Pulse

Pulse 2014;2:42–51
DOI: 10.1159/000369192
Published online: November 21, 2014

2235–8676/14/0024–0042$39.50/0
www.karger.com/pls

Review

Risk Associated with Pulse Pressure on Out-of-Office Blood Pressure Measurement

Yu-Mei Gu[a] Lucas S. Aparicio[b] Yan-Ping Liu[a] Kei Asayama[a, c] Tine W. Hansen[d] Teemu J. Niiranen[e] José Boggia[f] Lutgarde Thijs[a] Jan A. Staessen[a, g]

[a]Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium; [b]Servicio de Clínica Médica, Sección Hipertensión Arterial, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [c]Tohoku University Graduate School of Pharmaceutical Science and Medicine, Sendai, Japan; [d]Steno Diabetes Center, Gentofte, Denmark; [e]Population Studies Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Turku, Finland; [f]Centro de Nefrología and Departamento de Fisiopatología, Hospital de Clínicas, Universidad de la República, Montevideo, Uruguay; [g]VitaK Research and Development, Maastricht University, Maastricht, The Netherlands

Key Words
Pulse pressure · Thresholds · Blood pressure measurement · Epidemiology · Cardiovascular diseases

Abstract
Background: Longitudinal studies have demonstrated that the risk of cardiovascular disease increases with pulse pressure (PP). However, PP remains an elusive cardiovascular risk factor with findings being inconsistent between studies. The 2013 ESH/ESC guideline proposed that PP is useful in stratification and suggested a threshold of 60 mm Hg, which is 10 mm Hg higher compared to that in the 2007 guideline; however, no justification for this increase was provided. ***Methodology:*** Published thresholds of PP are based on office blood pressure measurement and often on arbitrary categorical analyses. In the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) and the International Database on HOme blood pressure in relation to Cardiovascular Outcome (IDHOCO), we determined outcome-driven thresholds for PP based on ambulatory or home blood pressure measurement, respectively. ***Results:*** The main findings were that for people aged <60 years, PP did not refine risk stratification, whereas in older people the thresholds were 64 and 76 mm Hg for the ambulatory and home PP, respectively. However, PP provided little added predictive value over and beyond classical risk factors.

Jan A. Staessen, MD, PhD, Studies Coordinating Centre
Research Unit Hypertension and Cardiovascular Epidemiology
Department of Cardiovascular Sciences, University of Leuven
Kapucijnenvoer 35, Box 7001, BE–3000 Leuven (Belgium)
E-Mail jan.staessen@med.kuleuven.be

Introduction

Pulse pressure (PP), the difference between systolic and diastolic blood pressure, depends on left ventricular ejection, the elasticity of the central arteries, as well as on the timing and intensity of the backward wave originating at reflection sites in the peripheral circulation. PP widens in the elderly as with advancing age, systolic blood pressure continues to rise, whereas the age-related increase in diastolic blood pressure levels off or even reverses in the fifth decade of life [1].

PP as a Cardiovascular Risk Factor

Previous studies have shown that peripheral PP as measured by conventional sphygmomanometry is an independent risk factor in patients with hypertension [2–5], coronary heart disease [2] or severe renal dysfunction [6], or in different populations [7–12]. However, other studies [13–15] were contradictory in that cardiovascular risk was not associated with PP. Several limitations of previous studies likely contributed to these contradictory findings in the literature. They mostly used the office blood pressure measurement or only recorded fatal endpoints [6, 8, 10–14], or applied recruitment criteria confined to high-risk patients [2–6, 14], a narrow age range [8, 12] or elderly [5, 11], or reported that the association between outcome and PP was present only in diabetic [10] or treated hypertensive patients [4].

