

# The International Database of Central Arterial Properties for Risk Stratification: Research Objectives and Baseline Characteristics of Participants

Lucas S. Aparicio<sup>1,2,\*</sup>, Qi-Fang Huang<sup>3,\*</sup>, Jesus D. Melgarejo<sup>2</sup>, Dong-Mei Wei<sup>2</sup>, Lutgarde Thijs<sup>2</sup>, Fang-Fei Wei<sup>2,4</sup>, Natasza Gilis-Malinowska<sup>5</sup>, Chang-Sheng Sheng<sup>3</sup>, José Boggia<sup>6</sup>, Teemu J. Niiranen<sup>7,8</sup>, Augustine N. Odili<sup>9</sup>, Katarzyna Stolarz-Skrzypek<sup>10</sup>, Jessica Barochiner<sup>1</sup>, Daniel Ackermann<sup>11</sup>, Kalina Kawecka-Jaszcz<sup>10</sup>, Valérie Tikhonoff<sup>12</sup>, Zhen-Yu Zhang<sup>2</sup>, Edoardo Casiglia<sup>12</sup>, Krzysztof Narkiewicz<sup>5</sup>, Jan Filipovský<sup>13</sup>, Aletta E. Schutte<sup>14,15</sup>, Wen-Yi Yang<sup>2,16</sup>, Antti M. Jula<sup>7</sup>, Angela J. Woodiwiss<sup>17</sup>, Murielle Bochud<sup>18</sup>, Gavin R. Norton<sup>17</sup>, Ji-Guang Wang<sup>3</sup>, Yan Li<sup>3,t</sup>, Jan A. Staessen<sup>19,20,t</sup>, and the International Database of Central Arterial Properties for Risk Stratification (IDCARS) Investigators<sup>‡</sup>

## OBJECTIVE

To address to what extent central hemodynamic measurements, improve risk stratification, and determine outcome-based diagnostic thresholds, we constructed the International Database of Central Arterial Properties for Risk Stratification (IDCARS), allowing a participant-level meta-analysis. The purpose of this article was to describe the characteristics of IDCARS participants and to highlight research perspectives.

## METHODS

Longitudinal or cross-sectional cohort studies with central blood pressure measured with the SphygmoCor devices and software were included.

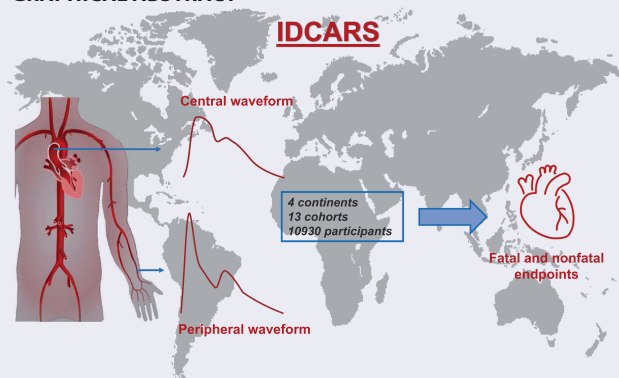
## RESULTS

The database included 10,930 subjects (54.8% women; median age 46.0 years) from 13 studies in Europe, Africa, Asia, and South America. The prevalence of office hypertension was 4,446 (40.1%), of which 2,713 (61.0%) were treated, and of diabetes mellitus was 629 (5.8%). The peripheral and central systolic/diastolic blood pressure averaged 129.5/78.7 mm Hg and 118.2/79.7 mm Hg, respectively. Mean aortic pulse wave velocity was 7.3 m per seconds. Among 6,871 participants enrolled in 9 longitudinal studies, the median follow-up was 4.2 years (5th–95th percentile interval, 1.3–12.2 years). During 38,957 person-years of follow-up, 339 participants experienced a composite cardiovascular event and 212 died, 67 of cardiovascular disease.

## CONCLUSIONS

IDCARS will provide a unique opportunity to investigate hypotheses on central hemodynamic measurements that could not reliably be studied in 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.

## GRAPHICAL ABSTRACT



**Keywords:** blood pressure; cardiovascular outcome; central blood pressure; hemodynamics; hypertension; pulse wave analysis; pulse wave velocity.

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Correspondence: Jan A. Staessen ([jan.staessen@appremed.org](mailto:jan.staessen@appremed.org); [jan.staessen@med.kuleuven.be](mailto:jan.staessen@med.kuleuven.be)).

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<sup>1</sup>Servicio de Clínica Médica, Sección Hipertensión Arterial, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; <sup>2</sup>Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium; <sup>3</sup>Center for Epidemiological Studies and Clinical Trials and Center for Vascular Evaluations, Shanghai Key Laboratory of Hypertension, Shanghai Institute of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; <sup>4</sup>Department of Cardiology, the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong, China; <sup>5</sup>Hypertension Unit, Department of

