Orthostatic Hypotension Is a More Robust Predictor of Cardiovascular Events Than Nighttime Reverse Dipping in Elderly

Robert H. Fagard, Paul De Cort

Abstract—Aims of the study were to assess in an elderly population the prevalences of orthostatic hypotension at different times after standing and of nighttime reverse dipping on ambulatory blood pressure monitoring, as well as their interrelationships and relative prognostic power for incident cardiovascular events. The study population consisted of 374 patients (225 women), aged 70.2±8.5 years, registered in 1 primary care practice and without major cardiovascular events or other comorbidities at baseline. They experienced 76 first cardiovascular events (death, myocardial infarction, or stroke) during 3406 years of follow-up. Systolic/diastolic orthostatic hypotension, defined as a decrease of systolic/diastolic blood pressure of ≥20/≥10 mm Hg, was present in 24.0%/13.3% of the patients immediately after standing, and in, respectively, 18.1%/10.5% and 12.4%/11.6% after 1 and 2 minutes, whereas systolic/diastolic reverse dipping occurred in 14.4%/9.5%. Orthostatic hypotension was 2 to 3 times more prevalent in reverse dippers than in dippers (P≤0.01). Systolic orthostatic hypotension was a significant and independent predictor of cardiovascular events, which was stronger during recovery than immediately after standing; in Cox regression analysis, the adjusted hazard ratio amounted to 2.38 (P<0.01) after 2 minutes. The independent predictive power of diastolic orthostatic hypotension was only significant soon after standing (P<0.05). Systolic and diastolic reverse dipping carried prognostic significance in univariable analyses (P<0.001) but not after adjustment for confounders, including 24-hour blood pressure. We conclude that orthostatic hypotension contributes to the phenomenon of reverse dipping but is a more robust predictor of cardiovascular events than reverse dipping in the elderly of the current study. (Hypertension. 2010;56:56-61.)

Key Words: ambulatory blood pressure monitoring ■ cardiovascular events ■ orthostatic hypotension ■ prevalence ■ prognosis ■ reverse dipping

A number of studies have assessed the prognostic significance of orthostatic hypotension (OH)1–12 or reverse dipping on ambulatory blood pressure (BP; ABP) monitoring (ABPM).13–19 Daytime ABP is usually higher than nighttime ABP, and the reverse diurnal pattern is independently associated with a higher incidence of cardiovascular events16,18,19 and mortality13,15,16,18,19 in most but not all studies.14,17 Also, OH carries a worse prognosis for all-cause4,9,11,12 and cardiovascular mortality,5,9 coronary heart disease (CHD),7,8,11,12 stroke,6 or an aggregate of cardiovascular events,12 although not all of the studies agree with regard to mortality1–3,10 or stroke.11,12 OH has been defined as a reduction of systolic BP of ≥20 mm Hg or of diastolic BP of ≥10 mm Hg within 3 minutes of standing,20 but this definition has been applied differently in the various prognostic studies. Some authors have reported on single BP measurements at different time intervals after standing,2–5,8,12 whereas others have averaged variable numbers of BP measurements6,7,9,10 or accepted OH if any of several BP measurements corresponded with the above definition.1,11 Furthermore, some studies reported separately on systolic and diastolic OH,2,5,8 but most studies accepted OH if either of the 2 was present. The prevalence of both OH and reverse dipping increases with age,21,22 and the 2 phenomena may be interrelated, because a lower BP in the upright position may contribute to a lower ABP during the day than during the night.23,24 However, no study has addressed the relative prognostic importance of OH and reverse dipping.

