# Natural History of Hypertension Subtypes in Young and Middle-Age Adults 

Francesca Saladini ${ }^{1}$, Francesca Dorigatti ${ }^{1}$, Massimo Santonastaso ${ }^{2}$, Lucio Mos ${ }^{3}$, Fabio Ragazzo ${ }^{1}$, Alessandra Bortolazzi ${ }^{4}$, Mauro Mattarei ${ }^{5}$, Guido Garavelli ${ }^{6}$, Paolo Mormino ${ }^{1}$ and Paolo Palatini ${ }^{1}$; The HARVEST Study Group

## BACKGROUND

The evolution of hypertension (HT) subtypes in young-to-middle-age subjects is unclear.

## METHODS

We did a prospective study in 1,141 participants aged 18-45 years from the HARVEST study screened for stage 1 HT , and 101 nonhypertensive subjects of control during a median follow-up of 72.9 months.

## RESULTS

At baseline, 13.8\% of the subjects were classified as having isolated systolic HT (ISH), $24.8 \%$ as having isolated diastolic HT (IDH), and $61.4 \%$ as having systolic-diastolic HT (SDH). All hypertensive groups developed sustained HT (clinic blood pressure $\geq 140 / 90 \mathrm{~mm} \mathrm{Hg}$ from two consecutive visits occurring at least after $\geq 6$ months of observation) more frequently than nonhypertensive subjects
( $P<0.001$ for all) with adjusted odds ratio of 5.2 (95\%Cl 2.9-9.2) among the SDH subjects, 2.6 ( $95 \% \mathrm{Cl} 1.5-4.5$ ) among the IDH subjects, and 2.2 ( $95 \% \mathrm{Cl} 1.2-4.5$ ) among the ISH subjects. When the definition of HT was based on ambulatory blood pressure (mean daytime blood pressure $\geq 135 / 85 \mathrm{~mm} \mathrm{Hg}, n=798)$, odds ratios were $5.1(95 \% \mathrm{Cl}$ $3.1-8.2$ ), 5.6 ( $95 \% \mathrm{Cl} 3.2-9.8$ ), and 3.3 ( $95 \% \mathrm{Cl} 1.7-6.3$ ), respectively. In the fully adjusted logistic model, the risk of ambulatory HT was smaller for the ISH than the IDH $(P=0.049)$ or SDH $(P=0.053)$ individuals.

## CONCLUSIONS

The present results indicate that young-to-middle-age subjects with ISH have a smaller risk of developing ambulatory HT than either subjects with SDH or IDH. Whether antihypertensive treatment can be postponed for long periods of time in young subjects with mild elevations of clinic systolic BP and low global cardiovascular risk should be examined in further studies.
Am J Hypertens 2009; 22:531-537 © 2009 American Journal of Hypertension, Ltd.

Hypertension (HT) subtypes defined by isolated or combined elevations of systolic and diastolic blood pressure (BP) may have different prognostic implications and require a different management of the patient. Isolated systolic HT (ISH) is the dominant form of HT from the sixth decade of life and beyond. ${ }^{1,2}$ In the elderly, high pulse pressure has been associated with progression of aortic atherosclerosis and the consequent loss of distensibility, and a body of evidence suggests the importance of pulse pressure in determining the risks of myocardial infarction and stroke in the old age. ${ }^{3-5}$ The mechanisms underlying elevated pulse pressure and the evolution of ISH in younger age groups have not been fully characterized. Traditionally, ISH in the young has been considered essentially as the result of increased cardiac output. ${ }^{6-8}$ However, according to a recent

[^0]study performed in young individuals, ISH appears to result from both an increased stroke volume and a decreased large artery distensibility. ${ }^{9}$ According to this view, ISH would be an ominous clinical condition predisposing to more severe HT and development of cardiovascular events also in young individuals. Isolated diastolic HT (IDH) is considered to be more benign than ISH being the consequence of an increase in arteriolar resistance without signs of atherosclerosis. ${ }^{10,11}$ However, according to a recent Framingham report, subjects with IDH have a high likelihood of developing systolic-diastolic HT (SDH) at follow-up and a cluster of features of increased cardiovascular risk. ${ }^{12}$

Little or no information is available on the long-term natural history and the clinical importance of ISH and IDH in the young. In particular, it is unclear whether the decline or even disappearance of ISH from youth to middle age, observed in cross-sectional studies, arises from a tendency to develop IDH or SDH. The first goal of the present study was thus to determine, by use of longitudinal follow-up in the HARVEST Study cohort, the risk for the development of sustained HT according to HT subtype. For a comparative analysis, we estimated the risk of developing sustained HT in a group of nonhypertensive subjects ( $\mathrm{BP}<140 / 90 \mathrm{mmHg}$, non-HT). The HARVEST Study is uniquely suited to explore these questions because it provides an
opportunity to describe the natural history of untreated HT in the young during the early phase, thus avoiding treatment bias.

