Risk of Cardiovascular Disease and Sudden Death in Schizophrenia

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Patients with schizophrenia are at higher risk for medical illnesses than people in the general population. Electrocardiographic and metabolic abnormalities that occur in patients with schizophrenia who are treated with antipsychotic medications have raised concerns about the safety of these medications. Concerns are amplified by the increased risk of atherosclerosis and sudden cardiac death in patients with schizophrenia regardless of the effect of antipsychotic agents. Because the modifiable risk factors for coronary atherosclerosis and sudden death are so prevalent within the schizophrenic population, it is important for clinicians treating patients with schizophrenia to know what these risks are and understand how they can contribute to increased mortality in these patients. The increased risk of atherosclerosis and sudden death in the schizophrenic population highlights a need for preventive services, which is further underscored by the numerous system- and patient-related barriers to preventive treatment. Clinicians must not only be aware of the modifiable risk factors, but they must also learn to manage the obstacles to prevention in conjunction with other health care specialists.

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Patients with schizophrenia are at higher risk for medical illnesses than people in the general population. They are 2 to 4 times more likely to die prematurely; on average, patients in the schizophrenic population die at least 10 years earlier than their age-matched counterparts.[1,2] Patients with schizophrenia are more likely to have abnormal variations in cardiac rate and are predisposed to obesity and type 2 diabetes.[3] It has been known for decades that patients with schizophrenia are at increased risk for sudden death and that antipsychotic drugs might increase that risk. The introduction of the novel antipsychotics focused attention on sudden death in patients with schizophrenia because the research of these drugs was conducted under rigorous regulatory guidelines that underscored drug safety and proper reporting of adverse events. Electrocardiographic and metabolic abnormalities that occur in patients with schizophrenia who are treated with atypical antipsychotics have raised concerns about the safety of antipsychotic medications in general. These concerns are amplified by the increased risk of atherosclerosis and sudden cardiac death in patients with schizophrenia regardless of the effect of antipsychotic agents.

SUDDEN CARDIAC DEATH

For sudden cardiac death to occur, it is necessary for a trigger to act upon a substrate to cause electrical instability and lethal arrhythmia. A trigger can be an electrolyte imbalance, stress, or a drug with arrhythmogenic potential. Substrates upon which a trigger acts are coronary atherosclerosis, myocardial hypertrophy, and myocardial ischemia. Coronary atherosclerosis is the most prevalent cause of myocardial ischemia, and myocardial ischemia is the most prevalent event leading to electrical instability and lethal arrhythmia. The atherosclerotic lesion of the coronary arteries constitutes a decisive step in the process leading to sudden death. The current understanding of an atherosclerotic lesion is that it is caused by a chronic inflammation of the arterial wall in response to injury produced by (1) a metabolic abnormality, such as dyslipidemia; (2) a mechanical abnormality, such as hypertension; or (3) an infectious organism. When this inflammatory response becomes excessive, it induces tissue proliferation, which in turn narrows the arterial lumen, beginning a process of arterial stenosis. If the source of injury persists, excess tissue proliferation creates atherosclerotic plaque and finally myocardial ischemia. The resulting myocardial ischemia leads to loss of cell membrane integrity, which disrupts both depolarization and repolarization and leads to electrical instability, cardiac arrhythmia, and sudden death.

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Table 1. Risk Factors for Coronary Atherosclerosis[a]

Modifiable	Nonmodifiable
Weight gain	Gender
Dyslipidemia	Age
Diabetes	Family history
Hypertension	
Smoking	
Psychological factors	
Medication	

[a]Data from Elisaf[4] and Welch and Chue.[5]

RISK FACTORS

A risk factor is a manifestation or a laboratory measurement that expresses the likelihood of an individual or a group to develop a disease over a defined period of time. A risk factor may play a causal role in the pathogenesis of the disease, like high cholesterol, or it may only be a marker of risk not directly related to the pathophysiology of the illness, such as the presence of abdominal fat. For a risk factor to be causally related to the disease, it must at least be present before the disease becomes manifest, and it must have biological plausibility.

