The International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome (IDACO): protocol and research perspectives

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Objectives **The International Database on Ambulatory Blood Pressure Monitoring (1993–1994) lacked a prospective dimension. We are constructing a new resource of longitudinal population studies to investigate with great precision to what extent the ambulatory blood pressure improves risk stratification.**

Methods **The acronym IDACO refers to the new International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome. Eligible studies are population based, have fatal as well as nonfatal outcomes available for analysis, comply with ethical standards, and have been previously published in peer-reviewed journals. In a meta-analysis based on individual patient data, composite and cause-specific cardiovascular events will be related to various indexes derived by ambulatory blood pressure monitoring. The analyses will be stratified by cohort and adjusted for the conventional blood pressure and other cardiovascular risk factors.**

Results **To date, the international database includes 7609 patients from four cohorts recruited in Copenhagen, Denmark ($n=2311$), Noorderkempen, Belgium ($n=2542$), Ohasama, Japan ($n=1535$), and Uppsala, Sweden ($n=1221$). In these four cohorts, during a total of 69 295 person-years of follow-up (median 9.3 years), 1026 patients died and 929 participants experienced a fatal or nonfatal cardiovascular event. Follow-up in five other eligible cohorts, involving a total of 4027 participants, is still in progress. We expect that this follow-up will be completed by the end of 2007.**

Conclusion **The international database of ambulatory blood pressure in relation to cardiovascular outcome will provide a shared resource to investigate risk stratification by ambulatory blood pressure monitoring to an extent not possible in any earlier individual study.** ***Blood Press Monit*** **12:255–262 © 2007 Lippincott Williams & Wilkins.**

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Introduction

In middle-aged and older individuals, hypertension is the predominant cardiovascular risk factor. Any man still normotensive at 50 years has a probability of over 90% to become hypertensive during the remainder of his lifetime [1]. Blood-pressure measurement is the basis for the diagnosis and treatment of hypertension. Conventional blood-pressure measurement by auscultation of the Korotkoff sounds is fraught with potential sources of error, which may arise in the patient, the observer, the

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sphygmomanometer, or in the overall application of the technique [2]. Ambulatory monitoring allows the registration of blood pressure throughout the whole day in patients engaged in their usual activities. Ambulatory blood-pressure recordings have high reproducibility, are not subject to digit preference, and avoid the transient rise of a patient's blood pressure in response to a medical environment, the so-called white-coat effect [2,3].

Collaborative meta-analyses of individual patient data constitute a powerful research tool to clarify the role of cardiovascular risk factors in relation to total and cause-specific mortality and morbidity, over and beyond the prognostic information generated by single cohort studies [4,5]. Earlier quantitative overviews published by the Prospective Studies Collaboration [6] and by the Asian Pacific Cohort Studies Collaboration [5] dramatically refined our understanding of the risk conferred by the conventionally measured blood pressure. Along similar lines, the international database on ambulatory blood-pressure monitoring [7] illustrated to what extent a meta-analysis of individual patient data can contribute to our understanding of the distribution [7,8] and the diurnal profile [7,9] of ambulatory blood pressure across ethnically diverse populations. This database constructed, in 1993–1994 [7], however, lacked a prospective dimension. We therefore planned to build a shared new resource of prospective studies conducted in the general population with the objective of elucidating with great precision to what extent ambulatory blood pressure improves risk stratification over and beyond conventional blood pressure. We chose IDACO as the acronym for the new International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome.

Methods

Study eligibility

Eligible studies are those performed in random population samples or those conducted in professional groups representative of a community. At least one baseline ambulatory blood-pressure recording and information on subsequent fatal and nonfatal outcomes should be available. Studies only qualify for inclusion in IDACO if they have been ethically approved, if at enrolment participants gave informed consent, and if they have stood the test of publication in peer-reviewed journals.