Therefore, the aims of the present study were to assess the following in an elderly population: (1) prevalence and prognostic significance of systolic and diastolic OH at different time intervals after standing; (2) prevalence and prognostic significance of systolic and diastolic reverse dipping; (3) interrelationships between OH and reverse dipping; and (4) the relative predictive power of OH and reverse dipping for cardiovascular events. The study was performed in subjects ≥60 years of age, registered in one primary care practice.25

Methods

Study Protocol

The study protocol was approved by the institutional ethics committee, and all of the participants gave informed consent after explanation of the protocol. The study was performed in one primary care practice in Flanders, Belgium, in which 2044 patients were registered, of whom 462 were ≥60 years old.25 Of the 462 patients, 63

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patients were excluded because they were bedridden (n=3), de-
demted on clinical grounds (n=2), admitted in a home for sick
elderly people (n=7), or had a history of myocardial infarction
(n=14), stroke (n=12), congestive heart failure (n=21), or myocar-
dial infarction plus stroke (n=2) or heart failure (n=2). We excluded
17 patients because no data were available on either OH or reverse
dipping, mainly because of a lack of collaboration or failed BP
measurements. An additional 8 patients were lost to follow-up,
leaving 374 analyzable patients for the current study.

Baseline examinations were performed between November 1990 and
May 1993 and were composed of a questionnaire, including medical
history, current smoking, and physical activity; a standard clinical
examination; and measurements of height, weight, and fasting serum
total cholesterol and glucose concentration. Any smoking was coded as
1 for current smoking, and a positive answer to the question, “Do you
practice any sports?” was coded as 1 for physical activity in the
statistical analyses; no smoking and no sports practice were coded as 0.
BP and heart rate measurements were performed in the patients’ homes,
most often by the general practitioner and otherwise by an assistant
physician. After 5 minutes of rest, BP was measured 3 times in the
sitting position by the auscultatory technique using a mercury sphyg-
momanometer and an appropriately sized cuff. Thereafter, BP was
measured 3 times in the supine position and 3 times after assumption of
the freestanding position, that is, immediately after standing and after 1
and 2 minutes. Heart rate was measured after each BP measurement,
except immediately after standing. Finally, 24-hour ABPM was per-
formed by use of a SpaceLabs 90202 or 90207 device, with appropriate
cuff size. ABP and heart rate were measured every 15 minutes from 8:00 AM
to 10:00 PM and every 30 minutes from 10:00 PM to 8:00 AM.
Daytime ABP was defined as the weighted average of all of the
measurements between 10:00 AM and 8:00 PM, and nighttime ABP was
the average ABP from 12:00 AM to 6:00 AM, which corresponds well
with the actual awake and asleep ABP.24 24-hour ABP was the
weighted average of all of the BP measurements. The same averages
were calculated for heart rate. OH was defined for systolic BP and
diastolic BP, or a combination of both, at each time interval after
standing, that is, a fall of systolic BP of ≥20 mm Hg and/or a fall of
diastolic BP of ≥10 mm Hg, and was also based on the difference
between the average of the 3 standing and the 3 supine BPs. Reverse
dippers had higher nighttime ABP than daytime ABP, and all of the
other patients were considered dippers in the current study.

Follow-Up

The vital and health status of the patients was ascertained between
January 2002 and December 2003. The aggregate of cardiovascular
death, nonfatal stroke, and myocardial infarction was the primary
end point of the current study, and cardiovascular death, fatal and
nonfatal CHD (myocardial infarction and sudden death), and all
strokes were secondary end points. All of the events were corrobo-
rated by the investigators according to established criteria27 and
without knowledge of the baseline data.

Statistical Analysis

Database management and statistical analyses were performed using
SAS software, version 9.1 (SAS Institute Inc). Data are reported as
mean±SD or as percentages. Differences between groups were
analyzed by unpaired t tests or by the χ² test for categorical data. We
used Cox regression analysis to assess the prognostic significance of
baseline characteristics, including OH, reverse dipping, or both. For
patients who experienced >1 event, analysis was restricted to the
first event under study. In multivariable Cox regression analysis, we
adjusted for age, sex, body mass index (BMI), heart rate, use of
BP-lowering drugs, smoking, diabetes mellitus, glycemia (after
logarithmic transformation because of the positively skewed distri-
bution), total cholesterol, and physical activity at baseline. When the
prognostic significance of OH was assessed, full adjustment included
average sitting BP and heart rate; for reverse dipping, we included
mean 24-hour BP and heart rate. Analyses were repeated with pulse
pressure instead of BP. We assessed whether the prognostic signif-
icance of OH and reverse dipping was different between men and
women by testing the appropriate interaction term in Cox models. A
2-tailed value of P≤0.05 was considered significant.