Studies in Patients

In the International Verapamil SR-Trandolapril Study (INVEST), Bangalore et al. [2] analyzed 22,576 hypertensive patients with coronary artery disease. The relation of the incidence and multivariable-adjusted hazard ratio (HR) for all-cause mortality, nonfatal myocardial infarction and nonfatal stroke with PP during follow-up was J- or U-shaped. When adjusted for baseline covariables, both the linear and quadratic terms of PP were significant ($p < 0.0001$) [2]. The nadir was at 54 mm Hg, with the 95% confidence interval (CI) derived by bootstrapping ranging from 42 to 60 mm Hg [2]. The relation of stroke with PP was linear [2].

Greenberg [4] analyzed 2,939 hypertensive patients aged 33–87 years enrolled in the Epidemiologic Follow-Up Study (NHEFS) of the First National Health and Nutrition Examination Survey (NHANES I). For cardiovascular mortality, the HRs associated with a 10-mm Hg increment in PP were 1.16 (95% CI, 1.08–1.25) and 1.12 (95% CI, 0.99–1.26) in treated and untreated hypertensive patients, respectively [4]. In the Systolic Hypertension in the Elderly Program (SHEP), Domanski et al. [5] demonstrated that with a 10-mm Hg increase in PP, the risk of all-cause mortality and that of fatal stroke increased by 16 and 11%, respectively.

Studies in Populations

In 2001, Framingham Heart Study, Franklin et al. [7] reported that with increasing age, there was a gradual shift from diastolic to systolic blood pressure and then to PP as predictors of coronary heart disease in the Framingham Heart Study. In 1989, Darne et al. [12] evaluated the risk associated with PP and mean arterial pressure, while addressing the colinearity between these two predictive variables. They used principal components analysis of systolic and diastolic blood pressure to generate a pulsatile and a steady component index of arterial pressure. The pulsatile component index was positively correlated with PP and the steady component index with mean arterial pressure; however, in statistical terms, the two new indices were completely unrelated. In 18,336 men and 9,351 women aged 40–69 years who

were followed for an average of 9.5 years, the investigators demonstrated that the steady component index of blood pressure was a strong predictor of all types of cardiovascular death in both sexes [12]. In contrast, the pulsatile component index was unrelated to prognosis in men, whereas in women it was positively and independently correlated with death from coronary heart disease and inversely correlated with stroke mortality [12]. However, the latter relations in women were based only on 15 deaths from myocardial infarction and on 22 deaths from stroke [12].

Along similar lines, Benetos et al. [8] recruited 19,083 French men aged 40–69 years at baseline and followed them for 19.5 years. A wide PP was an independent and significant predictor of all-cause mortality (odds ratio for a 10-mm Hg increase in younger participants vs. older participants, 1.28 vs. 1.19; $p < 0.05$), total cardiovascular mortality (1.36 vs. 1.24; $p < 0.05$), and especially coronary mortality (1.40 vs. 1.20; $p < 0.05$) [8]. In 1981, the National Institute on Aging initiated its epidemiologic studies of elderly people [11]. Glynn et al. [11] followed 9,431 participants aged 65–102 years for 10.6 years. In a sex- and age-adjusted survival analysis [11], both elevated systolic blood pressure >160 mm Hg and low diastolic blood pressure <70 mm Hg independently predicted total mortality [relative risk, 1.39 (95% CI, 1.26–1.53) for systolic and 1.27 (95% CI, 1.16–1.38) for diastolic blood pressure] and cardiovascular mortality [1.59 (95% CI, 1.39–1.81) for systolic and 1.38 (95% CI, 1.22–1.55) for diastolic blood pressure; $p < 0.001$]. PP was strongly correlated with systolic blood pressure ($r = 0.82$) [11], confirming the issue of colinearity introduced by Darne et al. [12]. Glynn et al. [11] reported that PP was a slightly stronger predictor of both total mortality [relative risk, 1.34 (95% CI, 1.23–1.46)] and cardiovascular mortality [1.57 (95% CI, 1.39–1.77)]. In contrast, in Japanese population studies, PP was only a weak predictor of stroke [16, 17] and did not predict myocardial infarction [18].

