

Letter Regarding Article by Segá et al, "Prognostic Value of Ambulatory and Home Blood Pressures Compared With Office Blood Pressure in the General Population"

To the Editor:

We read with interest the paper by Segá et al regarding the prognostic value of ambulatory, home, and office blood pressure in the PAMELA population.¹ However, we find that the main conclusions of the report may be driven by the lack of adjustment for confounders. The relationships between level of blood pressure and risk were not adjusted for age, which may have a major influence on risk over a long time span. There is indeed a relation between age and blood pressure,² and therefore, these results may be biased. The comparisons of the various blood pressures were also not adjusted for potential confounders, with the argument that "no adjustment for age, sex, and other cardiovascular risk factors was made because comparisons between the predictive value of various blood pressure values involved the same sample." However, it has been shown in a general Belgian population that the within-subject differences between office and ambulatory blood pressure measurements increased with older age and greater body mass index.³ In addition, in the Danish MONICA population, the within-subject differences between office and ambulatory blood pressure measurements increased with older age, diagnosis of hypertension, male gender, and presence of diabetes.⁴ So, to assess the true prognostic value of office blood pressure versus that of ambulatory blood pressure, it is mandatory to explore whether adjustments for other relevant cardiovascular risk factors would change the results. Recently, it was shown in the Danish MONICA population that ambulatory blood pressure was a much better predictor of all-cause mortality and cardiovascular mortality than office blood pressure, taking other relevant risk factors into account.⁵

Accordingly, to make the results from previous studies comparable to the PAMELA study, we would like to know the results of adjusted analyses. Until that time, the conclusion that "office, home, and ambulatory blood pressures are similarly predictive of the risk of cardiovascular and all-cause death" needs to be interpreted with caution.

Tine Willum Hansen, MD

*Research Center for Prevention and Health
Copenhagen, Denmark
Department of Cardiology
Bispebjerg University Hospital
Copenhagen, Denmark*

**Jørgen Jeppesen, MD, DMSc
Hans Ibsen, MD, DMSc**

*Medical Department M
Glostrup University Hospital
Copenhagen, Denmark*

1. Segá R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation*. 2005;111:1777–1783.
2. Kannel WB. Historic perspectives on the relative contributions of diastolic and systolic blood pressure elevation to cardiovascular risk profile. *Am Heart J*. 1999;138:205–210.
3. Staessen J, O'Brien E, Atkins N, Bulpitt CJ, Cox J, Fagard R, O'Malley K, Thijs L, Amery A. The increase in blood pressure with age and body mass index is overestimated by conventional sphygmomanometry. *Am J Epidemiol*. 1992;136:450–459.
4. Rasmussen SL, Torp-Pedersen C, Borch-Johnsen K, Ibsen H. Normal values for ambulatory blood pressure and differences between casual

blood pressure and ambulatory blood pressure: results from a Danish population survey. *J Hypertens*. 1998;16:1415–1424.

5. Hansen TW, Jeppesen J, Rasmussen S, Ibsen H, Torp-Pedersen C. Ambulatory blood pressure and mortality: a population-based study. *Hypertension*. 2005;45:499–504.

To the Editor:

Segá and coworkers¹ recently replicated the work of other investigators.^{2,3} In Italians randomly recruited from the population of Monza and enrolled in the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study,¹ they confirmed that per mm Hg, the risk of all-cause and cardiovascular mortality increased more with systolic than diastolic blood pressure (BP), more with nighttime than daytime ambulatory BP, and more with home or ambulatory than conventional BP measurement.

