

Double Product Reflects the Predictive Power of Systolic Pressure in the General Population: Evidence from 9,937 Participants

Rudolph Schutte,^{1,2} Lutgarde Thijs,¹ Kei Asayama,^{1,3} José Boggia,⁵ Yan Li,^{6,7} Tine W. Hansen,⁸ Yan-Ping Liu,¹ Masahiro Kikuya,³ Kristina Björklund-Bodegård,⁹ Takayoshi Ohkubo,^{3,4} Jørgen Jeppesen,¹⁰ Christian Torp-Pedersen,¹⁰ Eamon Dolan,¹¹ Tatiana Kuznetsova,^{1,14} Katarzyna Stolarz-Skrzypek,¹² Valérie Tikhonoff,¹³ Sofia Malyutina,¹⁴ Edoardo Casiglia,¹³ Yuri Nikitin,¹⁴ Lars Lind,⁹ Edgardo Sandoya,¹⁵ Kalina Kawecka-Jaszcz,¹² Jan Filipovský,¹⁶ Yutaka Imai,³ Jiguang Wang,⁶ Hans Ibsen,¹⁷ Eoin O'Brien,¹⁸ Jan A. Staessen,^{1,19} and on behalf of the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) Investigators

BACKGROUND

The double product (DP), consisting of the systolic blood pressure (SBP) multiplied by the pulse rate (PR), is an index of myocardial oxygen consumption, but its prognostic value in the general population remains unknown.

METHODS

We recorded health outcomes in 9,937 subjects (median age, 53.2 years; 47.3% women) randomly recruited from 11 populations and enrolled in the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) study. We obtained the SBP, PR, and DP for these subjects as determined through 24-hour ambulatory monitoring.

RESULTS

Over a median period of 11.0 years, 1,388 of the 9,937 study subjects died, of whom 536 and 794, respectively, died of cardiovascular (CV) and non-CV causes, and a further 1,161, 658, 494, and 465 subjects, respectively, experienced a CV, cardiac, coronary, or cerebrovascular

event. In multivariate-adjusted Cox models, not including SBP and PR, DP predicted total, CV, and non-CV mortality (standardized hazard ratio [HR], ≥ 1.10 ; $P \leq 0.02$), and all CV, cardiac, coronary, and stroke events (HR, ≥ 1.21 ; $P < 0.0001$). For CV mortality (HR, 1.34 vs. 1.30; $P = 0.71$) and coronary events (1.28 vs. 1.21; $P = 0.26$), SBP and the DP were equally predictive. As compared with DP, SBP was a stronger predictor of all CV events (1.39 vs. 1.27; $P = 0.002$) and stroke (1.61 vs. 1.36; $P < 0.0001$), and a slightly stronger predictor of cardiac events (1.32 vs. 1.22; $P = 0.06$). In fully adjusted models, including both SBP and PR, the predictive value of DP disappeared for fatal endpoints ($P \geq 0.07$), coronary events ($P = 0.06$), and stroke ($P = 0.12$), or DP was even inversely associated with the risk of all CV and cardiac events (both $P \leq 0.01$).

CONCLUSION

In the general population, we did not observe DP to add to risk stratification over and beyond SBP and PR.

Keywords: blood pressure; double product; systolic blood pressure; cardiovascular risk; hypertension; general population.

Correspondence: Jan A. Staessen (jan.staessen@med.kuleuven.be).

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¹Department of Cardiovascular Sciences, Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, University of Leuven, Leuven, Belgium; ²Department of Physiology, Hypertension in Africa Research Team (HART), North-West University, Potchefstroom, South Africa; ³Tohoku University Graduate School of Pharmaceutical Sciences, Sendai, Japan; ⁴Department of Health Science, Shiga University of Medical Science, Otsu, Japan; ⁵Centro de Nefrología and Departamento de Fisiopatología, Hospital de Clínicas, Universidad de la República, Montevideo, Uruguay; ⁶Center for Epidemiological Studies and Clinical Trials, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; ⁷Center for Vascular Evaluation, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; ⁸Research Center for Prevention and Health and the Steno

Diabetes Center, Gentofte, Denmark; ⁹Section of Geriatrics, Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden; ¹⁰Copenhagen University Hospital, Copenhagen, Denmark; ¹¹Cambridge University Hospitals, Addenbrook's Hospital, Cambridge, United Kingdom; ¹²First Department of Cardiology and Hypertension, Jagiellonian University Medical College, Kraków, Poland; ¹³Department of Clinical and Experimental Medicine, University of Padova, Padova, Italy; ¹⁴Institute of Internal Medicine, Novosibirsk, Russian Federation; ¹⁵Department of Cardiology, Asociación Española Primera de Socorros Mutuos, Montevideo, Uruguay; ¹⁶Faculty of Medicine, Charles University, Pilsen, Czech Republic; ¹⁷Aarhus University and Division of Cardiology, Holbak Hospital, Holbak, Denmark; ¹⁸Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland; ¹⁹Department of Epidemiology, Maastricht University, Maastricht, The Netherlands.