Risk Associated with Out-of-Office PP

International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes

To define outcome-driven thresholds for ambulatory PP, we did a subject-level meta-analysis of 9,938 patients recruited from 11 populations and enrolled in the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) [19]. Due to the results from the Framingham Heart Study [20] and the lower age boundary in several randomized clinical trials on antihypertensive treatment in the elderly [21], we stratified our analyses by 60 years of age. Exploratory analyses demonstrated that the association of endpoints with 24-hour PP was not always log-linear. To account for this nonlinear association, we applied the deviation from mean coding to compute HRs in deciles of the 24-hour PP distribution. This approach expresses the risk in each decile relative to the overall risk in the whole study population and allows computing 95% CIs for the HRs in all deciles without the definition of an arbitrary reference group. HRs relating endpoints to mean arterial pressure expressed the risk associated with a 1-SD increase in the level. We applied the generalized R^2 statistic to assess the risks additionally explained by 24-hour PP over and beyond mean arterial pressure and other covariables. In an attempt to refine the level of PP that was associated with a significantly increased risk, we performed a stepwise analysis. We calculated HRs for 1-mm Hg increments in PP for thresholds ranging from the 10th to the 90th percentile. These HRs expressed the risk in participants whose PP exceeded the cutoff point versus the average risk. We plotted these HRs and their 95% CIs versus the increasing cutoff points with the goal to determine at which level the lower confidence limit of the HRs crossed unity.

