FAQs on Cyscolin

1. What are the risk factors for stroke?

- There are more than 20 identified risk factors of stroke. Stroke can occur to anyone irrespective of age, gender or race
- The chances of having a stroke increase if a person has certain risk factors, or criteria that can cause a stroke. There are two types of risk factors for stroke:
  - Controllable and uncontrollable

- **Controllable risk factors** generally fall into two categories:
  - Lifestyle risk factors or medical risk factors
  - Lifestyle risk factors can often be changed, while medical risk factors can usually be treated

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- **Uncontrollable risk** factors include being over age 55, being male, being African American, Hispanic or Asian/Pacific Islander, or having a family history of stroke or transient ischemic attack (TIA)
- If people are aware up to 80 percent of strokes can be prevented, and the best way to protect yourself and loved ones from stroke is to understand personal risk and how to manage it

2. What is the type of patients at risk for stroke?

The following patients can be termed to be at risk of stroke
- Hypertensive patients with high BP >140/90 or unknown
- Patients with atrial fibrillation,
- with high cholesterol (>240 or unknown)
- patients with diabetes
- People with sedentary lifestyle
- Obese people

3. What are the most common stroke symptoms?

Symptoms can vary depending on whether the stroke is caused by a blood clot (ischemic stroke) or bleeding (hemorrhagic stroke), where the stroke occurs in the brain, and how bad it is. The general symptoms of Stroke include:

- Sudden numbness or weakness of face, arm or leg, especially on one side of the body
- Sudden confusion, trouble speaking or understanding
- Sudden vision changes (trouble seeing in one or both eyes)
- Sudden trouble walking, dizziness, loss of balance or coordination
- Sudden severe headache with no known cause

3. What is Transient ischemic attack (TIA)?

- Blood is carried to the brain via a complex network of arteries and vessels. A stroke occurs when one of these arteries becomes blocked or ruptures
- A stroke is a sudden interruption in the blood supply of the brain
- When the symptoms of a stroke last only a short time (less than an hour), this is called a transient ischemic attack (TIA) or mini-stroke
  - TIA symptoms are the same as for stroke
  - Transient ischemic attacks are serious warnings of an impending stroke
  - TIAs are brief episodes of stroke symptoms that resolve within minutes or hours, unlike stroke symptoms which can last longer.
  - Up to 40% of all persons who experience a TIA will go on to have a full stroke.
Within two days of a TIA, 5% of patients will have a stroke

Within 90 days of a TIA, 10% to 15% will have a stroke

Management of TIAs focuses on preventing a future stroke

4. What are the effects of a stroke?

• A stroke is a sudden interruption in the blood supply of the brain. Most strokes are caused by an abrupt blockage of arteries leading to the brain (ischemic stroke). Other strokes are caused by bleeding into brain tissue when a blood vessel bursts (hemorrhagic stroke). Because stroke occurs rapidly and requires immediate treatment, stroke is also called a brain attack.

• Every stroke is different. Every person affected by stroke will have different problems and different needs. The way in which you might be affected depends on where in the brain the stroke happens and how big the stroke is

• A stroke on the right side of the brain generally causes problems on the left side of the body. A stroke on the left side of the brain causes problems on the right side of the body

• Some strokes happen at the base of the brain and can cause problems with eating, breathing and moving. The right half of the brain controls the left side of the body and vice versa.
  
  o For example, weakness or paralysis in the left arm may result from a stroke in the right side of the brain. For most people, the left side of the brain controls language (talking, reading, writing, and understanding).
  
  o The right side controls perceptual skills (making sense of what you see, hear and touch) and spatial skills (judging size, speed, distance and position).

Stroke patients might have problems Such as:

- Weakness or lack of movement in your leg and/or arm (paralysis)
- Changes to the way you see things (perceptual or visual problems)
- Changes to the way you feel things e.g. touch (sensory problems)
- Problems thinking or remembering (cognitive problems)
• Trouble speaking, understanding, reading or writing
• Incontinence
• Shoulder pain or arm pain/stiffness
• Feeling worried or sad
• Problems controlling your feelings
• Problems with your sexuality

5. What are cerebral micro bleeds?

• Cerebral micro bleeds are tiny focal collections of blood breakdown products adjacent to histologically abnormal small vessels, resulting from blood leakage through the fragile vessel wall.
• Micro bleeds persist for many years, making them a potentially unique marker for an individual’s lifetime history of bleeding related to small vessel pathology.
• Cerebral micro bleeds (CMBs) are increasingly recognised neuroimaging findings in individuals with cerebrovascular disease and dementia, and in normal ageing.
• Special imaging technique (gradient echo MRI) has disclosed small, dot-like low signal areas in patients with haemorrhagic and ischemic stroke, hypertension, and in healthy elderly subjects.

