ORIGINAL RESEARCH

Twenty-Four-Hour Central Pulse Pressure for Cardiovascular Events Prediction in a Low-Cardiovascular-Risk Population: Results From the Bordeaux Cohort

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***Background*—**Central blood pressure (BP) is a promising marker to identify subjects with higher cardiovascular risk than expected by traditional risk factors. Significant results have been obtained in populations with high cardiovascular risk, but little is known about low-cardiovascular-risk patients, although the differences between central and peripheral BP (amplification) are usually greater in this population. The study aim was to evaluate central BP over 24 hours for cardiovascular event prediction in hypertensive subjects with low cardiovascular risk.

***Methods and Results*—**Peripheral and central BPs were recorded during clinical visits and over 24 hours in hypertensive patients with low cardiovascular risk (Systematic Coronary Risk Evaluation ≤5%). Our primary end point is the occurrence of a cardiovascular event during follow-up. To assess the potential interest in central pulse pressure over 24 hours, we performed Cox proportional hazard models analysis and comparison of area under the curves using the contrast test for peripheral and central BP. A cohort of 703 hypertensive subjects from Bordeaux were included. After the first 24 hours of BP measurement, the subjects were then followed up for an average of 112.5±70 months. We recorded 65 cardiovascular events during follow-up. Amplification was found to be significantly associated with cardiovascular events when added to peripheral 24-hour pulse pressure (P=0.0259). The area under the curve of 24-hour central pulse pressure is significantly more important than area under the curve of office BP (P=0.0296), and there is a trend of superiority with the area under the curve of peripheral 24-hour pulse pressure.

***Conclusions*—**Central pulse pressure over 24 hours improves the prediction of cardiovascular events for hypertensive patients with low cardiovascular risk compared to peripheral pulse pressure. **(*J Am Heart Assoc*. 2018;7:e008225. DOI: 10.1161/JAHA.117.008225.)**

Key Words: aortic pressure wave form • cardiovascular disease prevention • hypertension • pulse pressure

High blood pressure (BP) is the principal modifiable cardiovascular risk, and its prevalence increases with age.[1] Because a large proportion of the general population is affected by high BP, a desirable goal is to focus on prevention strategies in subjects most at risk of cardiovascular events. To this end, improvement of BP measurement has been identified as a priority.[2] Although office BP measurements are still useful, the superiority of ambulatory BP measurements over office measurements in cardiovascular prognosis has been shown,[3] and today ambulatory BP measurements serve as the reference for diagnosis of hypertension and assessment of BP phenotypes.[4-6] Central aortic BP is yet another interesting hemodynamic parameter, as it incorporates several components such as arterial stiffness (a determinant of aorta-to-peripheral pulse pressure amplification), location of reflecting sites, and the level of peripheral vascular resistance.

In essence, central BP measurements could be the ideal tool to assess cardiovascular risk.[7] A certain number of studies investigating subjects at high cardiovascular risk substantiate this argument[8-10]; however, data on subjects with low cardiovascular risk are less documented. Because BP amplification reduces with age and vascular aging,[11] the

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Clinical Perspective

What Is New?

- Central pulse pressure monitoring over 24 hours improves cardiovascular event prediction in the low-cardiovascular-risk hypertensive population.
- Monitoring central pulse pressure over 24 hours is easily feasible in clinical practice.

What Are the Clinical Implications?

- Central pulse pressure over 24 hours is helpful to identify young hypertensive patients with low cardiovascular risk who are in fact at risk of facing a cardiovascular event.
- It could then modify our medical strategies and encourage us to pay closer attention to these patients.

prognostic value of central BP is likely to be greater in young subjects with low cardiovascular risk, who are found to have the largest difference between central and peripheral pressure measurements. Our study therefore aimed to investigate if 24-hour monitoring of central BP in a young hypertensive population with a low cardiovascular risk (SCORE [Systematic Coronary Risk Evaluation] ≤5%) provides a more accurate assessment of cardiovascular risk than 24-hour monitoring of peripheral BP.

Materials and Methods

Study Population

The study population consists of a cohort of hypertensive subjects in Bordeaux, a prospective monocentric registry, which includes all patients who have been referred to our center for essential hypertension management before being initiated on any antihypertensive treatment.

