Prognostic Value of Morning Blood Pressure Surge in Clinical Events: A Meta-analysis of Longitudinal Studies

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Background: Cardiovascular (CV) events tend to occur more often in the morning. Thus, morning blood pressure surge (MS) may be related to the risk of CV events. The results of several studies evaluating the prognostic value of MS are inconsistent. In this study, we conducted a systematic review and meta-analysis to summarize the significance of MS in predicting future CV events. *Methods:* Among the related literature, we discovered 7 eligible longitudinal studies that had evaluated MS and had followed 14,133 patients with a mean follow-up period of 7.1 years. We evaluated the predictive value of MS for future CV events, stroke, and all-cause mortality in this meta-analysis. *Results:* For subjects with higher pre-waking MS than those with lower pre-waking MS, the pooled relative risk (RR) of all-cause mortality, stroke, and total CV events were 1.20 (95% confidence interval [CI]: .85-1.70, $P = .290$; 4 studies), 1.20 (95% CI: .94-1.53, $P = .146$; 3 studies), and 1.24 (95% CI: .60-2.53, $P = .562$; 3 studies), respectively. For subjects with higher sleep-trough MS, the pooled RR of all-cause mortality was 1.29 (95% CI: 1.11-1.52, $P = .001$; 4 studies). No significant publication bias was observed. *Conclusions:* Excess sleep-trough MS is a strong predictor for future all-cause mortality. Individuals with higher pre-waking MS showed a tendency for increased risk of CV outcomes, but the differences were insignificant. **Key Words:** Morning blood pressure surge—cardiovascular risk—stroke—prediction—meta-analysis.

Introduction

Several studies showed that cardiovascular (CV) complications, including stroke,[1] myocardial infarction,[2,3] and sudden death,[4] tend to peak in the morning. Blood pressure (BP) also rises sharply in response to the activation of the sympathetic nerve system in the early morning. Therefore, the high risk of CV complications is hypothesized to be associated with an excessive morning blood pressure surge (MS).[5,6] However, studies evaluating the prognostic value of MS have produced inconsistent results,[6-13] possibly because of the small number of events and different definitions of MS. To our knowledge, MS has 3 different definitions[5]: (1) sleep-trough surge: calculated as the morning BP (the mean BP during 2 hours after wake-up) minus the lowest night-time BP (1-hour average of 3 BP readings centered on the lowest nocturnal BP reading)[6,7,10-12]; (2) pre-waking surge: defined as the morning BP minus the pre-waking BP (2-hour average BP before wake-up)[6,7,10,12,13]; and (3) rising BP surge, defined as the BP

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on rising minus the last BP reading in the 30 minutes before rising.[8] Generally, researchers use only systolic BP, rather than diastolic BP, to calculate the MS. Given the diverse definitions of MS and inconsistent results about the predictive role of MS from different studies, an overview of relevant studies and assessment of robust quantitative estimates are necessary to compare the predictive value of MS in each definition. This article describes a systematic review and meta-analysis to evaluate the predictive role of excess MS in the future risk of major CV outcomes, including total CV events, stroke, and all-cause mortality.

Materials and Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[14]

Outcomes

The outcomes of interest were total CV events (fatal and nonfatal CV events, such as coronary events, heart failure, stroke, and myocardial infarction), stroke (fatal and nonfatal), and all-cause mortality.

Literature Search and Study Eligibility

We searched PubMed and Web of Science to retrieve eligible studies published before June 1, 2014. The search terms were "prediction," "risk," "death," "mortality," "outcome," "events," "stroke," "morning surge," "blood pressure surge," or "pressor surge." No restriction criteria were imposed. The strategy was followed with a manual retrieval of secondary sources, such as references from primary articles.

Studies were deemed eligible if they met the following criteria: (1) full-length original research articles published in peer-reviewed journals; (2) longitudinal studies; (3) had at least 1 definition of MS; (4) evaluated the relationship between MS and risk of CV events, stroke, or all-cause death; (5) provided the relative risks (RRs) or hazard ratio (HR) with confidence intervals (CIs) or sufficient data to calculate them.

Extraction of Data and Assessment of Study Quality

The literature search, study selection, and data extraction were performed independently by 2 reviewers (J.C.X. and H.Y). Disagreements were resolved by consensus. The extracted data included publication information (first author's last name and publication year), patients' characteristics (sample size, age, percentage of male, follow-up duration), MS results derived from ambulatory blood pressure monitoring (ABPM), cutoff value and risk estimates (HR, RR, or dichotomous frequency data of excess MS for total CV events, stroke, and all-cause mortality), and *P* values.

The methodological qualities of the included studies were assessed independently by 2 reviewers (J.C.X. and H.Y.) using the Newcastle–Ottawa Scale (NOS), a validated instrument in assessing the quality of observational and nonrandomized studies.[15] Disagreements were resolved through discussions with a senior reviewer (Y.X.Z.).

Statistical Analysis

RR was used as a common risk estimate across studies. We treated HR as RR. Given that no uniform cutoff is available for MS, patients were allocated to "higher MS" or "lower MS" groups according to cutoffs in each study (Table 1). In some studies, the adjusted risk estimates (adjusted HR or RR) from multivariate models were used when available.

Statistical heterogeneity across studies was calculated with the Cochran *Q* test and Higgins I^2 statistic.[16] A *P* value less than .05 and/or I^2 greater than 50% was treated statistically significant. A random effects model was used to obtain the pooled RR in the presence of significant heterogeneity, whereas a fixed effect model was used in the absence of heterogeneity. The RRs and CIs of comparable studies were illustrated with forest plots.

We then performed sensitivity analysis to detect the robustness of outcomes using a test of interaction and the source of heterogeneity.[17] Publication bias was assessed by a funnel plot with Egger's bias indicator test.[18,19] All analyses were performed using STATA software package (version 12.0; Stata Corp., College Station, TX).

Results

Qualitative Summary

We initially identified a total of 756 relevant publications, which were narrowed to 12 original articles[6-13,20-23] by excluding 231 duplicates and 513 unrelated articles. Three of those articles[9,22,23] were then excluded because the populations in these studies overlapped with those of other studies.[6,7] One article did not use one of the classic definitions of MS, so it was excluded.[20] Another article was excluded because of the small sample size and lack of essential data for calculating the risk estimates we needed.[21] Finally, 7 original articles were included in our meta-analysis.[6-8,10-13] Figure 1 shows the flow diagram of candidate article selection in this study.

Details of the 7 articles are shown in Table 1. A total of 14,133 subjects were included in this meta-analysis. All the studies are cohort studies. Hypertensive, diabetic, and general populations were included. The included subjects were from Denmark,[6] Belgium,[6] Russia,[6] Italy,[6,10,13] Poland,[6] France,[8] Israel,[12] Japan,[6,7] China,[6] Uruguay,[6] and Brazil.[11] The mean/median follow-up