Hypoglycemics, Metformins

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indications
glipizide/ metformin (Metaglip™)[1]	generic	▪ Initial therapy to improve glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise ▪ Second-line therapy in type 2 diabetics who have not achieved adequate glycemic control with a sulfonylurea or metformin alone
glyburide/ metformin (Glucovance®)[2]	generic	▪ Initial therapy to improve glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise ▪ Second-line therapy in type 2 diabetics who have not achieved adequate glycemic control with a sulfonylurea or metformin alone ▪ In combination with a TZD in patients who do not have adequate glycemic control with Glucovance alone
metformin (Glucophage®)[3]	generic	▪ Improvement of glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise in patients 10 years of age and older (including in combination with a sulfonylurea or insulin)
metformin ER (Fortamet™)[4]	Shionogi Pharma	▪ Improvement of glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise
metformin ER (Glumetza™)[5]	Depomed	▪ Improvement of glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise (including in combination with a sulfonylurea or insulin)
metformin XR (Glucophage XR®)[6]	generic	▪ Improvement of glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise (including in combination with a sulfonylurea or insulin)
metformin oral solution (Riomet™)[7]	Ranbaxy Pharmaceuticals	▪ Improvement of glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise in patients 10 years of age and older (including in combination with a sulfonylurea or insulin for ages 17 and older)

OVERVIEW

Approximately 25.8 million people, or 8.3 percent of the population in the United States have been diagnosed with diabetes mellitus.[8,9] In type 2 diabetes, insulin function may be impaired by defective insulin secretion and/or insulin resistance (decreased insulin sensitivity). Insulin resistance is typically the first to occur, leading to increased circulating insulin levels in the blood as a result of the decreased response from muscle tissues.

The initial impact of type 2 diabetes does not produce visible symptoms, often resulting in delayed diagnosis. In 2011, the estimated number of people in the United States diagnosed with diabetes was 18.8 million while there are still approximately seven million people living with undiagnosed diabetes.[10] The long-term effects of Type 2 diabetes include renal failure due to diabetic nephropathy, impaired vision due to diabetic retinopathy, loss of sensation and/or pain from diabetic neuropathy, and cardiovascular disease.

The primary objective of diabetes management is to achieve and maintain glycemic control and modify interventions when therapeutic goals are not being met. For most patients with type 2 diabetes, the initial treatment involves lifestyle changes. Lifestyle changes usually include healthier diets, increased exercise, and weight loss. Insulin sensitivity can be restored with continued practice of the lifestyle changes. If lifestyle modifications are not sufficient, oral medications are typically introduced. Oral drugs affect the insulin pathway by stimulating insulin production, regulating glucose release from the

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liver, and attenuating insulin resistance. When necessary, insulin therapy and other injectable drugs can be added to the treatment regimen.

The UK Prospective Diabetes Study (UKPDS) investigated whether intensive glucose control with metformin had any specific advantage or disadvantage. Intensive glucose control with metformin decreased the risk of diabetes-related endpoints in overweight diabetic patients and was associated with less weight gain and fewer hypoglycemic attacks than were insulin and sulfonylureas.[11] A ten-year follow-up to UKPDS revealed that patients treated with metformin continued to have significant risk reductions for any diabetes-related end point, as well as significant risk reductions for myocardial infarction (MI) and all-cause death.[12] Metformin has also proven to be as effective as a sulfonylurea at controlling blood glucose levels.

The 2013 ADA Standards of Medical Care in Diabetes recommends, except where contraindicated, the initiation of metformin at the time of type 2 diabetes diagnosis, along with lifestyle interventions, Furthermore, insulin therapy should be considered in newly diagnosed type 2 diabetic patients with highly symptomatic and/or elevated blood glucose levels or hemoglobin A1c (HbA1c), with or without additional agents, from the outset. The guidelines recommend maintaining an HbA1c goal of less than 7 percent for most patients.[13] These guidelines also include the use of a laboratory standardized HbA1c greater than or equal to 6.5 percent as a diagnostic indicator of diabetes. An additional category has been added to identify patients at risk for developing diabetes in the future as those with HbA1c value between 5.7 and 6.4 percent with impaired fasting glucose or impaired glucose tolerance. Therapy for patients with severe hypoglycemia, limited life expectancy, extensive comorbid conditions, advanced complications or longstanding diabetes with a history of difficulty in meeting goals using optimal therapy may include less stringent HbA1c target levels.