## METHODS

Study population. The study participants took part in the HARVEST, a long-term prospective study of 18- to 45-yearold individuals screened for stage 1 HT , initiated in April 1990, investigating the origin of HT with regard to clinical, ${ }^{13}$ physiological, ${ }^{14}$ and genetic characteristics. ${ }^{15}$ The study was conducted in 17 HT Units in Italy. Patients' recruitment was obtained with the collaboration of the local general practitioners who were instructed during local meetings. Consecutive patients with the above clinical characteristics seen in the offices of the participating general practitioners were eligible for recruitment and were referred to the HARVEST Centres. Participants were included in this investigation if they were not receiving antihypertensive treatment and had no history of cardiovascular disease. Baseline BP was the mean of six readings obtained during two visits performed 2 weeks apart. Diabetes was ruled out by fasting serum glucose test and renal impairment by serum creatinine and urinalysis. None of the patients had cardiac failure or evidence of coronary heart disease. One-hundred and one non-HT subjects with similar age ( $30.7 \pm 8.2$ years) and sex distribution (women $=28.7 \%$ ) to those of the hypertensive patients were taken as controls. They were recruited from the medical staff and their relations. All were asymptomatic, and were normal at physical examination. Their clinic BP measured six times over a 2 -week period was always $<140 / 90 \mathrm{~mm} \mathrm{Hg}$. The study was approved by the HARVEST Ethics Committee and by the Ethics Committee of the University of Padova, and written informed consent was given by the participants. The procedures followed were in accordance with institutional guidelines.

Procedures. The baseline data included a medical and family history and a questionnaire of current use of alcoholic beverages and tobacco and physical activity habits. ${ }^{13-15}$ All subjects underwent physical examination, anthropometry, blood chemistry, urine analysis, office BP, and 24-h BP measurements, echocardiogram, echocardiography, and 24-h urinary albumin measurement. Body mass index (BMI) was considered as an index of adiposity (weight divided by height squared). Twenty-four-hour BP monitoring was performed with Takeda A\&D TM2420 model 7 (A\&D, Tokyo, Japan) or ICR Spacelabs 90207 monitor (Spacelabs, Redmond, WA). The arithmetic average of the edited pressure was used as the ambulatory measurement. Other details on the methods used in the HARVEST study are reported elsewhere. ${ }^{13-15}$

Definitions. ISH at entry was defined as a systolic BP $\geq 140 \mathrm{mmHg}$ and diastolic BP $<90 \mathrm{mmHg}$, IDH was defined as a diastolic BP $\geq 90 \mathrm{~mm} \mathrm{Hg}$ and a systolic BP $<140 \mathrm{~mm} \mathrm{Hg}$, and SDH was defined as a diastolic BP $\geq 90 \mathrm{~mm} \mathrm{Hg}$ and a systolic $\mathrm{BP} \geq 140 \mathrm{mmHg}$. In the present report, development of clinic HT was defined as an average systolic BP $\geq 140 \mathrm{~mm} \mathrm{Hg}$ and/or a diastolic BP $\geq 90 \mathrm{~mm} \mathrm{Hg}$ from two consecutive visits occurring at least after $\geq 6$ months of implementation of
non pharmacological measures (clinic HT). Patients with $\mathrm{BP}<140 / 90 \mathrm{~mm} \mathrm{Hg}$ who needed treatment because of a high cardiovascular risk profile (including target organ involvement) were not included in the present study. Ambulatory HT was defined as an average daytime systolic BP $\geq 135 \mathrm{~mm} \mathrm{Hg}$ and/or daytime diastolic BP $\geq 85 \mathrm{~mm} \mathrm{Hg}$ (ambulatory HT). ${ }^{16,17}$

Follow-up. Follow-up visits were scheduled at 1, 2, 3 and 6 months and thereafter at 6 -month intervals. After each visit, the clinical investigators transferred all relevant information to the coordinating center in Padova. Subjects were followed until they developed HT requiring antihypertensive treatment according to guidelines criteria for young subjects at low cardiovascular risk available at the time of patient assessment. ${ }^{18-21}$ If at follow-up visits the BP level was above the operational threshold level, the patient was rescheduled for a visit within 2-4 weeks. If BP was still above the limit the patient was given antihypertensive treatment otherwise he or she was checked at monthly intervals. All data used for the present analysis were collected before starting the antihypertensive therapy. Ambulatory BP monitoring was performed at the baseline in all patients. In 11 centers, ambulatory monitoring was performed also after $5,8,10$, and 15 years, and/or just before starting therapy in the patients who needed antihypertensive treatment. The last available ambulatory BP monitoring was used for the analyses and was defined as final ambulatory BP. Final ambulatory BP was available in 798 subjects. For patients lost to follow-up, data available at the date of latest contact were used. Other details on follow-up procedures were reported elsewhere. ${ }^{13-15}$

Data analysis. Data are presented as mean $\pm$ s.d. unless specified. The distribution of clinical variables was compared across groups using the general linear model procedure and adjusting for age and sex. The Tukey-Kramer multiple comparisons post hoc test was used for contrasts. Kruskal-Wallis tests were applied to determine whether there was a statistically significant difference in follow-up duration. The significance of differences in categorical variables was assessed with the $\chi^{2}$ test. BP changes within groups were assessed with $t$-test for paired observations. A logistic regression model for a binary outcome was used to define the relationship between developing HT identified with either clinic BP or ambulatory BP and the HT category adjusting for age, sex, heart rate, and follow-up length and providing odds ratios (OR) for developing HT, using the subjects with BP $<140 / 90 \mathrm{~mm} \mathrm{Hg}$ as a reference group. Baseline BMI and body weight changes during follow-up were also included in the logistic model. Multicollinearity was tested by centering variables. A two-tailed probability value $<0.05$ was considered significant. All analyses were performed using Statistica version 6 (Stat Soft, Tulsa, OK) and Systat version 10 (SPSS, Evanston, IL).