Hypertension and Diabetology, Medical University of Gdańsk, Gdańsk, Poland;<sup>6</sup>Centro de Nefrología and Departamento de Fisiopatología, Hospital de Clínicas, Universidad de la República, Montevideo, Uruguay;<sup>7</sup>Department of Chronic Disease Prevention, Finnish Institute for Health and Welfare, Turku, Finland;<sup>8</sup>Department of Medicine, University of Turku and Turku University Hospital, Turku, Finland;<sup>9</sup>Department of Internal Medicine, Faculty of Clinical Sciences, College of Health Sciences, University of Abuja, Abuja, Nigeria;<sup>10</sup>First Department of Cardiology, Interventional Electrophysiology and Hypertension, Jagiellonian University Medical College, Kraków, Poland;<sup>11</sup>Clinic for Nephrology and Hypertension, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland;<sup>12</sup>Department of Medicine, University of Padua, Padua, Italy;<sup>13</sup>Faculty of Medicine, Charles University, Pilsen, Czech Republic;<sup>14</sup>Hypertension in Africa Research Team (HART), South African Medical Research Council and Unit of Hypertension and Cardiovascular Disease, North-West University, Potchefstroom, South Africa;<sup>15</sup>School of Population Health, University of New South Wales, The George Institute for Global Health, Sydney, Australia;<sup>16</sup>Department of Cardiology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China;<sup>17</sup>Cardiovascular Pathophysiology and Genomics Research Unit, Schools of Physiology, Faculty of Health

Sciences, University of the Witwatersrand, Johannesburg, South Africa;<sup>18</sup>Institute of Social and Preventive Medicine, University Hospital of Lausanne, Lausanne, Switzerland;<sup>19</sup>Research Institute Alliance for the Promotion of Preventive Medicine, Mechelen, Belgium;<sup>20</sup>Biomedical Sciences Group, Faculty of Medicine, University of Leuven, Leuven, Belgium.

\*Joint first authors who contributed equally to this work.

†Joint last authors who contributed equally to this work.

‡The International Database of Central Arterial Properties for Risk Stratification (IDCARS) Investigators are listed in the Appendix.

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## INTRODUCTION

Blood pressure is the major modifiable cardiovascular risk factor.<sup>1</sup> The Global Burden of Diseases Study reported that hypertension is the leading risk factor for ill health, causing 10.8 million deaths worldwide each year, which is more than half of the total cardiovascular mortality.<sup>2</sup> Based on the seminal work by Michel Safar<sup>3</sup> and Michael O'Rourke,<sup>4</sup> the perception that cardiovascular events are closer related to central than to brachial blood pressure has become a mainstream idea. The anatomical proximity of the aorta to the heart, brain and kidney, systolic augmentation from the central to the peripheral arteries, and the degradation of the arterial elastic properties with advancing age also contributed to the growing interest in the pathophysiological role of central blood pressure.

While theoretically sound,<sup>5–7</sup> the evidence supporting the association of cardiovascular events with central blood pressure, over and beyond brachial blood pressure, remains controversial. Roughly half of the published studies had a cross-sectional design with preclinical outcomes.<sup>8–15</sup> The longitudinal studies related a wide array of outcomes with central blood pressure, but applied different technologies to quantify the risk marker and not always accounted for peripheral blood pressure.<sup>10,11,16–25</sup> Other factors limiting the interpretation of the available literature are a sample size of less than 200 study participants,<sup>8,9,17,18,26–29</sup> a follow-up of 12 months or less,<sup>16–18</sup> selective enrollment of patients with hypertension,<sup>8,13,21,22,26,27,30,31</sup> chronic kidney disease,<sup>9,12,18</sup> or coronary heart disease.<sup>16,17,20</sup> To address this knowledge gap, we constructed the International Database of Central Arterial Properties for Risk Stratification (IDCARS), allowing a participant-level meta-analysis. The purpose of this article was to describe the baseline characteristics of IDCARS participants and to highlight research perspectives that will be pursued in the future, using the IDCARS resource.

## METHODS

### Identification of studies

Longitudinal cohort studies qualified for inclusion if information on brachial and central blood pressure and

cardiovascular risk factors was available at baseline, if the central blood pressure had been tonometrically measured, using SphygmoCor devices and software (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia and AtCor Medical Inc., Itasca, IL), if follow-up included both fatal and nonfatal endpoints, if study reports had been published in peer-reviewed articles, and if the study participants had been sampled from a population or in case of a convenience sample they were representative for the community from which they were enrolled. Cross-sectional studies of populations and hypertensive patients without information on fatal and nonfatal outcomes also qualified, provided that all other eligibility criteria were met. We identified studies qualifying for inclusion in the IDCARS resource by approaching investigators networked in the International Databases on Ambulatory (IDACO)<sup>32</sup> and Home (IDHOCO)<sup>33</sup> Blood Pressure in Relation to Cardiovascular Outcome.

All studies complied with the Helsinki Declaration on research in humans<sup>34</sup> and were approved by the competent Institutional Review Boards. Participants provided informed written consent. Before transfer to the coordinating office in Leuven, Belgium, the data were stripped from all personal identifiers, and if required by national legislations, additional ethical clearances were obtained. The [Supplementary Data](#) provides further study-specific information on the catchment areas, sampling strategies, recruitment, participation rate, the number of participants enrolled, and related literature sources ([Supplementary Tables S1 and S2](#) available in the [Supplementary Data](#)).

### Brachial blood pressure

Office blood pressure was measured in the sitting position by auscultation of the Korotkoff sounds or oscillometrically according to contemporary national or European guidelines, which did not substantially change over time.<sup>35</sup> Up to five consecutive readings were recorded ([Supplementary Table S3](#)), but for analysis only the first two were averaged. In some instances, only a single office reading was available. Office hypertension was a blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic or use of antihypertensive

drugs irrespective of the blood pressure level. Estimates of central blood pressure were calibrated, using one or the average of three additional blood pressure readings, which were obtained after the participants had rested in the supine position for at least 5 minutes, but in most instances for a longer period up to 15 minutes. If two blood pressure readings were obtained, the second was employed for calibration (Supplementary Table S3).

