Meta-analysis of association between visit-to-visit blood pressure variability and death: a linear relationship?

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Introduction

While the association between mean blood pressure (BP) and the risk of mortality is well known, in the last decades many studies suggested that visit-to-visit BP variability (BPV) may significantly improve the prediction of all cause and cardiovascular mortality. The aim of this meta-analysis was to investigate the BPV-death relationship and the presence of a BPV-threshold.

Methods

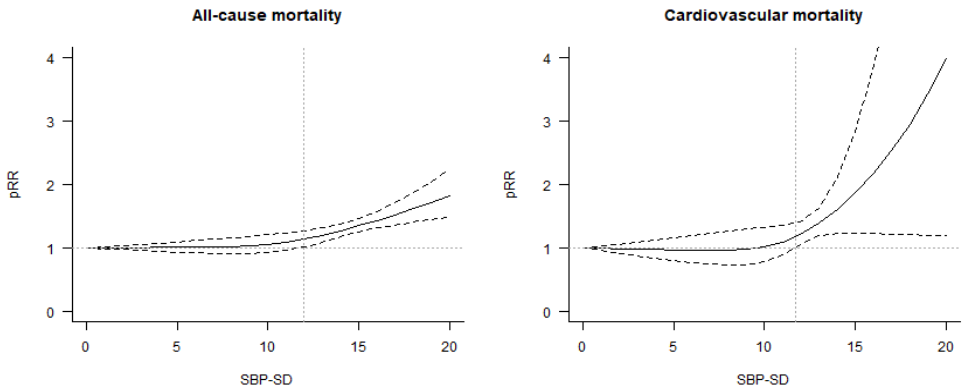
A Medline search was performed up to 21 April 2021 to identify all studies reporting the association between BPV and risk of death. Studies were included in the meta-analyses if:

i) were original observational studies or post-hoc analyses of randomized controlled trials (RCT);
ii) considered as exposure at least 3 categories, reporting the relative extreme values, mean value and number of events, of one or more of the following visit to visit systolic (SBPV) or diastolic (DBPV) blood pressure variability indexes: Standard deviation (SD), Average Real Variability (ARV), Coefficient of variation (CV), Residual, Variability independent of the mean (VIM);
iii) evaluated mortality outcomes (all-cause mortality, cardiovascular mortality);
iv) reported the association estimates between exposure and outcome (i.e. relative risk (RR), odds ratio (OR), hazard ratio (HR)) and the corresponding 95% confidence intervals or data allowing the estimation of relative standard error.

Following the approach by Orsini et al, restricted cubic spline random effects meta-regression models based on three knots set at 5th, 50th and 95th percentile of the BPV index distribution [1] were applied. Correlation between estimates belonging to the same study was taken into account using the Greenland and Longnecker approach [2].

Results

Bibliography search identified 4268 studies, 44 of them were included. The most frequently reported association estimates were related to SBPV and SD index (13 studies, 12 reporting all-cause mortality and 7 cardiovascular mortality). Five studies were based on the general population, 3 on subjects with hypertension and/or type II diabetes, 3 on subject with macrovascular disease or atrial fibrillation and 2 on subjects with stage 1-4 chronic kidney disease. In 3 studies SBPV calculation was based on 3 BP measurements, in 7 studies on 4 to at most 7 measurements and in 2 on 8 or more measurements. For one study the information on the number of measurement used was not available. The figures below show the curves derived from the parameters obtained from the meta-regression models aimed to assess the relationship between SBPV and the risk of all-cause and cardiovascular mortality respectively.



The results of the meta-regression analyses highlighted a non-linear relationship between SBPV and outcomes' risk, with a SBPV SD threshold (above which the risk of outcome becomes statistically significant) of 12.0 mmHg for all-cause mortality and 11.8 mmHg for cardiovascular mortality.

Conclusions

The lack of knowledge about the relationship between BPV and death as well as the lack of outcome-driven operational thresholds limit the clinical application of visit to visit BPV measurements. These findings could help clinicians in diagnosing and managing patients, although limited by heterogeneity in terms of population and number of BPV measurements.

References

1 Crippa Alessio, Orsini Nicola. Multivariate Dose-Response Meta-Analysis: The dosresmeta R Package
2 Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol. 1992;135(11):1301–1309