Managing risk factors to prevent stroke

Preventing stroke by modifying risk factors in the individual and the population as a whole still represents the most potent and cost-effective way of reducing the burden of stroke in our community. Important risk factors for stroke include elevated blood pressure, smoking, hypercholesterolaemia, diabetes mellitus, atrial fibrillation and lifestyle factors. Patients who have had a previous stroke or TIA are at especially high risk of further stroke and require early assessment and therapy.

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What is the burden of stroke?

Despite significant reductions in the mortality rates from stroke and ischaemic heart disease in the decades since 1950, stroke continues to rank as the third most common cause of death in Australia. About 50,000 people in Australia will experience a stroke in the next year and 12,000 people will die from their stroke within the first month of experiencing one. Of the survivors, 12,000 will be left disabled and requiring help with activities of daily living, whereas the other 26,000 people will often be left with significant impacts from their stroke – that is, physical, cognitive and emotional effects. The number of strokes and cost to society will continue to rise for at least the next 20 years due to an ageing population.

Three-quarters of strokes occur in people aged over 65 years and the most potent risk factor for stroke is increasing age. Many of the retired population continue to enjoy a good quality of life with high levels of participation in productive economic activity, such as child care and voluntary activities, even if they are no longer working full time. Most preventive strategies such as blood pressure and cholesterol lowering have been well tested in the older age group, in whom the absolute risk reduction with therapy is greater than in the middle aged. Preventive strategies in an older age group are often better accepted and more cost effective than in a younger age group.

IN SUMMARY

- **GPs have a critical role in stroke prevention by identifying patients with risk factors for stroke.**
- **Elevated blood pressure and cholesterol levels, smoking, atrial fibrillation, poor diet, overweight and sedentary lifestyle are modifiable risk factors for stroke.**
- **Patients at high risk of stroke, such as those presenting with transient ischaemic attack (TIA) or minor stroke, warrant urgent investigation and management. Therapy may include antiplatelet drugs, anticoagulants, carotid endarterectomy and aggressive risk factor management, aiming for target blood pressure levels of approximately 140/90 mmHg or lower, and total cholesterol levels of less than 4 mmol/L.**
- **Patient adherence to preventive treatments such as antihypertensives, anticoagulation and lipid-lowering agents remains poor, with education and reinforcement needed.**

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Treating both the individual and the population

In clinical practice we are often concerned with the patient sitting in front of us in the surgery, but the importance of reducing risk factors in the total population should not be ignored. Most lifestyle modifications in the individual can also be applied to the population as a whole (Figure 1). Much of the falling stroke mortality and morbidity in Western populations is associated more with population changes in risk factor prevalence rather than medical treatment *per se*. The two approaches are complementary: lifestyle changes in the population to reduce risk factors, and the addition of drug therapies in individuals at high risk of stroke. Prevention of stroke and stroke-related handicap can occur at a number of different stages, as shown in Figure 2. Primary prevention is obviously the most desirable, but secondary prevention in patients who have had a transient ischaemic attack (TIA) or minor stroke is very important because of the high absolute risk of stroke recurrence in such patients.

Important risk factors for stroke are those that are responsible for the greatest proportion of strokes occurring in the community. The importance of a particular risk factor is expressed as its population attributable risk (i.e. the percentage of strokes occurring in a population due to a particular risk factor = prevalence of the risk factor x relative risk of stroke associated with presence of the risk factor). A number of common risk factors for stroke are detailed in Table 1. When contemplating drug therapy or procedures that may be expensive or have significant side effects, it is important to target individuals at high absolute risk of stroke. We know that patients who have had a TIA or minor stroke are at a high risk of recurrent stroke, with up to a 10% risk of stroke per year.

In primary prevention, risk tables such as the cardiovascular risk calculator produced by the National Vascular Disease Prevention Alliance may be helpful to calculate the absolute risk of stroke and other cardiac events for an individual (see the website: www.nps.org.au/cv_risk_calculator). Atherosclerosis is a systemic disease and stroke victims are at risk of myocardial infarction, vascular death and other vascular events as well as recurrent stroke. Prevention of such events is also an added benefit of risk factor modification.