We limited our study sample to subjects with low cardiovascular risk (SCORE≤5%), as they are supposed to have a healthier arterial network and thus a more significant difference in BP between peripheral and central sites. Subjects should have a BP recorded over 24 hours coupled with the monitoring of timing of Korotkoff sounds (QKD), either at entry into the cohort, before any treatment, or during treatment follow-up. The first available record during the 24 hours is therefore considered as the starting point of the follow-up.

We excluded patients with atrial fibrillation or a thyroid dysfunction from our study because these are the limits of the QKD measurements.

Methods

The data, analytic methods, and study materials will be made available from the corresponding author to other researchers for purposes of reproducing the results or replicating the procedure on reasonable request.

Assessing Cardiovascular Risk Using the SCORE Model

The 10-year prediction of the occurrence of a fatal cardiovascular event is calculated using the SCORE, which is based on age, sex, systolic BP measured during an office visit, smoker status, and total cholesterol. The results of subjects diagnosed with diabetes mellitus were multiplied 2-fold for men and 4-fold for women.

Smokers are defined as active smokers or as former smokers who quit smoking less than 3 years before the study. Dyslipidemia in subjects is defined by a level of total cholesterol greater than 5.2 mmol/L or the use of statin treatments. Type 2 diabetes mellitus is defined by fasting blood glucose greater than 7 mmol/L or antidiabetic treatment intake.

BP Measurements

Office BP Measurements. Office BP measurements were carried out according to the European Society of Hypertension/European Society of Cardiology guidelines[12] by a trained nurse assigned to the hypertension unit or by a cardiologist in the unit. The subject was first made to sit down and rest for at least 5 minutes before the measurement. Three consecutive measurements with a mercury sphygmomanometer were taken and then averaged to obtain both systolic and diastolic BP. This measurement was done just before setting up the ambulatory BP monitoring.

Ambulatory BP Measurements. A DIASYS Integra II® monitor (Novacor®, Rueil-Malmaison, France) was used to measure peripheral BP. This involved an auscultatory method graded A/B by the British society of Hypertension.[13] BP was automatically measured and recorded every 15 minutes during daytime and nighttime. Only records with more than 50% of the measurements were validated and included in the study. We therefore were able to collect a minimum of 48 measurements, which largely meets the European Society of Cardiology quality criteria (14 daytime and 7 nighttime recordings).[14]

Measurements of Central BP. Central systolic BP measurements were obtained using the same measuring device and were based on the same 24-hour recordings as peripheral pressure measurements. The central systolic BP estimate was based on mean BP, arterial stiffness (QKD interval), heart rate, and height of subject. This technique was validated using invasive and noninvasive methods and through the dynamic fluctuations in BP induced by head-up tilt.[15,16]

The 24-hour peripheral pulse pressure (PP) is the difference between 24-hour peripheral systolic BP and 24-hour peripheral diastolic BP recorded.

The 24-hour central PP is the difference between 24-hour central systolic BP and 24-hour and peripheral diastolic BP.

Amplification is the difference between 24-hour peripheral systolic BP and 24-hour central systolic BP.

The PP ratio, another way to estimate amplification,[17] is calculated as the ratio of peripheral 24-hour PP to central 24-hour PP.

Follow-up and Cardiovascular Events. Information related to cardiovascular events was collected through regular contact with patients. The patients were contacted either during the follow-up visits in the health center or by telephone. Contact by telephone was systematically carried out every 2 years on average by a dedicated staff member (eg, the research coordinator). In case of an event of interest, the medical team thereafter verified the reported events based on the patients' medical files from the general practitioner and from hospitalization or operative reports. Recorded cardiovascular events included cardiovascular death, acute coronary syndromes with or without ST elevation, and ischemic or hemorrhagic cerebral strokes confirmed by cerebral computed tomography scan or magnetic resonance imaging. In the case of death, the cause was determined by the medical team using data collected from hospital records or by contacting the patient's general practitioner.

Ethical Considerations

Patients had to give their consent to participate in the study before being listed in the registry. The registry was thereafter approved by our local committee of ethics and protection for the individual (Committee for Protection of Persons in the South-West and Overseas III).

Statistical Analyses

The principal characteristics of patients were presented in a descriptive manner, with useful variables extracted for the calculation of the SCORE result.