### Pulse wave analysis

In most cohorts, experienced observers recorded the radial arterial waveform at the dominant arm during an 8-second period by applanation tonometry. They used a high fidelity SPC-301 micromanometer (Millar Instruments Inc., Houston, TX) interfaced with a SphygmoCor CvMS device and a laptop computer running SphygmoCor software. If multiple recordings were available from an individual, the record with the highest quality was selected for inclusion in the IDCARS database.

From the radial signal, the SphygmoCor software calculates the aortic pulse wave by means of a validated generalized transfer function.<sup>36,37</sup> The software returns the central systolic, diastolic and pulse pressure, and the pressure at the first and second peak (shoulder) of the central waveform (Supplementary Figure S1). The augmentation ratio and index are quotients of the second over the first peak of the central blood pressure wave and of the absolute difference between the second and first peak over central pulse pressure, both expressed as a percentage. For future analyses, a pressure-based triangular-flow wave separation algorithm will be applied,<sup>38</sup> as implemented in the SphygmoCor software, version 10, which allows computing the forward and backward pulse pressure amplitudes (Supplementary Figure S1) and the timing of their peak height, relative to the electrocardiographic QRS complex. Similarly, reimporting the SphygmoCor data files into software version 10 will also enable recalibrating the pulse wave analysis based on mean arterial pressure defined as diastolic blood pressure plus either 33% or 40% of pulse pressure, the difference between systolic and diastolic blood pressure.<sup>39</sup> The reflection index is the ratio of the backward to the forward pulse pressure amplitude, expressed as percentage.

In the cohort enrolled at Potchefstroom, South Africa, central blood pressure was recorded by the SphygmoCor XCEL, according to the procedures recommended by the manufacturer ([www.youtube.com/watch?v=cjps2t1f6X8](http://www.youtube.com/watch?v=cjps2t1f6X8)). This automated device has been validated against invasive recordings of central blood pressure<sup>40,41</sup> and manual tonometric measurements.<sup>42</sup>

### Pulse wave velocity

In most cohorts, aortic pulse wave velocity was measured by sequential electrocardiographically gated recordings of the arterial pressure waveform at the carotid and femoral arteries. The observers measured the distance from the suprasternal notch to the carotid sampling site (distance A), and from the suprasternal notch to the femoral sampling site (distance B). Pulse wave travel distance was calculated as

distance B minus distance A.<sup>43</sup> Pulse transit time was the average of 10 consecutive beats.<sup>44</sup> Carotid-femoral pulse wave velocity is the ratio of the travel distance in meters to transit time in seconds. Pulse wave velocity was discarded if the standard error of the mean of 10 beats was more than 10%. Participants enrolled at Potchefstroom, South Africa, had their pulse wave velocity measured using the SphygmoCor XCEL, according to the instructions of the manufacturer ([www.youtube.com/watch?v=7SPFDToCR0U](http://www.youtube.com/watch?v=7SPFDToCR0U)). This device has been validated for assessment of pulse wave velocity.<sup>42,45</sup> Carotid pulse waves were registered with a tonometer, as with the SphygmoCor device, whereas the femoral pulse wave was recorded, using a partially inflated oscillometric cuff positioned around the thigh.<sup>46,47</sup> Thus, in contrast to the SphygmoCor CvMS, the SphygmoCor XCEL allows simultaneous registration of the carotid and femoral pulse waves.

### Other baseline measurements

Data collection at baseline included information on each individual's medical history, smoking and drinking habits, and intake of medications. Body mass index was body weight in kilograms divided by height in meters squared. Serum levels of total and high-density lipoprotein (HDL) cholesterol and creatinine and blood glucose were determined at the study sites by automated techniques in certified laboratories. Diabetes mellitus was a self-reported diagnosis, a fasting or non-fasting blood glucose level of at least 126 mg per deciliter (7.0 mmol per liter) or 200 mg per deciliter (11.1 mmol per liter) or higher, or use of antidiabetic drugs.<sup>48</sup>

### Primary and secondary outcomes

The primary endpoint in future analyses will be a composite cardiovascular endpoint, including cardiovascular mortality, nonfatal myocardial infarction, heart failure and stroke, and surgical or percutaneous coronary revascularization or pacemaker implantation. Secondary endpoints include (i) all-cause, cardiovascular and noncardiovascular mortality, (ii) coronary events (mortality from ischemic heart disease and sudden death, nonfatal myocardial infarction, acute coronary syndrome and coronary revascularization, including or not including stable angina pectoris); (iii) cardiac events (coronary events, fatal and nonfatal heart failure, pacemaker implantation, and other cardiac deaths), (iv) and cerebrovascular events (fatal and nonfatal stroke, including or not including transient ischemic attack).

In terms of coding according to the international classification of diseases (ICD), stroke is defined as ICD-8 or ICD-9 codes 430–434 or 436, or ICD-10 codes I60–I64. Myocardial infarction is coded ICD-8 or ICD-9 code 410 or ICD-10 codes I21–I22, and heart failure as ICD8 codes 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 were unavailable in the transferred data,



the definition of events as provided by the investigators were accepted with reference to the publications on each cohort in the peer-reviewed literature.