## RESULTS

Of the HARVEST participants, $13.8 \%$ were classified as having ISH at entry, $24.8 \%$ as having IDH, and $61.4 \%$ as having SDH. The clinical characteristics of the three hypertensive groups

Table 1 | Baseline characteristics and follow-up metabolic data of the normotensive subjects, and of the three groups of hypertensive patients

| Variable | $\begin{aligned} & \text { Non-HT, } \\ & n=101 \end{aligned}$ | $\begin{gathered} \text { ISH, } \\ n=158 \end{gathered}$ | $\begin{gathered} \text { IDH, } \\ n=283 \end{gathered}$ | $\begin{gathered} \text { SDH, } \\ n=700 \end{gathered}$ | P value vs. Non-HT |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  |  | ISH | IDH | SDH |
| Sex, $n$ (\% women) ${ }^{\text {a }}$ | 29 (28.7) | 18(11.4) | 93 (32.9) | 201 (28.7) | <0.001 | 0.20 | 1.0 |
| Cigarette smokers, $n(\%)^{\text {a }}$ | 31 (30.7) | 34 (21.5) | 63 (22.3) | 137 (19.6) | 0.13 | 0.13 | <0.05 |
| Age (years) ${ }^{\text {a }}$ | $30.7 \pm 8.2$ | $25.7 \pm 6.9$ | $34.1 \pm 7.7$ | $34.6 \pm 8.2$ | <0.001 | <0.001 | <0.001 |
| Age at follow-up end (years) ${ }^{\text {a }}$ | $36.7 \pm 9.6$ | $32.3 \pm 8.1$ | $40.1 \pm 8.7$ | $40.5 \pm 8.8$ | <0.001 | <0.001 | <0.001 |
| Body mass index, $\mathrm{kg} / \mathrm{m}^{2}$ | $23.7 \pm 3.8$ | $24.8 \pm 2.9$ | $25.1 \pm 3.2$ | $25.8 \pm 3.6$ | <0.05 | <0.05 | <0.001 |
| Body mass index at follow-up end, $\mathrm{kg} / \mathrm{m}^{2}$ | $24.2 \pm 4.0$ | $25.5 \pm 3.3$ | $25.7 \pm 3.7$ | $26.1 \pm 3.5$ | <0.01 | <0.01 | <0.001 |
| Clinic systolic BP, mm Hg | $126 \pm 8$ | $150 \pm 9$ | $134 \pm 5$ | $150 \pm 8$ | <0.001 | $<0.001$ | <0.001 |
| Clinic systolic BP at follow-up end, mm Hg | $128 \pm 14$ | $142 \pm 13$ | $137 \pm 12$ | $147 \pm 14$ | <0.001 | <0.001 | <0.001 |
| Clinic diastolic BP, mm Hg | $81 \pm 8$ | $84 \pm 5$ | $94 \pm 3$ | $96 \pm 4$ | <0.001 | <0.001 | <0.001 |
| Clinic diastolic BP at follow-up end, mm Hg | $82 \pm 10$ | $88 \pm 9$ | $93 \pm 10$ | $95 \pm 10$ | <0.001 | <0.001 | <0.001 |
| Clinic heart rate, bpm | $71 \pm 10$ | $76 \pm 9$ | $72 \pm 9$ | $76 \pm 10$ | <0.001 | 0.44 | <0.001 |
| Clinic heart rate at follow-up end, bpm | $70 \pm 11$ | $72 \pm 11$ | $71 \pm 9$ | $73 \pm 10$ | 0.32 | 0.93 | 0.17 |
| Total cholesterol, mg/dl | $182 \pm 44$ | $185 \pm 36$ | $200 \pm 43$ | $202 \pm 39$ | 0.11 | <0.05 | $<0.05$ |
| Total cholesterol at follow-up end, mg/dl | $186 \pm 43$ | $191 \pm 42$ | $206 \pm 42$ | $210 \pm 41$ | 0.17 | <0.05 | $<0.01$ |
| HDL-cholesterol, mg/dl | $55 \pm 17$ | $53 \pm 14$ | $52 \pm 14$ | $52 \pm 15$ | 0.67 | 0.16 | 0.16 |
| HDL-cholesterol at follow-up end, mg/dl | $56 \pm 18$ | $52 \pm 13$ | $54 \pm 15$ | $53 \pm 15$ | 0.85 | 0.79 | 0.53 |
| Triglycerides, mg/dl | $111 \pm 69$ | $98 \pm 50$ | $115 \pm 75$ | $115 \pm 77$ | 0.82 | 0.99 | 0.97 |
| Triglycerides at follow-up end, mg/dl | $106 \pm 61$ | $101 \pm 65$ | $118 \pm 74$ | $124 \pm 85$ | 0.99 | 0.95 | 0.79 |
| Fasting glucose, mg/dl | $90 \pm 12$ | $91 \pm 11$ | $92 \pm 10$ | $94 \pm 12$ | 0.89 | 0.93 | 0.54 |
| Fasting glucose at follow-up end, mg/dl | $90 \pm 10$ | $92 \pm 18$ | $93 \pm 10$ | $95 \pm 14$ | 0.40 | 0.84 | 0.28 |