The risk factors for coronary atherosclerosis can be both modifiable and nonmodifiable. Nonmodifiable risk factors are gender, advancing age, and family history.[4] Modifiable risk factors are excessive weight, dyslipidemia, diabetes, hypertension, smoking, psychological factors,[4] and arythmogenic medication[5] (Table 1). The major risk factors are additive, which means that the total risk of a person is the sum of the risk conveyed by each of the major risk factors. Because the modifiable risk factors are so prevalent within the schizophrenic population, it is important for individuals caring for these patients to know what these risks are and understand how they can contribute to increased mortality in patients with schizophrenia.[6–8]

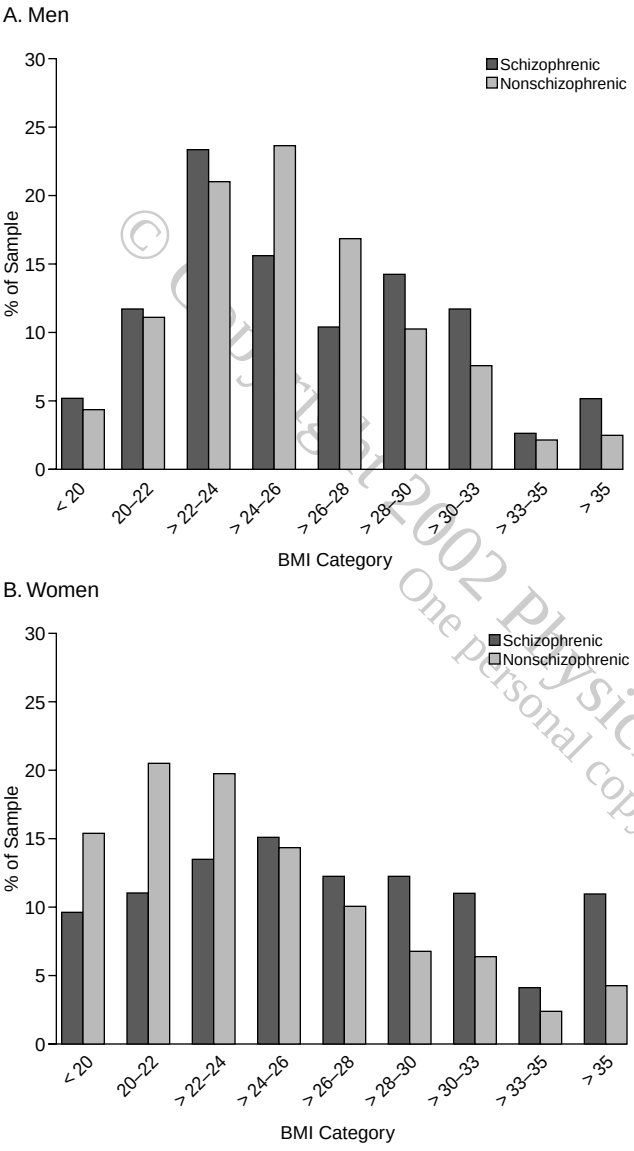
Weight Gain

Weight gain is associated with elevated triglyceride levels, diabetes, and hypertension. The relative risk of atherosclerosis in physically inactive individuals is approximately twice as high as in active individuals. The specific mechanism by which physical activity reduces mortality from cardiovascular disease is not known, but exercise has been shown to improve lipid profiles, glucose tolerance, obesity, and hypertension. Using the 1948 Framingham age and sex distribution data and the 1999 U.S. age and sex distribution data, Fontaine et al.[9] estimated the expected impact of weight gain on selected mortality rates and incidence rates of diabetes and hypertension among adults in the United States. They predicted that for all subjects combined, a mean weight gain of 2.5 kg (5.6 lb) would be expected to result in an additional 26 to 30 deaths per 100,000 people over 10 years. However, among people in the overweight or obese category (body mass index [BMI] > 27), the same weight gain would be expected to result in an additional 257 to 258 deaths per 100,000 people over 10 years. Similarly, a mean weight gain of 2.5 kg (5.6 lb) would be expected to result in an additional 350 cases of incident impaired glucose tolerance per 100,000 people over 10 years or 1850 additional cases of incident hypertension.