### Statistical analysis

For database management and statistical analysis, SAS software, version 9.4 (SAS Institute, Cary, NC) was used. For longitudinal studies, median follow-up time was estimated by the reverse Kaplan–Meier method. We standardized the time-dependent hemodynamic measurements, including the augmentation index and pressure amplification to a heart rate of 75 beats per minute. Means and proportions were compared between groups by the large sample z-test or ANOVA and by the  $\chi^2$  statistic, respectively. Statistical methods also included single and multiple regression analysis.

After stratification for cohort and sex, we interpolated missing values of body mass index and serum cholesterol levels from the regression slopes on age. In participants with unknown status of smoking, drinking, antihypertensive treatment, diabetes mellitus, or unknown history of cardiovascular disease, we set the indicator (dummy) variable to the cohort- and sex-specific mean of the codes (0, 1). Information on alcohol intake was not available for the cohort recruited in Buenos Aires, Argentina. Following methods applied in previous publications,<sup>49</sup> we extrapolated alcohol consumption in adult Argentinians from data stratified by sex and age.<sup>50–52</sup>

## RESULTS

### Characteristics of studies

Thirteen studies were included in the IDCARS database (Figure 1), of which eleven were population studies. Among the population studies (Supplementary Table S1), six were conducted in Europe, three in Africa, one in Asia, and one in South America. The sampling of participants was random, using a family-based ( $n = 7$ ) or age-stratified ( $n = 1$ ) sampling frame, or in the case of Finland and South Africa, a two-stage cluster sampling method with the goal to enroll individuals representative of the Finnish population ( $n = 1$ ) or a random sample of Black residents of Johannesburg ( $n = 1$ ) or a convenience sample of healthy volunteers, aged 20–30 years, who were stratified by ethnicity and recruited in Potchefstroom ( $n = 1$ ). Of the population studies (Supplementary Table S1), eight applied epidemiological and phenotyping methods similar to those used in the Flemish Study on Environment and Genes in Relation to Health Outcomes. The IDCARS database included two studies of hypertensive patients, respectively recruited in Buenos Aires, Argentina, and in Gdańsk, Poland. Supplementary Table S2 and the reference list available in the Supplementary Data provide the literature sources describing the design characteristics of the 13 studies in detail.

### Assessment of the central hemodynamics

Published articles describing the procedures for measuring the central hemodynamics are available for each study in Supplementary Table S2. In 12 studies (Supplementary Table

S3), the central hemodynamics were recorded by SphygmoCor CvMS devices and software versions ranging from 6.2 to 9.0. In Potchefstroom, South Africa, investigators used the SphygmoCor XCEL and software version 1.3 to acquire the hemodynamic data. To calibrate the pulse wave analysis with the signal recorded by the SphygmoCor CvMS approach, investigators measured brachial blood pressure by either Omron 705CP, Omron M6 or Omron 714/7220 devices, or by a standard mercury sphygmomanometer after participants had rested in the supine position for intervals ranging from 5 to 15 minutes (Supplementary Table S3). The number of readings obtained ranged from 1 to 3, but only the average or the last of two readings was used for calibration of the central pulse wave in IDCARS. At the acquisition stage, immediately prior to the SphygmoCor measurements, the pulse wave analysis was calibrated on brachial systolic and diastolic blood pressure, but recalibration to mean arterial and diastolic blood pressure will be implemented, using software version 10.0.

### Clinical and biochemical characteristics of participants

At the time of writing of this article, the IDCARS database included 10,930 individuals. Missing values at baseline, i.e., the date at which the hemodynamic measurements were obtained, were interpolated for body mass index ( $n = 32$ ), total ( $n = 483$ ) and high-density lipoprotein ( $n = 828$ ) serum cholesterol, serum creatinine ( $n = 704$ ), blood glucose ( $n = 322$ ), smoking ( $n = 344$ ) and drinking ( $n = 1,243$ ) status, use of antihypertensive medications at baseline ( $n = 77$ ), and history of cardiovascular disease ( $n = 513$ ).

The whole study population included 5,994 women (54.8%). The self-reported ethnicity was White in 6,391 participants (58.5%), Black in 2,389 (21.9%), Chinese in 2,069 (18.9%) and mixed or other in 81 (0.7%). The prevalence of office hypertension was 4,446 (40.7%), of which 2,713 (61.0%) were treated; 629 (5.8%) participants had diabetes. A history of cardiovascular disease, ischemic heart disease or stroke was reported in 1,052 (10.1%), 241 (2.6%), and 130 (1.3%) participants.

Mean age at baseline was 46.0 years (5th–95th percentile interval [PI5–95], 21.0–76.2 years). In all study participants (Table 1), mean values were 26.1 kg/m<sup>2</sup> (PI5–95, 19.0–36.7 kg/m<sup>2</sup>) for body mass index, 127.5/78.8 mm Hg (PI5–95, 100.0–166.0/61.0–98.5 mm Hg) for office systolic/diastolic blood pressure, 68.4 beats per minute (PI5–95, 52–87 beats per minute) for pulse rate, 184.8 mg/dL (PI5–95, 116.9–257.7 mg/dL) and 55.3 mg/dL (PI5–95, 31.9–83.6 mg/dL) for total and HDL serum cholesterol, 0.9 mg/dL (PI5–95, 0.6–1.3 mg/dL) for serum creatinine, and 88.8 mg/dL (PI5–95, 60.5–117.0 mg/dL) for blood glucose. The prevalence of smoking and drinking was 660 (11.4%) and 1,845 (35.1%) among women and 1,558 (32.6%) and 2,864 (64.7%) among men. The waist-to-hip ratio averaged 0.83 (PI5–95, 0.7–1.0) in women and 0.89 (PI5–95, 0.8–1.0) in men. Supplementary Tables S4–S16 provide detailed information on the baseline measurements in each of the 13 cohorts.