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An increased systolic blood pressure (SBP)^{1,2} and pulse rate (PR)^{3,4} are predictors of death and disability in the general population. The double product (DP), the product of SBP and PR, is an index of myocardial oxygen consumption.^{5,6} The DP was previously used during exercise testing in patients with coronary heart disease,^{5,6} in whom an attenuated increase in this index in response to exercise predicted cardiovascular (CV) mortality.^{7,8} Because of the positive predictive value of both SBP and PR in the general population, we assumed that the DP might be useful in stratification for CV risk.^{9–13} Preliminary findings in the Ohasama study¹³ suggested that the DP derived from self-measured home blood pressure (BP) was a more precise predictor of mortality than were the constituents of the product. However, the question remained of whether the DP is merely a mathematical entity or whether it does indeed outperform both SBP and PR in predicting the risk of CV mortality. We addressed this question in a study of 9,937 participants randomly recruited from 11 populations and enrolled in the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) study. We derived the DP for these individuals from 24-hour ambulatory BP recordings.

METHODS

Study population

At the time of writing of this paper, the IDACO database¹⁴ included 11 population cohorts and 12,148 randomly recruited participants for whom data were available on conventional and ambulatory BP. We excluded 2,211 participants because they were younger than 18 years of age ($n = 303$) or because they had fewer than 10 daytime or 5 nighttime BP readings ($n = 1,908$). Thus, the total number of subjects included in the present analysis was 9,937. For details, see the section on Supplementary Expanded Methods, which is available on-line at <http://ajh.oxfordjournals.org>.

The study complied with all applicable requirements of international regulations, and in particular with the Helsinki declaration of 1975 (as revised in 1983) for the investigation of human participants. The locally appointed ethics committee of each institution participating in the preparation of the study approved the study, and informed consent was obtained from each subject.

Blood-pressure measurement

Methods used for conventional and ambulatory BP measurement are described in detail in the Supplementary Expanded Methods available on-line. Hypertension was defined as a 24-hour ambulatory SBP of at least 130 mm Hg or diastolic BP (DBP) of at least 80 mm Hg or the use of antihypertensive drugs.¹⁵ The DP was the product of the 24-hour SBP and the 24-hour PR. We restricted our analysis to SBP because in middle-aged and older adults it is the predominant risk factor for coronary heart disease (CHD).¹⁶

Other measurements

We used the questionnaires originally administered to each of the study cohorts in the IDACO study to obtain information about each participant's medical history and smoking and drinking habits. Body mass index (BMI) was defined as body weight in kilograms divided by height in meters squared. We measured levels of serum cholesterol and blood glucose with automated enzymatic methods. Diabetes mellitus was defined as the use of antidiabetic drugs, a fasting blood glucose concentration of at least 7.0 mmol/l, a random blood glucose concentration of at least 11.1 mmol/l, a self-reported diagnosis of diabetes, or diabetes documented in practice or in hospital records.¹⁷

Ascertainment of events

We ascertained vital status and the incidence of fatal and nonfatal diseases from the appropriate sources in each country of origin of the population cohorts in the IDACO study, as described in previous publications.^{18–20} Fatal and nonfatal stroke did not include transient ischemic attacks. Coronary events encompassed death from ischemic heart disease, sudden death, nonfatal myocardial infarction, and coronary revascularization. Cardiac events comprised coronary endpoints and fatal and nonfatal heart failure. The composite CV endpoint included all of the endpoints named here plus CV mortality. In all outcome analyses we considered only the first event.

Statistical analysis

For database management and statistical analysis, we used SAS software version 9.1.3 (SAS Institute, Cary, NC). For comparison of means and proportions, we applied the large-sample z-test and the chi-squared statistic, respectively. In exploratory analyses we plotted incidence rates by quartiles of the distributions of SBP, PR, and DP, while standardizing by the direct method for cohort, sex and age (≤ 40 , 40–60, and ≥ 60 years). We used Kaplan–Meier survival function estimates and used the log-rank test to compare incidence rates across cohort- and sex-specific quartiles of SBP, PR, and DP. We applied Cox regression to compute standardized hazard ratios (HRs), which express the risk for an increase of one standard deviation (SD) in the independent variables. The predictive value of the DP, in addition to SBP and PR, was assessed by adding the term for the interaction between SBP and PR to a model already containing the composing terms. We checked the proportional hazards assumption with the Kolmogorov-type supremum test, as implemented in the PROC PHREG procedure of the SAS package. The HRs were adjusted for cohort, sex, age, BMI, smoking and drinking, serum cholesterol, diabetes mellitus, history of CV disease, and treatment with antihypertensive drugs. To adjust for cohort, we pooled participants recruited in the framework of the European Project on Genes in Hypertension (Kraków, Novosibirsk, Padova, and Pilsen). We tested heterogeneity in the HRs across subgroups by introducing the appropriate interaction term in the Cox model. We compared the HRs for SBP, PR, and DP through use of the Wald test as implemented in the TEST statement