We then built a Kaplan-Meier curve for time to event to illustrate the survival of the population sample.

We carried out survival analysis using a proportional-hazards model to evaluate the interest of PP in its different patterns (office, peripheral, and central over 24-hours) to predict future cardiovascular events. These 3 main variables are continuous, and we therefore verified their log-linearity. The time axis is represented by the follow-up period starting from the date of the first 24-hour BP measurement.

In a first step, analysis for each variable of interest was done in a univariate way and in a second step adjusted with age, sex, total cholesterol, and smoker status.

Then, to study the potential added value of the central BP parameters, we first built model 1, adding amplification to peripheral PP, and then model 2, adding PP ratio to peripheral PP adjusted for age, sex, dyslipidemia, and smoking status. The proportional-hazards assumption was verified by the Schoenfeld residuals for the selected variables.

Finally, we plotted receiver operating characteristic curves for PP measurements obtained during clinic visits, 24-hour peripheral PP, and 24-hour central PP. We then compared the areas under the curve (AUC) using the contrast test with the office peripheral PP measurement as reference.

The statistical threshold (α) is set to 5% without adjustment for multiplicity. The software SAS 9.4 (SAS Institute, Cary, NC) was used to carry out the analyses.

Results

A total of 703 subjects from the Bordeaux Hypertensive Cohort met the study inclusion criteria, having a SCORE result $\leq$5% (Table 1). The study sample comprised equal numbers of men and women, with a mean age of 51.5 ($\pm$13.6) years. From the first 24-hour BP measurement, the subjects were followed up for 112.5 ($\pm$70) months on average; 65 cardiovascular events were recorded over the course of the follow-up period including 4 deaths, 27 strokes, and 34 coronary

Table 1. Main Characteristics of Subjects, Bordeaux Hypertensive Cohort, N=703

	Mean (SD) or Proportion
Age, y	51.5 (13.6)
Male	49.8
BMI	25.6 (4.0)
SBP	151.0 (16.1)
DBP	92.5 (10.8)
24-h SBP	128.6 (15.0)
Amplification	4.9 (5.8)
24-h PP	44.0 (10.9)
Dyslipidemia	116 (16.5)
Smoker	110 (15.6)
Diabetes mellitus	0

Amplification in millimeters of mercury; dyslipidemia was defined by a cholesterol level greater than 5.2 mmol/L or a hypolipidemic treatment; smokers are defined as active smokers or as former smokers who quit smoking less than 3 years before the study; diabetic mellitus was defined by a level of fasting blood glucose greater than 7 mmol/L or the intake of antidiabetic treatment (oral treatment or insulin). BMI indicates body mass index; DBP, diastolic blood pressure (mm Hg); PP, pulse pressure (mm Hg); SBP, systolic blood pressure (mm Hg).

Table 2. Description of the Occurrence of a Cardiovascular Event, Bordeaux Hypertensive Cohort, N=703

	Cardiovascular Death	Stroke (Ischemic or Hemorrhagic)	Acute Coronary Syndrome or Revascularization	Total
N	4	27	34	65

syndromes (Table 2). The Kaplan-Meier curve illustrates the survival of our population sample (Figure 1).

In the univariate analysis, PP is associated with the outcome however it was measured. Hazard ratio (HR) increases from office PP (HR=1.023; confidence interval [CI] 1.004-1.041; *P*=0.0166) to 24-hour peripheral PP (HR=1.047; CI 1.026-1.069; *P*<0.001) and to 24-hour central PP (HR =1.071; CI 1.043-1.100; *P*<0.0001) (Table 3). After multiple adjustments, we confirm the previous observations (Table 4) (for office PP: HR=1.016; CI 0.996-1.037, *P*=0.1239, for peripheral 24-hour PP: HR=1.033; CI 1.011-1.056; *P*=0.0033, for central 24-hour PP: HR=1.062; CI 1.031-1.094; *P*<0.0001) (Table 4).

When amplification is added to peripheral 24-hour PP in the multivariate model (model 1), for every 1–mm Hg increase of amplification, the risk of a cardiovascular event is observed to decrease by 9%. This result is statistically significant with a *P*-value of 0.0032 (Table 4). With PP ratio instead of amplification (model 2), we note the same kind of result with a significant decrease of the HR to face a cardiovascular event (*P*=0.056) (Table 4).