### Hemodynamic measurements

Table 2 lists mean values of the peripheral (brachial) blood pressure levels as recorded in the supine position just prior

to the hemodynamic assessment, the central blood pressure levels, and the time-dependent hemodynamic measurement. The peripheral supine blood pressure averaged 129.5 mm Hg systolic and 78.7 mm Hg diastolic. The corresponding central values were 118.2 mm Hg and 79.7 mm Hg, respectively. Mean aortic pulse wave velocity was 7.3 m per second. [Supplementary Tables S4–S16](#) provide the similar information for each cohort and [Supplementary Table S17](#) highlights the sex differences in the peripheral and central blood pressure and in the time-dependent hemodynamic measurements.

### Incidence of events

Among 6,871 participants enrolled in nine longitudinal studies, the median follow-up was 4.2 years (PI5-95, 1.3–12.2 years). Across cohorts ([Supplementary Table S1](#)), the median follow-up ranged from 2.3 years (PI5-95, 1.4–3.1) to

14.1 years (PI5-95, 8.5–14.4 years). During 38,957 person-years of follow-up, 339 participants experienced a composite cardiovascular event (8.7 per 1,000 person-years) and 212 participants died (5.4 per 1,000 person-years), 67 (1.7 per 1,000 patient-years) of cardiovascular disease. [Table 3](#) lists the number of events by category that had accrued at the time of writing of this manuscript.

### DISCUSSION

This article describes the construction of the IDCARS database and the characteristics of the cohort studies and participants enrolled. Of the 13 included studies, eight applied epidemiological and phenotyping methods similar to those used in the Flemish Study on Environment and Genes in Relation to Health Outcomes. This is an important advantage, which greatly facilitated data harmonization. As shown in [Supplementary Tables S4–S16](#), IDCARS covers a wide

**Table 1.** Characteristics of 10,930 participants enrolled in 13 studies

Characteristic	No	Statistic before interpolation	Statistic with interpolation
No (%) of participants with characteristic			
Women	10,930	5,995 (54.8)	5,995 (54.8)
Region of enrolment			
Europe	10,930	4,140 (37.9)	4,140 (37.9)
JingNing, China	10,930	2,069 (18.9)	2,069 (18.9)
Africa	10,930	2,968 (27.2)	2,968 (27.2)
South America	10,930	1,753 (16.0)	1,753 (16.0)
Current smoking	10,586	2,218 (21.0)	2,218 (20.3)
Drinking alcohol	9,687	4,709 (48.6)	5,226 (47.8)
Hypertension	10,930	4,446 (40.1)	4,446 (40.1)
On antihypertensive treatment	10,853	2,713 (61.0)	2,713 (61.0)
Diabetes mellitus	10,930	629 (5.8)	629 (5.8)
History of cardiovascular disease	10,417	1,052 (10.1)	1,052 (10.1)
Mean ( $\pm$ SD) characteristic			
Age, y	10,930	46.0 $\pm$ 18.0	46.0 $\pm$ 18.0
Body mass index, kg/m <sup>2</sup>	10,898	26.1 $\pm$ 5.6	26.0 $\pm$ 5.6
Office systolic blood pressure, mm Hg	10,734	127.5 $\pm$ 20.4	127.5 $\pm$ 20.4
Office diastolic blood pressure, mm Hg	10,733	78.8 $\pm$ 11.3	78.8 $\pm$ 11.3
Heart rate, beats per minute	9,569	68.4 $\pm$ 11.0	68.4 $\pm$ 11.0
Serum total cholesterol, mg/dL	10,447	184.8 $\pm$ 43.2	185.1 $\pm$ 42.3
Serum high-density lipoprotein cholesterol, mg/dL	10,102	55.3 $\pm$ 16.1	55.2 $\pm$ 15.8
Total-to-high-density-lipoprotein cholesterol ratio	10,097	3.6 $\pm$ 2.6	3.6 $\pm$ 2.5
Serum creatinine, mg/dL	10,226	0.9 $\pm$ 0.3	0.9 $\pm$ 0.3
Blood glucose, mg/dL	10,608	88.8 $\pm$ 24.8	89.0 $\pm$ 24.5

Characteristics refers to baseline data of 6,871 participants enrolled in nine longitudinal cohort studies or to data at recruitment in 4,059 participants enrolled in four cross-sectional studies. No indicates the number of participants with available measurements. Hypertension was an office BP of  $\geq 140$  mm Hg systolic or  $\geq 90$  mm Hg diastolic or use of antihypertensive drugs. Diabetes mellitus was use of antidiabetic drugs, fasting blood glucose of  $\geq 126$  mg/dL (7.0 mmol/L), random blood glucose of  $\geq 200$  mg/dL (11.1 mmol/L), a self-reported diagnosis, or diabetes documented in practice or hospital records. Office blood pressure was the average of two readings in 9,787 participants or based on a single reading in 947 participants. Body mass index was body weight in kilogram divided by height in meters squared.

