

Nocturnal Hypertension: Neglected Issue in Comprehensive Hypertension Management

Andi Kristanto¹, Randy Adiwinata¹, Silvia Suminto¹, Benny N. Kurniawan¹, Finna Christianty¹, Robert Sinto²

¹ Faculty of Medicine, Atmajaya Catholic University of Indonesia, Jakarta, Indonesia.

² Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding author:

Robert Sinto, MD. Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro No. 71, Jakarta 10430, Indonesia. email: rsinto@yahoo.com, andi_kris@hotmail.com.

ABSTRAK

Irama sirkadian dalam tubuh, mempengaruhi variasi tekanan darah baik pada siang dan malam hari, sehingga didapatkan pola tekanan darah yang berbeda. Hipertensi nokturnal adalah peningkatan tekanan darah >120/70 mmHg pada malam hari akibat terganggunya irama sirkadian, dan berkaitan dengan peningkatan kejadian kardiovaskular, serebrovaskular, serta mortalitas pada pasien hipertensi. Hipertensi nokturnal dan perubahan pola penurunan tekanan darah, hanya dapat diketahui dengan cara melakukan pemeriksaan tekanan darah secara kontinyu selama 24 jam yang dikenal sebagai ambulatory blood pressure measurement (ABPM). Kronoterapi, menjadi salah satu strategi dalam menangani pasien dengan hipertensi nokturnal, yaitu dengan meminum obat anti hipertensi pada malam hari untuk mendapatkan penurunan tekanan darah yang sesuai irama sirkadian untuk meningkatkan kontrol tekanan darah.

Kata kunci: hipertensi nokturnal, pengukuran tekanan darah ambulatori, non-dipping, kronoterapi.

ABSTRACT

The body circadian rhythm affects blood pressure variability at day and night, therefore blood pressure at day and night might be different. Nocturnal hypertension is defined as increase of blood pressure >120/70mmHg at night, which is caused by disturbed circadian rhythm, and associated with higher cardiovascular and cerebrovascular events also mortality in hypertensive patients. Nocturnal hypertension and declining blood pressure pattern, can only be detected by continuous examination for 24 hours, also known as ambulatory blood pressure measurement (ABPM). Chronotherapy, has become a strategy for managing the hypertensive nocturnal patients, by taking hypertensive medication at night to obtain normal blood pressure decrease in accordance with the normal circadian rhythm and, improving blood pressure control.

Keywords: nocturnal hypertension, ambulatory blood pressure measurement, non-dipping, chronotherapy.

INTRODUCTION

Hypertension has been for long time well studied as one of the major cardiovascular disease risk factor, thus hypertension treatment in controlling blood pressure is important to prevent cardiovascular disease progression.¹ However, the diagnosis of nocturnal hypertension tend to be missed although it is an important predictor of all cause mortality and/or cardiovascular mortality.² Lack of awareness with hypertension cause patients to measure their blood pressure only during hospital visit. This factor contributed to the limited use of ambulatory blood pressure measurement (ABPM), and the possibility of nocturnal hypertension became overlooked.³ In this review, we described the definition, epidemiology, pathophysiology, clinical significance, diagnosis, and anti hypertension management of nocturnal hypertension.

DEFINITION

Hypertension is a major independent risk factor for the development of cardiovascular disease, and its variation at day or night of the blood pressure depends on circadian rhythm, which is associated with interaction of sympathetic nervous system and renin-angiotensin systems.⁴ This blood pressure variation phenomenon consist of dipping, extreme dipping, non dipping and riser or reverse dipping. Dipping phenomenon is defined as a decrease in systolic nighttime blood pressure 10-20% from daytime blood pressure and occurs as normal physiologic changes. The term “extreme dipping” is used when nighttime blood pressure decrease more than 20%. Meanwhile, in non dipping pattern, the decrease in blood pressure is only approximately 0-10% and the increase in blood pressure at night is called reverse dipping or riser. The latter pattern (non dipping and reverse dipping/riser) were associated with nocturnal hypertension. Nocturnal hypertension is defined as increase of blood pressure >120/70 mmHg at night.⁵⁻⁷