During the secondary analysis based on the receiver operating characteristic curve, the AUC for prediction of cardiovascular events is observed to increase between office peripheral PP and 24-hour PP curves, and with a maximum AUC observed for 24-hour central PP (Figure 2). This observed increase between 24-hour central PP and office peripheral PP is statistically significant (*P*=0.0296). On the other hand, the upward trend observed of the AUC between the 24-hour peripheral and central PP is not significant (Table 5).

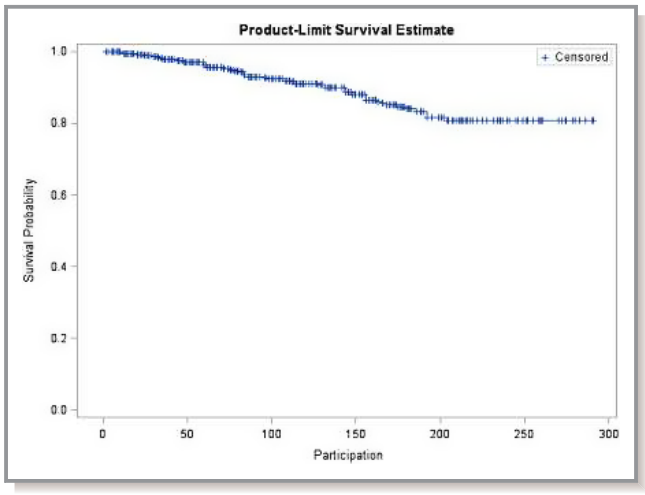

Figure 1. Kaplan-Meier survival curve; n=705, events=65.

Discussion

So far, a few studies about added value of central BP have been conducted on hypertensive subjects with medium to low cardiovascular risk. The Australian National Blood Pressure study is a randomized controlled trial studying elderly female hypertensive subjects (65-84 years) and compares 2 antihypertensive medications (diuretic or angiotension-converting enzyme inhibitor).[18] In this study, central BP measurements were carried out by applanation tonometry of the right common carotid using the SphygmoCor® (AtCor Medical, Sydney, Australia) device. Among 484 women with an average age of 72 years, 53 cardiovascular events were recorded. The key central parameters measured did not differ between women with and without a recorded cardiovascular event. On the other hand, peripheral measurements differed, with systolic BP and PP statistically greater in the subjects who had experienced a cardiovascular event (*P*<0.01 and *P*<0.001, respectively). Elderly female subjects are known to have the smallest pressure difference between the peripheral and aortic arteries (because of the age, sex, and height).[11] Thus, they were probably not the best population for studying the potential benefit of the central BP versus the peripheral BP.

The BP guide study is another randomized study that tests the hypothesis that knowledge of central BP will help provide better treatment for hypertensive patients at medium to low cardiovascular risk.[19] Consequently, 286 hypertensive subjects an average of 64 years of age were randomly assigned to 2 groups—a conventional control group with adjustment of treatment depending on existing knowledge (eg, out-of-office BP measurement, left ventricular hypertrophy) and an interventional group with an extra measurement of central BP in addition to the information provided for the control group. During the 12-month follow-up, it was shown that the use of central BP measurements significantly reduced the amount of antihypertensive treatments and improved quality of life while maintaining the same objectives as PP measurements.

Some authors examined the surrogate markers in hypertensive subjects with low cardiovascular risk. The first cross-sectional study subsequently included 153 hypertensive patients without any treatment.[19] Only 23 subjects were found to have high central BP according to the reference values established by Herbert et al.[11] These subjects had an inferior S-wave velocity across the mitral valve (*P*=0.05) and a greater proportion of glomerular filtration flow <60 mL/min (*P*=0.0125) compared with subjects with normal central pressure. There are, however, some limitations in this study,

Table 3. Cox Analysis: Results From the Univariate and Multivariate Analyses of Risk of Cardiovascular Events According to 24-Hour Pulse Pressure, N=703, Events=65

	Univariate Analysis			Multivariate Analysis		
Variable	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Office peripheral PP	1.023	1.004 to 1.041	0.0166	1.016	0.996 to 1.037	0.1239
24-h peripheral PP	1.047	1.026 to 1.069	<0.0001	1.033	1.011 to 1.056	0.0033
24-h central PP	1.071	1.043 to 1.100	<0.0001	1.062	1.031 to 1.094	<0.0001

Adjustment variables are sex, age, dyslipidemia, and smoking status. CI indicates confidence interval; HR, hazard ratio; PP, pulse pressure.

in particular the small sample size and the absence of longitudinal follow-up. Despite these limitations, the study raises questions about this low-risk population.