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Figure 1. Lifestyle modifications can reduce risk factors for stroke.

Common risk factors

Elevated blood pressure

Elevated blood pressure is the most important risk factor for both ischaemic stroke and haemorrhagic stroke in respect of its prevalence and response to therapy. A strong relation exists between increasing levels of diastolic and systolic blood pressure and risk of stroke in primary and secondary prevention. For every 7 mmHg increase in diastolic blood pressure and 13 mmHg increase in systolic blood pressure, the risk of stroke doubles. This applies throughout the range of 76 to 120 mmHg diastolic blood pressure and 130 to 180 mmHg systolic blood pressure.

In a multitude of randomised controlled clinical trials in primary prevention, consistent reductions in stroke risk have been demonstrated with a diversity of antihypertensive agents in a wide range of patient groups. Relative reductions in stroke risk are similar in the middle aged and elderly (including those aged over 80 years), with greater absolute reductions in stroke risk in the older age groups. Different drugs classes, including thiazide diuretics, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers and to a lesser extent β-blockers, all appear to reduce the relative risk of stroke by 30 to 40%. More recent studies have compared drugs from different therapeutic classes and combinations of drugs. The newer, more expensive agents such as

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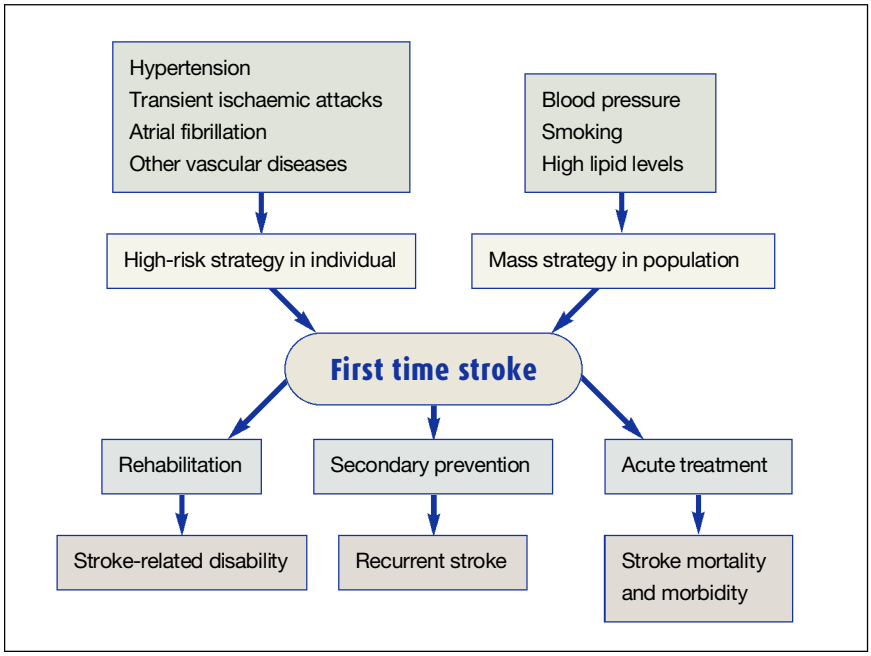

Figure 1. Ways of preventing stroke.

calcium channel blockers, ACE inhibitors or angiotensin II receptor blockers seem to be slightly more effective than the older, cheaper drugs such as thiazides and β-blockers. The target blood pressure for primary prevention is approximately 140/90 mmHg or lower, but for patients at higher risk of stroke a lower target is suggested because of other risk factors such as diabetes or chronic renal failure.