EPIDEMIOLOGY

As discussed above, the blood pressure changes at night was a physiologic changes

that occurs in healthy individual. However, these changes did not occur in some people. The non dipping pattern was found higher in Chinese, Japanese, and South Africans compared in Western and Eastern Europeans with the prevalence of 10.9% vs. 6.0%. The higher sodium and lower potassium intake among Asian than other population might be contribute to it.⁸ In a cohort study of Spanish Society of Hypertension Ambulatory Blood Pressure Monitoring Registry reported that from 42,947 hypertensive patients, there were 50.2% untreated patients and 40% treated patients had dipping pattern. At the same time, there were also 35% untreated patients and 40% treated patients had non dipping pattern.⁹ Non dipping pattern was associated with more severe target organ damage from chronic kidney disease (CKD), cardiovascular and cerebrovascular disease induced by hypertension.¹⁰

Non dippers were more prevalent in individuals with CKD and diabetic patients. Liu et al¹¹ found that non dipping phenomenon was commonly found in patients undergoing hemodialysis with the prevalence up to 70%. The possible mechanism is due to an inadequate blood pressure as a consequence of baroreflex or autonomic dysfunction in CKD patients, thus maintaining more adequate hemodialysis in these patients is needed to decrease cardiovascular complications. Also, in a study conducted by Cuspidi et al, found that non dipping prevalence was higher in hypertensive diabetic subjects than in hypertensive nondiabetic subjects after 24 hours ambulatory blood pressure monitoring. Renal hemodynamics, blood flow distribution, and plasma volume are thought to be affected by hyperglycemia state in diabetic patients.^{12,13}

PATHOPHYSIOLOGY OF NOCTURNAL HYPERTENSION

Many factors were postulated in disrupting the circadian rhythm, which in turn lead to attenuation of nocturnal blood pressure lowering phenomenon. The causes of abnormal circadian rhythm of blood pressure can be divided to hormonal metabolic factors and external factors such as smoking or aging. Some disease are implicated in the disruption, such as diabetes

mellitus, metabolic syndrome, chronic kidney disease, and obstructive sleep apnea (OSA).¹⁴ In this paper, we described the two most reported mechanisms of nocturnal hypertension, which were imbalance of nocturnal autonomic nervous system and limited sodium metabolism by kidneys.

Imbalance of Nocturnal Autonomic Nervous System Activation

In physiologic state, blood pressure levels is fluctuated along the day with peak in early morning and low during sleeping. Circadian rhythm is one of the contributors of the fluctuation which controlled from suprachiasmatic nuclei (SCN) of the anterior hypothalamus. Circadian rhythm mainly influenced by autonomic nervous system.¹⁵ In general, autonomic nervous system composed of sympathetic and parasympathetic nerves, which keep in balance to maintain physiologic state. Over dominance of sympathetic activation was postulated as the cause of nocturnal hypertension and attenuated the blood pressure dipping. Vardhan et al reported that, patients with obstructive sleep apnea (OSA) were having higher catecholamines plasma and urinary levels compared with control. This findings were correlated with hypertension in patient with OSA.¹⁶ Nielsen et al¹⁷, found that low degree of blood pressure dipping were related to sustained adrenergic activity which reflected by higher noradrenaline level and lead to decreased the peripheral vasodilatation capacity. Doxazosin, an alpha-1 adrenergic blocker drug, will effectively block the sympatethics activity which in turn lower the blood pressure while sleeping.¹⁸ These studies showed that non dipping phenomenon is caused by sympatethics system over activity.