Results

Patient Characteristics at Baseline

Age of the 374 patients (225 women) averaged 70.2±8.5
years, BMI averaged 27.5±4.7 kg/m², serum cholesterol
averaged 6.44±1.24 mmol/L (249±48 mg/dL), and glucose
averaged 5.05±1.56 mmol/L (91.0±28.0 mg/dL). Diabetes
mellitus was present in 7.0%, 19.1% were current smokers, and
18.4% practiced sports; 32.6% were on BP-lowering drug (diuretics: 10.2%, β-blockers: 12.0%, calcium antago-
nists: 9.4%, angiotensin-converting enzyme inhibitors: 6.7%,
others: 8.5%). The general characteristics were similar in the
354, 347, and 327 patients with data on, respectively, OH, the
standing positions, orthostatic BP change, and prevalence of
OH at baseline.

Table 1. Conventional BP Measurements in the Supine and
Standing Positions, Orthostatic BP Change, and Prevalence of
OH at Baseline

<table>
<thead>
<tr>
<th>Position</th>
<th>BP, mm Hg</th>
<th>Orthostatic BP</th>
<th>OH, n (%)</th>
</tr>
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<tbody>
<tr>
<td>Systolic</td>
<td>145.6±24.0</td>
<td>-10.0±17.5†</td>
<td>85 (24.0)</td>
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<tr>
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<td>Minute 1</td>
<td>Systolic</td>
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<td>-0.3±8.6</td>
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<tr>
<td>Minute 2</td>
<td>Systolic</td>
<td>140.4±23.3</td>
<td>-4.1±15.2†</td>
</tr>
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<tr>
<td>Average</td>
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Data are from 354 patients. Values are mean±SD or as
percentages. Differences between groups were analyzed by
unpaired t tests or by the χ² test for categorical data. We
used Cox regression analysis to assess the prognostic
significance of baseline characteristics, including OH, reverse
dipping, or both. For patients who experienced >1 event,
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positively skewed distribution), total cholesterol, and physical
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was assessed, full adjustment included average sitting BP and
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women by testing the appropriate interaction term in Cox models. A
2-tailed value of P≤0.05 was considered significant.
In the 347 patients with complete ABPM data, 24-hour, daytime, and nighttime ABP averaged, respectively, 126.2±13.6/72.8±8.4, 130.2±13.5/76.6±9.0, and 117.1±17.0/65.1±10.2 mm Hg. Reverse dipping was observed in, respectively, 50 (14.4%) and 33 patients (9.5%) for systolic and diastolic ABPs.

### Baseline Characteristics in Patients With OH and in Reverse Dippers

The 55 patients with OH based on the average systolic BP (149.9±24.1 versus 142.3±22.4 mm Hg; P<0.05) and higher pulse pressure (73.7±21.7 versus 67.3±19.8 mm Hg; P<0.05) than the 299 other patients. There were no significant differences with regard to age, sex, BMI, sitting heart rate, use of BP-lowering drugs, diabetes mellitus, cholesterol and glucose concentration, smoking, and physical activity; 17.0% of the women and 13.4% of the men had OH (P=0.36). None of the baseline characteristics differed significantly between patients with (n=32) and patients without diastolic OH (n=322).

As shown in Table 2, the 50 reverse dippers for systolic ABP were older than the 297 other patients, were composed of more women than men, and had higher average 24-hour systolic ABP, whereas the other patient characteristics were not different between the 2 groups; only age and 24-hour ABP remained significant in multivariable analysis. The 33 reverse dippers for diastolic ABP were older than the dippers, but none of the other variables differed significantly between the groups. In addition, the prevalence of OH was higher in reverse dippers than in dippers, and this was the case for each BP measurement after standing and for the average of the 3 BPs. The prevalence in reverse dippers was approximately twice the prevalence in dippers for systolic ABP and approximately 3 times the prevalence for diastolic ABP. These percentages hardly changed after adjustment for significant covariates. Furthermore, the correlation coefficient between the average orthostatic BP change and the day-night BP difference was 0.22 (P<0.0001) for systolic BP and 0.17 (P<0.0001) for diastolic BP; these relationships remained significant (P≤0.001) after full adjustment, including conventional sitting BP and mean 24-hour ABP.

