EXPANDED METHODS and DATA SUPPLEMENT

Risk Stratification by 24-Hour Ambulatory Blood Pressure and Estimated Glomerular Filtration Rate in 5322 Subjects from 11 Populations

Short title: Risk Stratification by ABP and eGFR

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Expanded Methods

Study Population

As described in detail elsewhere,[1] we constructed the International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO). Studies were eligible for inclusion, if they involved a random population sample, if baseline information on the ambulatory blood pressure and cardiovascular risk factors was available, and if the subsequent follow-up included both fatal and nonfatal outcomes.

The present study included 5322 participants: 190 residents from Copenhagen, Denmark;[2] 1072 subjects from Noorderkempen, Belgium;[3] 1040 older men from Uppsala, Sweden;[4] 241 subjects from Novosibirsk, the Russian Federation;[5,6] 185 inhabitants from Ohasama, Japan;[7] 346 villagers from the JingNing County, China;[8] 1082 subjects from Montevideo, Uruguay;[9] 165 from Pilsen, the Czech Republic;[6] 394 from Dublin, Ireland;[10] 306 from Padova, Italy;[6] and 301 from Kraków, Poland.[6] All participants gave informed written consent. Subjects recruited in Kraków, Novosibirsk, Pilsen, and Padova took part in the European Project on Genes in Hypertension (EPOGH).[6]

Blood Pressure Measurements

Conventional blood pressure was measured by trained observers with a mercury sphygmomanometer,[2,6,8,10] with validated auscultatory[7] (USM-700F, UEDA Electronic Works, Tokyo, Japan) or oscillometric[9] (OMRON HEM-705CP, Omron Corporation, Tokyo, Japan) devices, using the appropriate cuff size, with participants in the sitting[2,3,5-10] or supine[4] position. Conventional blood pressure was the average of 2 consecutive readings obtained either at the person's home[3,5,6,8,9] or at an examination center.[2,4,7,10] Office hypertension was a conventional blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic or the use of antihypertensive drugs.[11] We programmed portable monitors to obtain ambulatory blood pressure readings at 30 minute intervals throughout the whole day,[7,10] or at intervals ranging from 15[2] to 30[4] minutes during daytime and from 30[2] to 60[4] minutes at night. The devices implemented an auscultatory algorithm (Accutracker II) in Uppsala[4] or an oscillometric technique (SpaceLabs 90202 and 90207, Nippon Colin, and ABPM 630) in the other cohorts.[3-10]

The same SAS macro processed all ambulatory recordings, which generally stayed unedited. The Ohasama recordings were edited sparsely according to previously published criteria.[12] Within individual subjects, we weighted the means of the ambulatory blood pressure by the interval between readings.

When accounting for the daily pattern of activities of the participants, we defined daytime as the interval ranging from 1000 h to 2000 h in people from Europe[2-6,10] and South America,[9] and from 0800 h to 1800 h in those from Asia.[7,8] The corresponding night-time intervals ranged from midnight to 0600 h[2-6,9,10] and from 2200 h to 0400 h. [7,8] These fixed intervals eliminate the transition periods in the morning and evening when blood pressure changes rapidly, resulting in daytime and night-time blood pressure levels that are within 1–2 mm Hg of the awake and asleep levels.[8,13]

Assessment of Renal Function

To measure the serum creatinine concentration, all laboratories applied Jaffe's method[14] with the modifications described elsewhere[15,16] to overcome interferences and limitations. The samples were run on automated analyzers in certified laboratories that participated in external quality control programs. We used the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI)[17] to estimate the glomerular filtration rate (eGFR) from sex, age, and the serum creatinine concentration. In a subsample of 2962 participants (55.7%), we checked the presence of proteinuria by means of a semi-quantitative dipstick method (n=1287)[3,5-7] or by measurement of albumin in a 24-h urine collection (n=1675).[3,9] Proteinuria was a positive dipstick test (any degree of proteinuria) or a 24-h urinary albumin excretion of 30 mg or more.[18]

Calculation of the R^2 statistic

As proposed by Gillespie,[19] we applied the generalized R^2 statistic to assess the refinement in risk prediction by adding the 24-h blood pressure or eGFR to Cox models on top of other covariables. The formula for the calculation of R^2 is:

$$R^2 = 1 - \exp\left\{\frac{-2}{n}\left(\ln L(X2) - \ln L(X1)\right)\right\} = 1 - \exp\left\{\frac{-\chi 2}{n}\right\}$$

where Ln L (X2) and ln L(X1) are the log likelihood statistics of the extended and the nested reference model.