Limited Sodium Metabolism

Kidneys have a role in maintaining blood pressure, regulated by renin-angiotensin-aldosterone system and influenced by circadian rhythm. Non dipping patients are thought to be related with impaired capacity of kidneys to excrete sodium during daytime or increased tubular sodium reabsorption which was commonly caused by hyperaldosteronism.¹⁹ This theory was supported by data that the prevalence of non-dipper was increased in patient with low

glomerular filtration rate (GFR).²⁰ Wang et al²¹ reported among 540 Chinese CKD patients, total of 21.9% patients were riser, 36.1% patients were dipper, and 42% of patients were non-dipper.²¹ However, increased daily salt intake also found to be related with nocturnal hypertension. Kidneys will compensate high sodium intake by enhancing natriuresis during the night. Thus, blood pressure will remain elevated until kidneys succeed in reducing excess sodium.^{22,23}

CLINICAL IMPLICATIONS OF NOCTURNAL HYPERTENSION

Nocturnal hypertension phenomenon results in several clinical implications that have to be taken into consideration to predict complications and approach strategy to treat every individual with hypertension. There have been many studies conducted about circadian patterns and its clinical implications, especially those associated with cardiovascular, cerebrovascular, and renal diseases. Fagard et al²⁴, mentioned that cardiovascular complication in subject with non dipping circadian pattern is higher compared to subjects with dipping pattern. This statement is also supported by one of the studies that showed increasing 10 mmHg of nighttime systolic blood pressure would rise 35% possibility of cardiovascular risk in diabetic population.²⁵

The negative effect of cardiac function was described by Verdecchia et al²⁶. that non dipping group had greater risk of left ventricular hypertrophy (LVH) compared with dipping group. Groups with dipping circadian pattern had LVH risk at about 4%, while the risk of group with non dipping pattern increased to 15%. The thickening of carotid intima (>0.8 mm) also found higher in non dipping pattern than dipping, that will lead to atherosclerosis. OPERA study showed on their population based cohort study of 900 middle aged individuals, that mean carotid intima media thickness were higher in non-dipper (90 mm) compared to dipper (80 mm).²⁷ The association between carotid intima thickening and atherosclerosis plaque formation is supported by Salvetti et al²⁸. The results of ultrasonography showed that thickening of carotid intima and formation of plaque presence were 55% and 56% respectively in uncontrolled

hypertensive patients with non dipping circadian pattern, whereas in dipping circadian pattern were 24% and 33% respectively.

Persons who have high blood pressure in the night, which includes reverse dipping and non dipping had an increased risk of intracerebral hemorrhage (ICH). Sun et al⁶, found that probability of silent ICH in non dipping and reverse dipping group was 50.8%. Meanwhile, Tsivgoulis et al conducted a research on patients with ICH, and found that 74.4% of the patients with ICH were non dippers, while 43.8% of the patients were dippers.²⁹ Another study by Ma et al³⁰ showed, that several subjects with non dipping pattern had silent cerebral infarct. Non dipping are associated with lacunar cerebral infarct event which may leads to decline in verbal memory function.³¹

Kidney failure was also considered as another important clinical implication of the non dipping circadian pattern, reflected by presence of microalbuminuria and decreasing GFR. Kastarinen et al did a research of renal function on 460 subjects where 18.7% of the study population were non dipper. The mean eGFR of non dippers in this study were significantly lower compared with a mean eGFR in dipper patients.³² Meanwhile, Afsar et al³³ compared patterns of non dipping and 24 hour urinary albumin excretion (UAE) in 158 hypertensive patients (104 dippers; 54 non dippers). Among patients in the non dipper group, 17 patients had microalbuminuria, while only 9 patients in dipper group had microalbuminuria ($P < 0.0001$). The median UAE of dipper group was significantly lower (5.25 mg/day) when compared with non dipper group (23 mg/day).

SIGNIFICANCE OF AMBULATORY BLOOD PRESSURE MONITORING IN NON DIPPING HYPERTENSIVE PATIENT

There are several modalities of measuring blood pressure, which is divided into two categories, the clinic based measurement (auscultatory method, oscillometric method) and non clinic-based measurement (home blood pressure monitoring, ABPM).³⁴ ABPM itself has gained popularity as an alternative to traditional method for measuring blood pressure in clinical

setting.³⁵ In the ABPM technique, the patient wears a portable blood pressure measuring device for a certain period (usually 24 h). This periodically measures blood pressure (every 15–30 min during the day and every 30–60 min overnight) automatically and may provide information of blood pressure during normal daytime activities and importantly during sleep.^{36,37} The term ‘nocturnal hypertension’ or ‘non dipping’ pattern as described in above section become an important phenomenon to be considered by all clinicians and it can only be identified by 24 hour ABPM or other methods of recording the sleep blood pressure.^{38,39}