Data are mean $\pm$ s.d. unless specified, and are adjusted for age and sex. Follow-up data are also adjusted for length of follow-up.
BP, blood pressure; HT, hypertension; IDH, patients with isolated diastolic hypertension; ISH, patients with isolated systolic hypertension; Non-HT, subjects with blood pressure
$<140 / 90 \mathrm{~mm} \mathrm{Hg}$; SDH, patients with systolic-diastolic hypertension.
aUnadjusted.
and the non-HT subjects are reported in Table 1. ISH was more frequent among the male subjects and was inversely proportional to age being as prevalent as $48 \%$ among the men aged $18-21$ years and $\leq 1 \%$ in men and women aged $42-45$ years. Patients with ISH were younger and were more frequently men than non-HT subjects, whereas patients with IDH or SDH were older than non-HT. BMI was higher in all hypertensive groups than in non-HT subjects. Clinic heart rate was higher in ISH and SDH patients than non-HT subjects. Total cholesterol was higher among IDH and SDH patients than non-HT subjects. No significant differences in plasma glucose, high-density lipoprotein-cholesterol, triglycerides, or tobacco use were found between the groups.
The group with ambulatory BP data at the end of follow-up ( $n=798$ ) had similar baseline characteristics to those of the rest of the cohort (Table 2). Twenty-four-hour systolic BP was higher in SDH than IDH patients both at baseline and after 3 months ( $P<0.001$ ). The difference between the ISH and IDH participants did not reach the level of statistical significance ( $P=0.13$ at baseline; $P=0.11$ after 3 months). Baseline and 3-month 24-h diastolic BP was lower among the ISH patients than the other hypertensive groups (all $P<0.001$ ). $B P$ variability (SD of daytime $B P$ ) and the magnitude of the
mean $B P$ fall from day to night were similar in the four groups (data not shown). Baseline and 3-month ambulatory heart rates were higher in the IDH and SDH subjects than the ISH (all $P<0.05$ ) or the non-HT groups.

## Follow-up data

Median follow-up was 72.9 months (range, 6-193.9 months) for the whole cohort and 91.9 months (range, 6-193.9 months) for the 798 subjects who had final ambulatory BP. After 6 months of observation, clinic BP declined by $5 \pm 11 / 3 \pm 7 \mathrm{mmHg}$. A systolic BP $<140 \mathrm{mmHg}$ and a diastolic BP $<90 \mathrm{mmHg}$ were found in 47.7 and $36.4 \%$ of the subjects, respectively. At fol-low-up end, clinic BP declined by $2 \pm 14 / 1 \pm 9 \mathrm{mmHg}$ and $24-\mathrm{h}$ BP increased by $2 \pm 11 / 2 \pm 8 \mathrm{~mm} \mathrm{Hg}$. Body weight increased by $1.5 \pm 6.5 \mathrm{~kg}$ without significant differences between the groups. Between-group differences in metabolic data remained substantially unchanged at follow-up end (Table 1). During the follow-up, 28 non-HT (27.7\%) and 856 hypertensive (75.0\%) subjects developed clinic HT, whereas in the other 358 subjects BP fell to $<140 / 90 \mathrm{mmHg}$ threshold. Among the non-HT persons, one subject with optimal BP according to the $2007 \mathrm{ESC} /$ ESH guidelines ${ }^{17}(n=13)$, five subjects with normal BP $(n=29)$, and 22 subjects with high-normal BP $(n=59)$ developed clinic

Table $\mathbf{2}$ | Characteristics and $\mathbf{2 4 - h}$ blood pressure and heart rate of the $\mathbf{7 9 8}$ subjects who had ambulatory monitoring data at baseline and follow-up assessments

| Variable | Non-HT,$n=100$ | $\stackrel{\text { ISH, }}{n=81}$ | $\begin{gathered} \text { IDH, } \\ n=175 \end{gathered}$ | $\begin{gathered} \text { SDH, } \\ n=442 \end{gathered}$ | P value vs. Non-HT |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  |  | ISH | IDH | SDH |
| Sex, $n$ (\% women) ${ }^{\text {a }}$ | 29 (29.0) | 11 (13.6) | 55 (31.4) | 134 (30.3) | <0.05 | 0.67 | 0.79 |
| Age (years) ${ }^{\text {a }}$ | $30.7 \pm 8.3$ | $25.9 \pm 7.0$ | $34.7 \pm 7.9$ | $34.8 \pm 8.3$ | <0.001 | <0.01 | <0.001 |
| Age at follow-up end (years) ${ }^{\text {a }}$ | $36.7 \pm 9.7$ | $35.5 \pm 7.0$ | $42.3 \pm 8.6$ | $42.1 \pm 8.6$ | 0.76 | <0.001 | <0.001 |
| Average 24-h systolic BP at baseline | $122 \pm 13$ | $132 \pm 11$ | $127 \pm 10$ | $132 \pm 11$ | <0.001 | <0.01 | <0.001 |
| Average 24-h diastolic BP at baseline | $76 \pm 8$ | $75 \pm 8$ | $82 \pm 7$ | $83 \pm 8$ | 1.0 | <0.001 | <0.001 |
| Average 24-h heart rate at baseline, bpm | $70 \pm 9$ | $70 \pm 7$ | $73 \pm 7$ | $73 \pm 8$ | 0.91 | <0.01 | <0.001 |
| Average 24 -h systolic BP after 3 months | $122 \pm 12$ | $132 \pm 9$ | $127 \pm 10$ | $132 \pm 12$ | <0.001 | <0.001 | <0.001 |
| Average 24-h diastolic BP after 3 months | $76 \pm 8$ | $75 \pm 8$ | $82 \pm 6$ | $82 \pm 8$ | 0.94 | <0.001 | <0.001 |
| Average 24-h heart rate after 3 months, bpm | $71 \pm 10$ | $70 \pm 7$ | $73 \pm 7$ | $72 \pm 8$ | 0.62 | <0.05 | <0.05 |
| Average 24 -h systolic BP at follow-up end | $123 \pm 12$ | $133 \pm 11$ | $132 \pm 12$ | $135 \pm 12$ | <0.001 | <0.001 | <0.001 |
| Average 24-h diastolic BP at follow-up end | $77 \pm 8$ | $80 \pm 6$ | $85 \pm 8$ | $85 \pm 8$ | <0.01 | <0.001 | <0.001 |
| Average 24-h heart rate at follow-up end, bpm | $71 \pm 9$ | $70 \pm 7$ | $73 \pm 8$ | $73 \pm 9$ | 0.85 | <0.05 | <0.05 |

