Analysis of Recent Papers in Hypertension

Nighttime Administration of At Least One Antihypertensive Medication is Associated With Better Blood Pressure Control and Cardiovascular Outcomes in Patients With Type 2 Diabetes or Chronic Kidney Disease

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Blood pressure (BP) is not constant throughout the day. Ambulatory BP monitoring (ABPM) done outside of the normal office setting, in which BP measurements are taken at regular intervals (usually every 15 minutes while awake and 30 minutes while asleep) for at least 24 hours, has established the normal circadian pattern of BP. BP characteristically begins to increase between 3 AM and 6 AM and then rapidly increases (surges) on awakening. Over the next few hours after awakening, BP decreases gradually and then remains relatively constant throughout the remaining daytime hours. At night, BP normally "dips" 10% to 20% between midnight and 3 AM when the cycle repeats itself. It has long been known that clinical cardiovascular (CV) events including myocardial infarction (MI), stroke, and sudden cardiac death correlate with the morning BP surge. More recently, however, ABPM studies have informed us that the failure to demonstrate the normal dipping at night is also associated with an increase in CV events. In fact, a recent multivariate analysis has found that it is the nocturnal BP and not the early morning surge that is the key predictor of CV outcomes.

The tight relationship between nocturnal BP and CV events has led to the hypothesis that targeting antihypertensive therapy to particular times of day, known as "chronotherapy" may have clinical benefit. However, no previous well-designed prospective study has tested this hypothesis. As nocturnal hypertension frequently occurs in hypertensive individuals with diabetes and those with chronic kidney disease (CKD), evaluating the benefits of timed hypertension treatment on these two populations seems extremely important and an intriguing way to test the validity of the chronotherapy hypothesis. Accordingly, two prospective investigations from one large cohort of Spanish hypertensive patients with diabetes and CKD recently examined whether bedtime administration of at least one antihypertensive medication exerts better BP control and improves CV disease outcomes more than when all medications are taken early in the morning.

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COMMENTS

Current clinical practice finds that most patients take their antihypertensive medications in the morning, often when first arising. While both the Heart Outcomes Prevention Evaluation (HOPE) and Systolic Hypertension in Europe (SystEur) studies administered antihypertensive medication in the evening, no well-designed clinical hypertension outcome trial has specifically studied the concept of chronotherapy, randomizing patients to take their antihypertensive medications at different times of the day to prove whether this improves BP control and CV outcomes.

The present two publications, both from subset analysis of the Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular (MAPEC) trial database, found that shifting the timing of at least 1 of $\geq$3 antihypertensive medication(s) from morning to evening was more effective in controlling BP (both sleep and 24-hour ABPM) and associated with fewer CV events in patients with hypertension and diabetes or CKD.

While this finding is certainly intriguing and the magnitude of the benefit significant, since this is the first and only completed prospective study to favorably assess the role of ABPM and chronotherapy in patients with hypertension, caution must be exercised before we change clinical practice. Strengths of the MAPEC study include the large sample size, the considerable length of follow-up (more than 5 years), and the use of hard clinical endpoints. However, before we change our clinical practice on the basis of this single-center study from Spain, the results need to be replicated in a larger multicenter study evaluating a more diverse ethnic population such as we are likely to encounter in the United States. In addition, the use of baseline 48-hour ABPM that was repeated after any medication change or at least yearly throughout the study adds complexity and expense to the clinical design and is not consistent with usual clinical practice, even among most hypertension specialists, in the United States.

Study Methods for Study 1

In a subgroup of Spanish patients enrolled in MAPEC (Monitorizacion Ambulatoria para Prediccion de Eventos Cardiovasculares), 448 hypertensive individuals with type 2 diabetes from a single site were enrolled in a prospective, randomized, open-label,

blinded endpoint (PROBE) trial to either take all of their antihypertensive medications upon awakening (232 patients) or to take ≥1 of them at bedtime (216 patients). Patients who worked at night or did shift work, had secondary hypertension, type 1 diabetes, AIDS, or clinical CV disease or were pregnant were excluded. There were slightly more men (57%) than women (253 vs 195), with a mean age of 62.5±10.8 years. Body mass index averaged 32 kg/m^2. Other demographic and treatment variables between the groups were similar. All patients had baseline ABPM for 48 hours and then annually or 3 months after any medication change intended to improve BP control. In addition to the ABPM, all participants wore an actigraph that quantified physical activity at 1-minute intervals during each 48-hour ABPM. Hypertension was defined as awake ABPM ≥135/85 mm Hg or nocturnal BP ≥120/70 mm Hg. Median follow-up was 5.4 years.