Testing of antihypertensive drugs in randomised controlled trials in the secondary prevention of recurrent stroke has been conducted using ACE inhibitors, angiotensin II receptor blockers and indapamide. All three classes seem to prevent recurrent stroke and other vascular events in patients presenting with haemorrhagic or ischaemic stroke. Active treatment in the PROGRESS study of perindopril and indapamide reduced the relative risk of stroke by 26%, and stroke-related disability by 24%.[1] Relative risk reductions with active therapy were greatest in patients presenting with intracerebral haemorrhage. Patients in this study were treated irrespective of their blood pressure at randomisation, with the lowest stoke risk occurring in patients with an average blood pressure of 115 to 120/70 mmHg.

More recently, the ONTARGET trial (with over 25,000 participants) demonstrated that an ACE inhibitor (ramipril 10 mg) was equivalent in effectiveness to an angiotensin II receptor blocker (telmisartan 80 mg).[2] A third comparator group consisting of the combination of these two drugs lowered blood pressure by approximately 3 mmHg systolic and 1.5 mmHg diastolic compared with monotherapy, but did not demonstrate a further significant reduction in stroke risk. This combination therapy caused a significant excess of adverse events (including syncope, hypotensive events and renal dysfunction) in a population who were relatively young (mean age, 66 years).[2] Combination therapy with ACE inhibitors and angiotensin II receptor blockers is not applicable to most patients with hypertension and is associated with increased risks of side effects without any evidence of increased efficacy.

Lifestyle modifications, for example, weight loss, sodium restriction, potassium supplementation, alcohol restriction and increased exercise, are important factors in reducing blood pressure in low-risk

Table 1. Population attributable risk for various risk factors for stroke

Risk factors	Proportion of strokes occurring in the community*
Increasing age	(Not known)
Increasing blood pressure	30–50%
Cigarette smoking	25%
Having diabetes mellitus	10%
Having atrial fibrillation	10–15%
Increasing cholesterol levels	20%
Having vascular disease of heart/periphery	20%
Having carotid stenosis	5%
Poor diet with elevated homocysteine levels	(Not known)
Having obesity and undertaking low levels of exercise	(Not known)

* An individual may have multiple risk factors, hence the total is over 100%.

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Table 2. Individual and population interventions to reduce blood pressure, stroke and vascular disease

- Decrease weight
- Increase physical exercise (to at least 30 minutes three to five times per week)
- Reduce sodium salt consumption
- Decrease excess alcohol consumption (to one to two standard drinks per day or less)
- Increase unsaturated fat intake (to two to three fish meals per week, and use low-fat milk)
- Increase fresh fruit and vegetable intake
- Use drug therapy in high-risk individuals

patients, and also complement drug therapy in high-risk patients (Table 2).

Smoking

Smoking increases the risk of ischaemic and haemorrhagic stroke with a dose–response relationship. No randomised controlled trials have addressed smoking cessation in stroke prevention, but epidemiological observations suggest that ceasing smoking reduces the risk of stroke to a nonsmoking level five years after cessation. It is, therefore, never too late to stop smoking to reduce the risk of stroke.

Hypercholesterolaemia

The relation between total cholesterol levels and risk of ischaemic stroke is well established. What is not so clear is the relation between the risk of haemorrhagic stroke and cholesterol levels because patients with low levels of cholesterol seem to have an increased risk of haemorrhagic stroke in most epidemiological studies. In Western populations, where about 85% of strokes are ischaemic, this is not critical, but in Asian populations in which nearly 30% of strokes may be haemorrhagic, this dichotomy of effect may be important.

Randomised controlled trials in patients at high risk of coronary events have shown that the risk of stroke was reduced by about 20% in those allocated therapy with statins, such as simvastatin, pravastatin and atorvastatin. The picture in patients who have had previous stroke or TIA was less clear until the SPARCL trial demonstrated a 17% reduction in the risk of stroke when patients were allocated atorvastatin 80 mg daily.[3] There was an excess of haemorrhagic stroke in the atorvastatin group but this was outweighed by a significant reduction in ischaemic stroke and cardiac events. All patients with ischaemic stroke should be considered for statin therapy to prevent recurrent ischaemic stroke and cardiac events. This is especially important for long-term stroke survivors, who are more likely to die from a cardiac event than a stroke. The relation between cholesterol-lowering therapy and haemorrhagic stroke is the focus of ongoing research.