Data are mean $\pm$ s.d. unless specified, and are adjusted for age and sex. Blood pressure and heart rate at study end are adjusted also for length of follow-up. BP, blood pressure in mm Hg ; IDH, patients with isolated diastolic hypertension; ISH, patients with isolated systolic hypertension; Non-HT, subjects with blood pressure $<140 / 90 \mathrm{~mm} \mathrm{Hg}$; SDH, patients with systolic-diastolic hypertension.
${ }^{\text {a }}$ Unadjusted.


Figure 1 | Incidence of sustained hypertension (HT) in 101 normotensive subjects and 1,141 patients screened for stage 1 HT divided according to HT subtype at baseline assessment. $P$ values are adjusted for age, gender, heart rate, and follow-up length. (a) HT diagnosed with clinic blood pressure measurement. (b) HT diagnosed with ambulatory blood pressure monitoring. IDH, patients with isolated diastolic HT; ISH, patients with isolated systolic HT at entry; Non-HT, subjects with clinic blood pressure $<140 / 90 \mathrm{~mm} \mathrm{Hg}$; SDH, patients with systolic-diastolic HT.

HT. In the 884 subjects who developed HT, clinic BP rose from $147 \pm 10 / 94 \pm 5 \mathrm{mmHg}$ at baseline assessment to $149 \pm 12 / 97$ $\pm 8 \mathrm{mmHg}$ at final visit ( $P<0.001$ for both systolic and diastolic BPs). Conversely, in the 358 subjects who did not develop HT clinic BP fell from $141 \pm 11 / 91 \pm 7 \mathrm{mmHg}$ to $128 \pm 7 / 82 \pm$ $6 \mathrm{mmHg}(P<0.001$ for both systolic and diastolic BPs).

In Figure 1, the incidence of HT based on clinic BP during the follow-up in the three hypertensive groups and the non-HT individuals is shown. All hypertensive groups developed clinic HT more frequently than the non-HT subjects ( $\chi^{2}: 139.9$, $P<0.001$ ). However, the risk of HT development was greater among the SDH subjects (OR 5.2, 95\%CI 2.9-9.2) than the ISH (OR 2.2, 95\%CI 1.2-4.5, $P<0.001$ vs. SDH) or the IDH (OR


Figure $\mathbf{2}$ | Risk of incident hypertension $(\mathrm{HT})$ in patients with isolated systolic HT (ISH), the patients with isolated diastolic HT (IDH), and the patients with systolic-diastolic HT (SDH). Odds ratios were calculated from a logistic regression model adjusting for age, gender, heart rate, and follow-up length, using the subjects with clinic BP $<140 / 90 \mathrm{~mm} \mathrm{Hg}$ as a reference group (non-HT). (a) HT diagnosed with clinic measurement (blood pressure $\geq 140 / 90 \mathrm{~mm} \mathrm{Hg}$ ). (b) HT diagnosed with ambulatory measurement (daytime blood pressure $\geq 135 / 85 \mathrm{~mm} \mathrm{Hg}$ ).
2.6, $95 \%$ CI 1.5-4.5, $P<0.001$ vs. SDH) individuals (Figure 2). No significant difference was found between the ISH and IDH subjects. After inclusion of baseline BMI and body weight changes during follow-up in the regression model, OR (95\%CI) was 5.0 (2.9-8.8) in SDH, 2.2 (1.2-4.4, $P<0.001$ vs. SDH) in ISH, and 2.5 (1.4-4.4, $P<0.001$ vs. SDH) in IDH.

Only marginal changes in ambulatory BP and heart rate were seen in all groups after 3 months of observation. At follow-up end, among the ISH patients there was an increase in diastolic ( $P<0.001$ ) but not systolic $(P=0.55) 24-\mathrm{hBP}$. Among the IDH and SDH patients, a significant increase in 24-h BP was
observed for both systolic and diastolic BPs ( $P<0.001$ for all). Ambulatory heart rate remained substantially unchanged in all groups.
When the definition of HT was based on ambulatory BP, similar results to those obtained for clinic HT were observed ( $\chi^{2}: 45.4, P<0.001$, Figure 1). However, the risk of HT was similar in the SDH and IDH groups (ORs 5.1, 95\%CI 3.18.2 , and $5.6,95 \%$ CI $3.2-9.8$, respectively) and greater than among the ISH individuals (OR 3.3, 95\%CI 1.7-6.3, Figure 2). The differences with the ISH subjects were of borderline statistical significance ( $P=0.073$ vs. SDH, and $P=0.064$ vs. IDH). After inclusion of baseline BMI and body weight changes during follow-up in the regression model, the difference between ISH and SDH remained of borderline statistical significance ( $P=0.053$ ), and the difference between ISH and IDH reached the level of statistical significance ( $P=0.049$ ), with an OR ( $95 \% \mathrm{CI}$ ) of 1.9 (1.0-3.7).

