research conducted by (Dinaryanti et al., 2012) which states that the average monthly direct medical costs are influenced by the cost of other antidiabetic drugs such as in the insulin, metformin-insulin and metformin-acarbose-insulin groups, which are quite large compared to other therapies. This is because the price of antidiabetics, especially insulin, is much higher than the price of complication drugs and the cost of laboratory tests. Based on this, in all classes, the components of registration fees, doctor service fees, and laboratory fees occupy the same position so that they do not affect the overall direct medical costs.

The theoretical implication based on this study is that the average direct medical cost of metformin therapy is lower than that of metformin-glimepiride therapy. The use of metformin in Indonesia is

quite a lot, according to the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE) recommending treatment in type 2 DM can be started by giving metformin as a first line antidiabetic drug if blood glucose cannot be improved only with controlled lifestyle interventions. In addition, metformin is also able to reduce HbA1C by 1,0-2,0%. From the perspective of the price, metformin is classified as a cheap or low cost drug (Soelistijo et al., 2015). The practical implications of the results of this study can be used as a guide for health policy makers to make decisions related to drugs that have value commensurate with their costs to increase their efficiency, especially from the perspective of hospitals that can meet patient needs and are affordable by hospitals.

The limitations of the research at RSU Nene Mallomo Sidenreng Rappang were the limited data available both in the hospital management information system (SIM RS) and patient medical records, the limited number of patient data that met the research criteria and there were some patient data in the medical record that were not recorded Laboratory test result of Random Blood Glucose (RBG), either before receiving therapy, after receiving therapy or both. This makes the number of affordable population samples that meet the requirements much less than the total target population of DM patients. While the limitations of the research at the Galur II and Panjatan II Health Centers in Kulon Progo were the number of patient data that met the research criteria, but the patients data in the medical records did not record laboratory test results of Fasting Blood Glucose (FBG), either before receiving therapy, after receiving therapy or both.

## 5. Conclusion

Direct medical costs for T2DM patients who used metformin single therapy and metformin-glimepiride combination therapy at Nene Mallomo General Hospital were IDR 120.736 and IDR 126.298, respectively, while at Galur II Health Center and Panjatan II Health Center Kulon Progo, each was IDR 9.072, - and IDR 18.634. It can be concluded that the average direct medical cost of metformin therapy is lower than that of metformin-glimepiride therapy.

## Supplementary Materials

Table S1. Association between the average cost of antidiabetic oral of metformin and metformin-glimepiride. Figure 1. Data from 651 patients of DM type 2 including 501 patients at RSU Nene Mallomo and 150 patients at Galur II and Panjatan II Health centers were analyzed. Fulfilled inclusion criteria 14 patients were on metformin and 16 patients were on metformin-glimepiride. While at the Galur II and Panjatan II Health Center 15 patients were on metformin and 45 patients were on metformin-glimepiride.

**Author Contributions:** Conceptualization: S., S.H., W.S., D.A.P.; methodology: S., S.H., W.S., D.A.P. software: S., S.H., W.S., D.A.P. investigation: S., S.H., W.R., D.A.P.; resources: S., S.H., W.S., D.A.P. data curation: S., S.H., W.S. D.A.P.; writing-original draft preparation: S., W.S. D.A.P.; writing-review and editing: S., W.S.; supervision: S., W.S. D.A.P. All authors have read and approved of the manuscript and have made significant contributions to this study.

## Funding

This project was supported by grants from Directorate of Research and Community Service, Directorate General of Strengthening Research and Research Development, Technology/ National Research and Innovation Agency, Indonesia.

## Competing Interests

The authors declare no conflict of interest.

## Acknowledgment

The authors would like to thank the Directorate of Research and Community Service, Directorate General of Strengthening Research and Research Development, Technology/ National Research and Innovation Agency for the funding that has been provided with the contract number: PTM-011/SKPP.TT/LPPM UAD/VI/2020 Date 08 June 2020.

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