INTRODUCTION

Stroke is the second most common cause of death after ischemic heart disease and causes 9% of all deaths worldwide. In developed countries the annual incidence rate of stroke has been estimated to be 100 per 100,000 [95% confidence interval (CI), 80-119]. In a recent epidemiological carried out in urban Mumbai it has been estimated that the annual incidence of stroke is 145 per 100,000 persons (CI 95%: 120-170).  

There are many risk factors for stroke and transient ischemic attack (TIA). The non-modifiable factors are age, sex, heredity and ethnicity. The modifiable risk factors are hypertension, diabetes mellitus, hypercholesterolemia, smoking and physical inactivity among which hypertension is one of the most powerful predictor of stroke. It is conclusively proven that stroke risk is reduced by antihypertensive treatment. One systematic review showed that a diastolic blood pressure (BP) reduction of 5 to 6 mmHg results in 35 to 50% reduction in stroke risk. 

Cardiovascular events, including acute myocardial infarction and sudden cardiac death, display significant circadian variation in the timing of onset of symptoms. A meta-analysis which included 66635 acute myocardial infarctions, has demonstrated a 40% excess risk between 6 AM and noon compared with the rest of the day. This morning excess of cardiovascular risk is believed by some authorities to parallel the usual circadian pattern of physical activity, blood pressure, plasma catecholamines, and/or plasma cortisol. 

However in the case of acute stroke, many afflicted patients reported awakening with new neurologic deficits, and reports indicated that acute strokes tend to occur either during the evening hours or during sleep. This led to the conclusion that especially because acute therapies for stroke-in-evolution were not particularly effective, there was little reason to consider acute stroke as a medical emergency because the onset of symptoms was thought to occur during sleep, when most patients would not recognize them.

Later on, studies came which demonstrated the timing of acute stroke. In a study of 182 patients of acute stroke admitted within twelve hours of onset to a large teaching hospital in Mumbai, it was found that the frequency of onset of stroke was found to be highest between 6:01 am and 2:00 pm, in patients of infarct as well as haemorrhage. Patients of hypertension also showed a similar variation. Thus, the identification of periods of high risk, may help by matching drug doses with periods of vulnerability. This may decrease the risk of stroke in known hypertensives.

A metanalysis of 31 publications reporting the circadian timing of 11816 strokes was performed, subdividing by the type of stroke, according to the time of onset of symptoms. It was found that all subtypes of strokes displayed a significant circadian variation in time of onset, whether divided into 3-hour, 4-hour or 6-hour time periods (p<0.001). In this metanalysis there was a 49% increase (95% CI, 44% to 55%) in stroke of all types between 6 AM and noon, compared with expectations, if no circadian variation was present. There were 29% fewer strokes between midnight and 6 AM,
a 35% decrease compared with the other 18 hours of the day. The data are remarkably consistent across the various subtypes of stroke, and indicate, for ischemic stroke, hemorrhagic stroke, and even transient ischemic attacks, that the excess risk during the 6 AM to noon time period is significantly higher than would be expected by chance: 89%, 52%, and 80% (95% CI, 89% to 99%, 36% to 69%, and 43% to 126%, respectively, compared with the normalized risk for the other 18 hours of the day). Similarly, there is a significantly lower risk of stroke during the nighttime hours (midnight to 6 AM) for each stroke subtype: 30%, 54%, and 81% (95% CI, 26% to 33%, 48% to 60%, 72% to 87%, respectively, compared with the normalized risk for the other 18 hours of the day).

Therefore from data of this metanalysis it becomes apparent that the early morning hours have the highest risk of stroke onset. This is important since effective treatment of ischemic strokes is now increasingly available and strokes can be prevented by blood pressure management.

CLINICAL IMPLICATIONS
Hypertension and stroke have a very close relationship. Both diastolic and systolic hypertension cause significant cerebrovascular morbidity and mortality. A meta-analysis of 9 prospective observational studies involving more than 420,000 individuals free from known coronary or cerebral vascular disease at baseline followed up for 6 to 25 years (mean of 10 years) shows a direct, continuous and apparently independent association of diastolic blood pressure with both stroke and coronary artery disease.