Many studies compared ABPM and clinic-based measurement and concluded that ABPM is more superior in predicting cardiovascular event or other prognostic factor. ABPM may also reduce the incidence of white-coat effect and masked hypertension that were not detected in clinic-based measurement, and also predict all-cause mortality especially due to cardiovascular event than awake or clinic blood pressure.^{24,34,40} The results of the study showed that patients with an absence of normal dipping has higher mortality than the dipping one. The pattern of dipping that was detected will add clinical predictive information and further reinforcing the use of ambulatory monitoring in patient management.⁴⁰ Therefore, importance of nocturnal hypertension or ‘non dipping pattern’ of blood pressure strengthens the need for 24 hours ABPM.

THE IMPROVED STRATEGY IN HYPERTENSION MANAGEMENT

Standard Treatment of Hypertension

Nowadays, there are many different classes of antihypertensive drugs, such as diuretics, angiotensin-converting enzyme (ACE) inhibitor, angiotensin II-receptor-blockers (ARBs), β -blocker, and calcium antagonist, that have been used for the initiation and maintenance of antihypertensive treatment. Generally, a long-acting antihypertensive drug with 24 hours duration is used as an initial standard treatment of hypertensive patients in order to maintain blood pressure variability and adherence to therapy.^{41,42}

However, antihypertensive drugs used once daily are rarely effective from the morning dosing until the following morning. Many of the hypertensive patients, especially non dipper patients on standard antihypertensive drugs still have raised blood pressure on the morning. It is because the effect of antihypertensive drugs on the diurnal variation of blood pressure, depends not only on the mechanism of action of the drugs, but also on the time of administration, and the pharmacokinetics and pharmacodynamics of the drug.⁴³

In this regard, choosing the optimal timing for drug administration, especially a single dose antihypertensive drug, such as several kind of ACE inhibitor, ARB, or calcium antagonist should be considered. Also, we have discussed that the blood pressure (BP) is regulated by many different systems and its activity vary throughout the day. As drugs are developed that selectively block these systems, the reduction on the BP may not be consistent over 24 hours.^{4,44}

Chronotherapy: Improving the Hypertension Management

Chronotherapy is defined as administering drug while considering the optimal dosing time in purpose to enhance drugeffectiveness and tolerance. In hypertension, chronotherapy defined as taking hypertensive medication at night to obtain normal BP decrease in line with circadian rhythms, reduce the morbidity and mortality.^{45,46}

The MAPEC study compared the administration time between morning dose (taking all prescribed drugs in the morning) and bedtime doses (taking more than one drug at bedtime), and concluded that after a mean follow up of 5.6 years in 2156 subjects, the bedtime dose achieved better overall BP control. Also, subjects taking more than one drug at bedtime showed significantly lower relative risk of total cardiovascular disease events, compared to those taking all drugs in the morning. The prevalence of non-dipping significantly reduced in those receiving medication in the bedtime (34% vs. 62%) and higher prevalence of controlled ambulatory BP (62% vs. 53%).⁴⁵

The possibility to achieve better BP control using telmisartan administered at bedtime was

assessed in a study, in which telmisartan 80 mg given in 215 patients randomized to take the drug in the morning or bedtime. After 12 weeks of treatment, the reduction of BP was similar for both groups. However, subjects taking bedtime dose had reduced prevalence for non-dipper by 76%, without loss in 24 hour efficacy of telmisartan.⁴⁷ Similar results were found in other studies, in which olmesartan or valsartan taken at night provided 24 hours BP reduction while improving nocturnal BP fall more significantly than morning dosing, thus reducing the prevalence of non dipper.^{48,49}