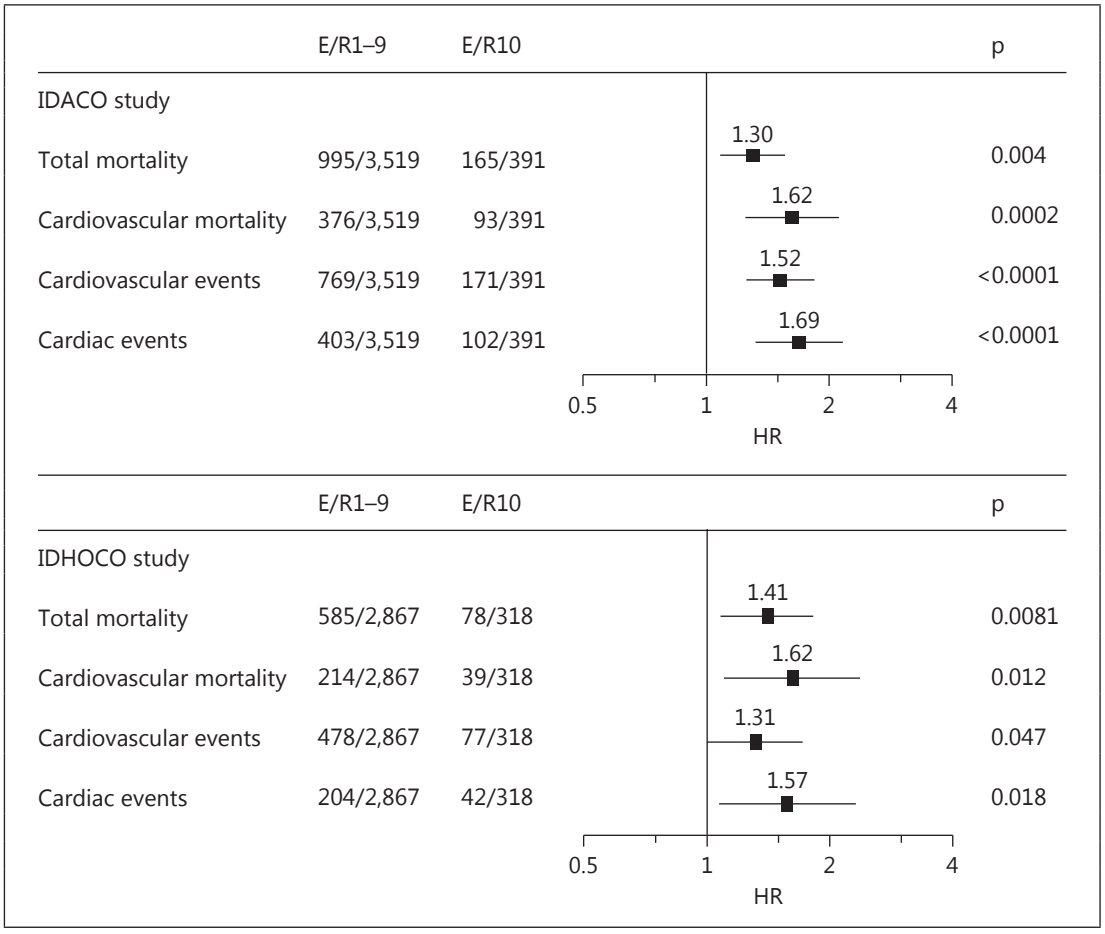

Fig. 1. Multivariable-adjusted HRs for outcomes in relation to 24-hour PP in the IDACO study (**a**) and to home PP in the IDHOCO study (**b**). The HRs, presented with 95% CIs, express the risk in the top decile compared with the average risk in the participants. All models were adjusted for cohort, sex, age, mean arterial pressure and pulse rate, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease and diabetes, and antihypertensive drug treatment. The p values are for the risk in the top decile relative to the overall risk in the whole study population. E/R1–9 = Number of events and participants at risk below the 90th percentile of the PP distribution. E/R10 = Number of events and participants at risk in the top decile, respectively. Reproduced with permission from Gu et al. [19] and Aparicio et al. [22].

In the 6,028 younger participants (<60 years), the median follow-up was 12.1 years. Over 68,853 person-years, 228 participants died and 221 experienced a fatal or nonfatal cardiovascular complication. Only in the highest decile of the PP distribution (threshold, ≥55.6 mm Hg; mean, 60.1 mm Hg) the risk of the composite cardiovascular endpoint was elevated [HR, 1.58 (95% CI, 1.11–2.25); p = 0.011] with a similar trend for cardiac endpoints [HR, 1.52 (95% CI, 0.99–2.33); p = 0.056]. Otherwise, the risks across deciles of the PP distribution did not deviate from the average risk (p ≥ 0.058). For stroke, Cox models across deciles of the PP distribution did not converge because of the low number of events (n = 63). While calculating the thresholds of 24-hour PP levels that stepwise increased by 1 mm Hg from the 10th to the 90th percentile, for all endpoints under study, the lower boundary of the 95% CIs of the successive HRs did not cross unity.

In the 3,910 older participants (≥60 years), the median follow-up was 10.7 years. Over 39,923 person-years, 1,160 participants died and 940 experienced a fatal or nonfatal cardio-