Identification of studies

On the basis of our knowledge of the literature, we identified 10 large-scale studies of ambulatory blood-pressure monitoring: the Flemish project on environment, genes and health outcomes [10], the Copenhagen monitoring of trend and determinants in cardiovascular diseases health survey [11], the Uppsala longitudinal study of adult men [12], the Ohasama study [13], the JingNing population study [8], the Allied Irish Bank study [14], the Montevideo study [15], the Leogra study [16], the European project on genes in hypertension [17], and the pressioni arteriose monitorate e loro associazioni study [18]. An electronic search of the literature (in English), using as search terms 'ambulatory blood pressure monitoring' and 'population' did not reveal any other eligible study in a general population. We will repeat searches at 6-monthly intervals.

Data collection

The IDACO database is constructed and maintained at the Studies Coordinating Centre in Leuven, Belgium. While respecting medical confidentiality and national legislations on the protection of privacy investigators will provide information in electronic format on each participant's baseline characteristics; anthropometrics, conventionally measured blood pressure, one 24-h ambulatory blood pressure recording, and cardiovascular risk factors. With regard to follow-up, the information to be computerized includes duration of follow-up, vital status at the end of follow-up, and the incidence of fatal and nonfatal events.

After integration of the participants' information into the database, each investigator will receive detailed summary statistics on his cohort. This process should help to ensure that the common database incorporates correct information and that there will be no conflicts between data to be used in the meta-analysis and those already reported by individual investigators in the literature [10–13]. The IDACO database will be held in strict confidence and will not be used in any publication without the permission of the investigators who have contributed data to a given analysis.

Conventional and ambulatory blood-pressure measurement

The conventional blood pressure should be measured by a standard mercury sphygmomanometer or a validated automated device, using the appropriate cuff size, after the patients have rested in the sitting [8,10,11,13–15,17] or supine [12,16] position for at least *2* [13] to 5 [8,11,12,14,15,17] minutes. The average of the first two conventional blood-pressure readings will be used for analysis. If available, blood-pressure readings obtained in the sitting position will be used. The thresholds proposed by the joint national committee on the prevention, detection, evaluation and treatment of high blood pressure [19], and the European societies of hypertension and cardiology [20] will be used for the classification of participants according to their conventional blood pressure. Patients on blood-pressure lowering drugs will be classified as hypertensive.

Ambulatory blood-pressure recordings cover at least 24 h and should be unedited or recorded with editing criteria set to limits as wide as possible. The monitors should

have been validated according to the guidelines of the European Society of Hypertension [2] and their calibration should have been checked during the period of data collection. For devices recording both auscultatory and oscillometric readings, only the latter will be analyzed.

At the studies coordinating office, the same SAS macro will process all individual ambulatory blood-pressure recordings. Only the first 24 h of each recording will be considered for analysis. Editing will be limited to the exclusion of measurements that are marked as technically inaccurate and those with a systolic blood pressure lower than or equal to the diastolic pressure. Within-patient averages of blood pressure over 24 h, daytime, and nighttime will be weighted by the time interval between consecutive readings. Recordings with less than 10 daytime readings and/or less than five nighttime readings will not be considered for analysis. Daytime and nighttime will be defined using short fixed clock-time periods [21], taking into account the daily pattern of activities of the study participants. Short fixed clock-time intervals eliminate the transition periods in the morning and evening, during which the blood pressure changes rapidly [7], and result in daytime and nighttime blood pressure levels that are within 1–2 mmHg of the awake and asleep levels [8,21]. In exploratory analyses, hourly blood-pressure means will be plotted for each cohort to ascertain that definitions of daytime and nighttime fit the actually observed diurnal blood-pressure profile and to find out whether sensitivity analyses should be performed to exclude the white-coat window [2] or the siesta period after lunch time.

The variability in the ambulatory blood pressure will be modeled, using the 24-h, daytime and nighttime within-patient standard deviations, the average real variability [22], the day-to-night blood-pressure ratio [9], the day-to-night blood-pressure difference [9], the blood-pressure load [23], the runs-test [24], Fourier analysis [24], cumulative sums [25], square wave modeling [21,26], the morning surge in blood pressure [27,28], and the time rate of variability [29]. Measures of blood-pressure variability will always be analyzed, when accounting or standardizing for the blood pressure level.