Prior to the first release of atypical antipsychotics in the United States, the 1989 National Health Interview Survey data revealed that a significantly greater proportion of women with schizophrenia had BMI distributions in the overweight and obese spectrum compared with their counterparts in the general medical population, and a trend toward greater BMI was also seen among men with schizophrenia (Figure 1).[10] Although antipsychotic-induced weight gain has been reported with the typical antipsychotic drugs, the introduction of the novel antipsychotics has focused attention on this adverse effect. Blockade of the 5-HT_2 and 5-HT_{1C} serotonin receptors and of histamine H_1 receptors has been invoked as a mechanism to explain atypical antipsychotic-induced weight gain for some agents. However, there are major gaps in both the serotonergic and the histaminergic explanation of weight gain. For example, the 2 antipsychotics most associated with weight gain have affinities for about 15 different types of receptors, which further complicates attempts to assign weight gain to any specific neurotransmitter-receptor interaction. Allison et al.[11] estimated and compared the effects of the newer antipsychotics on body weight after 10 weeks of treatment at a standard dose (Table 2). The highest mean weight change was with clozapine and olanzapine. Several studies have shown weight gain with olanzapine or clozapine exceeding 4.5 kg (10 lb) in less than 3 months of treatment in a large proportion of the treated patients.[12–16] The Allison et al. study was published before many data were available on the weight gain effects of quetiapine and ziprasidone. However, in premarketing studies, significantly more quetiapine-treated patients (23%) gained ≥ 27% of their body weight compared with placebo-treated patients (6%).[17] Ziprasidone appears to have a neglible effect on weight—in premarketing studies, only 10% of ziprasidone-treated patients gained ≥ 27% of their body weight compared with 4% of placebo-treated patients.[18]

Treating obesity and changing eating behaviors are challenging enough in individuals without a major mental illness, so the task of behavioral treatment of obesity in patients with schizophrenia can seem especially daunting. Unfortunately, however, excessive weight gain can greatly affect a patient's quality of life through increased comorbid medical illness, an increased relapse rate associated with noncompliance, or the social stigma associated with being obese (Table 3).[19] Obese patients are 13 times more likely to request discontinuation of their current antipsychotic medication because of concerns about weight gain and 3 times more likely to be noncompliant with treatment

Figure 1. Age-Adjusted BMI Distributions Among Schizophrenic and Nonschizophrenic Individuals in the 1989 NHIS Sample[a]



[a]Reprinted from Allison et al.[10] with permission. Abbreviations: BMI = body mass index; NHIS = National Health Interview Survey.

Table 2. Estimated Weight Change After 10 Weeks of Treatment With Atypical Antipsychotics[a]

Drug	Mean kg (lb)
Clozapine	4.45 (9.89)
Olanzapine	4.15 (9.22)
Risperidone	2.10 (4.67)
Sertindole	2.92 (6.49)
Ziprasidone	0.04 (0.09)

[a]Data from Allison et al.[11]

Table 3. Clinical Consequences of Antipsychotic-Induced Weight Gain in Patients With Schizophrenia[a]

Health risks
Hypertension
Atherosclerosis
Type 2 diabetes
Cardiovascular diseases
Stroke
Stigmatization
Noncompliance
Impairment of quality of life
Social withdrawal

[a]Reprinted from Kurzthaler and Fleischhacker[19] with permission.

compared with nonobese patients.[20] The essential points of weight loss intervention for the patient with schizophrenia are frequent monitoring of weight; nutritional and lifestyle counseling; and skills training that focuses on exercise, diet, health education, and behavioral techniques.[21] Weight loss intervention also includes the option to switch to an antipsychotic that may not cause weight gain.

Dyslipidemia

An abnormal lipid profile, or dyslipidemia, is a metabolic abnormality that, among other ill effects, causes injury to arterial walls and initiates the process leading to an atherosclerotic lesion. Dyslipidemia can include elevated serum total cholesterol (> 200 mg/dL), elevated serum low-density lipoprotein cholesterol (LDL) (> 130 mg/dL), elevated serum triglycerides (> 150 mg/dL), and/or low serum high-density lipoprotein cholesterol (HDL) (< 40 mg/dL).[22] Much of the investigation into how lipoproteins produce atherosclerosis has involved examination of the foam-cell formation that constitutes the initial atherosclerotic lesion. It is presumed that LDL is oxidized and then taken up by macrophages to become the atherogenic *foamy streak*. Drugs that lower blood cholesterol levels have been shown not only to have an impact on the risk of cardiovascular morbidity and mortality but also to have a direct effect on coronary structure and function. Dietary cholesterol intake is also significantly associated with risk for coronary atherosclerosis, independent of the serum cholesterol level.