**Table 2.** Hemodynamic characteristics of 10,930 participants enrolled in 13 studies

Characteristic	No	Statistic
Peripheral blood pressure		
Systolic pressure, mm Hg	10,834	129.5 ± 20.4
Diastolic pressure, mm Hg	10,836	78.7 ± 11.2
Pulse pressure, mm Hg	10,834	50.7 ± 15.6
Mean arterial pressure, mm Hg	9,637	97.3 ± 14.4
Central blood pressure		
Systolic pressure, mm Hg	10,834	118.2 ± 20.9
Diastolic pressure, mm Hg	10,835	79.7 ± 11.3
Pulse pressure, mm Hg	10,833	38.5 ± 15.1
Mean arterial pressure, mm Hg	10,835	96.1 ± 14.2
Time dependent central hemodynamics		
Augmentation index, %	10,812	22.2 ± 15.6
Augmentation index 75, %*	9,908	17.8 ± 15.2
Augmentation ratio, %	10,810	134.0 ± 27.4
Pressure amplification, mm Hg	10,811	9.9 ± 9.3
Pressure amplification 75, mm Hg*	7,320	8.3 ± 8.0
Aortic pulse wave velocity, m/s	7,601	7.3 ± 2.3

Values are mean ± SD. Hemodynamic characteristics refer to measurements obtained at baseline in 6,871 participants enrolled in nine longitudinal cohort studies or to measurements obtained at recruitment in 4,059 participants enrolled in four cross-sectional studies. No indicates the number of participants with available measurements. Peripheral blood pressure was measured in the supine position immediately prior to the tonometric assessment of the participants. These measurements were used to calibrate the central hemodynamic measurements. Mean arterial pressure was diastolic blood pressure plus one third of pulse pressure, the difference between systolic and diastolic blood pressure.

\*The time-dependent hemodynamic variables were standardized to a heart rate of 75 beats per minute.

diversity of ethnicities, the whole blood pressure spectrum from normotension up to hypertension, and an age span ranging from teenagers to the very old.

Meta-analytic methods involve combining and analyzing quantitative evidence from related studies to produce “new” results based on a comprehensive body of research. As such, meta-analyses are an integral part of evidence-based medicine.<sup>53</sup> Traditional meta-analyses synthesize aggregate data obtained from study publications or study authors, while IDCARS was designed as meta-analysis of individual participant data, in which raw data from each study were obtained and will be used for analysis. Although being more resource-intensive and time-consuming than the aggregate level approach, individual data-based meta-analyses have more power, allow the use of the same statistical approach across contributing studies, give more flexibility to extend or refine the planned analyses, and to account for heterogeneity across cohorts.<sup>53</sup> IDCARS, like its predecessors IDACO<sup>32</sup> and IDHOCO<sup>33</sup> should provide investigators the opportunity to investigate several hypotheses linking cardiovascular outcomes to central hemodynamic indexes that could not

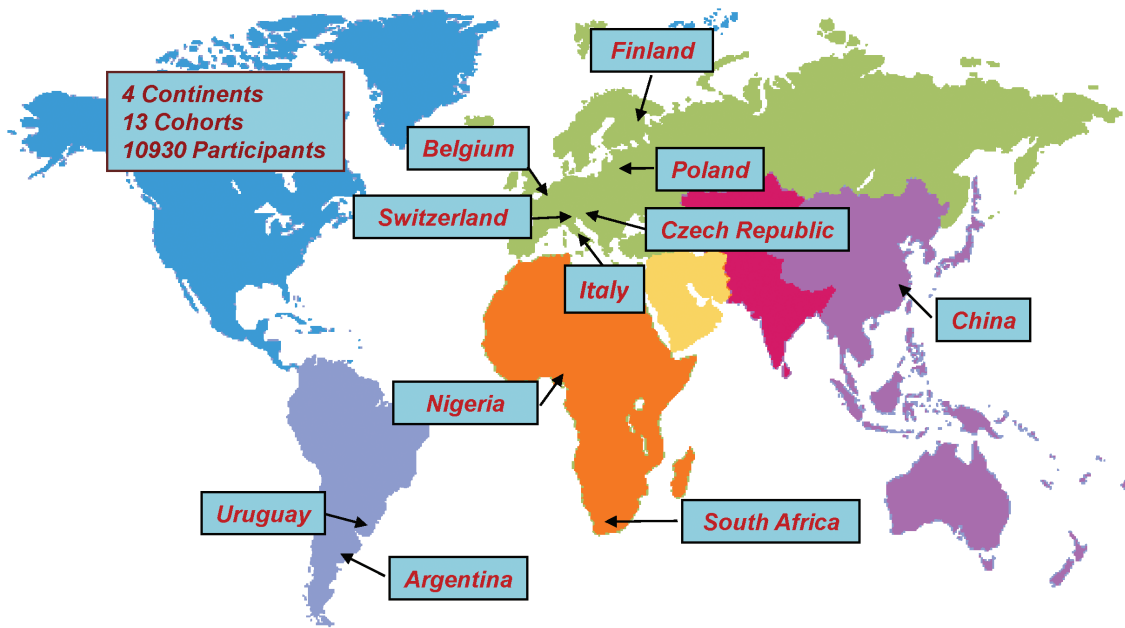
**Table 3.** Incidence of events in 6,871 participants enrolled in nine longitudinal studies