Other measurements

Data transfer will include detailed information on each patient's medical history, smoking and drinking habits, and intake of medications. Smoking and drinking are the current use of tobacco and alcohol. Body mass index will be calculated as body weight in kilograms divided by height in meters squared. Diabetes mellitus will be defined as a self-reported diagnosis, a fasting or random blood glucose level of at least 7.0 or 11.1 mmol per liter (126 or 200 mg/dl) [30], respectively, or the use of antidiabetic drugs. Previous cardiovascular disease includes cardiac and cerebrovascular disorders and peripheral vascular disease.

Definition of events

The primary endpoint consists of cardiovascular death, nonfatal myocardial infarction, surgical and percutaneous coronary revascularization, heart failure and stroke. If a patient experienced more than one cardiovascular event, only the first will be considered for analysis. Other endpoints are all-cause mortality, cardiovascular mortality, noncardiovascular mortality, stroke, cardiac disorders, and coronary heart disease. Coronary events consist of death from ischemic heart disease, sudden death, nonfatal myocardial infarction, and coronary revascularization. Cardiac complications include coronary events and fatal and nonfatal heart failure. Fatal and nonfatal stroke do not include transient ischemic attacks. If possible, stroke events will be differentiated into ischemic and hemorrhagic stroke.

In terms of coding according to the International Classification of Diseases (ICD), stroke will be defined as ICD-8 or ICD-9 codes 430–434 or 436, or ICD-10 codes I60–I64. Myocardial infarction will be defined as ICD-8 or ICD-9 code 410 or ICD-10 codes I21–I22, and heart failure as ICD-8 4270, 4271, 4280, 4290, 5191 or 7824, or ICD-9 codes 429 or 5184, or ICD-10 codes I50 or J81. Sudden death is ICD-8 code 4272 or 795, or ICD-9 code 4275 or 798, or ICD-10 codes I46 or R96. Peripheral arterial disease corresponds with ICD-8 or ICD-9 codes 441–444, or ICD-10 codes I71–I74, and includes surgical or peripheral revascularization procedures. In case ICD codes are not available in the transferred data, the definition of events as given by the investigators will be accepted with reference to the publication on each cohort in the peer-reviewed literature.

Statistical methods

For database management and statistical analysis, SAS software version 9.1 or higher (SAS Institute, Cary, North Carolina, USA) will be used.

All analyses will relate health outcomes to parameters derived from ambulatory blood-pressure recordings both in unadjusted and multivariate-adjusted analyses. In exploratory analyses, incidence rates will be plotted by quantiles of the ambulatory blood-pressure parameters, but standardizing will be done by the direct method for cohort. Next, the association between outcomes and the indexes derived from ambulatory blood-pressure recordings will be further assessed, using the Cox proportional-hazards model stratified by cohort. Adjusted analyses will consider the following covariates measured at baseline: sex, age, body mass index, smoking and drinking habits, total serum cholesterol, diabetes mellitus, antihypertensive drug treatment, and history of cardiovascular disease.

Sensitivity analyses will be undertaken to confirm the main conclusions of each analysis. As a general rule, subgroup analyses will search for consistency in the results according to sex, age group, antihypertensive treatment at enrolment, and history of cardiovascular disease. In addition, sensitivity analyses will also address the question of whether the inclusion of one or more cohorts biased the results in any direction.

Research objectives

Outcome-driven diagnostic thresholds for the ambulatory blood pressure

Although blood pressure is continuously distributed, clinicians need a diagnostic reference frame to interpret ambulatory blood-pressure values and to classify patients. Current guidelines propose operational thresholds for the ambulatory blood pressure [2,19,20], but these limits rely largely on the distribution of the ambulatory blood pressure in normotensive reference populations or on the regression of ambulatory on conventional blood pressure. Generating outcome-driven diagnostic thresholds for the ambulatory blood pressure was one of the major objectives motivating this research consortium to combine resources.

The relationship between cardiovascular outcomes and blood pressure, irrespective of the technique of measurement, is usually considered to be log-linear and continuous [4]. For the usual blood pressure on conventional measurement, the risk starts rising at levels of 115 mm Hg systolic and 75 mmHg diastolic [4]. According to current guidelines [2,19,20], these are blood-pressure values well within the normotensive range. One key issue in the determination of outcome-based thresholds is therefore the notion of the level of risk that is normal or acceptable.