The use of chronotherapy in other hypertensive drugs regimens had shown similar beneficial effects. Bedtime dosing of ramipril in at least two different studies were found to be effective in achieving nocturnal BP regulation.^{50,51} The role of chronotherapy in nifedipine GITS (Gastrointestinal-Therapeutic-System) formulation and amlodipine as calcium channel blocker class drugs also showed greater reduction of 24-hours ABPM and greater BP reduction at night compared with morning dosing.^{52,53}

A chronotherapy trial using combination antihypertensive drug also has been conducted by Hermida et al⁵⁴, using valsartan/amlodipine combination in 203 hypertensive subjects, and resulted that BP-lowering efficacy was highest when both antihypertensive drugs ingested at bedtime, compared to both ingested on awakening, or either of the drugs ingested on awakening and the other at bedtime. Moreover, chronotherapy was found to have useful effect in treatment of resistant hypertension. In a study of 250 patients with resistant hypertension that received three hypertensive drugs, ambulatory BP reduced by 9.4/6.0 mmHg when one of the drugs was administered at bed time. The percentage of dippers increased from 16% to 57% after 12 weeks of administering one drug at bedtime.⁵⁵

CONCLUSION

As conclusion, identifying the nocturnal hypertension as well dipping or non dipping status of patients are important for aiding the decision on the necessity of chronotherapy, withdrawal

or reduction of unnecessary medication, and monitoring hypertension treatment. Taking the antihypertensive medication in the night significantly improves the dipping pattern of hypertensive patient, thus chronotherapy is a improved strategy in hypertension management.

REFERENCES

1. Maraj I, Makaryus JN, Ashkar A, et al. Hypertension management in the high cardiovascular risk population. *Int J Hyper*. 2013;1-7.
2. Friedman O, Logan AG. Can nocturnal hypertension predict cardiovascular risk? *Integr Blood Press Control*. 2009;2:25-37.
3. Li Y, Wang JG. Isolated nocturnal hypertension: A disease masked in the dark. *Hypertension*. 2013;61(2):278-83.
4. Morgan TO, Anderson A. Different drug classes have variable effects on blood pressure depending on the time of day. *Am J Hypertens*. 2003;16:46-50.
5. Li L-H, Li Y, Huang Q-F, et al. Isolated nocturnal hypertension and arterial stiffness in a Chinese population. *Blood Press Monitoring*. 2008;13(3):157-9.
6. Sun J, Yang W, Zhu Y, et al. The relationship between nocturnal blood pressure and hemorrhagic stroke in Chinese hypertensive patients. *J Clin Hypertens*. 2014;16(9): 652-7.
7. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals. part 1: blood pressure measurement in humans. A statement for professionals from the subcommittee of professional and public education of the American heart association council on high blood pressure research. *Hypertension*. 2005;45:142-61.
8. Redon R, Lurbe E. Nocturnal blood pressure versus non-dipping pattern what do they mean? *Hypertension*. 2008;51:41-2.
9. Sierra ADL, Redon J, Banegas JR, et al. Prevalence and factors associated with circadian blood pressure patterns in hypertensive patients. *Hypertension*. 2009;53:466-72.