of the PROC PHREG procedure of the SAS software. Lastly, we plotted the 10-year risk of all-cause mortality, non-CV mortality, CV mortality, and composite CV endpoints in relation to the SBP and PR.

RESULTS

Baseline characteristics

The study population consisted of 6,622 Europeans (66.6%), 1,877 Asians (18.9%), and 1,438 South Americans (14.5%). The 9,937 participants included 4,702 women (47.3%). Hypertension was present in 4,459 participants (44.9%), and 1,946 (19.6%) were taking antihypertensive drugs. At enrollment, 2,788 participants (28.3%) were smokers and 4,759 (52.2%) reported intake of alcohol. Conventionally measured SBP averaged (\pm SD) 130.2 ± 20.3 mm Hg and conventionally measured DBP averaged 79.4 ± 11.5 mm Hg,

and the average 24-hour ambulatory SBP and DBP were 123.5 ± 14.0 mm Hg and 73.6 ± 8.4 mm Hg, respectively. As shown in Table 1, the baseline characteristics of the study subjects were significantly different across cohort- and sex-specific quartiles of the DP with the exception of drinking (P for trend = 0.43) and a history of CV disease (P for trend = 0.16). The cohort- and sex-specific quartiles of the DP are shown in Supplementary Table S1, available online.

Incidence of events

The median follow-up of the entire study population was 11.0 years (5th–95th percentile interval, 2.5–18.1 years). Across cohorts, the median follow-up ranged from 2.5 years (5th to 95th percentile interval, 2.3–2.6 years) in JingNing to 17.6 years (16.4–18.2 years) in Dublin. During 108,758 person-years of follow-up, 1,388 participants died (12.8

Table 1. Baseline characteristics of study participants

Characteristic	Quartiles of double product			
	Low	Medium-Low	Medium-High	High
Number (%) with characteristic				
All subjects in category	2,484	2,485	2,484	2,484
European	1,655 (66.6)	1,656 (66.6)	1,655 (66.6)	1,656 (66.7)
Asian	469 (18.9)	470 (18.9)	469 (18.9)	469 (18.9)
South American	360 (14.5)	359 (14.4)	360 (14.5)	359 (14.5)
Women	1,175 (47.3)	1,175 (47.3)	1,176 (47.3)	1,175 (47.3)
Antihypertensive treatment	444 (17.9)	400 (16.1)	464 (18.7)	637 (25.6)
Smokers	568 (22.9)	624 (25.1)	725 (29.2)	871 (35.1)
Using alcohol	1,170 (47.1)	1,201 (48.3)	1,198 (48.2)	1,193 (48.0)
Diabetes mellitus	104 (4.2)	137 (5.5)	166 (6.7)	251 (10.1)
History of cardiovascular disease	193 (7.8)	174 (7.0)	187 (7.5)	236 (9.5)
Mean \pm SD of characteristic				
Age, years	51.5 \pm 16.1	51.8 \pm 15.7	52.9 \pm 15.7	54.7 \pm 15.4
Body mass index, kg/m ²	24.5 \pm 3.6	25.1 \pm 4.1	25.5 \pm 4.2	26.3 \pm 4.6
Conventional blood pressure, mm Hg				
Systolic	122.7 \pm 18.3	126.1 \pm 17.7	131.4 \pm 19.0	140.7 \pm 21.4
Diastolic	74.6 \pm 9.9	77.7 \pm 10.2	80.4 \pm 10.7	85.0 \pm 12.5
24-hour ambulatory measurements				
Systolic, mm Hg	114.3 \pm 10.1	119.6 \pm 10.2	124.9 \pm 11.3	135.2 \pm 14.6
Diastolic, mm Hg	67.8 \pm 5.9	71.5 \pm 6.2	74.8 \pm 6.9	80.4 \pm 8.6
Pulse rate, bpm	63.6 \pm 6.5	70.2 \pm 6.2	74.3 \pm 6.5	80.5 \pm 7.8
Double product, mm Hg•bpm	7,230 \pm 574	8,348 \pm 386	9,220 \pm 451	10,822 \pm 1131
Blood glucose, mg/dl	90.6 \pm 18.9	93.2 \pm 24.1	94.8 \pm 24.7	98.4 \pm 29.9
Serum cholesterol, mg/dl	213.5 \pm 45.2	215.1 \pm 44.4	217.8 \pm 44.4	220.5 \pm 45.2