We chose to conform with the general consensus in current guidelines [2,19,20]. We therefore planned to determine levels of the ambulatory blood pressure yielding risks equivalent to those associated with optimal and normal blood pressure and hypertension on conventional measurement. As an alternative approach, we will also calculate the levels of the ambulatory blood pressure resulting in a 5% or 10% overall cardiovascular risk over 10 years. The latter procedure does not involve any assumption of risk associated with the conventional blood pressure.

Ambulatory blood-pressure measurement to refine risk stratification

In clinical practice, ambulatory blood-pressure monitoring is a diagnostic instrument geared at refining risk stratification. Along this line, IDACO will constitute a powerful resource to address several issues related to the prognostic significance of the ambulatory blood pressure. The preliminary list of ambulatory blood-pressure indexes, of which the predictive value will be investigated, includes the following: (i) white-coat and masked hypertension; (ii) the blood-pressure levels during daytime and nighttime, and their ratio; (iii) measures of diurnal blood-pressure variability, including the morning surge in blood pressure [27,28] and the time rate of variability [29]; (iv) the ambulatory heart rate; and (v) pulse pressure and the ambulatory arterial stiffness index [31–33]. In addition, we will investigate to what extent diabetes mellitus or a history of cardiovascular disease, as compared with the absence of these conditions, impacts on the prognostic accuracy of the ambulatory blood pressure. All aforementioned analyses will explore whether the indexes derived from ambulatory monitoring are predictive over and above those derived from conventional blood-pressure readings. Results from analyses, which require a dichotomization of the study population, such as for instance those of white-coat and masked hypertension or nighttime dipping status, will be confirmed by analyses that include the exposure variables as continuous measurements. Sample size permitting, it is also our intention to construct risk charts similar to those derived from Framingham [34] or the SCORE system [35], but including the ambulatory blood pressure as an additional risk factor.

Results

After contacting the investigators of 10 eligible studies, nine studies [8,10–17], representing six European [10–12,14,16,17], two Asian [8,13] and one South American [15] cohort qualified for incorporation into the IDACO database. Of these nine studies [8,10–17], four [10–13] had outcome data available at the time of writing of this manuscript and are, therefore, already included in the database.

Cohorts with outcome data available in the IDACO database

Currently, the IDACO database includes 7609 patients: 2311 residents of Copenhagen, Denmark [11]; 2542 residents of Noorderkempen, Belgium [10]; 1535 residents of Ohasama, Japan [13]; and 1221 men from Uppsala, Sweden [12]. Table 1 lists the characteristics of these patients by cohort. Overall, these four cohorts include 3399 women (44.7%), 2220 smokers (29.5%), 3586 alcohol consumers (53.1%), 530 diabetic patients (7.0%), and 640 participants with a previous history of cardiovascular disease (8.4%). Median age (5th to 95th percentile points) was 59 years (23–73). The conventional blood pressures were obtained either at the patient's home ($n = 2536$) or at an examination center ($n = 4853$), and were measured either in the sitting ($n = 6173$) or the supine ($n = 1216$) position. Conventional blood-pressure measurements were not available in 220 patients. Mean values in the remaining 7389 patients were 131.3 ± 19.8 mmHg systolic and 79.0 ± 11.6 mmHg diastolic. Of the 3314 hypertensive patients (43.6%),