### Prognostic Significance of OH and Reverse Dipping

Median follow-up time of the 374 patients was 11.0 years (range: 0.04 to 13.0 years), and total follow-up time amounted to 3406 patient-years. The total number of events during follow-up, including first and subsequent events, consisted of 59 cardiovascular deaths, 40 cases of fatal or nonfatal CHD, and 24 strokes. The primary end point was composed of 76 first events, consisting of 46 cardiovascular deaths, 19 nonfatal myocardial infarctions, and 11 nonfatal strokes.

As shown in the Figure, systolic OH at each time interval after standing was a significant predictor of cardiovascular events, both before and after full adjustment. The relationship became stronger from the assessment immediately after standing onward to the 2-minute recovery measurement. Only age (P<0.001) and male sex (P<0.01) were significant and independent predictors of cardiovascular events in the multivariable analyses. Sitting systolic BP and heart rate were not significant, and this was also the case for pulse pressure. There was no significant interaction between OH and sex. The predictive power was strongest when OH was based on the average BPs (hazard ratio [HR]; 2.80 [95% CI: 1.63 to 4.82]; P<0.001). As for the secondary end points and based on the average BPs, the fully adjusted HR amounted to 2.08 (95% CI: 1.11 to 3.89; P<0.05) for cardiovascular death (n=52 events), 2.72 (95% CI: 1.30 to 5.69; P<0.01) for CHD (n=38), and 2.45 (95% CI: 0.90 to 6.68; P=0.08) for stroke (n=21). By contrast, both crude and fully adjusted HRs for diastolic OH were only significant for the immediate BP measurement after standing and became nonsignificant thereafter, also when based on the average BPs. When the diagnosis of OH was based on systolic or diastolic BP, the HRs were somewhere between the results obtained with systolic and diastolic BP, and there was no evidence of superior predictive power.

In the 347 patients with complete ABPM data, who experienced 70 cardiovascular events during follow-up, reverse dipping was a significant and strong predictor before adjustment (HR: 2.73 [95% CI: 1.60 to 4.68] for systolic BP and 3.45 [95% CI: 1.94 to 6.1] for diastolic BP; P<0.001 for both) but was not a significant predictor after full adjustment (HR: 1.19 [95% CI: 0.001) for both).
0.65 to 2.18] for systolic BP and 1.33 [95% CI: 0.72 to 2.47] for diastolic BP). Age (P < 0.001), male sex (P < 0.05), and systolic but not diastolic 24-hour ABP (P < 0.05) were independent predictors of cardiovascular events in the multivariable analyses. Twenty-four-hour pulse pressure was not a significant and independent predictor. The interaction between reverse dipping and sex was not significant.

Table 3 summarizes the prognostic significance of OH and reverse dipping when both variables were included in the same model. Before adjustment, OH and reverse dipping were significant and independent predictors of cardiovascular events for systolic BP, whereas only reverse dipping was significant for diastolic BP. After full adjustment, including conventional sitting BP and heart rate and 24-hour mean ABP and heart rate, systolic OH was the only significant predictor of cardiovascular events.

Discussion

The main findings of the present study in elderly subjects registered in 1 primary care practice are as follows: (1) OH is most pronounced immediately after active standing; (2) OH is more prevalent in reverse dippers than in dippers; (3) systolic OH is a better predictor of cardiovascular events than diastolic OH; (4) diastolic OH is only predictive shortly after standing, whereas systolic OH is most predictive during recovery; and (5) OH is a more robust predictor of cardiovascular events than reverse dipping.