Since treatment with antipsychotics is associated with weight gain, and weight gain is associated with elevated triglyceride blood levels, it is not surprising that this observation has been highlighted by the introduction of the atypical antipsychotics such as clozapine, olanzapine, and quetiapine.[14,16,22,23] There is evidence that some atypical antipsychotics are more associated with lipid changes than others. In a retrospective comparison of lipid changes in inpatients treated with risperidone or olanzapine for 1 year,[24] the mean increase in triglyceride levels was 104.8 mg/dL in the olanzapine-treated patients versus 31.7 mg/dL in the risperidone-treated patients.

Diabetes

Diabetes is another risk factor for coronary atherosclerosis that is associated with metabolic abnormalities that

result in changes in the transport, composition, and metabolism of lipoproteins. Even preclinical diabetes, which can manifest as abnormal glucose tolerance, increases the risk of cardiovascular disease. Insulin resistance and the resulting hyperinsulinemia, which can occur at least 20 years before the clinical onset of hyperglycemia, can damage the arterial wall. Both insulin resistance and hyperinsulinemia are associated with hypercholesterolemia, obesity, and hypertension. Heart disease death rates in adults with diabetes are about 2 to 4 times higher than those of people without diabetes.[25] Premenopausal women with diabetes lose their protection from heart disease and have an even more markedly increased risk.[26] Hyperinsulinemia, hypertriglyceridemia, low HDL levels, visceral obesity, and hypertension are all risk factors for cardiovascular disease that tend to be higher or more common in hyperglycemic patients compared with normoglycemic patients.[25]

An increased prevalence of impaired glucose tolerance, including the onset or exacerbation of diabetes mellitus, has been reported with some of the atypical antipsychotics, including clozapine[26] and olanzapine.[14,27,28] Newcomer et al.,[29] in a recent study, examined glucose regulation in 48 schizophrenic patients being treated with the atypical antipsychotics clozapine, olanzapine, or risperidone or conventional antipsychotics and in 31 untreated healthy control subjects. Olanzapine-treated patients had significant glucose elevations at all time points compared with patients receiving conventional antipsychotics and the control subjects. Clozapine-treated patients had significant glucose elevations at the fasting measurement and the measurement made 75 minutes after the oral load in comparison to patients receiving conventional antipsychotics and untreated control subjects. No differences in mean plasma glucose level were found when risperidone-treated patients were compared with patients treated with conventional antipsychotics or untreated controls.

Sometimes the onset of diabetes is unrelated to weight gain. In an analysis of 45 published cases of new-onset diabetes and diabetic ketoacidosis associated with atypical antipsychotics, Jin et al.[30] found that half the patients manifested no weight gain at the time they presented with diabetes or DKA, although 84% were overweight at the start of antipsychotic treatment.

Hypertension

Hypertension is classified by the National Heart, Lung, and Blood Institute[31] of the National Institutes of Health as a blood pressure reading of ≥ 140/90 mm Hg or current use of hypertensive medication. Hypertension is a cardiovascular risk factor because it produces structural changes within the arteries that narrow the arterial lumen and lead to aneurysms and necrosis. The sequelae of hypertension are manifested after many years and are greatly affected by comorbidities such as dyslipidemia, smoking, diabetes, obesity, lack of physical activity, sodium intake, and stress. Effective treatment dramatically changes the natural history of hypertension-related dysfunctions, but again, patients with schizophrenia are likely to have poor access to medical care and poor compliance with medical care once it becomes accessible.