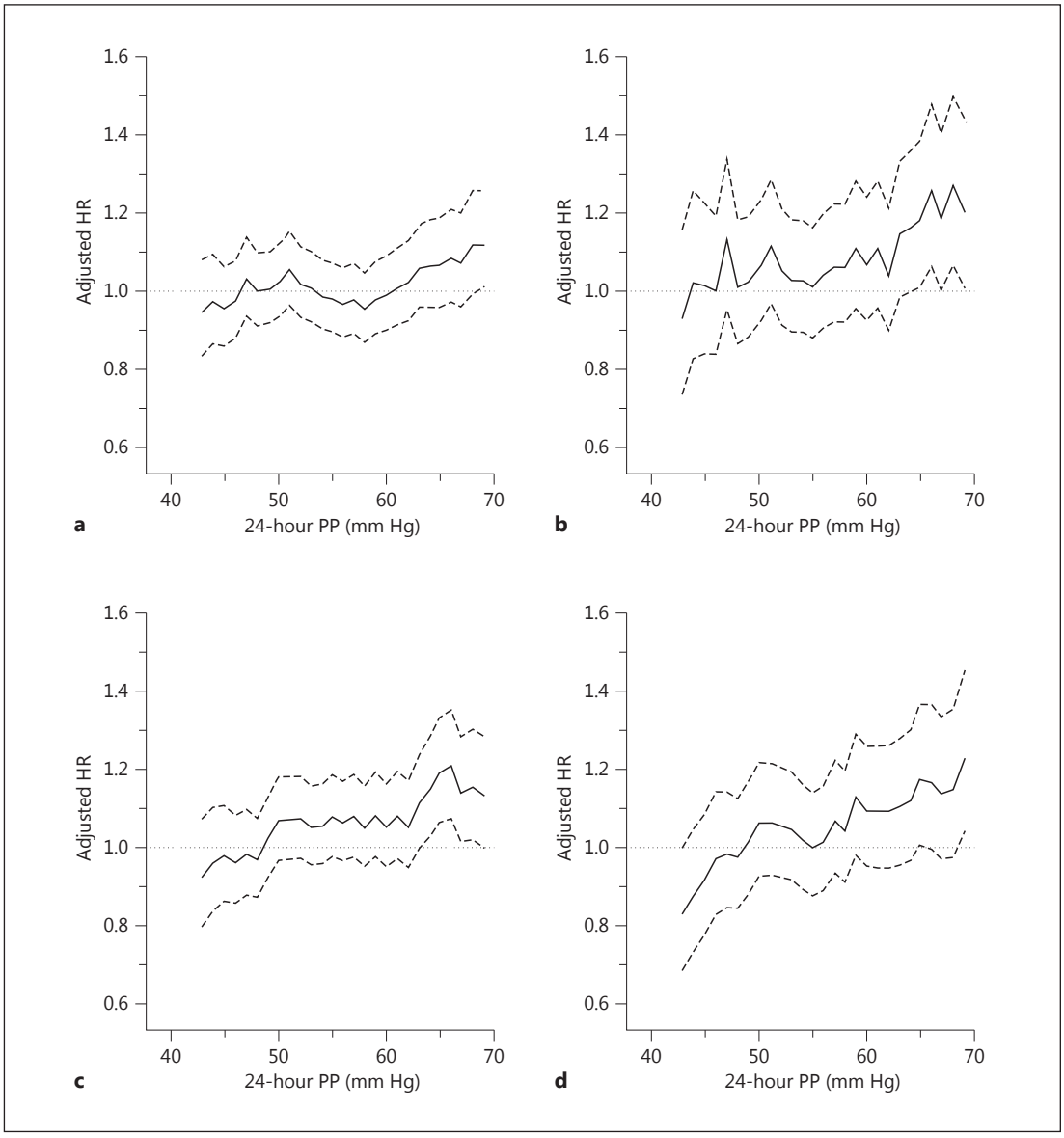

Fig. 2. HRs according to 24-hour PP levels ranging from the 10th to the 90th percentile in 3,910 older participants. HRs for all-cause (**a**) and cardiovascular (**b**) mortality as well as for cardiovascular (**c**) and cardiac (**d**) events express the risk at each level of PP compared with the average risk. Solid and dotted lines denote the point estimates and the 95% CIs, respectively. The HRs were adjusted as in figure 1. Reproduced with permission from Gu et al. [19].

vascular complication. The risk of any death, cardiovascular mortality, a composite cardiovascular endpoint, or a cardiac event was consistently elevated in the top decile of the PP distribution (threshold, ≥68.8 mm Hg; mean, 76.1 mm Hg; fig. 1). The HRs were 1.30 for all-cause mortality, 1.62 for cardiovascular mortality, 1.52 for a composite cardiovascular endpoint, and 1.69 for a cardiac event (fig. 1). The HR for stroke in the top decile of the PP distribution was 1.40 ($p = 0.028$). Otherwise, the risks across the deciles of the PP distribution did not deviate from the average risk. The R^2 statistic for adding a design variable coding for the top decile of the 24-hour PP distribution to Cox models including all other covariables was