A recent large randomised controlled trial, the JUPITER trial, investigated the role of rosuvastatin in primary prevention of vascular events in people with elevated levels of the inflammatory marker C Reactive Protein (CRP) and normal levels of low-density lipoprotein cholesterol.[4] This followed the observation that such patients were at elevated risk of vascular events irrespective of their level of other vascular risk factors such as cholesterol level or blood pressure. Although the relative reduction in the risk of stroke was an impressive 48%, the absolute risk was small meaning that nearly 300 people would need to be treated for two years to prevent one of them having a stroke.[4]

Diet and antioxidants

Epidemiological research has identified poor diet with low intake of fresh fruit and vegetables as a risk factor for stroke. This risk may be related to saturated fat intake or other dietary risk factors and health habits. A low fresh fruit and vegetable intake is associated with elevated levels of homocysteine, which are in turn associated with higher risks of primary and secondary stroke and cardiac events.

Antioxidant vitamin supplements such as folic acid and vitamins B_6 and B_{12} have been shown to lower homocysteine levels. A 3 µmol/L lower level of plasma homocysteine is associated with a 10% reduction in stroke risk and a 26% reduction in cardiac events. Unfortunately, the randomised controlled trials conducted to date have been unable to demonstrate any significant clinical benefits with vitamin supplementation although significant reductions in homocysteine levels have been achieved. The reports from the largest trial to date in this area, the VITATOPS study, are still awaited. On the epidemiological evidence available, it seems prudent to advise patients to have a healthy diet with low levels of saturated fat, a low sodium salt intake and an adequate intake of fresh fruit and vegetables.

Alcohol

The relation between alcohol consumption and stroke risk follows a 'J' curve with stroke risk minimised by an alcohol intake of one to two standard drinks per day, and an increased risk of ischaemic and haemorrhagic stroke at levels above this.

Diabetes mellitus

Diabetes mellitus remains an independent risk factor for stroke and cardiac disease even after controlling for other known risk factors. The relative risk of stroke in a patient with diabetes is about twice that in a person without diabetes. Controlling risk factors such as elevated blood pressure and cholesterol levels in patients with diabetes thus yields high absolute benefits. Target levels for blood pressure (130/85 mmHg or lower) and total cholesterol levels (less than 4 mmol/L) are the same as those for secondary prevention in patients with diabetes. Tighter control of diabetes has not been demonstrated to prevent

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Risk stratification in patients with atrial fibrillation using $CHADS_2$ criteria[11]

The $CHADS_2$ score is a clinical prediction rule for estimating the risk of stroke in patients with atrial fibrillation. It can also determine what treatment is necessary for individual patients.

Letter	Risk factor	Points
C	Congestive heart failure	1
H	Hypertension	1
A	Age 75 years or older	1
D	Diabetes mellitus	1
S	Prior stroke/TIA	2

Using the table above, a $CHADS_2$ score can be obtained by adding together the points that correspond to the risk factors in an individual patient. Using the table below, the annual stroke risk can then be calculated and the preferred treatment regimen determined.

$CHADS_2$ score	Annual stroke risk*	Preferred treatment
0	Low risk (2%)	Aspirin
1	Moderate risk (3%)	Warfarin or aspirin
2 to 6	High risk (4 to 18%)	Warfarin (INR target of 2 to 3)

*Annual stroke risk varies from 2% for a score of 0, 3% for a score of 1, 4% for a score of 2, 6% for a score of 3, 8% for a score of 4, 12% for a score of 5, to 18% for a score of 6.

ABBREVIATIONS: TIA = transient ischaemic attack; INR = international normalised ratio.