6. How CMBs are identified?

• There has been substantial progress in the understanding of CMBs in recent years, particularly in the development of newer MRI methods for the detection of CMBs and the application of these techniques to population-based samples of elderly people.
• Gradient-echo (also termed T2*-weighted) MRI is exquisitely sensitive to blood breakdown products (including haemosiderin, deoxyhaemoglobin and ferritin) which are paramagnetic and cause local dephasing of the MR signal.
• Cerebral micro bleeds are thus well seen as small, round, dark dots of 2-5mm diameter, though the actual physical size of micro bleeds is likely to be less than a millimetre.
7. What causes cerebral micro bleeds?

- Micro bleeds are associated with lacunar infarcts and clinical syndromes, and with white matter lesions, suggesting that they result from small vessel damage.
- Moreover, in most studies micro bleeds are more common in patients with hypertension, diabetes, obesity, smoking and aging.

8. Who gets cerebral micro bleeds - and what is their significance?

**Healthy individuals with no history of stroke**

- Micro bleeds are found in about 5% of the normal population in their fifth to eighth decades, increasing in prevalence with age to about 7-8% of patients over 70 having MRI for non-stroke indications. The clinical significance of cerebral micro bleeds in an otherwise healthy individual is unknown, but they may predict an increased future cerebrovascular risk.

**Primary Intracerebral haemorrhage**

- Primary intracerebral haemorrhage (PICH) accounts for about 20% of all strokes, and is usually caused by rupture of a small or medium-sized arterial wall (trauma, arteriovenous malformations or intracranial aneurysms are conventionally excluded from this diagnostic group)
- Cerebral micro bleeds are found in between 54% and 71% of PICH and are especially common in Asian populations, which to date have been the most extensively studied
- Cerebral amyloid angiopathy (CAA) is less common (though probably under-recognized) and causes recurrent, often non-disabling, PICH in a ‘lobar’ distribution, especially in elderly patients
- CAA is due to amyloid deposition in small to medium leptomeningeal and cortical vessels making them fragile and prone to bleeding
- *Greenberg* reported micro bleeds in 80% of elderly patients with lobar haemorrhage compatible with presumed cerebral amyloid angiopathy
Ischemic stroke patients

- Micro bleeds are found in between 18% and 65% of patients with ischemic stroke. The wide variation reflects study population differences (hospital versus community; different proportions of stroke subtypes; and different demographic groups).
- Micro bleeds are consistently more common in Asian patients and those with lacunar infarction compared with atherothrombotic or cardioembolic ischemic stroke.
- It was suggested that micro bleeds may predict the risk of hemorrhagic transformation after acute cerebral infarction, particularly after thrombolysis.

9. Do micro bleeds cause symptoms?

- Micro bleeds have been considered to be asymptomatic, but recent studies suggest that they may not be as clinically silent as was first thought.
- In a study, the investigators studied the cognitive function in patients with cerebral micro bleeds compared to a non-micro bleed control group matched for age, white matter changes on MR, stroke subtype and associated large-vessel stroke.
- Executive dysfunction was twice as common in micro bleed patients (60% vs. 30%) and was related to micro bleed burden in the frontal lobes and basal ganglia, suggesting that cognitive impairment could result from disruption of strategic frontal basal ganglia circuits.
- These findings may assist the assessment of stroke patients with cognitive impairment, and influence the use of antihypertensive and antiplatelet treatments.

10. What is the role of citicoline in excitotoxicity and neurorepair in stroke?

- Moro et al provide recent evidence showing that citicoline may increase ATP availability in neurons and increase membrane levels of glutamate transporters in neurons. These factors might contribute to reduce excitotoxicity after acute stroke.
- Moreover, Moro et al also describe some potential neurorepair effects of citicoline, including an increase in dendritic spines and an augmented density of pyramidal cells.
• According to the authors, these actions might explain the improved behaviour and function shown by animals treated with citicoline after experimental stroke. 

(Ref: Management and Prevention Symposium: Preface Proceedings of Recent Developments and Future Directions in Stroke Stroke 2011, 42:S1-S2)

11. Does citicoline have a role in hemorrhagic stroke?

Yes. Many studies show that treatment with citicoline in experimental intracerebral haemorrhage improves neurological functional outcome and reduces the volume of the ischemic injury surrounding the hematoma.  

(Ref: Citicoline Preclinical and Clinical Update 2009-2010; Stroke 2011; 42; S36-S39)

12. Is there any Indian study for the right dose and usage of Citicoline?

• Numerous clinical trials performed over many years have documented the excellent tolerance and reliable efficacy of citicoline in patients with stroke over the globe.