## DISCUSSION

The present results show that the risk of developing HT over the years may vary according to HT subtype in the screening phase. Young-to-middle-age subjects with ISH at baseline screening had an increased likelihood of developing HT during subsequent years compared to subjects with BP $<140 / 90 \mathrm{~mm} \mathrm{Hg}$. However, the risk was smaller than in persons with SDH. Subjects with IDH at entry also had an increased likelihood of developing clinic HT at follow-up, with a significant adjusted odds ratio only slightly greater than those with ISH (adjusted ORs of 2.6 and 2.2, respectively). However, when the diagnosis of HT was based on the ambulatory measurement, subjects with IDH at entry had a $90 \%$ greater risk of ambulatory HT than subjects with ISH similar to that in patients with SDH. Thus, according to this HARVEST report, the view that IDH is a low-risk condition should be reconsidered in young-to-middle-age individuals.

The HARVEST investigators had the unique opportunity to track the natural history of the distinct HT subtypes over the long term in subjects initially screened for stage 1 HT , in the absence of the confounding effect of antihypertensive treatment or prior cardiovascular events. According to international guidelines, subjects with low cardiovascular risk profile and BP within the stage 1 hypertensive range, such as those enrolled in the HARVEST, should be monitored for extended periods with only nonpharmacological treatment. ${ }^{18-21}$ As a matter of fact, in many of the HARVEST participants, clinic BP decreased to $<140 / 90 \mathrm{~mm} \mathrm{Hg}$ during the first 6 months of follow-up, and in the whole cohort clinic BP declined by $5 / 3 \mathrm{~mm} \mathrm{Hg}$. In the 358 participants who did not develop clinic HT, mean final clinic BP was $128 / 82 \mathrm{~mm} \mathrm{Hg}$. The BP decline in the latter subjects may be ascribed to several factors, including regression to the mean, ${ }^{22}$ adaptation to the medical environment, ${ }^{23}$ and improvement of unhealthy lifestyle, which occurred in about $40 \%$ of the HARVEST participants. ${ }^{24}$
The BP follow-up in different BP categories has been studied in several analyses from the Framingham study, ${ }^{12,25}$ but little information was available on evolution of HT subtypes
for young subjects. In 20 men and 13 women with ISH aged $30-39$ years, Sagie et al. found that the risk of developing SDH was higher than in a group of normotensive controls but no comparison was made with subjects with initial IDH or SDH. ${ }^{25}$ In older people, ISH results from increased elastic artery stiffness, which increases pulse-wave velocity and wave reflection amplitude. ${ }^{26}$ Within this clinical scenario, high pulse pressure is considered as an ominous hemodynamic parameter as it proved to be a strong precursor of cardiovascular disease ${ }^{4,5}$ and its impact on the cardiovascular system is thought to be greater than that of mean BP among old individuals. ${ }^{27}$ The mechanisms underlying ISH in younger individuals are poorly understood. In a recent cross-sectional study ISH appeared to result from both an increased stroke volume and aortic stiffness, suggesting that ISH in young individuals may not be benign. ${ }^{9}$ According to others, exaggerated pulse pressure amplification may be responsible for ISH of the young which is often defined as spurious HT. ${ }^{28,29}$ The high clinic systolic BP in ISH subjects might also be due to a pronounced alarm reaction to the BP measurement which would attenuate only partially with time. This would explain the different impact of ISH relative to IDH on the development of clinic HT compared to ambulatory HT.

Little is known on the evolution of IDH. In a cohort of normotensive and hypertensive subjects with a mean age of 48.5 years, Franklin et al. observed a much higher risk of developing SDH among subjects with IDH at initial screening than among subjects with ISH. ${ }^{12}$ Previous studies have shown that the relative importance of systolic BP tends to decrease with decreasing age. ${ }^{30,31}$ For subjects aged $\leq 45$ years, diastolic BP was found to be a stronger predictor of coronary heart disease morbidity and mortality than was systolic BP. ${ }^{30}$ In subjects $<50$ years of age, pulse-wave velocity, an indicator of aortic stiffness, resulted to be more closely correlated with diastolic BP than systolic BP. ${ }^{31}$ In the Framingham study, IDH subjects were characterized as being overweight or obese and having increased risk for clinical events. ${ }^{12}$ In the present study, total cholesterol measured either at baseline or at follow-up end was increased in the IDH subjects compared to the non-HT individuals. These findings question the concept that IDH is a benign clinical condition as suggested by previous reports ${ }^{10,11,32}$ and indicate that in young and middle-age individuals IDH is associated with increased cardiovascular risk.