Baseline characteristics of participants by cohort and sex-specific quartiles of the 24-hour double product. All linear trends were significant ($P < 0.0001$) except for drinking ($P = 0.43$) and a history of cardiovascular disease ($P = 0.16$). Because quartiles were cohort- and sex-specific, the proportions of Europeans, Asians, and South Americans, and of women and men, were similar across quartiles. To convert cholesterol and glucose from mg/dl to mmol/l, multiply by 0.0259 and 0.0555, respectively.

per 1,000 person-years) and 1,161 experienced a fatal or nonfatal CV complication (11.0 per 1,000 person-years). Mortality included 536 CV and 794 non-CV deaths, 40 deaths of unknown cause, and 18 deaths from renal failure. Considering cause-specific CV events, the incidences of fatal and nonfatal stroke were 86 and 379, respectively. Cardiac events consisted of 86 fatal and 217 nonfatal cases of acute myocardial infarction, 77 deaths from ischemic heart disease, 12 sudden deaths, 29 fatal and 170 nonfatal cases of heart failure, and 67 cases of surgical or percutaneous coronary revascularization.

Exploratory analyses

In exploratory analyses, we plotted death (Figure 1A-C) and event (Figure 1D-F) rates standardized for cohort, sex, and age across quartiles of SBP, PR, and DP (Figure 1). Total ($P < 0.0001$), CV ($P < 0.0001$), and non-CV ($P = 0.0006$) mortality increased with an increased DP. Total mortality also increased with an increased SBP and PR ($P < 0.0001$).

Cardiovascular mortality ($P < 0.0001$), but not non-CV mortality ($P = 0.10$), increased with an increased SBP. Conversely, non-CV mortality ($P = 0.0007$), but not CV mortality ($P = 0.10$), increased with an increased PR. Similarly, all CV, cardiac, and stroke events increased with an increased DP ($P < 0.0001$). These associations were driven by SBP ($P < 0.0001$), and not by PR, which was not associated with all CV ($P = 0.43$), cardiac ($P = 0.22$), or stroke ($P = 0.14$) events. We obtained similar findings by plotting Kaplan-Meier survival function estimates (Supplementary Figure S1) for total mortality and the composite CV endpoints by cohort- and sex-specific quartiles of SBP, PR, and DP. Values of P of the corresponding log-rank tests were significant ($P < 0.0001$), with the exception of that for PR ($P \geq 0.09$).

Mortality

Systolic blood pressure, PR, and DP fulfilled the proportional hazard assumption ($P \geq 0.09$), with the exception of SBP ($P = 0.005$) and PR ($P = 0.05$) in relation to