Event	n	Fatal	Nonfatal
Total mortality	...	212	...
Cardiovascular mortality	...	67	...
Sudden death	...	7	...
Ischemic heart disease	...	10	...
Heart failure	...	14	...
Peripheral arterial disease	...	2	...
Other cardiovascular disease	...	6	...
Stroke	...	28	...
Noncardiovascular mortality	...	123	...
Death from renal failure	...	3	...
Cause of death unknown	...	19	...
Composite cardiovascular endpoint			
Coronary heart disease	176		
Sudden death	7	7	...
Myocardial infarction	43	5	38
Coronary revascularization	73	...	73
Other ischemic heart disease	53	...	53
Heart failure	70	14	56
Stroke	93	28	65
Other nonfatal cardiovascular outcomes			
Atrial fibrillation	61	...	61
Pacemaker implantation	13	...	13
Transient ischemic attack	22	...	22

Median follow-up of the 6,871 participants was 4.2 years (5th to 95th percentile interval, 1.3–12.2 years). The composite and nonfatal events do not add up, because within each category only the first event was analyzed. An ellipsis indicates not applicable.

be reliably studied in the smaller cohorts of the contributing studies.

The central concept in the clinical application of central blood pressure is that target organ damage is more closely associated with aortic than with peripheral blood pressure. However, 70% of individuals with high-normal brachial pressure had similar aortic pressures as those with stage-1 hypertension.<sup>54</sup> The added prognostic value of central over peripheral blood pressure still remains controversial.<sup>6</sup> A first IDCARS report demonstrated that in adults older than 30 years the associations of the primary and secondary cardiovascular IDCARS endpoints with central systolic blood pressure and pulse pressure were not tighter than with their peripheral counterparts.<sup>55</sup> Future IDCARS analyses will enable to address several issues. First, we will investigate the prognostic information generated by various indexes derived from the radial, carotid and central pulse waveforms, such as but not limited to forward and backward pulse pressure amplitude, the augmentation indexes, and pulse wave velocity. Next, for the indexes showing association with adverse health outcomes, we will derive outcome-driven



**Figure 1.** Geographical spread of IDCARS participants. Two cohorts were enrolled in Poland and South Africa.

thresholds and construct predictive models in an attempt to clarify whether these arterial phenotypes improve the currently applied risk scores.<sup>56,57</sup>

For the noninvasive assessment of carotid-femoral pulse wave velocity the estimation of the pulse wave travel distance is critical. In 135 patients, aortic pulse wave velocity was invasively measured during cardiac catheterization, from the delay in wave foot and the distance travelled as the catheter was withdrawn from the ascending aorta to the aortic bifurcation.<sup>43</sup> On the next day, noninvasive the carotid-femoral pulse wave velocity was assessed, using the SphygmoCor system, relating the delay between carotid and femoral wave foot to travel distance, estimated with five different methods on body surface.<sup>43</sup> The best agreement with the invasive measurements was found for the subtraction method (Spearman's  $R$ , 0.77),<sup>43</sup> as applied in the IDCARS centers. On the other hand, in 98 healthy volunteers, the true anatomical carotid-femoral travel path length was measured by MRI (reference) and compared with 11 estimates of aortic path length, nine based on tape measures and two based on body height. The tape measure distance from carotid to femoral artery, multiplied by 0.8, yielded the best agreement with the reference aortic path length.<sup>58</sup> Subsequently, a European consensus document provided arguments for the use of 80% of the direct carotid-femoral distance as the most accurate estimate of aortic pulse wave travel distance.<sup>59</sup> However, multiplying the subtraction-derived travel path by 1.25 provides the aortic length estimated by direct measurement of the carotid-femoral distance. Multiplication by this constant will not affect the significance of the association sizes of endpoints with carotid-femoral pulse wave velocity.

In IDCARS, a single noninvasive system (SphygmoCor) has been used for the estimation of the central hemodynamic traits via a generalized transfer function.<sup>36,37</sup> As stated in the Methods, quality control of the arterial phenotypes was rigorously standardized. While the use

of a single system might be considered as a strength in terms of the standardization of the arterial phenotypes, it might also limit generalizability. Among the noninvasive instruments used to estimate central blood pressure, the SphygmoCor apparatus is classified as a type-1 device,<sup>60</sup> which provides an estimate of the central blood pressure relative to the measured brachial blood pressure and which generates a relatively accurate pressure difference between peripheral and central blood pressure. The accuracy in deriving the central blood pressure is critically dependent on the calibration of the waveform recorded at the carotid or radial artery. The estimated central blood pressure is most accurate, if these peripheral waveforms are calibrated against the invasively measured blood pressure.<sup>61,62</sup> However, in IDCARS, the brachial cuff blood pressure was used for calibration. This introduces error as a consequence of the recognized underestimation of intra-arterial brachial systolic blood pressure together with overestimation of intra-arterial brachial diastolic blood pressure.<sup>62,63</sup> Furthermore, amplification of systolic blood pressure from the brachial to radial arteries may compound the error in the underestimation of the central systolic blood pressure and central pulse pressure, when radial artery waveforms are calibrated using brachial systolic and diastolic blood pressure.<sup>64</sup> Data from a meta-analysis indicated that using mean arterial pressure and diastolic blood pressure could be the preferred calibration option to provide a relatively more accurate noninvasive estimation of central systolic blood pressure.<sup>65</sup> Most IDCARS centers (Supplementary Table S3) used oscillometric devices to measure brachial blood pressure. These devices derive mean arterial pressure from the envelope drawn around the maximal pressure oscillations in the brachial cuff, an argument in favor of the calibration involving mean arterial pressure, and extrapolate systolic and diastolic blood pressure by the embedded proprietary



software.<sup>66,67</sup> Alternatively, mean arterial pressure may be calculated from the brachial cuff blood pressure as diastolic plus 33% or 40% of pulse pressure.<sup>39</sup>