Stoke studies mentioned in this article

BAFTA study
Birmingham Atrial Fibrillation Treatment of the Aged study

CAPRIE study
Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events study

CHARISMA trial
Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance trial

JUPITER
Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin

MATCH trial
Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke trial

ONTARGET
Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial

PRoFESS trial
Prevention Regimen for Effectively Avoiding Second Strokes trial

PROGRESS
Perindopril Protection Against Recurrent Stroke Study

SPARCL trial
Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial

VITATOPS trial
Vitamins to Prevent Stroke trial

macrovascular events. However, the use of metformin in patients with type 2 diabetes mellitus seems to have unique effects in lowering vascular events independent of the degree of diabetic control achieved.

Preventive treatment for high-risk patients

Antiplatelet therapy

Randomised controlled trials that have included thousands of patients presenting with ischaemic stroke or TIA have shown that antiplatelet drugs such as aspirin, clopidogrel, ticlopidine and the combination of aspirin and dipyridamole reduce the relative risk of vascular events by 22%. An absolute risk reduction of 20 events per thousand patients treated per year was demonstrated (i.e. 50 people would need to be treated to prevent one of them having a vascular event).[5] This is a very cost-effective intervention with an inexpensive therapy such as low-dose aspirin costing $40 to 50 per year.

The combination of aspirin plus dipyridamole is more expensive ($400 per year), as is also clopidogrel ($1000 per year). Both dipyridamole and clopidogrel have been studied in large randomised controlled trials in comparison with aspirin. The CAPRIE study demonstrated a relative risk reduction in vascular events of approximately 9% with clopidogrel 75 mg daily compared with aspirin 325 mg daily.[6] The absolute risk reduction was 0.5% (i.e. 200 people would need to be treated each year to prevent one of them having a vascular event). Various subgroup analyses from this trial have attempted to try and demonstrate a greater risk reduction in some patient groups (e.g. those with diabetes or peripheral vascular disease) or a greater effectiveness in preventing cardiac events compared with strokes, but these analyses are

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statistically unsound and should be treated with great caution. The combination of aspirin and dipyridamole has been compared with aspirin alone in two large randomised controlled trials with a 20% relative risk reduction in vascular events demonstrated. This translates into an absolute risk reduction of 1% per year (i.e. 100 people each year would need to be treated to prevent one of them having a vascular event).[7]

More recently, the PRoFESS trial directly compared the combination of aspirin and dipyridamole with clopidogrel in nearly 20,000 people with minor stroke or TIA.[8] There was no statistical difference in efficacy identified between the two drug regimens overall, or in any subgroup of patients. Both regimens were equally effective in preventing individual endpoints such as stroke, nonfatal myocardial infarction and vascular death. This trial could be labelled as a very expensive exercise to prove drug equivalence, but does reassure the clinician that both regimens are comparable in efficacy and that the choice between agents can be determined on the basis of side effects, cost and drug sensitivity. Dipyridamole causes headache and nausea in about 20% of people, whereas clopidogrel may cause diarrhoea and rash and is indicated for patients who are allergic or intolerant to aspirin.

The combination of aspirin and clopidogrel in stroke prevention was tested in the CHARISMA and MATCH trials, and was shown to have no demonstrable benefit over aspirin or clopidogrel monotherapy.[9,10] The combination of aspirin and clopidogrel carries a significantly increased haemorrhagic risk, which may be why the promising advantage of this combination for the short-term therapy of unstable angina, acute myocardial infarction and coronary angioplasty has not translated into benefits in stroke prevention over a longer duration in older patients.

Anticoagulant therapy

The use of warfarin in the prevention of stroke has been assessed in a number of randomised controlled trials, with clear efficacy demonstrated in patients with constant and paroxysmal atrial fibrillation. Nonrandomised studies suggest warfarin may also be useful in patients at high risk of cardioembolism because of mitral stenosis, prosthetic valve replacement, recent myocardial infarction with mural thrombus, cardiomyopathy with mural thrombus and cryptogenic stroke with a demonstrated patent foramen ovale. Patients with atrial fibrillation remain by far the largest group at risk of stroke, with a prevalence of up to 15% in those

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aged over 80 years. Superiority of warfarin over aspirin has not been demonstrated in patients whose major risk factor for stroke is atherosclerotic disease (e.g. high-grade intracranial stenosis, or routinely after TIA or minor stroke).