Anti hypertensive therapy is vital to primary and secondary prevention of stroke. Randomized controlled trials have shown that a cornerstone of primary stroke prevention is based on treating hypertension. Subsequent other trials came to show that antihypertensive therapy in the post stroke period is crucial to prevent recurrent stroke. Important amongst them, the Hypertension Outcomes Prevention Evaluation (HOPE) a trial of Ramipril in 9297 patients with high vascular risk in which 1013 patients had a history of previous stroke. Within this subgroup, Ramipril was effective at reducing BP (by 11/4 mm Hg) whereas the composite outcome of stroke, myocardial infarction (MI), and vascular death was reduced by 30%. The largest trial to date was the Perindopril pROtection aGainst RECurrent Stroke Study (PROGRESS), which assessed a treatment regime based on another ACE-I, Perindopril, given with or without Indapamide in 6105 patients with previous ischemic stroke or primary intracerebral hemorrhage. This was validated in the Indian population too. In a multicentre, prospective observational study of Indian stroke patients, receiving perindopril with or without indapamide it was found that there were 2.7% recurrent strokes with a Kaplan-Meier estimate of strokes plus TIA of 3.3%, which suggests that perindopril ± indapamide based prevention may be effective in reducing risk of recurrent stroke.

THERAPEUTIC IMPLICATIONS
With the knowledge that the early morning hours (and not the nighttime hours) have the highest risk of the onset of stroke, this is useful in timing anti-hypertensive therapy. Similarly blood pressure varies throughout the day, being highest on awakening in the morning and lowest during sleep. The sleep blood pressure predicts cardiovascular and cerebrovascular ischemic events better than the awake blood pressure, which predicts hemorrhagic strokes. Therefore antihypertensive agents that specifically target the early morning rise in blood pressure and heart rate, without reducing blood pressure severely during the night, might be more advantageous in controlling the rise in blood pressure during the hours around awakening, although, ideally blood pressure should be controlled throughout 24 hours of its variability. An ideal antihypertensive agent is one when administered in the morning has a long duration of action to still have an effect on the early morning rise in blood pressure. This would be effective not only in stroke prevention but in prevention of myocardial infarction since morning hours are also the time of day associated with an increased risk myocardial infarction and sudden cardiac death.

In this regard ambulatory blood pressure (BP) monitoring has become very useful in the diagnosis and management of selected hypertensives. Circadian variation of BP patterns is known to predict cardiovascular and cerebrovascular outcomes and other target organ damage and as mentioned earlier the sleep blood pressure predicts cardiovascular and cerebrovascular ischemic events better than the awake blood pressure, which predicts hemorrhagic strokes. On an average, each 5% attenuation in the decline in nocturnal SBP/DBP confers a 20% rise in the risk of cardiovascular mortality.

The prevalence of circadian BP patterns and the clinical factors associated with the non-dipping pattern was assessed in a large cross-sectional study involving 42,947 hypertensive
A normal dipping pattern (dipper) was diagnosed when the reduction in the average SBP during the night period was >10% of mean SBP during the day. When this proportion was >20%, the patient was classified as an extreme dipper. An abnormal dipper pattern (nondipper) was diagnosed when the night average SBP reduction was 10% with respect to day values. When the mean night SBP was higher than the day one, the patient was classified as a riser. There were 34,563 patients who were on stable antihypertensive treatment and there were 8384 patients who were not currently receiving antihypertensive treatment. In the cohort of untreated patients, the prevalence of dipping (dippers/extreme dippers) and nondipping (nondippers/risers) patterns was 59% and 41%, respectively. In the cohort of patients receiving antihypertensive treatment, the prevalence of dipping (dippers/extreme dippers) and nondipping (nondippers/risers) patterns was 47.2% and 52.8%, respectively. Nondippers had a significant association with advanced age, obesity, diabetes mellitus and overt cardiovascular/cerebrovascular or renal disease. In treated patients, nondipping was associated with the use of higher number of drugs but not with the time of day at which antihypertensive drugs were administered. This finding is in contrast to what was earlier found that the administration of nondiuretic antihypertensive drugs at bedtime can improve blood pressure control and restore the dipping pattern in a substantial number of patients with refractory or resistant hypertension.17