The 2012 ADA and European Association for the Study of Diabetes (EASD) Consensus Statement on the Medical Management of Hyperglycemia in type 2 diabetes indicate that HbA1c targets and blood glucose lowering medications should be individualized.[14] The consensus statement recommends lifestyle modifications and initiation of metformin as first line in managing hyperglycemia in patients with type 2 diabetes. However if lifestyle interventions and metformin fail to produce or maintain glycemic goals, the 2012 consensus statement recommends choosing an anti-hyperglycemic agent based on individual patient needs, preferences and benefits versus risks analysis due to a lack of comparative data among anti-diabetic medications. In order to assist with product selection, a color-coded chart depicts strict versus less stringent management based on a number of factors, including risk of hypoglycemia, patient motivation, life expectancy, disease duration, and comorbidities. Due to the fact that patients with type 2 diabetes are at increased risk of complications from cardiovascular disease, aggressive management of cardiovascular risk factors such as blood pressure and hyperlipidemia should be part of the multifactorial risk reduction approach.[15]

Metformin reduces HbA1c by 1.5 to 2 percent and fasting plasma glucose (FPG) levels by about 20 percent or 60 to 70 mg/dL.[16] Metformin also has favorable effects on serum triglycerides, total cholesterol and LDL-C, and a possible modest increase in HDL-C.[17]

In 2013, the American Academy of Clinical Endocrinologists (AACE) released an algorithm and consensus statement for type 2 diabetes treatment with a goal HbA1c of ≤6.5% for healthy patients with low hypoglycemic risk.[18] The 2013 AACE algorithm replaces the 2009 AACE/ACE diabetes algorithm for glycemic control. For patients with concurrent illness and at risk of hypoglycemia goal HbA1c is >6.5%. Lifestyle modification, including medically assisted weight loss, underlies all of the

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treatments. The guidelines state the choice of therapy must be based on the individual patient, medications, cost, ease of use, other risk factors, and patient's initial HbA1C level: < 7.5%, ≥7.5%, and >9%. It suggests patients with an HbA1C <7.5% start with monotherapy; whereas patients with an HbA1C ≥7.5% begin with dual therapy. Patients with an HbA1C >9% and no symptoms may start either dual or triple antihyperglycemic therapy; patients with an HbA1C >9% with symptoms should begin insulin therapy with or without other agents. The HbA1C should be reassessed every three months and failure to improve may warrant additional complementary therapy for optimal glycemic control. The guidelines provide prescribers a hierarchical order of the usage of drugs where metformin is the preferred treatment of choice for monotherapy and first-line agent for dual and triple therapy. For patients <7.5% at entry, monotherapy options considered safer are metformin, a GLP-1 receptor agonist, a DPP-4 inhibitor, or an alpha-glucosidase inhibitor. Medications to be used with caution, include sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors, thiazolidinediones, sulfonylureas, and meglitinides.

The 2013 American Academy of Pediatrics (AAP) guidelines for Management of Newly Diagnosed Type 2 Diabetes Mellitus in Children, recommends a lifestyle modification program, including nutrition and physical activity, and metformin as first-line therapy for children and adolescents (ages 10- 18 years) at the time of diagnosis and who are not ketotic or in diabetic ketoacidosis.[19] Insulin therapy should be initiated in patients with ketosis or ketoacidosis.

PHARMACOLOGY

Metformin, a biguanide, decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Glyburide and glipizide, the sulfonylurea components of Glucovance and Metaglip, respectively, lower blood glucose by stimulating the release of insulin from the pancreas.

PHARMACOKINETICS

Metformin has a bioavailability of 50 to 60 percent. Bioavailability decreases with increasing doses due to a decrease in absorption rather than a change in elimination. Metformin is eliminated by the kidney (greater than 90 percent within 24 hours) with no hepatic metabolism. The half-life is approximately 6.2 hours. Tubular secretion plays a role in elimination, as the elimination rate of metformin is approximately 3.5 times greater than the creatinine clearance.[20]

The glipizide and metformin components of Metaglip are bioequivalent to coadministered Glucotrol® and Glucophage.[21]

The pharmacokinetics of metformin in the combined product, Glucovance, are similar to the pharmacokinetics of metformin as a single agent. The pharmacokinetics of glyburide as a combination product are different than those of glyburide as the Micronase® product. The area under the plasma concentration time curve (AUC) was greater for glyburide in the combination product, Glucovance, versus glyburide as the Micronase product.[22]

The rate and extent of absorption of metformin oral solution (Riomet) was found to be comparable to that of metformin tablets under fasting or fed conditions.[23]

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Metformin ER (Fortamet) uses single-composition osmotic technology. Upon ingestion, the drug is dissolved inside the tablet and slowly released through laser-drilled ports. Drug release is dependent on a constant osmotic gradient and continues until this gradient is no longer present.[24]

Metformin ER (Glumetza) is a polymer-based oral drug delivery system.[25] The tablets swell in the stomach allowing increased gastric retention time for delivery of metformin at a designed rate.