Two large, prospective, population-based studies, in which mean age averaged 46 years and 52 years, respectively, estimated the prevalence of OH defined as a reduction of systolic BP of ≥20 mm Hg or diastolic BP of ≥10 mm Hg based on 1 BP measurement within 3 minutes of standing. Although these authors observed prevalences of 6% and 5%, respectively, the prevalence amounted to 19% in our study when we used a similar definition of OH, confirming the higher prevalence of OH in the elderly. In the population-based studies, OH was independently associated with all-cause mortality,9,12 cardiovascular mortality,9 and CHD,7,12 but this was only the case for stroke in one study.6 Most studies reported on older subjects,1–5,8,10,11 and the results have not always been consistent. OH was independently predictive of all-cause mortality in some3,11 but not all studies1,2,10 and significantly predicted cardiovascular mortality in one5 but not in another study.2 CHD was consistently predicted,8,11 whereas stroke and heart failure were not independently predicted in the one study in which these outcomes were reported.11 Differences among studies may be attributed to the selected study population, whether institutionalized patients or patients with cardiovascular disease and other comorbidities were included, the use of variable definitions of OH though within the consensus definition,20 measurement of ≥1 BP at different times after standing, and the use of systolic BP, diastolic BP, or a combination of both. We, therefore, analyzed the importance of different BP measurements after standing and found that, overall, systolic BP was a better predictor of cardiovascular events than diastolic BP and that combining systolic and diastolic OHs did not improve prediction. Furthermore, the prognostic power of diastolic BP was best immediately after standing and that of systolic BP was best during recovery, which, together with the fact that systolic and diastolic OHs were concordant in only one third of
the patients with OH, supports previous suggestions that systolic and diastolic OHs may represent different pathophysiological entities. It is of note that the HRs were approximately similar for CHD and stroke. As for the pathophysiology of our findings, the BP decrease on standing, which is mainly related to the displacement of blood from the thorax to the lower parts of the body, is counteracted by baroreceptor deactivation and stimulation of the sympathetic nervous system, and this response becomes more sluggish with aging. Our results suggest that inappropriate recovery from orthostatic BP fall is prognostically more important than the immediate BP fall itself.

Reverse dipping was present in 14.4% of the patients for systolic ABP and in 9.5% for diastolic ABP. A number of studies reported on the prognostic significance of reverse dipping in the population, or in hypertensive patients, with appropriate adjustment for relevant covariates and 24-hour ABP. Ohkubo et al observed in a population-based study on individuals aged ≥40 years that cardiovascular mortality was significantly higher in reverse dippers than in dippers. In a large meta-analysis of prospective population studies, reverse dipping was independently associated with mortality and an aggregate of fatal and nonfatal cardiovascular events. Ben-Dov et al reported on patients referred for ABPM and found that all-cause mortality was significantly higher in reverse dippers than in dippers. In a meta-analysis of prospective studies in hypertensive patients, reverse dipping predicted mortality and aggregates of cardiovascular events, irrespective of the presence of cardiovascular disease at baseline. In elderly patients with hypertension, stroke incidence and cardiovascular mortality were higher in reverse dippers than in other dipping categories, but this was not significant after full adjustment including 24-hour ABPM. Finally, in a small number of octogenarians, stroke incidence was not different according to the dipping pattern. We observed that reverse dipping was strongly associated with future cardiovascular events in univariable Cox regression analysis, but this relationship was no longer significant after full adjustment. Age, male sex, and 24-hour BP were the stronger predictors in the multivariable models.

It has been suggested that OH is associated with lower BP in the upright position during daytime and may, therefore, contribute to the abnormal diurnal BP pattern. Kario et al observed in elderly hypertensive patients that OH, defined as a systolic BP decrease of ≥20 mm Hg during 70° head-up tilt, was found in 27% of reverse dippers and in, respectively, 9% and 7% of dippers and extreme dippers. Ejaz et al reported that reversal of the circadian BP pattern was frequently observed when ABPM was performed in patients who presented for evaluation of OH, many of whom had comorbid conditions. By contrast, no significant correlation was found between standing-lying BP difference and nocturnal ABP fall in young, mild hypertensives. In our elderly study population, we did observe a 2- to 3-times higher prevalence of systolic and diastolic OH in reverse dippers than in dippers, which was independent of confounding factors, supporting the contribution of OH to the phenomenon of reverse dipping.