Warfarin reduces the relative risk of stroke in patients with atrial fibrillation by two-thirds (absolute risk reduction up to 8%; number needed to treat [NNT] = 12), whereas aspirin reduces the relative risk by about 20% (absolute risk reduction, 2.5%; NNT = 40). The risk of stroke in patients with atrial fibrillation is best assessed using the $CHADS_2$ criteria (see the box on page 64).[11] The risk of serious haemorrhage in patients taking warfarin is probably 0.5 to 1% per year, which is two to five times the bleeding risk in patients taking aspirin. The need for blood tests and the possible interactions with other drugs may also increase the cost and side effects of warfarin use. Each individual must, therefore, be assessed based on his or her personal risk of stroke, balanced against the risk of side effects of bleeding (Table 3), with a personal preference for outcomes often being the deciding factor.

The BAFTA study has recently demonstrated that warfarin can safely be given to patients of an older age group (aged over 75 years). Age alone, therefore, should not be an exclusion criterion for the use of anticoagulation.[12]

Unfortunately, attempts to maintain sinus rhythm in patients with atrial fibrillation by electrical or drug means have not demonstrated a reduction in stroke or cardioembolic risks.

Carotid endarterectomy and angioplasty

The effectiveness of carotid endarterectomy in patients with carotid territory minor stroke or TIA and severe (>70%) ipsilateral carotid stenosis has been demonstrated in two major surgical trials. Carotid endarterectomy reduces the relative risk of ipsilateral stroke by 50% over and above best medical therapy (absolute risk reduction, 15%; NNT = 7).[13] The role of carotid endarterectomy in patients with asymptomatic carotid stenosis remains contentious with an absolute risk reduction of approximately 2% (NNT = 50) and a negligible benefit or even harm in older age groups or females. Carotid angioplasty and stenting has been proposed as a less invasive and safer means of treating carotid stenosis, but none of the randomised controlled trials published to date have supported this proposition. Carotid endarterectomy performed by an appropriate surgeon remains the treatment of first choice in most of these patients.

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Table 3. Factors associated with a higher bleeding risk in patients taking warfarin

- Presence of bleeding diasthesis
- Untreated gastrointestinal bleeding source
- Presence of haemorrhagic retinopathy
- Intracerebral bleeding source
- Uncontrolled hypertension
- Presence of bacterial endocarditis
- Heavy alcohol intake
- Presence of cognitive impairment
- High risk of falls
- Poor compliance with therapy or monitoring
- Unstable international normalised ratio results during therapy
- Increase in age

The timing of surgical intervention is critical, with the greatest benefit in patients having surgery within two weeks of symptom onset. Males, patients with a more severe stenosis and those aged over 75 years also seem to have a greater absolute benefit from surgery.

Conclusion and guidelines

We now have excellent data to support a number of interventions to reduce the risk of stroke by modifying risk factors and targeting disease processes. The major problem now lies in making sure that adequate screening for stroke risk factors occurs and that patients adhere to recommended therapy. Adherence to preventive strategies remains poor; only half of patients with hypertension are identified and only half of those taking therapy are controlled. Hypercholesterolaemia is also treated in only half of patients with the condition and controlled in only 30% of those treated.

Opportunistic screening by GPs in the course of their routine practice is very cost effective. Each full-time working GP in Australia will see in an average week about 80 people aged between 30 and 80 years who have at least one risk factor for stroke. Identification and management of such individuals will reduce the burden of vascular disease in the community. Identification and prompt referral of patients presenting with minor stroke or TIA will ensure that appropriate investigations and preventive strategies are started early.

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COMPETING INTERESTS: None.

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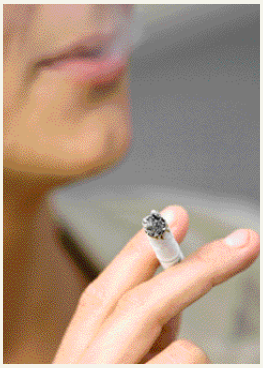

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