The reconstruction of the aortic pulse wave from the radial or brachial pulse wave requires the application of a generalized transfer function, which has been validated,<sup>36,37</sup> but which has also been criticized.<sup>68</sup> Although the SphygmoCor device uses a single sensor for applanation tonometry, some validation studies of the generalized transfer function have utilized a servo-controlled automated tonometric system based on an arrayed sensor to avoid issues related to a manually operated single sensor.<sup>69,70</sup> Given the scepticism surrounding the SphygmoCor technology,<sup>71</sup> possible differences in successive software versions and the issues related to calibration, the SphygmoCor data files will be reimported in version 10 of the software. This will enable recalibrating the pulse wave analysis based on mean arterial pressure<sup>39</sup> and diastolic blood pressure. Furthermore, in experienced hands, version 10 of the SphygmoCor software also allows pulse wave decomposition and computing the forward and backward pulse pressure amplitudes (Supplementary Figure S1) and the timing of their peak height, relative to the electrocardiographic QRS complex. Wave decompositions is opening new research horizons, in particular in the identification of vascular risk factors<sup>72</sup> or ventriculoarterial coupling,<sup>73</sup> which both might adversely affect the IDCARS study endpoints.

While the IDCARS database is a powerful resource, some limitations in its exploitation must also be acknowledged. First, the anthropometric characteristics, the period of recruitment, and the assessment of endpoint data differed between cohorts. However, analyses will be adjusted for cohort as a random effect and analyses will be stratified by cohort, as appropriate. Participant-level meta-analyses allow applying the same statistical methods to all contributing cohorts and to assess and account in detail for the heterogeneity across cohorts, for instance by excluding cohorts in sensitivity analyses.<sup>53</sup> This statistical approach proved to be feasible.<sup>55</sup> Moreover, the diversity of the IDCARS cohorts might strengthen the generalizability of the project's results. Second, confounding factors, such as antihypertensive treatment, smoking and drinking status, or renal dysfunction, were only assessed at baseline so that they cannot be accounted for in a time dependent manner. However, we intend to update the IDCARS database at 5-year intervals in the same way as we did for IDACO<sup>32</sup> and IDHOCO.<sup>33</sup> Finally, IDCARS will generate information on the association of adverse health outcomes with central hemodynamic measurements. Reference values for the parameters derived by pulse wave analysis have been proposed for Blacks born and living in Africa,<sup>74</sup> Chinese<sup>75,76</sup> and White Europeans,<sup>77</sup> and for pulse wave velocity by consensus among experts.<sup>59</sup> While in the hierarchy of evidence, longitudinal studies outperform cross-sectional analyses, the ultimate validation of the clinical utility of such parameters must come from randomized clinical trials. The design of such trials will be challenging considering the choice of drugs<sup>22</sup> or dietary interventions<sup>72</sup> that might reduce central blood pressure more than peripheral blood pressure. For example, in the Conduit Artery Function Evaluation Study,<sup>22</sup> 2,199 patients were randomized to treatment

with atenolol ± bendroflumethiazide or amlodipine ± perindopril. Although brachial systolic blood pressure was similar in both treatment groups (difference, 0.7 mm Hg;  $P = 0.2$ ), the amlodipine-based regimen produced substantial reductions ( $P < 0.0001$ ) in central systolic blood pressure (4.3 mm Hg) and central pulse pressure (3 mm Hg). However, the multivariable-adjusted hazard ratios relating peripheral and central pulse pressure to the post-hoc defined composite endpoint consisting of total cardiovascular events/procedures and the development of renal impairment were similar (1.10 [ $P = 0.050$ ] vs. 1.11 [ $P = 0.048$ ]).<sup>22</sup> The multi-ethnic IDCARS data might inform the sample size calculations of future trials in this field of clinical research.

IDCARS is a unique data resource that will provide an opportunity to investigate several hypotheses relating adverse health outcomes to central hemodynamic indexes with greater statistical power and accuracy than possible in the individual studies included in the database. Results of such analyses might inform guidelines, the conduct of clinical trials and be of help to clinicians involved in the management of patients with suspected or established arterial disease and cardiovascular risk factors, such as hypertension.

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None of the authors declares a conflict of interest.

## APPENDIX

**Argentina, Buenos Aires:** LS Aparicio, J Barochiner;

**Belgium, Noordkempen:** D-M Wei, JD Melgarejo, L Thijs, JA Staessen, F-F Wei, W-Y Yang, Z-Y Zhang;

**China, Jing Ning:** DW An, YB Cheng, QH Guo, JF Huang, QF Huang, Y Li, CS Sheng, JG Wang;

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**Poland, Gdańsk:** W Kucharska, K Kunicka, N Gilis-Malinowska, K Narkiewicz, W Sakiewicz, E Swierblewska;

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**South Africa, Potchefstroom:** C Mels, R Kruger, G Mokwatsi, AE Schutte;

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## SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* online.

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