Metformin XR (Glucophage XR) is a dual hydrophilic matrix consisting of polymers that hydrate and swell after contact with the GI tract. Drug diffusion is independent of pH and provides a slow release of metformin.[26]

CONTRAINDICATIONS/WARNINGS[27, 28, 29, 30, 31, 32]

Any product containing metformin is contraindicated in patients with any of the following: renal disease or renal dysfunction (SCr ≥1.5 mg/dL for males and ≥1.4 mg/dL for females), acute or chronic metabolic acidosis including diabetic ketoacidosis, acute myocardial infarction, septicemia, pregnancy, or known hypersensitivity to metformin or other ingredients in the drug formulation. Metformin products once carried a contraindication in congestive heart failure patients but that has now been removed. Patients with congestive heart failure still have a higher risk of lactic acidosis.

Lactic acidosis is a rare, but potentially fatal, complication of metformin therapy. Use caution in patients with renal insufficiency or patients undergoing radiologic procedures who receive intravenous iodinated contrast agents.

Caution should be used with metformin in patients experiencing hypoxic states or undergoing surgical procedures and in patients with hepatic impairment or with excessive alcohol intake. Due to the age-related decline of renal function, do not titrate metformin to the upper dosage range in elderly patients (>80 years of age) even for patients with serum creatinine levels within the normal range.

DRUG INTERACTIONS[33, 34, 35, 36, 37, 38]

Exercise caution when using with drugs that are known to exacerbate hyperglycemia.

Cationic drugs such as amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin that are eliminated by renal tubular secretion have a theoretical potential interaction with metformin by competing for common renal tubular transport systems. No specific dosing changes are recommended. Increased metformin plasma concentrations are seen with concurrent administration of cimetidine, furosemide, and nifedipine. No specific dosing changes are recommended. Contrast agents increase the risk of metformin-induced lactic acidosis.

The same drug interactions can occur with glipizide/metformin or glyburide/metformin as with each individual agent. Consult package inserts for detailed information.

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ADVERSE EFFECTS

Drug	Diarrhea	Headache	Nausea/ Vomiting	Abdominal Pain	Dizziness
glipizide/metformin 5/500 mg (Metaglip)[39] n=87	18.4	12.6	8.0	5.7	nr
glipizide 5 mg n=84	13.1	6	6.0	8.3	nr
metformin 500 mg n=75	17.3	5.3	8.0	6.7	nr
glyburide/metformin (Glucovance)[40] n=642	17	8.9	7.6	6.9	5.5
glyburide n=324	6.2	11.4	5.2	3.1	5.6
metformin n=312	20.5	9.3	12.2	8	3.8
metformin (Glucophage)[41] n=141	53.2	5.7	25.5	6.4	nr
placebo n=145	11.7	4.8	8.3	4.8	
metformin ER (Fortamet)[42] n=424	16.7	4.7	8.5	nr	nr
metformin IR n=430	11.9	5.1	7.4		
metformin ER (Glumetza) + sulfonylurea[43] n=431	12.5	nr	6.7	nr	nr
placebo + sulfonylurea n=144	5.6		4.2		
metformin ER (Glucophage XR)[44] n=781	9.6	nr	6.5	nr	nr
placebo n=195	2.6		1.5		

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. nr=not reported

Adverse effects for metformin solution are similar to those for metformin.

Monitoring

Monitor renal function initially and annually. Monitor when renal function may be compromised (intravenous iodinated contrast media, hypoxic states or surgical procedures) or when concomitant drug therapy may interfere with drug clearance. Monitor FPG periodically and HbA1c every three months to determine if treatment goals are met.

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SPECIAL POPULATIONS[45, 46, 47, 48, 49, 50]

Pediatrics

Metformin (Glucophage, Riomet) can be used in patients 10 years of age and older according to the prescribing information. Other metformin-containing products have not been evaluated in pediatric patients.

Pregnancy

All products in this review are rated Pregnancy Category B except for metformin solution and glipizide/metformin combination which are Pregnancy Category C.

Renal Impairment

As renal clearance rate declines, elimination of metformin is reduced proportionally. Patients with creatinine clearance less than the upper limit of normal for their age should not receive metformin.