While confirmatory, the report by Segá et al leaves many issues unaddressed. First, it deviates from current standards by not accounting for sex, age, and other cardiovascular risk factors. The authors argued that comparisons between the various types of BP measurement involved the same subjects and confounding factors; however, we previously demonstrated in 2 independent populations that the parameters of the relations between BP and age or body mass index significantly differed according to the type of BP measurement.⁴ Thus, in Cox regression, the relative hazard ratios associated with each type of BP measurement might be substantially different depending on the inclusion of other explanatory variables. For instance, in Belgian and Irish subjects, the within-subject differences between office and ambulatory blood pressure measurements increased with age and body mass index.⁴ Second, Segá et al presented the likelihood ratio test statistic only for comparisons of various combinations of systolic BP measurement in relation to cardiovascular mortality. They did not report these test statistics for comparisons between the different types of BP measurement, between daytime and nighttime BP, or between systolic and diastolic BP. Third, over the last decennium, the introduction of invasive therapies drastically reduced the case-fatality rate of major cardiovascular complications, in particular those related to the coronary complications of hypertension. The report by Segá et al spans 10.9 years of follow-up that ended on December 31, 2003. This probably explains why the 56 cardiovascular deaths only represented 30.1% of all-cause mortality.¹ Not accounting for nonfatal events is important for the generalization of the results of the study by Segá et al. Finally, in Figures 2, 3, and 4, Segá and coworkers duplicated the unadjusted results already presented in the continuous risk functions given in Figure 1. Because of the low number of cardiovascular deaths, the vertical scale of the Kaplan-Meier estimates only spanned 5%. Because these estimates remained unadjusted for confounders, they cannot be extrapolated to other populations with different age distribution or cardiovascular risk profiles.

**Eamon Dolan, MD
Eoin T. O'Brien, MD**
*Beaumont Hospital
Dublin, Ireland*

Jan A. Staessen, MD
*Hypertension Unit
University of Leuven
Leuven, Belgium*

1. Segá R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) Study. *Circulation*. 2005;111:1777–1783.

- Hansen TW, Jeppesen J, Rasmussen S, Ibsen H, Torp-Pedersen C. Ambulatory blood pressure and mortality: a population-based study. *Hypertension*. 2005;45:499–504.
- Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Den Hond E, McCormack P, Staessen JA, O'Brien E. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension*. 2005;46:156–161.
- Staessen J, O'Brien E, Atkins N, Bulpitt CJ, Cox J, Fagard R, O'Malley K, Thijs L, Amery A. The increase in blood pressure with age and body mass index is overestimated by conventional sphygmomanometry. *Am J Epidemiol*. 1992;136:450–459.

To the Editor:

Sega and colleagues¹ compared the prognostic value for mortality risk of home and ambulatory blood pressure (BP) measurement with office BP measurement in a Italian general population using 11-year follow-up data from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. They reported that the overall ability to predict death was not greater for home and ambulatory than for office BP measurement.

In a Japanese general population (the Ohasama study), we previously reported that the prognostic value of home and ambulatory BP measurement was superior to office BP measurement for mortality risk.^{2,3} More recently, using 10-year follow-up data, we have demonstrated that home and ambulatory BP measurement is also superior to office BP measurement in predicting the risk of stroke.^{4,5}

The mostly nonsignificant difference among predictive powers of the 3 methods of BP measurement in the PAMELA study¹ would be attributable to the smaller statistical power due to a smaller number of events (56 cardiovascular deaths¹) compared with the recent data of the Ohasama study (136 fatal and nonfatal stroke events⁴ and 152 composite events of cardiovascular death and nonfatal stroke⁵). The less remarkable predictive power of home BP in the study by Sega et al would also be attributable to the smaller number of home BP measurements in the PAMELA population (average of only 2 home BP values obtained in the morning and in the evening within a day) compared with that used in our Ohasama study (average of 21 home BP values), because we demonstrated that the predictive power of home BP measurement linearly increased with an increase in the number of home BP measurements taken.⁴ The authors' conclusions from the PAMELA study should be interpreted with caution, because their results might not be applicable to the predictive power of home BP obtained by multiple self-measurements. Comparison of the prognostic value of multiple self-measurements of home BP and ambulatory BP awaits further follow-up results from the Ohasama study.

Takayoshi Ohkubo, MD, PhD

*Department of Planning for Drug Development and Clinical Evaluation
Graduate School of Pharmaceutical Science
Tohoku University
Sendai, Japan*

Yutaka Imai, MD, PhD

*Department of Clinical Pharmacology and Therapeutics
Graduate School of Pharmaceutical Science and Medicine
Tohoku University
Sendai, Japan*

- Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) Study. *Circulation*. 2005;111:1777–1783.
- Ohkubo T, Imai Y, Tsuji I, Nagai K, Kato J, Kikuchi N, Nishiyama A, Aihara A, Sekino M, Kikuya M, Ito S, Satoh H, Hisamichi S. Home blood

pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. *J Hypertens*. 1998;16:971–975.