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Table S1: Cohort- and Sex-Specific Quantiles of Serum Creatinine (mg/dl)

Center	Women						Men					
	N	P10	P25	P50	P75	P90	N	P10	P25	P50	P75	P90
Copenhagen	99	0.68	0.73	0.79	0.90	1.02	91	0.90	0.96	1.02	1.13	1.24
Ohasama	136	0.70	0.70	0.80	0.90	0.90	49	0.70	0.90	1.00	1.05	1.20
Noorderkempen	539	0.75	0.80	0.90	1.00	1.11	533	0.93	1.01	1.10	1.21	1.31
Uppsala	…	…	…	…	…	…	1040	0.89	0.95	1.03	1.13	1.21
Montevideo	610	0.77	0.83	0.92	1.05	1.15	472	0.93	1.02	1.14	1.26	1.38
JingNing	188	0.85	0.89	0.95	1.02	1.07	158	0.97	1.04	1.11	1.20	1.28
Novosibirsk	136	0.77	0.83	0.90	1.00	1.09	105	0.89	0.97	1.03	1.12	1.22
Pilsen	90	0.77	0.84	0.89	0.96	1.05	75	0.93	0.97	1.05	1.12	1.20
Dublin	158	0.76	0.82	0.90	0.95	1.01	236	0.89	0.99	1.08	1.16	1.24
Padova	172	0.70	0.70	0.80	0.80	0.90	134	0.80	0.90	0.99	1.05	1.10
Kraków	165	0.64	0.74	0.84	0.96	1.04	136	0.79	0.86	0.95	1.09	1.17

N indicates the number of women or men. P10, P25, P50 P75 and P90 are the center and sex specific quantiles. An ellipsis indicates unavailable data.

Table S2: Cohort- and Sex-Specific quantiles of the Estimated Glomerular Filtration Rate (ml/min/1.73 m^2)

Center	Women						Men					
	N	P10	P25	P50	P75	P90	N	P10	P25	P50	P75	P90
Copenhagen	99	60.0	69.1	81.0	81.7	95.4	91	62.5	69.9	79.4	80.0	91.9
Ohasama	136	60.3	68.7	77.6	87.7	93.8	49	64.1	70.8	80.4	92.0	99.6
Noorderkempen	539	55.3	63.4	76.7	89.9	100.3	533	60.8	67.9	78.9	90.4	100.7
Uppsala	…	…	…	…	…	…	1040	59.6	65.1	72.6	80.0	86.2
Montevideo	610	50.7	59.9	72.0	85.1	95.4	472	54.36	63.4	75.0	88.3	99.6
JingNing	188	58.8	65.2	71.8	80.1	87.7	158	60.2	70.0	78.8	90.3	95.3
Novosibirsk	136	58.8	69.8	80.9	91.2	102.6	105	72.3	79.7	91.9	101.5	113.0
Pilsen	90	65.5	71.3	83.6	93.4	98.4	75	68.3	80.0	91.5	100.1	112.3
Dublin	158	70.8	76.5	84.9	95.0	105.5	236	70.3	78.3	87.0	96.2	108.5
Padova	172	74.4	84.4	95.9	102.5	118.1	134	81.4	85.9	99.2	106.6	117.4
Kraków	165	63.6	76.5	86.7	102.4	117.8	136	76.6	85.9	100.9	117.0	124.7

N indicates the number of women or men. P10, P25, P50 P75 and P90 are the center and sex specific quantiles. An ellipsis indicates unavailable data.

Table S3. Standardized Hazard Ratios in Relation to 24-h Diastolic Blood Pressure and Estimated Glomerular Filtration Rate in 5322 Participants

Endpoint (number)	Model	**24-h Diastolic Pressure**		**1/HR eGFR**	
		Hazard Ratio	*P*	Hazard ratio	*P*
Mortality					
All causes (513)	A	1.11 (1.02-1.22)	0.023	1.05 (0.91-1.20)	0.50
	FA	1.11 (1.01-1.22)	0.024	1.05 (0.91-1.20)	0.53
Cardiovascular (206)	A	1.32 (1.14-1.52)	0.0001	1.34 (1.07-1.67)	0.012
	FA	1.31 (1.14-1.51)	0.0002	1.33 (1.06-1.66)	0.014
Noncardiovascular (275)	A	0.99 (0.87-1.13)	0.90	0.89 (0.74-1.08)	0.24
	FA	0.99 (0.87-1.13)	0.91	0.89 (0.74-1.08)	0.24
Fatal Plus Nonfatal Events					
All cardiovascular (555)	A	1.32 (1.22-1.44)	<0.0001	1.15 (1.01-1.31)	0.035
	FA	1.32 (1.22-1.44)	<0.0001	1.14 (1.00-1.30)	0.044
Cardiac (335)	A	1.23 (1.10-1.37)	0.0002	1.08 (0.91-1.27)	0.40
	FA	1.23 (1.10-1.37)	0.0002	1.07 (0.90-1.27)	0.44
Coronary (257)	A	1.15 (1.02-1.31)	0.025	1.07 (0.89-1.30)	0.46
	FA	1.15 (1.02-1.31)	0.026	1.07 (0.89-1.29)	0.48
Stroke (218)	A	1.47 (1.29-1.68)	<0.0001	1.33 (1.08-1.64)	0.009
	FA	1.47 (1.29-1.68)	<0.0001	1.33 (1.08-1.64)	0.009