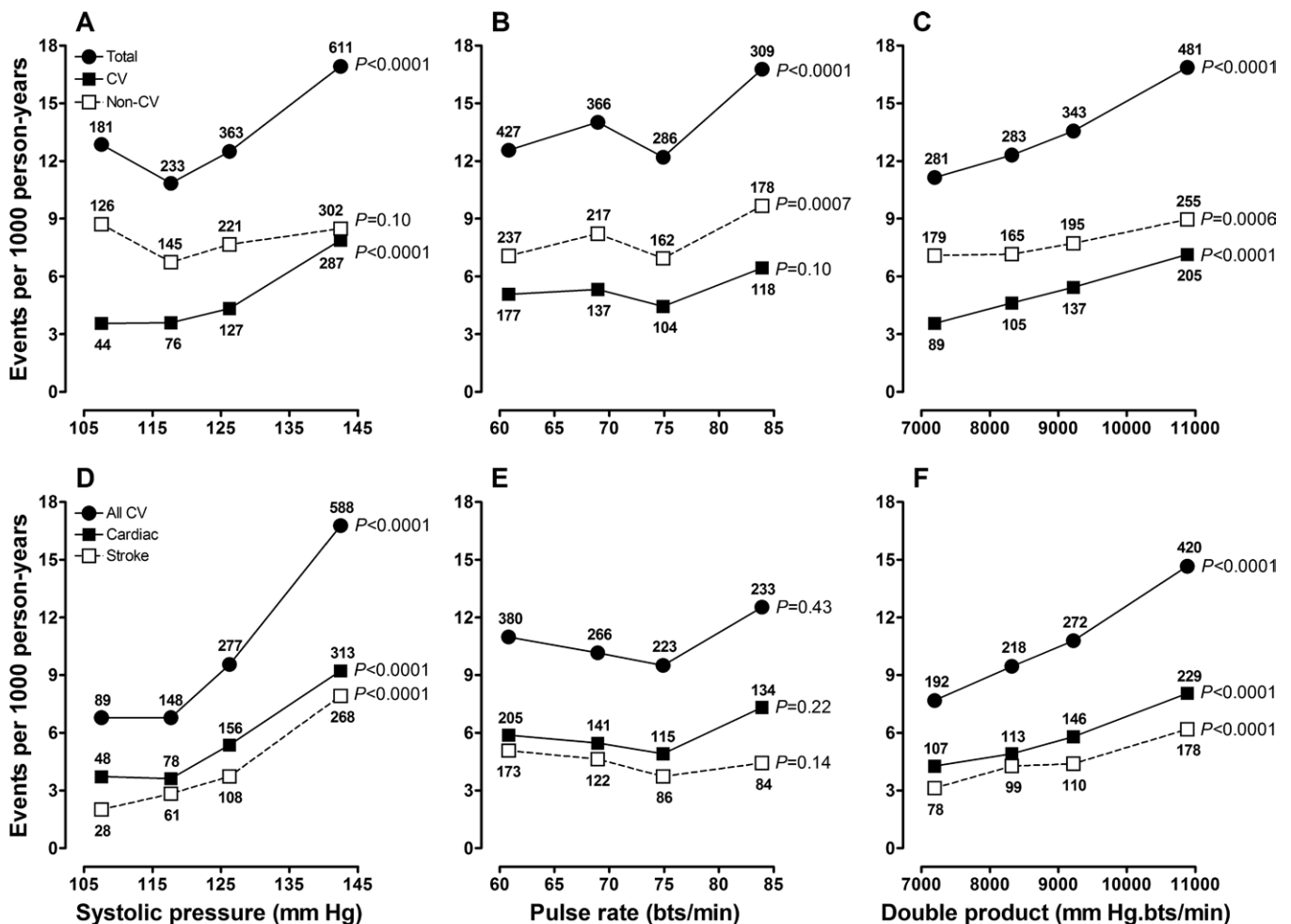


Figure 1. Incidence of mortality (A-C) and of cardiovascular (CV) events (D-F) in relation to systolic blood pressure (A, D), pulse rate (B, E), and double product (C, F) in 9,937 study participants. Incidence rates were standardized for cohort, sex, and age by the direct method. Mortality rates are plotted separately for total, CV, and non-CV mortality. Cardiovascular events include the composite of all fatal plus nonfatal CV events, fatal plus nonfatal cardiac events, and fatal plus nonfatal stroke. The number of endpoints contributing to the rates are presented. Values of P refer to significance for trend.

total mortality and SBP in relation to non-CV mortality ($P = 0.008$). In multivariate Cox regression models (Table 2), we adjusted for cohort, sex, age, BMI, smoking and drinking, serum cholesterol, diabetes mellitus, history of CV disease, and antihypertensive drug treatment. Both SBP ($P = 0.0002$) and PR ($P < 0.0001$) predicted total mortality, but SBP was a stronger predictor of CV mortality than was PR (HR, 1.34 vs. 1.17; $P = 0.04$). Conversely, PR was a stronger predictor of non-CV mortality than was SBP (HR, 1.16 vs. 1.00; $P = 0.01$). When they were adjusted for each other, the predictive value of both SBP and PR in relation to fatal endpoint remained unchanged (Table 2).

In adjusted models not including SBP and PR, the DP predicted total ($P < 0.0001$), CV ($P < 0.0001$), and non-CV ($P = 0.02$) mortality. For CV mortality, SBP and the DP were equally predictive (HR, 1.34 vs. 1.30; $P = 0.71$), and PR and the DP had similar predictive value for non-CV mortality (HR, 1.16 vs. 1.10; $P = 0.11$). However, in models including both SBP and PR, the predictive value of DP not only became borderline significant or disappeared ($P \geq 0.06$), but showed an inverse relationship to total, CV, and non-CV mortality. Figure 2A–C shows the 10-year absolute risk of total, CV, and non-CV mortality associated with SBP and

PR, confirming the predictive value of SBP ($P < 0.0001$) for CV mortality (Figure 2B) and of PR ($P = 0.0007$) for non-CV mortality (Figure 2C).

Fatal and nonfatal cardiovascular events

Systolic blood pressure, PR, and DP fulfilled the proportional hazard assumption ($P \geq 0.23$), with the exception of SBP in relation to all cardiac events ($P = 0.04$). Systolic blood pressure predicted ($P < 0.0001$) all CV, cardiac, coronary and stroke events, whereas PR was predictive only of the composite CV endpoint (HR, 1.09; $P = 0.02$) in models not including SBP (Table 2). In models including SBP, PR was not significant (HR, 1.05; $P = 0.17$).