Smoking

Smoking is probably the most prevalent risk factor for cardiovascular disease, and it is a common habit within the schizophrenic population. Between 50% and 90% of patients with schizophrenia are nicotine dependent.[8] Smokers are 3 times more likely than nonsmokers to experience a major coronary event, and smokers have twice the risk for sudden cardiac death.[32] Smoking contributes to the formation of arteriosclerotic plaque by damaging the endothelium, increasing the proliferation of smooth muscle, and promoting adherence of platelets to the arterial wall. Smoking also promotes thrombosis by increasing fibrinogen levels, plasma viscosity, and arterial wall stiffness and enhances the release of catecholamines, which increases blood pressure and heart rate and decreases the threshold for a lethal arrhythmia. Smoking also increases the heart's demand for oxygen while reducing the capacity of hemoglobin to carry oxygen. The net result of insufficient myocardial oxygen is myocardial ischemia.

Smoking also increases the metabolism of antipsychotic drugs, which necessitates higher dosages to achieve the desired clinical effect,[2] and patients taking higher dosages of antipsychotic medications are more susceptible to greater weight gain. Although the side effects of weight gain and withdrawal make smoking cessation difficult, cessation is a highly effective means to reduce the risk of cardiovascular disease. Unfortunately, patients with schizophrenia find it particularly difficult to refrain from smoking. In addition to the various reasons that all smokers initiate and continue the habit, it is conceivable that patients with schizophrenia also use smoking as an attempt to ameliorate the cognitive dysfunction that is associated with the illness. Less educated and less affluent individuals, who comprise the majority of patients with schizophrenia, are also more likely to be smokers. Members of the more disadvantaged class have less access to smoking cessation programs and information about the negative health effects of smoking, and they are more likely to use smoking as a strategy to alleviate stress and depression. The need for smoking cessation programs within this population cannot be overemphasized.

PSYCHOLOGICAL FACTORS

Stress, hostility, depression, and high demand at work coupled with low control over the work environment have been associated with increased risk for cardiovascular disease.[33] Posttraumatic depression has been associated with arrhythmic deaths, and anxiety has been strongly associ-

Table 4. Barriers to Health Care for Patients With Schizophrenia[a]

System-Related Barriers
Lack of insurance coverage
Lack of access to health care
Stigmatization by health care providers
Lack of understanding of benefits of preventive services by health care workers
Lack of integration of medical and mental health systems
Patient-Related Barriers
Poverty
Noncompliance
Poor communication skills
Denial of illness
Psychosis
Increased pain tolerance

[a]Adapted from Goldman.[8]

ated with acute coronary events.[34] Acute myocardial infarction (MI) is often attributed to heavy physical work, violent quarrel, or unusual mental stress, and stress reduction has been shown to produce some benefit in reducing the risk of cardiovascular disease.[35]

Medication

An examination by Ray et al.[32] of all sudden deaths in the Tennessee Medicaid database for the period January 1, 1988, to December 31, 1993, found that there were twice as many sudden deaths in those taking phenothiazines than in those who were not. The cohort included Tennessee Medicaid enrollees. Persons who received Medicaid were identified by an enrollment file that indicated the periods of enrollment and enrollee demographic characteristics. The enrollment file was linked with Tennessee death certificates, which identify date and recorded cause of death. Enrollee files record prescriptions filled at the pharmacy, outpatient visits, inpatient admissions, and nursing home stays. These data were used to identify the study cohort to determine periods of exposure to study drugs, identify potential cases of sudden cardiac death, and classify cohort members according to preexisting cardiovascular and other diseases.

There were 1483 cases of sudden cardiac death confirmed in the cohort.[32] Twenty percent of those identified as taking phenothiazines were taking thioridazine, which is considered the most problematic agent, and about 20% were taking haloperidol, which is considered a relatively safe drug.[36–38] The most important feature of the study[32] was that each person who died suddenly was evaluated for preexisting cardiovascular risk factors, and a metric was used for establishing severity of risk. The metric included hospital admissions, emergency room visits, physician visits with cardiovascular diagnoses, the use of medications to treat cardiovascular disease or its predisposing conditions, and the use of medications to treat diabetes or to lower lipid levels. The risk factors were adjusted for age and sex, and each case was carefully determined to be sudden death from a cause most likely consistent with an arrhythmia. For cohort members with none, mild, moderate, and severe cardiovascular disease, the respective age- and sex-standardized death rates were 6.2, 10.0, 22.5, and 147.4 deaths per 10,000 person-years. The number of excess sudden cardiac deaths for every 10,000 person-years of follow-up in the population taking at least 100 mg/day of thioridazine or its equivalent with none, mild, moderate, or severe cardiovascular disease was 4, 21, 23, and 372. The increased number of deaths in those taking phenothiazines was attributed to a variety of factors including overweight, lack of exercise, smoking, and stress, as well as medication. These data indicate that even prior to the introduction of the atypical antipsychotic drugs, sudden death occurred more frequently in patients with serious mental illness who had existing cardiovascular risk factors than in the general population.