## Limitations

Because of the narrow diagnostic thresholds that define and separate nonhypertensive status and hypertensive subtypes from each other, there is the possibility of misclassification of baseline and follow-up BP categories. To minimize this problem, we defined both baseline and follow-up BP categories on the basis of six BP readings recorded at two consecutive visits. Another limitation of our study is that the criteria for treating the HARVEST participants changed several times from 1990 to 2006. Thus, the use of the $140 / 90 \mathrm{~mm} \mathrm{Hg}$ threshold for defining HT in the present study was a post hoc definition. However, a strength of our study is that we used also ambulatory

BP to identify HT during the follow-up. In contrast with the well-known tendency for clinic BP to decline in hypertensive subjects during a period of observation, ${ }^{22,23}$ a phenomenon observed also in the present study, ambulatory BP did not show a regression to the mean effect, as documented by the ambulatory measurement after 3 months, which yielded essentially identical results to those of baseline assessment. Thus, the changes in ambulatory BP that we observed at the end of follow-up in our patients represent a true hemodynamic change and are not a statistical artifact.

## Conclusions

Several studies have shown that among treated hypertensive subjects, those with uncontrolled systolic BP were at greater risk of cardiovascular disease than those with uncontrolled diastolic BP indicating that effective systolic BP control should be the main focus of treatment. ${ }^{33,34}$ However, this concept stems from results obtained in populations of middle-age to elderly patients whereas little is known on whether high systolic BP should be treated aggressively also in young individuals. The present results indicate that ISH subjects 45 years of age or younger have a smaller risk of developing ambulatory HT during subsequent years than patients with IDH or SDH. Whether antihypertensive treatment can be postponed for long periods of time in young subjects with mild elevations of clinic systolic BP and low global cardiovascular risk should be examined in further studies.

## APPENDIX

## List of the centers participating in the HARVEST study

Belluno-Cardiologia: G. Catania, R Da Cortà; CremonaDiv. Medica: G Garavelli; Dolo-Div. Medica: F Pegoraro, S Laurini; Mirano - Cardiologia: D D’Este; Padova-Clinica Medica 4: F Dorigatti, V Zaetta, P Frezza, P Bratti, D Perkovic, C Guarnieri; Pordenone-Centro Cardioreumatologico: G Cignacco, G Zanata; Rovereto-Ala-Div. Medica: M Mattarei, T Biasion; Rovigo-Cardiologia: P Zonzin, A Bortolazzi; San Daniele del Friuli-Area di Emergenza: L Mos, S Martina, O Vriz; San Donà di Piave-Cardiologia: L. Milani, C Canali; Trento-Div. Medica: P Dal Ri, M Dal Follo; Treviso-Div. Nefrologia: G Calconi, P. Gatti; Vittorio Veneto-Div. Medica: M Santonastaso, E Cozzutti, R Garbelotto, A Mazzer. Trial Coordinator: P Palatini.

Acknowledgments: The study was funded by the University of Padova, Padova, Italy, and by the Associazione"18 Maggio 1370,"San Daniele del Friuli, Italy.

Disclosure: The authors declared no conflict of interest.