Table 1. Characteristics of 24-hour PP by age group and blood pressure status

Characteristic	Normotension	White-coat hypertension	Masked hypertension	Sustained hypertension
<60 years (n = 6,028)				
Participants	4,189 (69.5)	430 (7.1)	605 (10.1)	804 (13.3)
24-hour PP, mm Hg	44.8±5.9	47.2±5.8	50.0±8.8	51.8±8.8
≥60 years (n = 3,910)				
Participants	1,403 (35.9)	655 (16.7)	481 (12.3)	1,371 (35.1)
24-hour PP, mm Hg	48.6±6.4	51.3±6.3	58.6±9.0	62.7±10.7
PP level ≥64 mm Hg	16 (0.41)	15 (0.38)	112 (2.86)	562 (14.4)

Values are presented as n (%) or mean ± SD. Conventional hypertension was defined as a conventional blood pressure of ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic). Ambulatory hypertension was defined as a 24-hour blood pressure level of ≥130 mm Hg (systolic) or ≥80 mm Hg (diastolic). Normotension and sustained hypertension were consistently normal or elevated blood pressure levels on both conventional and ambulatory measurements. White-coat hypertension was conventional hypertesion in the presence of a normal ambulatory blood pressure. Masked hypertension was ambulatory hypertesion in the presence of a normal conventional blood pressure. In participants aged <60 years, the analyses did not identify a risk-conferring threshold; in older participants the risk of all-cause mortality increased significantly at a PP level of ≥64 mm Hg. All between-group differences in PP characteristics according to blood pressure status were significant ($p \leq 0.05$).

0.10% for total and 0.12% for cardiovascular mortality, and 0.27, 0.21, and 0.09% for the composite cardiovascular endpoint, all cardiac events, and stroke, respectively. For most endpoints under study (fig. 2), with the exception of stroke, the lower boundary of the 95% CIs of the successive HRs crossed the reference line at levels ranging from 64 mm Hg (composite cardiovascular endpoint) to 69 mm Hg (total mortality and cardiac events).

Table 1 shows the prevalence of normotension, white-coat hypertension, masked hypertension, and sustained hypertension among younger (<60 years) and older (≥60 years) participants. In addition, table 1 shows that there were significant differences in PP according to the cross-classification based on conventional (≥140/90 mm Hg) and 24-hour ambulatory blood pressure (≥130/80 mm Hg). The prognostic value of these differences in PP remains to be established. Indeed, the prevalence of a PP >64 mm Hg only exceeded 10% in patients with sustained hypertension (table 1).

International Database on Home Blood Pressure in Relation to Cardiovascular Outcome

We analyzed the International Database on HOme blood pressure in relation to Cardiovascular Outcome (IDHOCO) data [22] following the same methods as described above for the IDACO study. In the 3,285 younger subjects, the median follow-up was 8.3 years. Over 32,671 person-years of follow-up, 149 participants died and 161 experienced a fatal or nonfatal cardiovascular complication. The cause of death was cardiovascular in 41 participants. The association between outcome and PP did not deviate significantly from log-linearity ($p \geq 0.092$). Table 2 shows the standardized HRs associated with home mean blood pressure and home PP. When adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, home pulse rate, history of cardiovascular disease, diabetes mellitus, and antihypertensive treatment, the home PP significantly predicted all outcomes, except for fatal and nonfatal stroke. After further adjustment for mean arterial pressure, PP only predicted all-cause and cardiovascular mortality (table 2). The low number of events precluded an analysis by the deciles of the PP distribution in the younger participants.