A recent work studied 208 hypertensive patients aged 57±12 years, 34% women. Office (mean of 4 measurements) and 24-hour central and peripheral BP were measured by the oscillometric Mobil-O-Graph device (I.E.M. GmbH, Stolberg, Germany).[20] Peripheral systolic or pulse pressures were associated with left ventricular hypertrophy, arterial stiffness, and renal abnormalities after multiple adjustments, but central BP was not. However, the small sample size and the cross-sectional design are 2 major limits that should attenuate this study's conclusions.

With a cohort of 703 hypertensive subjects and a mean follow-up of 10 years, our study is the first to offer a long enough follow-up to present data on the occurrence of hard clinical end points in a low-risk population.

Nevertheless, justifying the contribution of a new cardiovascular risk marker in the domain of hypertension is always difficult. In essence, the majority of cardiovascular risk markers are strongly interconnected, and this interconnection is evident between peripheral and central BP. The choice of selecting hypertensive patients with a SCORE of <5% as an inclusion criterion was taken on the ground that studying a homogeneous sample of patients might allow limiting the number of variables in statistical analysis and thereby improve the chance to show a different predictive value of central versus peripheral PP. Moreover, splitting central BP as peripheral PP and amplification limits the risk of overadjustment bias.[21] As a second step, the comparison of AUC for the 3 levels of PP supports the findings from the survival analysis.

Clinical implications include identifying hypertensive patients with a high risk of a cardiovascular event, which is an important goal. Apart from the question of the BP threshold, there is the question of what component of BP we have to measure. Vascular aging is a process that makes our BP components evolve through our lifetime.[20]

BP and arterial stiffness are known to be 2 major components of central BP, and both have been shown to be predictive of cardiovascular events. BP and arterial stiffness increase with aging with the consequences of a reduced amplification and an increase in BP variability. It explains that the best markers of cardiovascular events may change with aging: central BP for young patients and possibly BP variability for older patients.[22,23] Our work supports the interest of monitoring central BP for hypertensive patients with low cardiovascular risk.

Table 4. Cox Analysis: Results From the Multivariate Analyses of Risk of Cardiovascular Events According to 24-Hour Pulse Pressure and Amplification (Model 1) or Pulse Pressure Ratio (Model 2) After Adjustment for Age, Sex, Dyslipidemia, and Smoking Status, N=703, Events=65

Variable	HR	95% CI	*P* Value
Model 1			
Peripheral 24-h PP	1.067	1.035 to 1.100	<0.0001
Amplification	0.912	0.858 to 0.970	0.0032
Model 2			
Peripheral 24-h PP	1.054	1.027 to 1.081	<0.0001
PP ratio	0.038	0.004 to 0.385	0.0056

Amplification is peripheral 24-hour PP minus central 24-hour PP; PP ratio is peripheral 24-hour PP/central 24-hour PP. CI indicates confidence interval; HR, hazard ratio; PP, pulse pressure.

Limitations

Our technique to measure central BP is not considered as the gold standard even if it has been developed and validated in different population samples against invasive central BP[15] and against noninvasive "gold standard": the SphymoCor®.[16] With a mean 24-hour amplification of 5 mm Hg in a population with average age of 50 years (4 mm Hg for women and 6 mm Hg for men), our results are consistent with the reference values established recently.[11] Indeed, the expected amplification at this age is about 6 mm Hg for women and 9 mm Hg for men based on office pressure measurements, whereas our method is based on 24-hour BP measurements, which could smooth the results.