10. Routledge F, McFetridge-Durdle J. Nondipping blood pressure patterns among individuals with essential hypertension: a review of the literature. *Eur J Cardiovasc Nurs*. 2007;6(1):9-26.
11. Liu M, Takahashi H, Morita Y, et al. Non-dipping is a potent predictor of cardiovascular mortality and is associated with autonomic dysfunction in haemodialysis patients. *Nephrol Dial Transplant*. 2003;18(3):563-9.
12. Cuspidi C, Meani S, Fonati L, et al. Short-term reproducibility of a non-dipping pattern in type 2 diabetic hypertensive patients. *J Hypertens*. 2006;24(4):647-53.
13. Leitao CB, Canani LH, Silveiro SP, et al. Ambulatory blood pressure monitoring and type 2 diabetes mellitus. *Arq Bras Cardiol*. 2007;88(2):315-21.
14. Kanbay M, Turgut F, Uyar ME, et al. Causes and mechanisms of nondipping hypertension. *Clin Exp Hypertens*. 2008;30(7):585-97.
15. Biaggioni I. Circadian clocks, autonomic rhythms, and blood pressure dipping. *Hypertension*. 2008;52(5):797-8.
16. Vardhan V, Shanmuganandan K. Hypertension and catecholamine levels in sleep apnoea. *Med J Armed Forces India*. 2012;68(1):33-8.
17. Nielsen FS, Hansen HP, Jacobsen P, et al. Increased sympathetic activity during sleep and nocturnal hypertension in type 2 diabetic patients with diabetic nephropathy. *Diabet Med*. 1999;16(7):555-62.
18. Yasuda G, Hasegawa K, Kuji T, et al. Effects of doxazosin on ambulatory blood pressure and sympathetic nervous activity in hypertensive type 2 diabetic patients with overt nephropathy. *Diabet Med*. 2005;22(10):1394-400.
19. Bankir L, Bochud M, Maillard M, et al. Nighttime blood pressure and nocturnal dipping are associated with daytime urinary sodium excretion in African subjects. *Hypertension*. 2008;51(4):891-8.
20. Isobe S, Ohashi N, Fujikura T, et al. Disturbed circadian rhythm of the intrarenal renin-angiotensin system: relevant to nocturnal hypertension and renal damage. *Clin Exp Nephrol*. 2014;19(2):231-9.
21. Wang C, Zhang J, Liu X, et al. Reversed dipper blood-pressure pattern is closely related to severe renal and cardiovascular damage in patients with chronic kidney disease. *PLoS ONE*. 2013;8(2):e55419.
22. Shin J, Xu E, Lim YH, et al. Relationship between nocturnal blood pressure and 24-h urinary sodium excretion in a rural population in Korea. *Clin Hypertens*. 2014;20(1):9.
23. Kimura G, Dohi Y, Fukuda M. Salt sensitivity and circadian rhythm of blood pressure: the keys to connect CKD with cardiovascular events. *Hypertens Res*. 2010;33(6):515-20.
24. Fagard RH, Celis H, Thijs L, et al. Daytime and night-time blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension* 2008;51:55-61.
25. Atabek ME, Akyurek N, Eklioglu BS, et al. impaired systolic blood dipping and nocturnal hypertension: an independent predictor of carotid intima-media thickness in type 1 diabetic patients. *J Diab Compl*. 2014;51-5.
26. Verdecchia P, Schillaci G, Guerrieri M, et al. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. *Circulation*. 1990;81:528-36.
27. Vasunta RL, Kesäniemi YA, Ylitalo A, et al. Nondipping pattern and carotid atherosclerosis in a middle-aged population: OPERA study. *Am J Hypertens*. 2012;25:60-6.