In adjusted analyses (Table 2) not including SBP and PR, the DP was predictive of the composite CV endpoint ($P < 0.0001$) and of cardiac ($P < 0.0001$), coronary ($P < 0.0001$), and stroke events ($P < 0.0001$). Systolic blood pressure was a stronger predictor of all cardiovascular events than was the DP (HR, 1.39 vs. 1.27; $P = 0.002$), and was also a stronger predictor of stroke (HR, 1.61 vs. 1.36; $P < 0.0001$), as well as being a slightly stronger predictor of cardiac events (HR, 1.32 vs. 1.22; $P = 0.06$), and was similar to the DP in

Table 2. Standardized hazard ratios in relation to systolic blood pressure, pulse rate, and double product in 9,937 study participants

Endpoint (n)	Model	SBP	PR	DP
		Hazard ratio	Hazard ratio	Hazard ratio
Mortality				
All causes (1,388)	A	1.13 (1.06–1.20)‡	1.17 (1.10–1.25)§	1.18 (1.12–1.25)§
	FA	1.11 (1.05–1.19)‡	1.16 (1.09–1.24)§	0.54 (0.28–1.06)
Cardiovascular (536)	A	1.34 (1.22–1.48)§	1.17 (1.06–1.30)†	1.30 (1.19–1.43)§
	FA	1.33 (1.21–1.46)§	1.14 (1.03–1.26)*	0.36 (0.13–1.05)
Non-cardiovascular (794)	A	1.00 (0.91–1.09)	1.16 (1.06–1.26)‡	1.10 (1.02–1.19)*
	FA	0.98 (0.90–1.07)	1.16 (1.07–1.27)‡	0.69 (0.28–1.73)
Fatal plus nonfatal events				
All cardiovascular (1,161)	A	1.39 (1.31–1.48)§	1.09 (1.01–1.16)*	1.27 (1.20–1.35)§
	FA	1.38 (1.30–1.47)§	1.05 (0.98–1.13)	0.36 (0.18–0.73)†
Cardiac (658)	A	1.32 (1.21–1.43)§	1.08 (0.99–1.18)	1.22 (1.13–1.32)§
	FA	1.31 (1.21–1.42)§	1.05 (0.96–1.15)	0.31 (0.13–0.77)*
Coronary (494)	A	1.28 (1.16–1.41)§	1.09 (0.98–1.21)	1.21 (1.10–1.32)§
	FA	1.27 (1.15–1.40)§	1.07 (0.96–1.18)	0.37 (0.13–1.03)
Stroke (465)	A	1.61 (1.46–1.77)§	1.03 (0.92–1.15)	1.36 (1.24–1.50)§
	FA	1.61 (1.46–1.77)§	0.98 (0.87–1.10)	0.41 (0.13–1.26)

* $P < 0.05$

† $P < 0.01$

‡ $P < 0.001$

§ $P < 0.0001$

Systolic blood pressure, PR, and DP were recorded through 24-hour ambulatory blood-pressure monitoring. Hazard ratios, presented with 95% confidence intervals, express the risk associated with a 1-SD increase in SBP, PR, and DP. All models were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, diabetes mellitus, history of cardiovascular disease, and antihypertensive treatment. Adjusted models (A) include either SBP, PR, or DP, whereas in fully adjusted models, SBP is adjusted for PR and vice versa and the DP is adjusted for both SBP and PR. All-cause mortality included 40 deaths of unknown origin and 18 deaths from renal causes.

Abbreviations: A, adjusted model; DP, double product; FA, fully adjusted model; PR, pulse rate; SBP, systolic blood pressure.