• As per Gupta et al. study, 500 mg is optimal and in fact drug of choice in Indian population in terms of safety and efficacy as add on.  

(Ref: Role of Citicoline in Ischemic Stroke. S.K Gupta*, Anupriya Gupta, Deeraj Gondhotra, Ajay Gupta, Shruti Gupta)

13. What is the action of citicoline on membrane stability and protecting integrity?

• Evidence of citicoline’s role as a phosphatidylcholine precursor has been found in animal studies.

• The brain uses choline preferentially for acetylcholine synthesis, which can limit the amount of choline available for phosphatidylcholine production.

• When the demand for acetylcholine increases or choline stores in the brain are low, phospholipids in the neuronal membrane can be catabolised to supply the needed choline.

• Exogenous citicoline thus helps preserve the structural and functional integrity of the neuronal membrane.
14. What is the role of citicoline in neuronal repair in prestroke and poststroke patients?

Three mechanisms are postulated for citicoline in neuronal repair:

- Repair of neuronal membranes via increased synthesis of phosphatidylcholine
- Repair of damaged cholinergic neurons via potentiation of acetylcholine production
- Reduction of free fatty acid build-up at the site of stroke-induced nerve damage

In addition to phosphatidylcholine, citicoline serves as an intermediate in the synthesis of sphingomyelin, another neuronal membrane phospholipid component. Citicoline has shown the potential to restore post-ischemic sphingomyelin levels.

15. What is the role of citicoline in head trauma?

- Citicoline facilitates memory rehabilitation in brain trauma patients by restoring blood flow to the lesion site
- In a single-blind, randomized trial, 216 head injury patients were assigned to two treatment groups:
  - one received conventional treatment, while the other received conventional treatment plus 1,000 mg I.V. citicoline daily
  - The proportion of patients showing improvements in cognitive and motor symptoms was greater in the citicoline group

16. What will be the dosage of Cyscolin in acute stage of cerebral infarction? How long Cyscolin should be continued?

- The recommended dose of Cyscolin is 500 – 1000mg daily which can be given as o.d or b.d dosing. Cyscolin can be given up to 2g safely. When it is given above 1g some incidence of dizziness have been reported
- Cyscolin can be used safely with minimal side effects in acute stroke treatment
- Cyscolin appears to improve functional outcome and reduce neurologic deficit with 500 – 100mg of Cyscolin appearing to be the optimal dose
• For minimal benefits to be clinically visible, Cyscolin should be continued for 3-6 months.

17. **Why piracetam should be used in stroke with utmost caution?**

- Piracetam is contraindicated in hemorrhagic strokes because of its anti-platelet aggregate effect and should be used with caution in patients using anticoagulants or platelet antiaggregant drugs including low-dose aspirin.
- Piracetam leads to neuronal excitation, which is not required during the stroke, when the neuronal damage is maximum.
- Piracetam has no role in preventing auto-cannibalization, which leads to increased neuronal damage.
- Piracetam significantly increases blood flow & volume, which is dangerous as this can predispose to recurrent stroke like hemorrhagic stroke.

18. **Explain the use and linking of CMB in pre-stroke?**

- Even in healthy elderly individuals, silent brain infarctions and sub-cortical white matter lesions are generally thought to be strong risk factors for subsequent stroke.
- These asymptomatic ischemic lesions often coexist with micro bleeds (MBs) in patients with stroke.
- Hypertension and diabetes is top among the list. Thus, it is important to understand the individual contributions of these conditions to stroke onset.
- A recent meta-analysis revealed that MBs were present in 44% of patients with recurrent ischemic stroke and 83% with recurrent ICH (Intracerebral haemorrhage).
- On the other hand, MBs only occur in approximately 5% to 6% of subjects without cerebrovascular disease or neurological symptoms.
19. Explain Kaplan Meier Curves of stroke free survival rate given in the Visual aid?

- Kaplan Meir curves are used to explain survival analysis in clinical trials.
- It is used to estimate survival probabilities and to compare survival of different groups.
- In clinical trials the investigator is often interested in the time until participants in a study present a specific event or endpoint. This event usually is a clinical outcome such as death, disappearance of a tumor, etc.
- The participants will be followed beginning at a certain starting-point, and the time will be recorded needed for the event of interest to occur.
- Usually, the end of the study is reached before all participants have presented this event, and the outcome of the remaining patients is unknown. Also the outcome is unknown of those participants who have withdrawn from the study.
- The graph in the VA explains the survival rate of people without and with CMBs.
- More than 2000 people were followed for seven years and evaluated for the linkage between CMBs and stroke.
- The analysis was that the people with CMB are more prone to stroke and the stroke free survival rate was about 40%.