

Night-time blood pressure: dipping into the future?

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Journal of Hypertension 2002, 20:2131–2133

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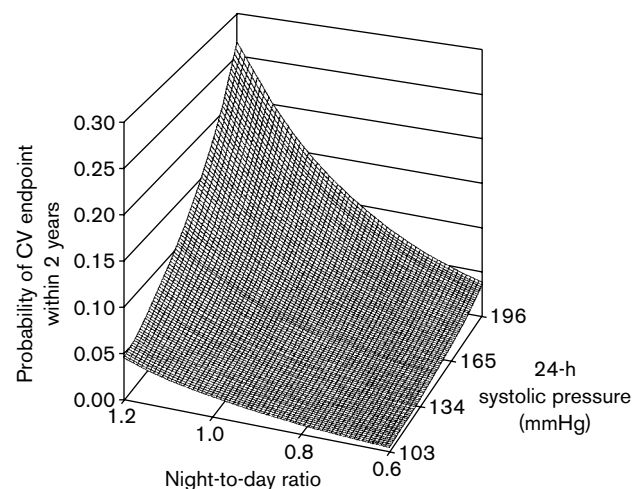
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In this issue of the journal, Ohkubo *et al.* [1] extend their previous preliminary findings [2] in 1542 inhabitants of Ohasama, Japan by increasing mean follow-up from 4.1 years to 9.2 years. The Japanese researchers [1] noticed a linear and inverse relationship between cardiovascular mortality and the nocturnal decline in blood pressure, which was independent of the overall blood pressure load during 24 h and other cardiovascular risk factors. Overall, each 5% increment in the systolic or diastolic night-to-day ratio was associated with a 20% rise in the risk of cardiovascular death, even when 24-h ambulatory blood pressure was within the normotensive range (< 135/80 mmHg) [1]. In keeping with many other investigators, a categorical analysis was used in which a 'non-dipper' was arbitrarily defined as an individual with a nocturnal decline in systolic or diastolic blood pressure of less than 10%. Compared with the reference group of normotensive dippers, hypertensive non-dippers experienced a more than five-fold increase in the relative hazard rate of cardiovascular mortality while, in normotensive non-dippers and hypertensive dippers, the relative risk rose two- to three-fold [1].

The 'dipper/non-dipper' classification was first introduced in 1988 when a retrospective analysis suggested that non-dipping hypertensive patients had a higher risk of stroke than the majority of patients with a dipping pattern [3]. On balance, most large-scale prospective studies currently support the concept that a diminished nocturnal blood pressure fall is associated with a worse prognosis [4,5]. In older patients with isolated systolic hypertension [4], the relative hazard rate of all cardiovascular end-points rose by 19% for each 5% increment in the systolic night-to-day blood

pressure ratio, independent of the 24-h blood pressure level (Fig. 1). In the PIUMA study [5], cardiovascular morbidity, expressed as the number of combined fatal and non-fatal cardiovascular events per 1000 patient-years, was 4.7 in the normotensive group, 17.9 in dippers and 49.9 in non-dippers with ambulatory hypertension, with a 5% increment in the systolic night-to-day ratio leading to a 20 to 30% increase in the overall

Fig. 1



Night-to-day ratio and 24-h systolic blood pressure at entry as independent predictors of the 2-year incidence of cardiovascular (CV) end-points in the placebo group. Using multiple Cox regression, the event rate was standardized to female sex, 69.6 years (mean age), no previous cardiovascular complications, non-smoking status and residence in Western Europe. Incidence is given as a fraction (i.e. 0.02 is an incidence of two events per 100 people followed for 2 years). Reproduced with permission [4].

cardiovascular risk. Verdecchia *et al.* [6] also evaluated incident cardiovascular morbidity in tertiles of the night-to-day blood pressure ratio. With adjustments applied for age, diabetes mellitus and average 24-h systolic pressure, men and women belonging to the highest third of the distribution (mean ratio approximately 0.96) compared with the remainder of the patients (mean ratio approximately 0.83) had relative hazard rates of 1.96 and 1.70, respectively, approximately corresponding to 29 and 23% risk increase for each 5% increment in the night-to-day ratio [6]. Thus, in two cohorts of middle-aged and older hypertensive patients [4–6], estimates of relative risk associated with the systolic night-to-day blood pressure ratio were almost identical with the population-based outcome data from the Ohasama study [1].