Geriatrics

Metformin (Glucophage, Riomet) should not be initiated in patients ≥ 80 years of age unless serum creatinine clearance levels are not reduced. Metformin should be titrated carefully in older patients. Due to reduced renal function in patients of advanced age and thereby increased risk of lactic acidosis, geriatric patients should be monitored regularly for reduced renal function and managed appropriately.

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DOSAGES

Drug	Parameters	Initial Dosage	Availability
glipizide/metformin (Metaglip)[51]	First-line therapy for FPG < 280 mg/dL	2.5 mg/250 mg daily with a meal	2.5 mg/250 mg 2.5 mg/500 mg 5 mg/500 mg tablets
	First-line therapy for FPG 280-320 mg/dL	2.5 mg/500 mg twice daily with meals	
	Second-line therapy	2.5 mg/500 mg or 5 mg/500 mg twice daily with meals	
glyburide/metformin (Glucovance)[52]	Initial therapy	1.25 mg/250 mg once or twice a day with meals	1.25 mg/250 mg, 2.5 mg/500 mg, 5 mg/500 mg tablets
	Initial therapy with HbA1c > 9% or FPG > 200 mg/dL	1.25 mg/250 mg twice daily with meals	
	Second-line therapy	2.5 mg/500 mg or 5 mg/500 mg twice daily with meals	
metformin (Glucophage)[53]	Initial therapy	500 mg twice daily or 850 mg daily with meals	500, 850, 1,000 mg tablets
metformin ER (Fortamet)[54]	Initial therapy	1,000 mg daily with evening meal	500, 1,000 mg tablets
metformin ER (Glumetza)[55]	Initial therapy	1,000 mg daily with evening meal	500, 1,000 mg tablets
metformin XR (Glucophage XR)[56]	Initial therapy	500 mg daily with evening meal	500, 750 mg tablets
metformin oral solution 100 mg/mL (Riomet)[57]	Initial therapy	500 mg (5 mL) twice daily or 850 mg (8.5 mL) daily with meals	100 mg/mL oral solution

Combination therapy

Once metformin is used at maximum daily dose and hyperglycemia is not controlled, changing therapy to metformin XR 1,000 mg twice daily with meals is an alternative. If an adequate response is not seen within two to three months, initiate combination therapy with other antidiabetic agents.

CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers,

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the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

glipizide/metformin (Metaglip)

In a multicenter, double-blind trial, 247 patients were randomized to glipizide 30 mg, metformin 500 mg, or glipizide/metformin 5/500 mg for 18 weeks.[58] Maximum doses allowed were glipizide 30 mg, metformin 2,000 mg, and glipizide/metformin 20/2,000 mg. Patients were generally obese (mean BMI=31.3 kg/m^2), had moderate to severe hyperglycemia (mean HbA1c 8.7 percent), and had a mean duration of diabetes of 6.5 years. Glipizide/metformin tablets controlled the HbA1c level more effectively than did either glipizide or metformin monotherapies (mean treatment differences, in favor of glipizide/metformin, of -1.06 percent and -0.98 percent, respectively, p<0.001). Glipizide/metformin tablets also reduced the fasting plasma glucose (FPG) level and the three-hour postprandial glucose area under the concentration-time curve more effectively than did either monotherapy, without increasing the fasting insulin level. The greatest blood glucose control with glipizide/metformin tablets was achieved at a mean daily dose of glipizide/metformin 17.5/1,747 mg compared with mean doses of glipizide 30 mg or metformin 1,927 mg.

glyburide/metformin (Glucovance)

In a placebo-controlled, double-blind, multicenter study, 806 patients with type 2 diabetes and HbA1c greater than seven percent were randomized to four weeks of therapy with glyburide 2.5 mg, metformin 500 mg, glyburide/metformin 1.25/250 mg, glyburide/metformin 2.5/500 mg, or placebo once daily.[59] Doses could be titrated over the next eight weeks based on glycemic response up to a maximum of four tablets per day. At 20 weeks, patients taking the combination therapy had greater reductions in HbA1c levels (-1.48 and -1.53 percent, respectively) compared with glyburide (-1.24 percent; both p<0.001), metformin (-1.03 percent; p=0.016 and 0.004, respectively), or placebo (0.21 percent; both p<0.001). FPG and postprandial glucose were reduced significantly more in the glyburide/metformin groups. These effects were achieved with lower doses of each agent in the combination therapy. Higher incidences of gastrointestinal effects were noted in the metformin groups versus glyburide alone and placebo.