When reverse dipping and OH were both included in Cox regression models without adjustment for baseline characteristics, reverse dipping appeared to be the better predictor of cardiovascular events for diastolic BP and shortly after standing for systolic BP. However, only systolic OH remained significant after full adjustment, with inclusion of sitting BP and 24-hour ABP. We, therefore, conclude that particularly systolic OH is a more robust predictor of cardiovascular events than reverse dipping in the elderly of the current study.

Our study has strengths and limitations. To the best of our knowledge, it is the first to compare the prognostic significance of OH and reverse dipping in the same population. The study has been performed in one primary care practice in which registered patients were familiar with the physician, the technique, and circumstances of the BP measurement. However, it is not certain whether the results can be extrapolated to randomly recruited elderly or to measurements in other conditions. Unlike many other studies, we excluded patients with major cardiovascular disease or other comorbidities, which might have influenced the results. In addition, although no specific tests have been performed, there was no evidence of coexisting conditions responsible for autonomic failure. Approximately one third of the patients were on BP-lowering drugs, but treatment was not a significant determinant of OH, reverse dipping, or prognosis. The effect of tranquilizers or sleeping pills could not be assessed, because this information was not available. As in the other studies, the diagnoses of OH and reverse dipping were based on single evaluations, so that the question of whether their predictive power would be improved by repeated assessments remains unanswered. Finally, as in most other studies, management of hypertension and other clinical conditions was not standardized or assessed during follow-up.

### Table 3. Crude and Adjusted HRs for Cardiovascular Events With OH and Reverse Dipping Included in the Same Model

<table>
<thead>
<tr>
<th>BP Measurement</th>
<th>Crude</th>
<th>Adjusted$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OH immediate</td>
<td>1.72</td>
<td>1.81</td>
</tr>
<tr>
<td>Reverse dipping</td>
<td>2.06</td>
<td>0.86</td>
</tr>
<tr>
<td>OH minute 1</td>
<td>2.03</td>
<td>2.65</td>
</tr>
<tr>
<td>Reverse dipping</td>
<td>2.01</td>
<td>0.68</td>
</tr>
<tr>
<td>OH minute 2</td>
<td>2.16</td>
<td>2.10</td>
</tr>
<tr>
<td>Reverse dipping</td>
<td>1.97</td>
<td>0.80</td>
</tr>
<tr>
<td>OH average</td>
<td>2.69</td>
<td>2.69</td>
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<tr>
<td>Reverse dipping</td>
<td>1.98</td>
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<tr>
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</tbody>
</table>

Data are from 327 patients and 63 cardiovascular events. Values are HRs (95% CIs).

*P<0.05 significance of HR.
†P<0.01 significance of HR.
‡P<0.001 significance of HR.
§Data were adjusted for age, sex, BMI, BP-lowering drugs, diabetes mellitus, cholesterol and glucose concentration, smoking, physical activity, and sitting and 24-h systolic or diastolic BP and heart rate.

*The effect of tranquilizers or sleeping pills could not be assessed, because this information was not available. As in the other studies, the diagnoses of OH and reverse dipping were based on single evaluations, so that the question of whether their predictive power would be improved by repeated assessments remains unanswered.

**Finally, as in most other studies, management of hypertension and other clinical conditions was not standardized or assessed during follow-up.**
Perspectives
Current guidelines for the management of hypertension in the elderly recommend that BP should be measured also in the erect posture because of the increased risk of OH. The current study emphasizes that standing BP is not only of clinical but also of prognostic importance. Although ABPM may be indicated for various reasons, including the proven prognostic value of average ABP, our results show that the simple measurement of orthostatic BP change appears to be prognostically more relevant than the ABPM-derived variable nighttime reverse dipping. Our study also suggests that a more precise definition of OH is warranted, because the current definition leaves room for interpretation and has indeed been applied differently in various studies, which hampers their comparability. Finally, future studies should address the question of how to manage patients with OH, reverse dipping, or both to improve prognosis.

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Disclosures
None.

References
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