Table 1 Baseline characteristics of cohorts with outcome data

Characteristic	Copenhagen [11]	Noorderkempen [10]	Ohasama [13]	Uppsala [12]
Number of patients	2311	2542	1535	1221
Women, no (%)	1130 (48.9)	1298 (51.1)	971 (63.3)	0
Age (years)	56.4 (10.2)	42.6 (17.0)	61.7 (10.7)	71.0 (0.6)
Body mass index (kg/m^2)[a]	26.1 (4.1)	25.1 (4.5)	23.4 (3.1)	26.3 (3.4)
Weight (kg)	75.1 (14.1)	71.0 (14.7)	54.3 (9.3)	80.4 (11.5)
Height (cm)	169 (9)	168 (10)	152 (9)	175 (6)
Blood pressure (mmHg)				
Conventional systolic	131.3 (19.3)	123.9 (17.0)	131.2 (18.5)	146.8 (18.5)
Conventional diastolic	83.4 (10.8)	75.3 (11.0)	74.1 (11.3)	83.8 (9.5)
24-h systolic	128.6 (12.8)	118.8 (11.1)	123.1 (13.2)	132.9 (15.6)
24-h diastolic	75.1 (8.5)	71.3 (7.4)	71.9 (7.7)	75.1 (7.7)
Daytime[b] systolic	136.7 (13.8)	123.8 (11.0)	128.8 (14.3)	140.3 (16.3)
Daytime[b] diastolic	80.6 (9.3)	76.1 (8.1)	75.9 (8.8)	79.8 (8.7)
Nighttime[b] systolic	115.8 (14.0)	108.5 (12.2)	111.7 (14.8)	119.3 (18.6)
Nighttime[b] diastolic	65.7 (9.1)	61.8 (8.2)	63.5 (8.3)	66.9 (9.0)
Serum cholesterol (mg/dl)[c]	239 (42)	208 (44)	193 (34)	225 (39)
Smokers, no (%)	998 (43.3)	692 (27.5)	285 (18.6)	245 (20.8)
Drinkers, no (%)	1983 (86.2)	645 (25.8)	278 (22.5)	680 (94.1)
Diabetes mellitus, no (%)	71 (3.1)	61 (2.4)	267 (17.4)	131 (10.8)
Cardiovascular disease, no (%)	137 (5.9)	188 (7.4)	98 (6.4)	217 (17.8)
Hypertension, no (%)[d]	1037 (44.9)	659 (26.0)	710 (46.3)	908 (74.5)
Antihypertensive treatment, no (%)	346 (15.0)	318 (12.6)	549 (35.8)	427 (35.3)

Data are mean (SD) or number of patients(%).
[a]Body mass index is body weight in kilograms divided by height in meters squared.
[b]Daytime ranged from 10:00 to 20:00 h in Europeans and from 08:00 to 18:00 h in Japanese. The corresponding nighttime intervals ranged from 00:00 to 06:00 h and from 22:00 to 04:00 h, respectively.
[c]To convert serum total cholesterol levels to millimoles per liter, divide by 38.67.
[d]Hypertension is a conventional blood pressure of at least 140 mmHg systolic or 90 mmHg diastolic or the use of antihypertensive drugs.

1640 (49.5%) were taking blood-pressure-lowering drugs. The ambulatory blood pressure was not measured during nighttime in 1623 of the 7609 patients. In addition, less than 10 daytime readings and/or less than five nighttime readings were available in 22 and 67 patients. The mean 24-h systolic and diastolic blood pressures in the remaining 5897 patients averaged 126.1 ± 14.0 mmHg for systolic and 73.6 ± 8.2 mmHg for diastolic.

Table 2 shows the number of events in each cohort currently included in the database. Median follow-up ranged from 8.3 years (5th to 95th percentile interval, 1.6–15.3 years) in Noorderkempen to 10.4 years (4.7–13.3 years) in Ohasama. In the overall study population, during a total of 69 295 person-years of follow-up, 1026 patients died and 929 participants experienced a fatal or nonfatal cardiovascular event. The unadjusted incidence of fatal and nonfatal cardiovascular complications averaged 13.4 events per thousand person-years, ranging from 5.5 to 31.4 events per thousand person-years in Noorderkempen and Uppsala, respectively.

Eligible cohorts still awaiting completion of follow-up

Table 3 lists the baseline characteristics of the patients, whose follow-up data are still being collected and who were therefore not yet included in the database.

Discussion

The main objective of the IDACO project is to refine current knowledge of ambulatory blood-pressure monitoring as a diagnostic instrument in the stratification of cardiovascular risk. Meta-analyses of individual patient data are more resource-intensive and time-consuming than meta-analyses based on summary statistics of published reports. We, nevertheless, decided to perform a meta-analysis based on individual patient data for various reasons. First, in most cases, the statistics of interest are not available from published reports. Second, it has been shown that an aggregate-level analysis always has less power than an investigation of individual patient analysis [36]. Third, an individual patient meta-analysis allows the use of the same statistical approach and quality standards across studies. For instance, in IDACO, the same SAS macro will process all individual ambulatory blood-pressure recordings. Fourth, heterogeneity between cohorts can be better assessed. Heterogeneity can be caused not only by differences in study design or geographic location, but also by differences in the characteristics of the individual patients. Finally, the availability of individual patient data gives more flexibility to extend or refine the planned analyses than an aggregate level approach would do.