In a multicenter, double-blind trial of 486 patients with type 2 diabetes who were treatment-naïve, therapy was initiated with glyburide/metformin 1.25/250 mg, metformin 500 mg, or glyburide 2.5 mg.[60] After 16 weeks, patients in the glyburide/metformin group had superior mean reductions in HbA1c from baseline (-2.27 percent versus metformin –1.53 percent and glyburide –1.9 percent; p=0.0003). Glyburide/metformin also significantly reduced FPG and two-hour postprandial glucose values compared with either monotherapy. The final mean doses of glyburide/metformin (3.7/735 mg) were lower than those of metformin (1,796 mg) and glyburide (7.6 mg).

metformin (Glucophage)

In a study to evaluate the effect of metformin in intensive blood glucose control with insulin or sulfonylureas, 753 patients with newly-diagnosed type 2 diabetes were randomized to diet alone (n=411) or intensive blood glucose control with metformin (n=342).[61] Patients were followed for a mean duration of 10.7 years for the occurrence of any diabetes-related clinical endpoint, diabetes-

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related deaths, and all-cause mortality. The metformin group was also compared to patients on chlorpropamide (n=265), glyburide (n=277), or insulin (n=409) for the same endpoints. The median HbA1c in the metformin group was 7.4 percent compared with eight percent in the diet alone group. Metformin patients had relative risk reductions of 32 percent (p=0.002) for any diabetes-related endpoint, 42 percent (p=0.017) for diabetes-related death, and 36 percent (p=0.011) for all-cause mortality compared to the diet alone group. Compared to the other pharmacologic therapies, metformin had a greater effect on any diabetes-related endpoint (p=0.0034), all-cause mortality (p=0.021), and stroke (p=0.032). The findings of this study help substantiate the use of metformin as a first line agent in the treatment of type 2 diabetes mellitus.

metformin XR (Glucophage XR)

A multicenter, double-blind trial enrolled 217 patients with type 2 diabetes who had HbA1c values less than or equal to 8.5 percent and mean fasting glucose concentrations of <200 mg/dL while receiving metformin 500 mg twice daily for eight weeks.[62] Patients were randomly assigned to metformin XR 1,000 or 1,500 mg once daily or metformin 500 mg twice daily for 24 weeks. All three treatment groups had similar changes in HbA1c at weeks 12 and 24 compared to baseline. At week 12, the mean change from baseline in HbA1c was -0.15 percent for metformin, -0.23 percent for metformin XR 1,000 mg, and -0.04 percent for metformin XR 1,500 mg.

In Protocol 1 of a randomized, double-blind, placebo-controlled study, 240 patients were randomized to receive metformin XR 1,000 mg once daily or placebo.[63] In Protocol 2, 742 patients were randomized to receive metformin XR 500 mg once daily, 1,000 mg once daily, 1,500 mg once daily, 2,000 mg once daily, 1,000 mg twice daily, or placebo. The primary endpoint in each study was the change from baseline in HbA1c at 12 weeks (Protocol 1) or 16 weeks (Protocol 2). Metformin XR reduced HbA1c in Protocol 1 with mean treatment differences for 1,000 mg once daily versus placebo of -0.7 percent at 12 weeks and -0.8 percent at 24 weeks (p<0.001 for each). In Protocol 2, a clear dose-response relationship was evident at doses up to 1,500 mg with treatment differences versus placebo of -0.6 percent (500 mg once daily), -0.7 percent (1,000 mg once daily), -1 percent (1,500 mg once daily), and -1 percent (2,000 mg once daily). Efficacy of metformin XR 2,000 mg once daily and 1,000 mg twice daily were similar. More patients achieved HbA1c less than seven percent with metformin XR versus placebo in Protocol 1 (29 percent versus 14 percent at 12 weeks) and with once daily metformin XR in Protocol 2 (up to 36 percent versus 10 percent at 16 weeks). Total cholesterol and LDL-C improved (p<0.05, p<0.001) in metformin XR groups in Protocol 2. Metformin XR was well tolerated.

SUMMARY

Metformin is an effective agent for the management of hyperglycemia in patients with type 2 diabetes mellitus. Metformin (Glucophage, Riomet) are FDA-approved in pediatric patients. The metformin immediate-release and extended-release formulations provide similar effects on HbA1c and FPG with once daily dosing to enhance patient compliance.

The combination of glyburide/metformin has been shown to significantly decrease HbA1c and FPG more than either agent alone. Adverse effects of the combination product were not significantly different than either agent used alone. The other combination product, glipizide/metformin (Metaglip), also has been shown to be more effective than either agent used alone with adverse effect

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profiles similar to each individual agent. The combination products allow for using fewer tablets per day and may provide an incentive for increased adherence.

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