eGFR is the glomerular filtration rate estimated from the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI), as given in reference 17. Hazard ratios, presented with 95% confidence interval, express the risk associated with a 1-SD increase in 24-h diastolic blood pressure (8.3 mm Hg) or a 1-SD decrease in eGFR (16.7 ml/min/1.73 m^2). For eGFR, the inverse of the hazard ratio is presented, so that higher values, associated with lower eGFR, reflect higher risk. All models were adjusted for center, sex, age, body mass index, smoking and drinking, serum cholesterol, diabetes mellitus, history of cardiovascular disease, and antihypertensive treatment. Adjusted models (A) include either the 24-h diastolic blood pressure or eGFR, while fully adjusted models (FA) include both 24-h diastolic blood pressure and eGFR in addition to the aforementioned covariables.

Table S4. Predictive Value of the Cox Regression models.

Models	Cardiovascular mortality			Cardiovascular events			Stroke		
	Likelihood ratio	*P*	R^2 (%)	Likelihood ratio	*P*	R^2 (%)	Likelihood ratio	*P*	R^2 (%)
Basic model	445.4	…	8.03	809.7	…	14.1	353.0	…	6.40
24-h diastolic pressure added to basic model	14.0	0.0001	0.26	41.2	<0.0001	0.77	30.5	<0.0001	0.57
eGFR added to basic model	6.4	0.011	0.12	4.46	0.035	0.08	7.0	0.009	0.13
eGFR added to basic model also including 24-h diastolic pressure	6.1	0.0002	0.02 0	4.08	<0.0001	–0.33	7.0	<0.0001	–0.30

The basic model included cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, and treatment with antihypertensive drugs. *P*-values are for the improvement of the fit across nested models.
Values are likelihood ratios and associated *P*-values and generalized R^2-statistics for adding 24-hour diastolic blood pressure or eGFR to the reference model.

Table S5. Sensitivity Analyses for Cardiovascular Mortality in Relation to the 24-H Ambulatory Blood Pressure and eGFR Excluding One Center at a Time

Center	At risk	Events	24-H Systolic Pressure		1/HR eGFR	
			Hazard ratio (CI)	*P*	Hazard ratio (CI)	*P*
All centers	5322	206	1.33 (1.18–1.50)	<0.0001	1.35 (1.07–1.69)	0.01
Excluded center						
Ohasama	5137	199	1.31 (1.15–1.48)	<0.0001	1.37 (1.09–1.73)	0.007
JingNing	4976	200	1.29 (1.13–1.46)	<0.0001	1.35 (1.07–1.69)	0.011
Copenhagen	5132	202	1.33 (1.18–1.51)	<0.0001	1.34 (1.07–1.69)	0.012
Dublin	4928	201	1.34 (1.18–1.51)	<0.0001	1.32 (1.05–1.67)	0.017
Noorderkempen	4250	161	1.26 (1.10–1.45)	0.0007	1.54 (1.18–1.99)	0.001
Uppsala	4282	89	1.67 (1.37–2.05)	<0.0001	1.41 (1.01–1.96)	0.045
EPOGH	4309	200	1.31 (1.16–1.49)	<0.0001	1.33 (1.06–1.67)	0.016
Kraków	5021	204	1.33 (1.17–1.50)	<0.0001	1.35 (1.07–1.69)	0.011
Novosibirsk	5081	202	1.32 (1.16–1.49)	<0.0001	1.34 (1.06–1.68)	0.013
Padova	5016	206	1.33 (1.18–1.50)	<0.0001	1.33 (1.06–1.67)	0.013
Pilsen	5157	206	1.33 (1.18–1.50)	<0.0001	1.35 (1.08–1.70)	0.010
Montevideo	4240	190	1.34 (1.18–1.52)	<0.0001	1.24 (0.97–1.57)	0.080

eGFR is the glomerular filtration rate estimated from the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI), as given in reference 17. Hazard ratios, presented with 95% confidence interval (CI), express the risk associated with a 1-SD increase in 24-h systolic blood pressure (14.2 mm Hg) or a 1-SD decrease in eGFR (16.7 ml/min/1.73 m^2). For eGFR, the inverse of the hazard ratio is presented, so that higher values, associated with lower eGFR, reflect higher risk. All models were adjusted for center, sex, age, body mass index, smoking and drinking, serum cholesterol, diabetes mellitus, history of cardiovascular disease, and antihypertensive treatment and include both the 24-h systolic blood pressure or eGFR. EPOGH (European Project on Genes in Hypertension) includes participants recruited at Kraków, Novosibirsk, Padova and Pilsen.