In IDACO, we opted not to combine cohorts of hypertensive patients with patients randomly recruited from the general population. The external validity and generalizability of population-based results are obviously larger than those emerging from cohorts of referred hypertensive patients. In addition, we considered that, in hypertensive patients, blood-pressure-lowering treatment might be a confounder with too large an impact to adjust

Table 2 Incidence of events per cohort

Statistic	Copenhagen [11]	Noorderkempen [10]	Ohasama [13]	Uppsala [12]	Four cohorts
Number of participants	2311	2542	1535	1221	7609
Median follow-up (years)	9.3	8.3	10.4	9.9	9.3
Total person-years	20 602	22 028	15 313	11 353	69 295
Fatal events					
All	264	171	242	349	1026
Unknown cause	9	33	1	2	45
Noncardiovascular	150	79	155	193	577
Cardiovascular	105	59	86	154	404
Stroke	24	12	45	21	102
Ischemic heart disease	46	18	16	75	155
Sudden death	22	3	6	0	31
Heart failure	…	14	9	4	…
Peripheral arterialdisease	…	3	2	26	…
Other cardiovascular	13	9	8	28	116
Fatal plus nonfatal events					
All cardiovascular[a]	272	121	179	357	929
Stroke	111	32	143	145	431
Cardiac events	173	86	31	207	497
Coronary events[b]	127	63	22	163	375
Myocardial infarction	97	31	12	134	274
Coronary revascularization	2	35	…	…	…
Heart failure	74	32	9	74	189

An ellipsis (…) indicates unavailable data.
[a]Cardiovascular deaths plus stroke and cardiac events. Nonfatal events do not add up because composite end points include only the first event.
[b]Mortality from coronary heart disease, including sudden death, plus myocardial infarction and coronary revascularization.

Table 3 Baseline characteristics of eligible cohorts still under follow-up

Characteristic	Allied Irish Bank Study [14]	EPOGH [17]	JingNing [8]	Leogra [16]	Montevideo [15]
Number of patients	815	1106	716	265	1925
Women, no (%)	416 (51.0)	611 (55.2)	389 (54.3)	128 (48.3)	1142 (59.3)
Age (years)	36.3 (11.7)	38.4 (14.3)	48.0 (15.4)	71.1 (4.9)	50.0 (15.7)
Body mass index (kg/m^2)[a]	24.1 (2.8)	25.4 (4.8)	22.4 (3.0)	27.5 (3.9)	26.9 (4.9)
Weight (kg)	68.2 (12.8)	72.3 (14.9)	54.6 (9.2)	74.0 (13.5)	73.4 (15.5)
Height (cm)	168 (9)	168 (9)	156 (8)	164 (8)	165 (10)
Blood pressure (mmHg)					
Conventional systolic	119.2 (15.3)	128.9 (19.3)	131.2 (25.2)	173.4 (21.5)	129.2 (24.2)
Conventional diastolic	73.1 (10.0)	81.1 (12.0)	78.8 (13.1)	94.1 (10.0)	80.4 (12.1)
24-h systolic	118.3 (11.4)	120.5 (12.0)	122.8 (17.2)	142.7 (13.0)	120.7 (14.8)
24-h diastolic	72.4 (7.5)	72.8 (8.2)	78.1 (10.8)	79.0 (6.7)	75.6 (9.2)
Daytime[b] systolic	124.7 (12.8)	126.9 (12.3)	128.0 (17.3)	149.1 (14.3)	123.9 (15.3)
Daytime[b] diastolic	78.7 (8.6)	78.1 (8.3)	82.4 (11.0)	83.6 (7.9)	78.5 (9.9)
Nighttime[b] systolic	106.4 (11.5)	109.3 (13.1)	113.7 (19.1)	131.3 (16.4)	111.5 (20.7)
Nighttime[b] diastolic	61.9 (8.3)	63.5 (9.5)	70.9 (12.0)	71.9 (8.6)	65.2 (10.4)
Serum cholesterol (mg/dl)[c]	Unavailable	198 (46)	191 (39)	233 (46)	221(44)
Smokers, no (%)	229 (28.1)	290 (26.2)	209 (29.2)	30 (11.3)	430 (22.3)
Drinkers, no (%)	658 (80.7)	394 (35.6)	387 (54.1)	215 (81.1)	548 (28.5)
Diabetes mellitus, no (%)	23 (2.8)	40 (3.6)	9 (1.3)	27 (10.2)	128 (6.6)
Cardiovascular disease, no (%)	26.3 (3.2)	72 (6.5)	6 (0.8)	61 (23.0)	132 (6.8)
Hypertension, no (%)[d]	0	368 (33.3)	267 (37.3)	263 (99.2)	762 (39.6)
Antihypertensive treatment, no (%)	0	183 (16.5)	97 (13.6)	74 (27.9)	350 (18.2)