BARRIERS TO PREVENTION

Because patients with schizophrenia are faced with an increased risk for cardiovascular disease and sudden death, it is only reasonable that physicians recommend appropriate primary and secondary preventive measures. The need for prevention is further underscored by the fact that patients with schizophrenia are less likely than the general population to receive adequate health care for reasons that can be attributed to both the health care system and to the patients themselves (Table 4).[8] A patient with schizophrenia who is hospitalized for acute MI is less than half as likely to receive revascularization by angioplasty or bypass surgery as a patient without mental illness.[39] Despite a proven and recognizable need for preventive measures, there are significant barriers to implementation.

System-Related Barriers

Insurance reimbursement is not always available for preventive services, even though these services help avoid costlier procedures in the long run. There is often a lack of adequate access to health care services for patients with schizophrenia because physicians are much more likely to engage in activities that result in immediate gratification, like pharmacologic relief of angina, than in preventive activities, which provide only delayed benefits and cannot be easily quantified in individual patients. In addition, there can often be stigmatization of mental illness by health care providers, which can cause patients with schizophrenia to avoid treatment, and sometimes health care workers do not understand the magnitude of the benefits of preventive interventions. Further, the lack of integration of the medical and mental health care systems can result in serious diagnostic difficulties.

Patient-Related Barriers

Patients with less education and lower incomes are less likely to comply with rehabilitation and educational

programs, and unfortunately, the majority of patients with schizophrenia fall into this socioeconomic category. They have difficulty understanding the benefits of a program and often cannot comprehend that no-cost programs are affordable. Psychosis and denial of illness are also barriers to adequate health care for the patient with schizophrenia. Also, patients with schizophrenia seem to have an extremely high threshold for pain, which may hinder a physician's ability to diagnose a serious medical condition. For example, it is common for schizophrenics to report a lack of pain with MI; Dworkin[40] noted that only 18% reported pain as compared with 90% in the general population.

CONCLUSION

Although specialists often manage comorbid medical conditions, the particular difficulties presented by patients with schizophrenia require that clinicians become familiar with assessing cardiovascular risk and the options available to reduce that risk. In general, for patients to be considered low risk for developing cardiovascular disease, they must be nonsmoking and nondiabetic, their blood pressure must be < 120/80 mm Hg, and their total cholesterol must be < 200 mg/dL. On the basis of the Framingham study and classification,[41] patients who have already manifested cardiovascular disease in the form of MI, angina, aortic aneurysm, or peripheral vascular disease are considered high risk. These patients have a 20% to 30% chance of developing MI over the next 10 years. Patients already diagnosed with type 2 diabetes fall into the same high risk category even if they have not yet manifested a cardiovascular disease-related event. There are a number of dilemmas in predicting risk for cardiovascular disease and selecting the appropriate intervention. For example, what action does a clinician take if a nondiabetic patient who has not yet manifested cardiovascular disease has a positive family history or elevated blood pressure? Should that patient be assigned to intervention reserved for low-risk patients, or should the patient undergo further evaluation to identify subclinical cardiovascular disease, and therefore be classified as higher risk and treated more aggressively? Should a diagnosis of schizophrenia increase the classification of risk beyond that of the regular Framingham classification? Despite the undeniable benefits of the atypical antipsychotics, to what extent should the cardiovascular disease risk profile be considered in selecting an antipsychotic drug?

As difficult and as frustrating as it might occasionally seem, it is incumbent upon clinicians to implement preventive measures and encourage a healthy lifestyle including a nutritious diet, physical exercise, and smoking cessation.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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