A SCORE result ≤5% determined which subjects were included in the study sample. However, the study sample was

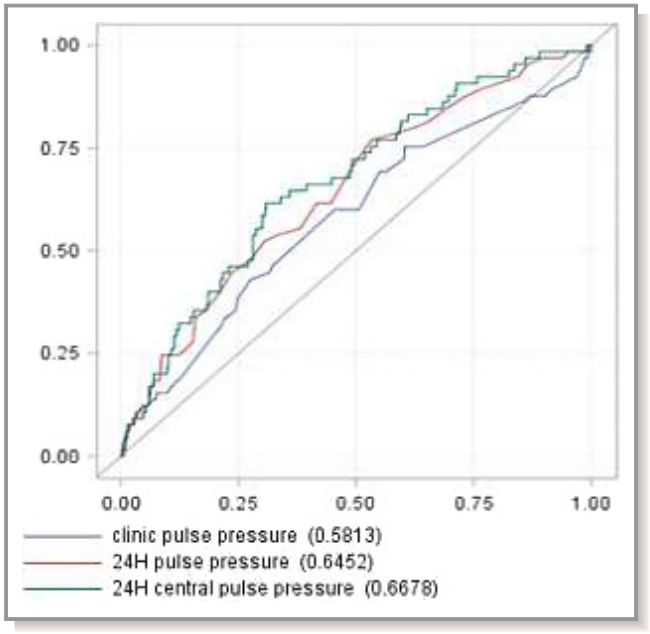

Figure 2. Receiver operating characteristic curve for each pulse pressure component with its respective area under the curve (AUC). 24H indicates 24-hour.

somewhat heterogeneous, as a proportion of the subjects did not undergo ambulatory BP monitoring at the time of hypertension diagnosis, and as a result, the antihypertensive treatments received from the time of diagnosis to the ambulatory BP monitoring may have modified our findings. With this taken into consideration, a longitudinal follow-up approach was put into practice starting from the first ambulatory BP measurement and therefore does not question the statistical analysis. On the other hand, the proportion of subjects treated for hypertension underestimates a priori the strength of the study and consequently does not cast doubt on the results.

The improvement of the prediction by using the central PP rather than the peripheral PP remains modest. Regardless of the comparison of AUC, the improvement is not significant between central and peripheral PP even if there is a positive trend. Our study sample has a low cardiovascular risk, and so a long follow-up is required to collect cardiovascular events.

Table 5. Comparison of AUC by the Contrast Test With Office Peripheral Pulse Pressure as Reference (AUC=0.5813), N=703

Contrast	β	95% CI	*P* Value
24 h-peripheral PP (AUC=0.6452)	0.064	−0.014 to 0.142	0.1093
24 h-central PP (AUC=0.6678)	0.087	0.008 to 0.164	0.0296

Data show results from the Bordeaux hypertensive cohort, AUC indicates area under the curve; CI, confidence interval; PP, pulse pressure.

However, the observation of a larger AUC from the office to 24 hours of central PP favors the interest in measuring central BP, which must be confirmed by other studies.

Conclusion and Perspectives

Central PP over 24 hours improves the cardiovascular prognosis prediction compared with peripheral PP (both office and 24 hours) in hypertensive subjects with low cardiovascular risk.

Because this population represents a large majority of hypertensive patients, it could help to identify patients with a higher risk of cardiovascular complications.

If these results are supported by further research, we could open the door for interventional trials to investigate central BP thresholds in this population of interest.

Disclosures

None.