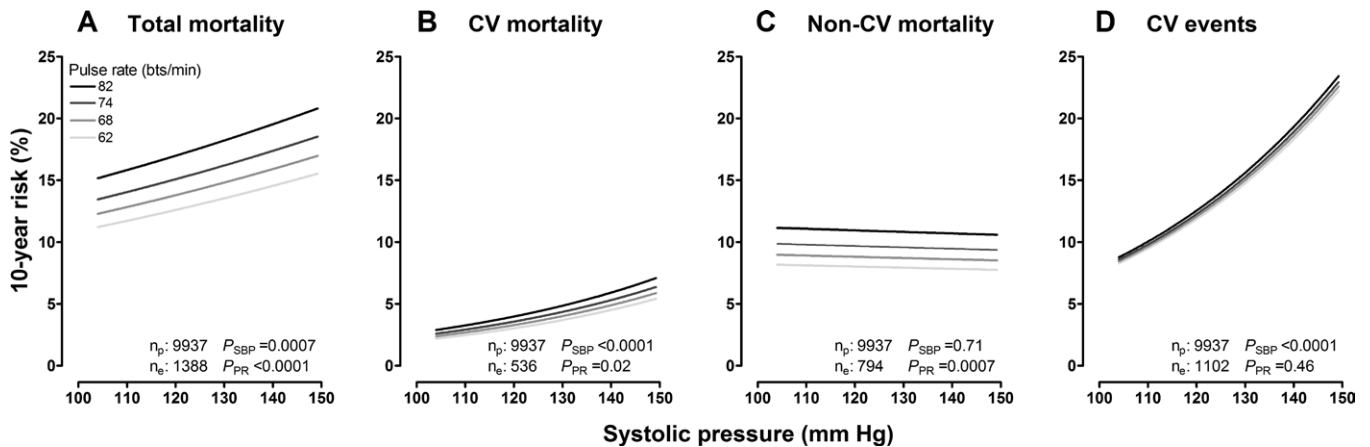


Figure 2. Ten-year absolute risk of total (A), cardiovascular (CV) (B), and non-CV (C) mortality and the composite CV endpoint (D). Risk-function estimates were standardized to the mean distribution in the whole study population of cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, diabetes mellitus, history of CV disease, and treatment with antihypertensive drugs. The 24-hour pulse rate is represented by four risk functions corresponding to 62, 68, 74, and 82 bpm (approximate quartile midpoints). Plotted values of 24-hour systolic blood pressure span the interval from the 5th to the 95th percentiles. Values of P are for the independent effect of blood pressure (P_{SBP}) and pulse rate (P_{PR}), and n_p and n_e indicate the number of participants at risk and the number of events, respectively.

predicting coronary events (HR, 1.28 vs. 1.21; $P = 0.26$). In fully adjusted models including SBP and PR (Table 2), the predictive value of the DP disappeared for coronary ($P = 0.06$) and stroke ($P = 0.12$) events, and was inversely associated with the risk of all CV ($P = 0.004$) and cardiac ($P = 0.01$) events. Figure 2D shows the 10-year absolute risk of the combined CV endpoint associated with SBP and PR, confirming the predictive value of SBP ($P < 0.0001$) and the absence of a predictive value of PR ($P = 0.46$).

Sensitivity analyses

Sensitivity analyses, in which we stratified for sex, age (above or below 60 years), history of CV disease, antihypertensive treatment, presence or absence of hypertension, smoking, use of alcohol, and European, Asian, and South American ethnicity (Supplementary Table S2) or from which we excluded one cohort at a time (Supplementary Table S3), were confirmatory. The only exception was a significant interaction between treatment status and the DP in the prediction of CV mortality and all CV events ($P \leq 0.02$) and between alcohol use and the DP in the prediction of all CV events ($P = 0.02$). We therefore excluded 659 patients being treated with beta-blockers and 4,759 users of alcohol, but this did not materially change the HRs as reported in Table 2. Lastly, ambulatory BP is often found to be a stronger predictor than conventional clinic BP and may therefore drive these findings. Because ambulatory blood pressure monitoring (ABPM) is not always used in the clinical setting, we repeated our analyses using conventional BP measurements (from 9 of the 11 centers with conventional BP data), which did not change our findings (Supplementary Table S4).

DISCUSSION

This study investigated the prognostic value of the DP and found that it does not add to the prediction of CV risk beyond that provided by SBP or PR. The predictive value

of the DP for CV mortality and events was either similar to or weaker than that of SBP and was similar to that of PR. These findings remained the same after the exclusion of patients treated with beta-blockers as well as after various stratifications, after the exclusion of one study cohort at a time, and after repeating our analyses using conventional BP measurements.

The first prognostic evidence for the DP appeared recently in the Ohasama population study, in which BP and PR were measured at rest during home BP measurement.¹³ In this prospective study, the respective increases in risk for total, CV and non-CV mortality were 15.1%, 17.6%, and 13.9% for every 1,000 mm Hg.bpm increment in the DP. Additionally, both SBP (for which the risk increased by 8.3% per 10 mm Hg increase) and PR (for which the risk increased by 23.0% per 10 mm Hg increase) predicted total mortality. In accord with our findings, SBP predicted CV mortality (with an increased risk of 16.7% per 10 mm Hg increase in BP) and PR predicted non-CV mortality (with an increased risk of 25.5% per 10 mm Hg increase in BP). On the basis of the improvement in the goodness of fit of their models when they added the DP to SBP or PR, the investigators in the Ohasama study¹³ concluded that the strongest association was between the DP and CV and non-CV mortality.¹³ However, to show that the DP adds predictive value independent of SBP and PR, they had to add the DP to a model already including both SBP and PR. Furthermore, the HRs in the Ohasama investigators' report¹³ were not standardized, which prevents a direct comparison of the effect sizes of SBP, PR and DP.