Data are mean (SD) or number of patients (%). EPOGH indicates the European project on genes in hypertension, including participants recruited in Cracow, Poland (n=321), Novosibirsk, Russian Federation (n=304), Mirano, Italy (n=310), and Pilsen, the Czech Republic (n=171).
[a]Body mass index is body weight in kilograms divided by height in meters squared.
[b]Daytime ranged from 08:00 to 18:00 h in Chinese and from 10:00 to 20:00 h in the other studies. The corresponding nighttime intervals ranged from 22:00 to 04:00 h and from 00:00 to 06:00 h, respectively.
[c]To convert serum total cholesterol levels to millimoles per liter, divide by 38.67.
[d]Hypertension is a conventional blood pressure of at least 140 mmHg systolic or 90 mmHg diastolic or the use of antihypertensive drugs.

for. Indeed, in the older patients with isolated systolic hypertension randomized to placebo (n = 393) in the Systolic Hypertension in Europe trial [37], the 24-h, daytime (10:00 to 20:00 h) and nighttime (from 00:00 to 06:00 h) systolic blood pressures all predicted the incidence of cardiovascular complications, even after further adjustment for office blood pressure. In contrast, in the active-treatment group (n = 415), systolic blood pressure at entry did not significantly predict cardiovascular endpoints, regardless of the technique of blood-pressure measurement [37]. In the four cohorts currently included in the database, only one-fifth of the patients

were on antihypertensive drug treatment at baseline. All analyses will be adjusted for antihypertensive drug treatment. In addition, a sensitivity analysis in untreated patients is planned to show indisputably whether or not the results are confounded by antihypertensive drug treatment.

In contrast to several other studies [18,38] relating cardiovascular outcomes to the ambulatory blood pressure, we will analyze both fatal and nonfatal outcomes. The introduction of stroke units and the wide availability of invasive coronary care and thrombolysis recently reduced the case-fatality rate of most cardiovascular complications of hypertension. Not accounting for nonfatal events therefore limits the generalizability of some reports [18,38].

IDACO will provide the means to test several hypotheses that cannot be reliably analyzed in individual studies, because of low event rates or short follow-up. An important issue to be addressed is the prognostic significance of white-coat hypertension and masked hypertension. The interpretation of earlier studies on white-coat and masked hypertension is difficult, because of varying cut-off limits for hypertension on ambulatory measurement, because of the confounding effect of antihypertensive drug treatment in the hypertensive cohorts [39–43], and/or because of the restriction of outcome to a composite cardiovascular endpoint or mortality [18,44]. Special attention will be paid to the subgroup of patients with diabetes mellitus. As for conventional blood pressure [20], more conservative diagnostic thresholds for ambulatory blood pressure in this high-risk subgroup might be warranted.

In conclusion, IDACO will provide a unique opportunity to investigate several hypotheses that could not reliably be studied from individual studies. The results of these analyses might inform guidelines and be of help to clinicians involved in the management of patients with suspected or established hypertension.

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Appendix

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