The daily variation in blood pressure is partly explained by the changing activity of the sympathetic and the renin-angiotensin systems. When awake, the sympathetic activity is relatively high and baroreceptors control BP, keeping it relatively constant despite widely varying inputs. During sleep, sympathetic activity is reduced and renin secretion increases and is probably the essential controller of blood pressure. Therefore, drugs like diuretics and calcium channel blockers which act independently of these systems can be administered in the morning and their action is expected to be similar during sleep and wake hours. However there is increased responsiveness to ACE-inhibitors during sleep hours, while beta blockers do not work well during sleep hours.18 Therefore ACE-inhibitors and angiotensin receptor blockers are better administered during night. Amlodipine, has been shown to be effective in reducing BP throughout the day and night, independent of dosing time. Beta blockers, diuretics are to be administered during the morning hours. Thus control of morning surge of BP and consequently prevention of strokes and cardiac ischemic events can be achieved.

Calcium antagonist Nifedipine reduces the incidence of stroke in Eastern Asia, as shown by the Shanghai Trial Of Nifedipine in the Elderly (STONE) and the Systolic Hypertension in China (Syst-China) trials. A trial from Japan has shown that benidipine may be more efficient than Nifedipine in preventing strokes in the elderly.19 The result of this study are: 1) benidipine and nifedipine reduce 24-h daytime (10:00-20:00) and nighttime (00:00-06:00) averages of SBP and DBP ($P$ < 0.001); 2) the circadian double amplitude of BP is decreased after treatment with benidipine (from 28.6 to 21.1 mm Hg SBP and from 19.7 to 15.2 mm Hg DBP; $P$ < 0.05), while the day-night difference in SBP is increased after treatment with nifedipine (18.6 vs 27.9 mm Hg, $P$ < 0.01); and 3) the increase in the day-night difference of heart rate (HR) is significant after treatment with benidipine (13.6 vs 18.8 beats per minute, bpm; $P$ < 0.05), but not with nifedipine. The fact that benidipine reduces the circadian BP amplitude may be one reason for the superiority of this treatment over nifedipine in preventing an adverse outcome.

TIMING OF ANTI-PLATELET THERAPY

It has been demonstrated that platelet activation significantly increases during acute ischemic stroke and substantially decreases thereafter. Moreover platelet aggregation is higher during early morning hours. Conventionally for prevention patients take aspirin in the morning. Obviously the highest plasma level of the drug occurs in the after noon hours (outside the peak thrombo-embolic incidence hours), lowering the protective efficacy of the drug. This method of daily aspirin administration has its lowest protective value against cardiovascular events during the night and early morning, when the lack of physical activity further augments the cascade of hemorheological events favoring platelet aggregation and subsequent ischemia. Hence it has been proposed that aspirin should be administered in the late evening (10 PM) so that highest plasma levels would be reached in the early morning hours.20 Experts believe that this time shift in the administration of aspirin would fit better in the circadian scheme of the occurrence of stroke, thus resulting in a more effective prevention.

In CONCLUSION, it is stated that:
1. It is important to be aware of the fact there is excess risk of stroke in the early morning hours.
2. It is also important to treat hypertensives especially with the aim to reduce the early morning rise of BP, which is
associated with higher risk of both adverse cardiovascular and cerebrovascular outcomes.

3. Ambulatory blood pressure monitoring is very important to help in identifying the nondippers who are a subset group of hypertensives who have a higher risk of adverse cardiovascular and cerebrovascular and renal profiles.

4. Administration of nondiuretic antihypertensive drugs at bedtime can improve blood pressure control and restore the dipping pattern in a substantial number of patients with refractory or resistant hypertension.

5. ACE-inhibitors and angiotensin receptor blockers are better administered during the night, when the renin secretion increases. Beta blockers, diuretics and calcium channel blockers can be given in the morning hours.

6. As for now hypertensive therapy needs to be tailored according to patient need and requirement, since the impact of chronotherapy, not merely on the circadian pattern, but also on the cardiovascular and cerebrovascular outcome, still remains an open question and needs to be answered in a prospective, controlled clinical trial.

REFERENCES
13. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet 2001;358:1033- 41