Table 2. Standardized HRs relating outcomes to home PP by age group

	Age <60 years			Age ≥60 years		
	events, n	mean blood pressure	PP	events, n	mean blood pressure	PP
Mortality						
All causes						
A	149	1.24 (1.01–1.51)*	1.28 (1.08–1.52)**	663	1.04 (0.95–1.13)	1.14 (1.05–1.25)**
FA		1.08 (0.86–1.37)	1.24 (1.01–1.51)*		0.96 (0.86–1.06)	1.17 (1.06–1.30)**
Cardiovascular						
A	41	1.44 (0.98–2.10)	1.56 (1.15–2.11)**	253	1.08 (0.94–1.24)	1.22 (1.07–1.40)**
FA		1.15 (0.75–1.77)	1.47 (1.03–2.10)*		0.96 (0.82–1.14)	1.25 (1.06–1.47)**
Fatal plus nonfatal events						
All cardiovascular						
A	161	1.50 (1.24–1.80)****	1.34 (1.15–1.56)****	555	1.26 (1.15–1.38)****	1.25 (1.14–1.36)****
FA		1.35 (1.09–1.68)**	1.18 (0.98–1.41)		1.18 (1.06–1.32)**	1.14 (1.02–1.27)*
Cardiac						
A	90	1.66 (1.31–2.10)****	1.38 (1.15–1.66)***	246	1.01 (0.88–1.16)	1.12 (0.98–1.27)
FA		1.50 (1.12–2.00)**	1.15 (0.92–1.45)		0.91 (0.77–1.09)	1.18 (1.00–1.39)
Coronary						
A	76	1.54 (1.20–2.00)***	1.26 (1.03–1.55)*	175	1.03 (0.87–1.21)	1.15 (0.99–1.34)
FA		1.49 (1.08–2.06)*	1.05 (0.81–1.35)		0.90 (0.73–1.11)	1.22 (1.00–1.49)*
Stroke						
A	73	1.25 (0.94–1.68)	1.31 (1.01–1.71)*	320	1.51 (1.34–1.70)****	1.37 (1.21–1.56)****
FA		1.13 (0.82–1.56)	1.25 (0.94–1.68)		1.42 (1.23–1.63)****	1.14 (0.98–1.32)

HRs, presented with 95% CIs, express the risk associated with a 1-SD increase in mean home blood pressure (11.7 and 11.2 mm Hg in subjects aged <60 years and ≥60 years, respectively) or a 1-SD increase in home PP (8.8 and 13.4 mm Hg, respectively). All models were stratified for cohort and adjusted for sex, age, body mass index, smoking and drinking, serum cholesterol, home pulse rate, diabetes mellitus, history of cardiovascular disease, and antihypertensive treatment. Adjusted models (A) include either the mean blood pressure or PP, while fully adjusted models (FA) include both mean blood pressure and PP in addition to the aforementioned covariates. Significance of the HRs: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$. Reproduced with permission from Gu et al. [19].

In the 3,185 older subjects, the median follow-up was 8.2 years (5th–95th percentile interval, 7.2–16.8 years). Over 26,655 person-years of follow-up, 663 participants died and 555 experienced a fatal or nonfatal cardiovascular complication. The cause of death was cardiovascular in 253 participants. Considering fully adjusted models, the home PP predicted all of the endpoints ($p \leq 0.044$), except for fatal combined with nonfatal cardiac events ($p = 0.052$) and stroke ($p = 0.083$). The generalized R^2 statistics for adding home PP as the predictor of outcome over and beyond mean arterial pressure was ≤0.20%.

Figure 1 shows the multivariable-adjusted HRs for outcomes in the top decile of the distribution of home PP versus the average risk in all of the elderly subjects. The HRs reached statistical significance in the upper decile for total mortality, cardiovascular mortality, all cardiovascular events, all cardiac events, and all coronary events. The risk of stroke in the upper decile did not exceed the average risk among all elderly. PP in the 9th and top deciles of the distribution of home PP averaged 71.3 mm Hg (range, 67.8–75.9 mm Hg) and 84.9 mm Hg (range, 76.0–125.8 mm Hg), respectively.