28. Salvetti M, Muiesan ML, Rizzoni D, et al. Night time blood pressure and cardiovascular structure in a middle-aged general population in northern Italy: The Vobarno study. *J Hum Hypertens*. 2001;15:879–85.
29. Tsigoulis G, Konstantinos V, Nikolaos Z, et al. Associated of blunted nocturnal blood pressure dip with intracerebral hemorrhage. *Blood Press Monitor*. 2005;10(4):189-95.
30. Ma JF, Sun JL, Zhao J, et al. Relationship between nocturnal blood pressure variation and silent cerebral infarction in Chinese hypertensive patients. *J Neurol Sci*. 2010;294(1-2):67-9.
31. Boxtel MPJ, Henskens LHG, Kroon AA, et al. Ambulatory blood pressure, asymptomatic cerebrovascular damage and cognitive function in essential hypertension. *J Human Hypertens*. 2006;20:5-13.
32. Kastarinen H, Vasunta RL, Ukkola O, et al. Glomerular filtration rate is related to dipping pattern in ambulatory blood pressure monitoring – a cross-sectional population based study. *J Human Hypertens*. 2010; 24:247–53.
33. Afsar B, Elsurer R. Urinary albumin excretion among nondipper hypertensive patients is closely related with the pattern of nondipping. *J Am Soc Hypertens*. 2010; 4(4):196-202.
34. Piper MA, Evans CV, Burda CU, et al. Screening for high blood pressure in adults: A systematic evidence review for the U.S. Preventive services task force. *AHRQ Publication*. 2014;13.
35. Vollmer WM, Appel LJ, Svetkey LP, et al. Comparing office-based and ambulatory blood pressure monitoring in clinical trials. *J Human Hypertens*. 2005;19:77-82.
36. Head GA, McGrath BP, Mihailidou AS, et al. Ambulatory blood pressure monitoring in Australia: 2011 consensus position statement. *J Hypertension*. 2012;30(1).
37. National Heart Foundation and High Blood Pressure Research Council of Australia Ambulatory Blood Pressure Monitoring Consensus Committee. Ambulatory blood pressure monitoring. *Australian Family Physician*. 2011;40(11).
38. Mahabala C, Kamath P, Bhaskaran U, et al. Antihypertensive therapy: nocturnal dippers and nondippers. Do we treat them differently? *Vasc Health Risk Manag*. 2013;9:125-33.
39. Christian H. Blood pressure variability: Prognostic value and therapeutic implications. *ISRN Hypertension*. 2013.
40. Ben-Dov IZ, Kark JD, Ishay DB, et al. Predictors of all-cause mortality in clinical ambulatory monitoring unique aspects of blood pressure during sleep. *Hypertens*. 2007;49:1235-41.
41. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31(7):1281-357.
42. Flack JM, Nasser SA. Benefits of once-daily therapies in the treatment of hypertension. *Vasc Health Risk Manag*. 2011;7:777-87.
43. Kario K. Morning hypertension: A pitfall of current hypertensive management. *Clinic*. 2005;18:21.
44. Fujimura A. Chronotherapy-present and future. *Nihon Rinsho*. 2013;71:2097-101.
45. Hermida RC, Diana EA, Artemio M, et al. Influence of circadian time of hypertension treatment on cardiovascular risk: Results of the Mapec Study. *Chronobiol Int*. 2010;27(8):1629-51.
46. Gorostidi M. Effect of Olmesartan-based therapy on therapeutic indicators obtain through out-of-office blood pressure. *Cardiol Ther*. 2015;4(1):S19-S30.
47. Hermida RC, Ayala DE, Fernandez JR, et al. Comparison of the efficacy of morning versus evening administration of Telmisartan in essential hypertension. *Hypertension*. 2007;50(4):715-22.
48. Povedano T, Santiago, Villa BGD. 24-Hour and night time blood pressures in type 2 diabetic hypertensive patients following morning or evening administration of Olmesartan. *J Clin Hypertens*. 2009;11(8):426-31.
49. Hermida RC, Calvo C, Ayala DE, et al. Decrease in urinary albumin excretion associated with the normalization of nocturnal blood pressure in hypertensive subjects. *Hypertension*. 2005;46(4):960-8.
50. Hermida RC, Ayala DE. Chronotherapy with the angiotensin-converting enzyme inhibitor Ramipril in essential hypertension: Improved blood pressure control with bedtime dosing. *Hypertension*. 2009;54(1):40-6.
51. Svensson P, Faire UD, Sleight P, et al. Comparative effect of Ramipril on ambulatory and office blood pressure a HOPE substudy. *Hypertension*. 2001;38:e28-e32.
52. Hermida RC, Ayala DE, Mojon A, et al. Chronotherapy with nifedipine GITS in hypertensive patients: improved efficacy and safety with bedtime dosing. *Am J Hypertens*. 2008;21(8):948–54.
53. Qiu YG, Chen JZ, Zhu JH, et al. Differential effects of morning or evening dosing of amlodipine on circadian blood pressure and heart rate. *Cardiovasc Drugs Ther*. 2003;17(4):335–41.
54. Hermida RC, Ayala DE, Fontao MJ, et al. Chronotherapy with valsartan/amlodipine fixed combination: improved blood pressure control of essential hypertension with bedtime dosing. *Chronobiol Int*. 2010;27(6):1287-303.
55. Hermida RC, Ayala DE, Fernandez JR, et al. Chronotherapy improves blood pressure control and reverts the nondipper pattern in patients with resistant hypertension. *Hypertension*. 2008;51(1):69-76.