1. Staessen J, Amery A, Fagard R. Isolated systolic hypertension in the elderly. JHypertens 1990; 8:393-405.
2. Kannel WB, Dawber TR, McGee DL. Perspectives on systolic hypertension. The Framingham Study. Circulation 1980;61:1179-1182.
3. Laurent S, Katsahian S, Fassot C, Tropeano AI, Gautier I, Laloux B, Boutouvrie P. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. Stroke 2003; 34:1203-1206.
4. Nielsen WB, Vestbo J, Jensen GB. Isolated systolic hypertension as a major risk factor for stroke and myocardial infarction and an unexploited source of cardiovascular prevention: a prospective population-based study. J Hum Hypertens 1995; 9:175-180.
5. Staessen JA, Gasowski J, Wang JG, Thijs L, Hond ED, Boissel JP, Coope J, Ekborm T, Gueyffier F, Liu L, Kerlikowske K, Pocock S, Fagard RH. Risk of the untreated and treated isolated systolic hypertension in the elderly: meta analysis of outcome trials. Lancet 2000; 355:865-872.
6. Lund-Johansen P. Hemodynamics in essential hypertension at rest and during exercise—a 20-year follow-up study. Ann Clin Res 1988;20(Suppl 48):31-38.
7. Eich RH, Peters RJ, Cuddy RP, Smulyan H, Lyons RH. The hemodynamics in labile hypertension. Am HeartJ 1962;63:188-195.
8. Andersson OK, Suurkula MB, Sannersyedt, Magnusson M, Sivertsson. Does hyperkinetic circulation constitute a pre-hypertensive stage? A 5-year follow-up of hemodynamics in young men with mild blood pressure elevation. J Intern Med 1989; 226:401-408.
9. Mc Eniery CM, Wallace YS, Maki-Petaya K, McDonnell B, Sharman JE, Retallick C, Franklin SS, Brown MJ, Lloyd RC, Cockcroft JR, Wilkinson IB. Increased stroke volume and aortic stiffness contribute to isolated systolic hypertension in young adults. Hypertension 2005;46:221-226.
10. Fang J, Madhavan S, Cohen H, Alderman MH. Isolated diastolic hypertension: a favorable finding among young and middle-aged hypertensive subjects. Hypertension 1995; 25:377-382.
11. Kelly TN, Gu D, Chen J, Huang JF, Chen JC, Duan X, Wu X, Yau CL, Whelton PK, He J. Hypertension subtype and risk of cardiovascular disease in Chinese adults. Circulation 2008; 118:1558-1566.
12. Franklin SS, Pio JR, Wong ND, Larson MG, Leip EP, Vasan RS, Levy D. Predictors of new-onset diastolic and systolic hypertension: the Framingham Heart Study. Circulation 2005; 111:1121-1127.
13. Palatini P, Mormino P, Mos L, Mazzer A, Dorigatti F, Zanata G, Longo D, Garbelotto R, De Toni R, Graniero G, Pessina AC. Microalbuminuria, renal function and development of sustained hypertension: a longitudinal study in the early stage of hypertension. J Hypertens 2005; 23:175-182.
14. Palatini P, Graniero G, Mormino P, Nicolosi L, Mos L, Visentin P, Pessina AC. Relation between physical training and ambulatory blood pressure in stage I hypertensive subjects. Results of the HARVEST trial. Circulation 1994; 90:2870-2876.
15. Sartori M, Semplicini A, Siffert W, Mormino P, Mazzer A, Pegoraro F, Mos L, Winnicki M, Palatini P. G-protein beta3-subunit gene 825T allele and hypertension: a longitudinal study in young grade I hypertensives. Hypertension 2003;42:909-914.
16. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P; European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. J Hypertens 2003; 21:821-848.
17. 2007 Guidelines for the Management of Arterial Hypertension. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007; 25:1105-1187.
18. Treating mild hypertension. Report of the British Hypertension Society working party. BMJ 1989; 298:694-698.
19. Sever P, Beevers G, Bulpitt C, Lever A, Ramsay L, Reid J, Swales J. Management guidelines in essential hypertension: report of the second working party of the British Hypertension Society. BMJ 1993; 306:983-987.
20. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Sub-Committee. Blood Press 1999;1 Suppl:9-43.
21. European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003; 21:1011-1053.
22. Bland JM, Altman DG. Statistics notes: some examples of regression towards the mean. BMJ 1994; 309:780.
23. Asmar R, Safar M, Queneau P. Evaluation of the placebo effect and reproducibility of blood pressure measurement in hypertension. Am J Hypertens 2001; 14:546-552.
24. Winnicki M, Somers VK, Dorigatti F, Longo D, Santonastaso M, Mos L, Mattarei M, Pessina AC, Palatini P. Lifestyle, family history and progression of hypertension. J Hypertens 2006; 24:1479-1487.
25. Sagie A, Larson MG, Levy D. The natural history of borderline isolated systolic hypertension. N Engl J Med 1993; 329:1912-1917.
26. Safar H, Chahwakilian A, Boudali Y, Debray-Meignan S, Safar M, Blacher J. Arterial stiffness, isolated systolic hypertension, and cardiovascular risk in the elderly. Am J Geriatr Cardiol 2006; 15:178-182.
27. Sesso HD, Stampfer MJ, Rosner B, Hennekens CH, Gaziano JM, Manson JE, Glynn RJ. Systolic and diastolic blood pressure, pulse pressure, and mean arterial pressure as predictors of cardiovascular disease risk in Men. Hypertension 2000; 36:801-807.
28. O'Rourke MF, Vlachopoulos C, Graham RM. Spurious systolic hypertension in youth. Vasc Med 2000; 5:141-145.
29. Mahmud A, Feely J. Spurious systolic hypertension of youth: fit young men with elastic arteries. Am J Hypertens 2003; 16:229-232.
30. Antikainen R, Jousilahti P,Tuomilehto J. Systolic blood pressure, isolated systolic hypertension and risk of coronary heart disease, strokes, cardiovascular disease and all-cause mortality in the middle-aged population. J Hypertens 1998; 16:577583.
31. Millasseau S, Ritter JM, Chowienczyk P. Relationship between blood pressure and aortic pulse wave velocity in young and old subjects with essential hypertension. JHypertens 2003; 21 (Suppl 4):S253. Abstract.
32. Nielsen WB, Lindenstrom E, Vestbo J, Jensen GB. Is diastolic hypertension an independent risk factor for stroke in the presence of normal systolic blood pressure in the middle-aged and elderly? Am J Hypertens 1997; 10: 634-639.
33. Stokes GS. Treatment of isolated systolic hypertension. Curr Hypertens Rep 2006; 8:377-383.
34. Mancia G, Pessina AC, Trimarco B, Grassi G; SILVIA (Studio Italiano Longitudinale sulla Valutazione della Ipertensione Arteriosa nel 2000) Study Group. Blood pressure control according to new guidelines targets in low- to high-risk hypertensives managed in specialist practice. J Hypertens 2004; 22:2387-2396.

[^0]:    ${ }^{1}$ Department of Clinical and Experimental Medicine, University of Padova, Padova, Italy; ${ }^{2}$ Department of Internal Medicine, Town Hospital, Vittorio Veneto, Italy; ${ }^{3}$ Department of Emergency Area, Town Hospital, San Daniele del Friuli, Italy; ${ }^{4}$ Department of Cardiology, Town Hospital, Rovigo, Italy; ${ }^{5}$ Department of Internal Medicine, Town Hospital, Rovereto, Italy; ${ }^{6}$ Department of Internal Medicine, Town Hospital, Cremona, Italy. Correspondence: Paolo Palatini (palatini@unipd.it)

    Received 11 June 2008; first decision 19 July 2008; accepted 10 January 2009; advance online publication 19 February 2009. doi:10.1038/ajh.2009.21
    © 2009 American Journal of Hypertension, Ltd.