Interpretation

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [23] proposed that PP is only marginally stronger than systolic blood pressure for risk stratification in individuals aged ≥60 years, and that for those aged <60 years, PP is not predictive. According to the 2007 European guideline [24], PP is a derived measure, which combines the imprecision of the original systolic and diastolic mea-

surements. This guideline stated that, although levels of 50–55 mm Hg have been suggested, no practical cutoff values separating PP normality from abnormality are available. The 2013 European guideline [25] increased this threshold to 60 mm Hg without providing any justification. The IDACO analyses [19] established that for people aged <60 years, a 24-hour PP level of about 60 mm Hg might be associated with increased risk, but that a safe threshold could not be established. Among the elderly participants, a 24-hour PP of about 76 mm Hg was definitely associated with higher risk, and levels <64 mm Hg were probably safe. Using intra-arterial monitoring, Khattar et al. [26] observed that survival rates were highest among individuals aged <60 years, if the 24-hour PP was <70, and lowest among elderly patients with a 24-hour PP of ≥70 mm Hg. To our knowledge, Khattar et al.'s [26] report is the only other study proposing an outcome-driven threshold for 24-hour PP. However, this article does not include any justification as to why 70 mm Hg was chosen as the threshold in a dichotomized analysis. The results were based on an unadjusted Kaplan-Meier survival function analysis, and the study population consisted of patients with essential hypertension, in whom treatment had been withdrawn for 8 weeks [26]. All other proposals for PP thresholds relied on conventional blood pressure measurements. In analyses adjusted but not stratified for age, 2 studies [3, 9] derived a threshold from the 66th percentile of the PP distribution. Madhavan et al. [3] proposed a threshold of 63 mm Hg based on the incidence of myocardial infarction in 2,207 hypertensive patients aged 55 years, and Borghi et al. [9] suggested a threshold of 67 mm Hg based on the incidence of cardiovascular disease among 2,939 Italian patients (aged 14–84 years). Asmar et al. [27] derived a threshold of 65 mm Hg from the mean PP plus 2 SDs in 61,724 French patients (aged 16–90 years). The IDHOCO analyses [22] established that, for patients aged <60 years, total and cardiovascular mortality were log-linearly associated with home PP, but that due to the small number of events, no outcome-driven threshold could be established. In the elderly, home PP predicted all endpoints with the exception of stroke, but the refinement of prognostication over and beyond traditional risk factors and the steady component of blood pressure was small. Among elderly, the threshold delineating an increased risk of death is around 68 mm Hg, and for fatal combined with nonfatal cardiovascular events it is 76 mm Hg.

Conclusions

After review of the available literature, we did a subject-level meta-analysis to derive outcome-driven thresholds for PP based on 24-hour ambulatory monitoring or self-reported blood pressure measured at home. All results are generalizable because they originate from 14 randomly recruited population samples, representing 13 countries and 3 continents. For subjects aged <60 years, irrespective of the measurement method, PP did not add to risk stratification. However, for those aged ≥60 years, higher PP conferred an increased cardiovascular risk. However, while accounting for all covariables, a PP in the top decile of the distribution contributed <0.3% to the overall risk among the elderly. The proposed thresholds are ≥70 mm Hg for 24-hour PP and 76 mm Hg for home PP. These observations could inform guidelines and be of help to clinicians in diagnosing and managing patients.

Acknowledgments

The European Union (HEALTH-2011.2.4.2-2-EU-MASCARA, HEALTH-F7-305507 HOMAGE and the European Research Council Advanced Researcher Grant 2011-294713-EPLORE), the Fonds voor Wetenschappelijk Onderzoek Vlaanderen, Ministry of the Flemish Community, Brussels, Belgium (G.0881.13 and G.0880.13), and the International Zinc and Lead Research Organization currently support the Studies Coordinating Centre in Leuven, Belgium.

Disclosure Statement

The authors have no conflicts of interest to declare.

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