References

1. Forouzanfar MH, Alexander L, Anderson HR, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the global burden of disease study 2013. *Lancet*. 2015;386:2287–2323.
2. Blacher J, Levy BI, Mourad JJ, Safar ME, Bakris G. From epidemiological transition to modern cardiovascular epidemiology: hypertension in the 21st century. *Lancet*. 2016;388:530–532.
3. Clement DL, De Buyzere ML, De Bacquer DA, de Leeuw PW, Duprez DA, Fagard RH, Gheeraert PJ, Missault LH, Braun JJ, Six RO, Van Der Niepen P, O'Brien E. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med*. 2003;348:2407–2415.
4. Boggia J, Li Y, Thijs L, Hansen TW, Kikuya M, Bjorklund-Bodegard K, Richart T, Ohkubo T, Kuznetsova T, Torp-Pedersen C, Lind L, Ibsen H, Imai Y, Wang J, Sandoya E, O'Brien E, Staessen JA. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. *Lancet*. 2007;370:1219–1229.
5. Roush GC, Fagard RH, Salles GF, Pierdomenico SD, Reboldi G, Verdecchia P, Eguchi K, Kario K, Hoshide S, Polonia J, de la Sierra A, Hermida RC, Dolan E, Zamalloa H. Prognostic impact from clinic, daytime, and night-time systolic blood pressure in nine cohorts of 13,844 patients with hypertension. *J Hypertens*. 2014;32:2332–2340; discussion 2340.
6. Palatini P, Reboldi G, Beilin LJ, Casiglia E, Eguchi K, Imai Y, Kario K, Ohkubo T, Pierdomenico SD, Schwartz JE, Wing L, Verdecchia P. Added predictive value of night-time blood pressure variability for cardiovascular events and mortality: the ambulatory blood pressure-international study. *Hypertension*. 2014;64:487–493.
7. McEniery CM, Cockcroft JR, Roman MJ, Franklin SS, Wilkinson IB. Central blood pressure: current evidence and clinical importance. *Eur Heart J*. 2014;35:1719–1725.
8. Safar ME, Blacher J, Pannier B, Guerin AP, Marchais SJ, Guyonvarc'h PM, London GM. Central pulse pressure and mortality in end-stage renal disease. *Hypertension*. 2002;39:735–738.
9. Roman MJ, Devereux RB, Kizer JR, Lee ET, Galloway JM, Ali T, Umans JG, Howard BV. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the strong heart study. *Hypertension*. 2007;50:197–203.
10. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *Eur Heart J*. 2010;31:1865–1871.
11. Herbert A, Cruickshank JK, Laurent S, Boutouyrie P. Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk factors. *Eur Heart J*. 2014;35:3122–3133.

12. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1281–1357.
13. O'Brien E, Waeber B, Parati G, Staessen J, Myers MG. Blood pressure measuring devices: recommendations of the European Society of Hypertension. *BMJ*. 2001;322:531–536.
14. O'Brien E, Asmar R, Beilin L, Imai Y, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. *J Hypertens*. 2005;23:697–701.
15. Cremer A, Butlin M, Codjo L, Coulon P, Ranouil X, Joret C, Coste P, Asmar R, Avolio A, Gosse P. Determination of central blood pressure by a noninvasive method (brachial BP and QKD interval). *J Hypertens*. 2012;30:1533–1539.
16. Cremer A, Codjo L, Butlin M, Papaioannou G, Yeim S, Jan E, Kiat H, Avolio A, Gosse P. Determination of central blood pressure by a noninvasive method (brachial blood pressure and QKD interval): a noninvasive validation. *J Hypertens*. 2013;31:1847–1852.
17. Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. *J Physiol*. 2000;525(Pt 1):263–270.
18. Dart AM, Gatzka CD, Kingwell BA, Willson K, Cameron JD, Liang YL, Berry KL, Wing LM, Reid CM, Ryan P, Beilin LJ, Jennings GL, Johnston CI, McNeil JJ, Macdonald GJ, Morgan TO, West MJ. Brachial blood pressure but not carotid arterial waveforms predict cardiovascular events in elderly female hypertensives. *Hypertension*. 2006;47:785–790.
19. Sharman JE, Marwick TH, Gilroy D, Otahal P, Abhayaratna WP, Stowasser M. Randomized trial of guiding hypertension management using central aortic blood pressure compared with best-practice care: principal findings of the BP guide study. *Hypertension*. 2013;62:1138–1145.
20. Wilkinson IB, Franklin SS, Hall IR, Tyrrell S, Cockcroft JR. Pressure amplification explains why pulse pressure is unrelated to risk in young subjects. *Hypertension*. 2001;38:1461–1466.
21. Wu YT, Fratiglioni L, Matthews FE, Lobo A, Breteler MM, Skoog I, Brayne C. Dementia in Western Europe: epidemiological evidence and implications for policy making. *Lancet Neurol*. 2016;15:116–124.
22. Schillaci G, Pucci G, Parati G. Blood pressure variability: an additional target for antihypertensive treatment? *Hypertension*. 2011;58:133–135.
23. Parati G, Ochoa JE, Bilo G. Blood pressure variability, cardiovascular risk, and risk for renal disease progression. *Curr Hypertens Rep*. 2012;14:421–431.