Table S6. Sensitivity Analyses for All Cardiovascular Events in Relation to the 24-H Ambulatory Blood Pressure and eGFR Excluding one center at a time

Center	At risk	Events	24-H Systolic Pressure		1/HR eGFR	
			Hazard ratio (CI)	*P*	Hazard ratio (CI)	*P*
All centers	5322	555	1.37 (1.27–1.47)	<0.0001	1.15 (1.01–1.32)	0.033
Excluded center						
Ohasama	5137	530	1.35 (1.25–1.45)	<0.0001	1.17 (1.02–1.34)	0.027
JingNing	4976	547	1.35 (1.25–1.46)	<0.0001	1.15 (1.01–1.31)	0.040
Copenhagen	5132	531	1.35 (1.26–1.46)	<0.0001	1.16 (1.01–1.33	0.033
Dublin	4928	550	1.37 (1.27–1.47)	<0.0001	1.15 (1.01–1.31)	0.041
Noorderkempen	4250	465	1.36 (1.25–1.47)	0.0007	1.20 (1.03–1.38)	0.016
Uppsala	4282	263	1.56 (1.38–1.77)	<0.0001	1.02 (0.85–1.21)	0.82
EPOGH	4309	523	1.36 (1.26–1.47)	<0.0001	1.14 (0.99–1.31)	0.061
Kraków	5021	550	1.37 (1.27–1.47)	<0.0001	1.16 (1.01–1.32)	0.030
Novosibirsk	5081	539	1.36 (1.26–1.47)	<0.0001	1.13 (0.98–1.29)	0.085
Padova	5016	545	1.36 (1.27–1.47)	<0.0001	1.16 (1.01–1.32)	0.032
Pilsen	5157	554	1.37 (1.27–1.48)	<0.0001	1.16 (1.02–1.32)	0.029
Montevideo	4240	476	1.36 (1.25–1.47)	<0.0001	1.23 (1.06–1.43)	0.006

eGFR is the glomerular filtration rate estimated from the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI), as given in reference 17. Hazard ratios, presented with 95% confidence interval (CI), express the risk associated with a 1-SD increase in 24-h systolic blood pressure (14.2 mm Hg) or a 1-SD decrease in eGFR (16.7 ml/min/1.73 m^2). For eGFR, the inverse of the hazard ratio is presented, so that higher values, associated with lower eGFR, reflect higher risk. All models were adjusted for center, sex, age, body mass index, smoking and drinking, serum cholesterol, diabetes mellitus, history of cardiovascular disease, and antihypertensive treatment and include both the 24-h systolic blood pressure or eGFR. EPOGH (European Project on Genes in Hypertension) includes participants recruited at Kraków, Novosibirsk, Padova and Pilsen.

Table S7. Sensitivity Analyses for Cardiovascular Mortality and All Cardiovascular Events in Relation to the 24-H Ambulatory Blood Pressure and eGFR in Participants with and without Proteinuria

Endpoint	At risk	Events	24-H Systolic Pressure		1/HR eGFR	
			Hazard ratio (CI)	*P*	Hazard ratio (CI)	*P*
Cardiovascular mortality						
All	2962	62	1.57 (1.25–1.97)	0.0001	1.28 (0.83–1.99)	0.27
Without proteinuria	2716	47	1.61 (1.24–2.10)	0.0004	1.00 (0.60–1.67	0.99
With proteinuria	246	15	1.24 (0.75–2.06)	0.41	2.33 (0.75–7.21)	0.14
Cardiovascular events						
All	2962	183	1.43 (1.25–1.63)	<0.0001	0.98 (0.78–1.24)	0.89
Without proteinuria	2716	145	1.43 (1.23–1.65)	<0.0001	1.03 (0.80–1.34	0.81
With proteinuria	246	38	1.34 (0.96–1.86)	<0.084	0.74 (0.44–1.25)	0.27

eGFR is the glomerular filtration rate estimated from the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI), as given in reference 17. Hazard ratios, presented with 95% confidence interval (CI), express the risk associated with a 1-SD increase in 24-h systolic blood pressure or a 1-SD decrease in eGFR. For eGFR, the inverse of the hazard ratio is presented, so that higher values, associated with lower eGFR, reflect higher risk. See Methods for the definition of proteinuria. All models were adjusted for center, sex, age, body mass index, smoking and drinking, serum cholesterol, diabetes mellitus, history of cardiovascular disease, and antihypertensive treatment and include both the 24-h systolic blood pressure or eGFR.