Our findings discourage the use of the DP in the clinical setting because of the lack of evidence that it adds to risk prediction over and beyond that provided by SBP. The DP in regression models already including SBP and PR is simply the interaction term between these two variables. It verifies whether the effect of PR depends on the level of SBP and *vice versa*. When the DP is measured at rest or during daily activities, the interpretation of its significance is difficult,

especially if one considers the variability of its individual components. For example, the body attempts to stabilize the DP under normal conditions via the baroreflex²¹; and PR tends to be higher in women than in men,²² whereas BP is higher in men than in age-matched premenopausal women,²³ a situation that is reversed after menopause; and BP increases²⁴ and PR decreases²⁵ with age in both men and women. The negative relationship between the DP and some of the outcome measures in our study in models including both SBP and PR compounds the complexity of its statistical and ultimately physiological interpretation.

The DP is related to myocardial oxygen consumption,^{5,6} and physiologically its use was justified during exercise testing in patients with ischemic heart disease.^{5,6} Stated simply, an attenuation in coronary blood flow would also decrease the DP because the PR would decrease in an attempt to limit or prevent myocardial necrosis.²⁶ Indeed, the DP increases during augmented coronary flow in response to atrial pacing, as shown by Anderson et al.²⁷ Not surprisingly, an attenuated response of the DP to physical activity is predictive of cardiovascular mortality, as shown in 6,251 survivors of myocardial infarction⁷ and in 1,749 patients referred for exercise testing.⁸ It is therefore a decrease in the DP during exercise that is predictive and mechanistically interpretive.^{7,8} The fact that PR also predicts non-CV mortality,⁴ possibly reflecting poor overall health or other pre-existing disease states,²⁸ makes the interpretation of the DP even more difficult. The positive relationship of the DP to CV mortality and to events at rest or during ambulatory monitoring, in accord with our results, therefore seems merely to be the independent predictive value of its constituents.¹⁻⁴

Despite the lack of clarity of the DP beyond its meaning in exercise testing, comparative clinical trials have been done to determine the superiority of one drug over another in reducing the DP, such as during the morning surge in BP^{10,11} and over a 24-hour period.¹² For example, White et al.¹² conducted a randomized clinical trial for 8 weeks to compare the efficacy and tolerability of a calcium-channel blocker (amlodipine besylate) and a beta-blocker (metoprolol succinate) in reducing the DP over 24-hours and in the early morning (upon awakening) in 35 hypertensive patients. The authors concluded that the beta-blocker provided more effective control of the DP. However, the significant reduction in the 24-hour DP and morning DP effected by the beta-blocker as compared with the calcium-channel blocker was due to the result of a decrease in the PR (-11.2 bpm vs. +2.4 bpm, and -11.1 bpm vs. +3.6 bpm, respectively, both $P < 0.0001$), and not to a lowering of SBP (-14.0 mm Hg vs. -10.6 mm Hg, $P = 0.11$; and -13.0 mm Hg vs. -10.4 mm Hg, $P = 0.35$). In our population sample drawn from a general population, the exclusion of patients treated with beta-blockers made little difference in the risk-predictive effect of the DP. This is an example of the mixed messages that reach clinicians, who already face the challenge of effective BP management in their patients. Our study suggests that the reporting of new risk markers without their verification in randomized clinical trials of CV outcome must be avoided, and that the focus in reducing CV risk should remain on BP management, as set out in the ESC-ESH practice guidelines for the management of hypertension.¹⁵

The current study must be interpreted within the context of its potential limitations. We included 9,937 randomly selected individuals from 11 different countries in the study, but our results could still not be generally applicable. Even though our results were adjusted for multiple variables and were consistent in sensitivity analyses after the exclusion of patients treated with beta-blockers as well as after various stratifications, after the exclusion of one cohort at a time, and after the analyses were repeated with the use of conventional clinical measurements of BP, we cannot exclude the possibility of residual confounding. Furthermore, ABPM of the study subjects was not standardized in terms of device type and intervals between successive readings. On the other hand, our use of a single SAS macro ensured that daytime was always defined in the same way in our analyses of data, with short fixed clock-time intervals, and that the time-weighted means in our results were calculated identically across cohorts. Lastly, no information was available about the subjects' physical activity, and we did not adjust for serum creatinine because data about this was missing for 44% of the subjects, which in our data analyses may have been confounding factors.

In conclusion, our data do not support the hypothesis that the DP is superior to SBP in predicting CV events and mortality in the general population. Current guidelines for the management of hypertension must be followed.

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DISCLOSURES

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