The agreement between these three large prospective studies is to be welcomed because the prognostic value of a non-dipping diurnal blood pressure profile has long been the source of controversial debate. Lack of standardization, arbitrary dichotomization of a continuous and variable measurement (night-to-day ratio), inappropriate selection of cases (non-dippers) and controls (dippers), insufficient sample size and failure to account for confounding issues can all influence conclusions based on nocturnal blood pressure. Another methodological problem is poor reproducibility of the night-to-day ratio [7,8] and a ‘regression-to-the-mean’ phenomenon when ambulatory blood pressure recordings are repeated in subjects classified as extreme dippers or non-dippers on the first ambulatory recording [7]. Ironically, despite poor reproducibility of the night-to-day ratio, it may be that night-time blood pressure is more standardized and consequently more reproducible than daytime blood pressure (sleep being a more stable state than activity), and that it is this feature that gives nocturnal blood pressure its predictive value.

Wrist actigraphy and keeping a diary during monitoring may help to increase reproducibility of the awake and sleeping blood pressures. The application of short, fixed clock-time intervals to define daytime and night-time blood pressure is an alternative and simple approach [9]. To increase consistency between studies, definitions of dipping status should be based on systolic as well as diastolic blood pressures [10]. Finally, to facilitate comparisons between studies, future reports should include a continuous analysis of the night-to-day blood pressure ratios.

Whereas it is becoming increasingly clear that a diminished nocturnal blood pressure fall leads to a worse cardiovascular prognosis [1,4,5], much research still needs to be carried out to elucidate the underlying pathogenetic mechanism. A simple explanation might be that patients, whose health is impaired and who are

at high risk of cardiovascular complications, are physically inactive and therefore show only a small rise in their daytime blood pressure with a flattened diurnal blood pressure profile [11]. An alternative explanation for the close correlation between cardiovascular risk and a high night-time blood pressure might be that both factors are linked to a common pathophysiological mechanism, such as a raised sympathetic tone [12] or an increased renal reabsorption of sodium, necessitating a higher night-time blood pressure to drive pressure natriuresis [13]. The disappearance of the normal diurnal blood pressure profile in patients with hyperaldosteronism, pheochromocytoma, renovascular hypertension or renal failure is in keeping with the latter hypothesis [14,15]. Furthermore, some studies have shown a significant relationship between blood pressure and night-time sodium excretion or the restoration of a dipping diurnal blood pressure profile in non-dipping hypertensive patients given a low-salt diet [13,16]. In this context, ethnicity may account for the excess stroke mortality in the Ohasama population versus what might be expected in Western populations [1]. Evidence that salt is an independent risk factor for stroke [17] adds strength to the salt hypothesis as the pathogenetic mechanism in non-dippers. Finally, the higher cardiovascular risk attributable to non-dipping may simply be due to the cardiovascular system having to sustain a persistent unrelenting blood pressure load throughout the whole day and night.

With the evidence therefore strongly pointing to nocturnal hypertension as an independent risk factor for cardiovascular complications in hypertensive (and non-hypertensive) subjects, we must next ask what the implications of this finding hold for clinical practice? There are a number of issues that clinicians managing hypertension will have to consider. First, a non-dipping nocturnal pattern can only be diagnosed by performing 24-h ambulatory monitoring. If ‘non-dippers’ are at greater risk than ‘dippers’, it becomes important to diagnose the phenomenon as part of the risk stratification. Moreover, recent evidence that extreme nocturnal dipping may also affect the occurrence of cardiovascular events [18] further strengthens the case for the wider application of the technique of ambulatory blood pressure measurement in clinical practice. Verdecchia [19] has proposed a two-stage decision approach. First, ambulatory blood pressure measurement should be used to identify the low-risk subgroup of patients with office hypertension, but with a normal ambulatory blood pressure (white-coat hypertension). In a second step, diagnosis of a non-dipping pattern among patients with sustained hypertension may delineate a high-risk subgroup, in which more vigorous antihypertensive treatment is warranted [19].

The second issue of importance for clinical practice is

how to treat nocturnal hypertension. This consideration raises two further questions. First, should blood pressure be lowered over the whole day to prevent cardiovascular complications? Several placebo-controlled trials in hypertension using antihypertensive drugs without 24-h efficacy have demonstrated significant benefit [20], but this does not preclude the possibility that better results would be obtained by achieving 24-h control of blood pressure in patients with nocturnal hypertension. Second, should it be an aim of good management to restore the dipping diurnal blood pressure profile in hypertensive patients with a non-dipping profile so as to improve cardiovascular outcome? The findings of Ohkubo *et al.* [1] make the answers to these questions a research priority.

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