- Ohkubo T, Imai Y, Tsuji I, Nagai K, Watanabe N, Minami N, Itoh O, Bando T, Sakuma M, Fukao A, Satoh H, Hisamichi S, Abe K. Prediction of mortality by ambulatory blood pressure monitoring versus screening blood pressure measurements: a pilot study in Ohasama. *J Hypertens*. 1997;15:357–364.
- Ohkubo T, Asayama K, Kikuya M, Metoki H, Hoshi H, Hashimoto J, Totsune K, Satoh H, Imai Y. How many times should blood pressure be measured at home for better prediction of stroke risk? 10-year follow-up results from the Ohasama study. *J Hypertens*. 2004;22:1099–1104.
- Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Prognosis of “masked hypertension” and “white-coat” hypertension detected by 24-h ambulatory blood pressure monitoring: 10-year follow-up from the Ohasama study. *J Am Coll Cardiol*. 2005;46:508–515.

Response

We read with interest the letters commenting on the results of our study.¹ Our reply to the remarks are as follows.

Home blood pressure (BP). Our data do not disagree with the results of the Ohasama Study² on the clinical importance of home BP, because (1) the goodness-of-fit to the model predicting cardiovascular or all-cause mortality was, if anything, higher than that of office or 24-hour BP measurement; (2) this was the case even if only 2 home BP measurements were available, which did not allow us to fully explore the potentials of this approach; and (3) combining office with home BP values improved the predictive ability of the model.

Comparisons of statistical tests. The likelihood ratio test cannot be used to compare differences in the goodness of fit between different BPs. The question seems to us somewhat irrelevant, however, because the goodness-of-fit values were not lower for office than for ambulatory BP measurements,¹ which justifies our conclusion about the noninferiority of its prognostic importance.

Adjustment for “confounders.” We decided (see Methods) not to adjust for other variables because office, home, and ambulatory BPs were obtained at the same time in the same subjects, ie, we dealt with a within-sample comparison that did not require adjustments for differences that simply did not exist. Moreover, in general, we are against the habit of drawing conclusions based on extensive adjustment of original data because (1) this does not guarantee that the role played by factors other than that under study is eliminated, a goal that can be achieved, whenever possible, by recollection of data devoid of the previously observed differences, and (2) the statistical attempt to dissociate the role of factors that are intimately related can be biologically artificial and in some instances can distort the inherent features of the phenomenon under study, thus introducing rather than removing confounders. This applies to the increasing difference between office and ambulatory or home BP with aging (reported years ago in a PAMELA report³), which characterizes the overall relationships and behavior of these pressures and thus must not be arbitrarily corrected. The above does not exclude that other factors can differently modify the effects of office, home, or ambulatory blood pressure, eg, that gender, age, or blood glucose interacts with office values differently than it does with ambulatory values. It also does not mean that the conclusion reached for the whole population sample applies to all subsamples, eg, old versus young subjects, males versus females, hypertensive versus normotensive individuals; however, these are additional issues that we did not address, also because of the limited number of fatal events we could count on.

Novelty of data. It is somewhat contradictory to define the data as “confirmatory” and at the same time disagree with their conclusion. Our data confirm some previous results, often obtained, however, in selected groups of subjects, and none of

which had office, home, and ambulatory values all available. In addition, the evidence comes from a large population and a very long follow-up. Finally, much more than previous contributions, the results emphasize the prognostic importance of office BP and show the flatter slope of its relationship with events to be the clearest prognostic difference from the other pressures.

Roberto Sega, MD
Rita Facchetti, PhD
Michele Bombelli, MD
Giancarlo Cesana, MD
Giovanni Corrao, MD
Guido Grassi, MD
Giuseppe Mancia, MD

Clinica Medica
Dipartimento di Medicina Clinica
Prevenzione e Biotecnologie Sanitarie

Universita Milano-Bicocca
Ospedale San Gerardo
Monza, Italy

1. Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation*. 2005;111:1777–1783.
2. Ohkubo T, Imai Y, Tsuji I, Nagai K, Kato J, Kikuchi N, Nishiyama A, Aihara A, Sekino M, Kikuya M, Ito S, Satoh H, Hisamichi S. Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. *J Hypertens*. 1998;16:971–975.
3. Sega R, Cesana G, Milesi C, Grassi G, Zanchetti A, Mancia G. Ambulatory and home blood pressure normality in the elderly: data from the PAMELA population. *Hypertension*. 1997;30:1–6.