Study Results From Study 1

Most patients were taking ≥3 antihypertensive medications at baseline and about 70% in each group were "nondippers." There was no difference in the number of antihypertensive agents or drug classes used between the two groups. Patients randomized to take at least 1 antihypertensive medication at bedtime (bedtime group) had significantly better 24-hour BP control and a lower rate of CV events (CV death, MI, stroke) (hazard ratio [HR], 0.25; 95% confidence interval [CI], 0.1–0.61; *P*=.003]. The percentage of nondippers in the bedtime group decreased from 70% to 49.5%, while in the group taking all of their medications upon awakening, the prevalence of nondipping (76%) was unchanged from baseline. For each 5-mm Hg decrease in nocturnal BP there was a 12% reduction in CV events. In type 2 diabetic hypertensive patients taking ≥3 medications, 24-hour BP control and CV outcome was significantly improved by shifting one antihypertensive drug from morning to evening. This chronotropic effect was independent of the number of antihypertensive drugs required and the class of antihypertensive drug shifted. The authors conclude that sleep-time BP is the most significant prognostic marker of CV events in diabetics. A simple intervention of giving 1 of ≥3 antihypertensive agents at bedtime in these patients favorably reduces CV risk and improves dipping status in hypertensive patients with diabetes.[1]

Study Methods for Study 2

Between 2000 and 2007, 695 hypertensive individuals 18 years and older with CKD (estimated glomerular filtration rate [eGFR] <60 mL/min per 1.73 m^2, urinary albumin excretion ≥30 mg per 24-hour urine or both), on at least two occasions at least 3 months apart were assessed for enrollment at a single Spanish site. From these, 661 (396 men and 265 women, with a mean age of 59 years) were enrolled in this PROBE trial. Hypertension was diagnosed based on accepted ABPM criteria: an awake BP mean ≥135/85 mm Hg or an asleep BP mean ≥120/70 mm Hg. Patients were randomized to take either all of their antihypertensive medications upon awakening (332 patients) or to take ≥1 of them at bedtime (329 patients). Those randomized to the bedtime-treatment group never ingested in the morning any of the medications ingested at bedtime. Exclusion criteria included night or shift work employment, pregnancy, secondary hypertension, type 1 diabetes, AIDS, clinical alcohol or drug abuse, or clinical CV disease. Body mass index averaged 32 kg/m^2. All other demographic and treatment variables between the groups were similar.

All patients had baseline ABPM for 48 hours (every 20 minutes between 7 AM and 11 PM and every 30 minutes during the night) with a calibrated Spacelabs 90207 ABPM monitor (Spacelabs Inc, Issaquah, WA) and then annually or 3 months after any medication change intended to improve BP control. In addition to the ABPM, all participants wore an actigraph that quantified physical activity at 1-minute intervals during each 48-hour ABPM. Blood samples were obtained between 8 AM and 9 AM after an overnight fast the same week that the 48-hour ABPM was done. Median follow-up was 5.4 years.

Study Results From Study 2

Patients who took at least one BP-lowering medication at bedtime had an adjusted risk for CV events (a composite of death, MI, angina, revascularization, heart failure, lower extremity arterial occlusion, retinal artery occlusion, and stroke) approximately one third of patients who took all medications on awakening (adjusted HR, 0.31; 95% CI, 0.21–0.46; *P*<.001). Bedtime dosing also reduced the composite risk of CV death, MI, and stroke (adjusted HR, 0.28; 95% CI, 0.13–0.61; *P*<.001). Furthermore, patients who took at least one medication at bedtime had a significantly lower mean sleep-time BP and better ABPM control (56% vs 45%, *P*=.003). During follow-up, each 5-mm Hg decrease in mean sleep-time systolic BP was associated with a 14% reduction in the risk of CV events (*P*<.001). Among patients with CKD and hypertension, taking at least one antihypertensive medication at bedtime improves control of BP and reduces the risk for CV events.[2]

FINAL THOUGHTS

The American Diabetes Association in their 2012 Standards of Care provides a new recommendation (level of evidence A) to give at least one antihypertensive medication in the evening if several are required to control BP in a diabetic hypertensive patient. While this report from MAPEC certainly supports that recommendation, and extends it to patients with CKD, these finding should be replicated in a well-designed multicenter US study in a diverse population before this type of chronotherapy becomes the standard of care. Of course, pending the results of such a trial,

since this is a low-cost (really no cost) intervention that is not likely to be associated with adverse effects, clinicians can consider shifting at least one medication to bedtime administration in cases of resistant hypertension, recognizing that the data are not definitive.

Other important issues and questions are raised by these data, including the fact that it is still unclear which class (or classes) of antihypertensive drug is best to give at bedtime. Also, these findings add to the controversy as to whether ABPM should become a routine tool for the diagnosis and management of hypertension.

The bottom line is that the magnitude of the benefit seen in MAPEC makes it imperative that we further test the chronotherapy hypothesis in future well-designed clinical trials. We need a large multicenter trial of US patients designed to strengthen the level of evidence for its use before we implement chronotherapy in clinical practice.

References

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