Change in cardiovascular risk profile by echocardiography in low- or medium-risk hypertension

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Background **Clinical decision-making in hypertensive patients is largely based upon assessment of total cardiovascular risk. World Health Organization–International Society of Hypertension (WHO–ISH) guidelines suggest delaying or withholding drug treatment in individuals assessed as at low risk on the basis of a suggested work-up that does not include echocardiography.**

Objective **To assess the impact of echocardiography on risk stratification in never-treated individuals classified as at low cardiovascular risk.**

Design **A retrospective analysis of a prospective survey.**

Setting **Outpatient hypertension clinics of three community hospitals.**

Patients **A total of 792 hypertensive adults classified as at low or medium risk, drawn from a larger sample of 1322 never-treated hypertensive patients.**

Main outcome measures **Change in risk class and need of immediate treatment after echocardiographic evaluation of left ventricular hypertrophy.**

Results **Those at low and medium risk according to WHO–ISH (to receive delayed treatment) represented 17 and 43%, respectively, of the whole hypertensive population. The prevalence of left ventricular hypertrophy on echocardiography was 21 and 32% in low- and medium-risk groups, respectively (29% on average).**

Conclusions **In untreated hypertensive individuals without overt target-organ damage, in whom treatment would be postponed or avoided according to current WHO–ISH guidelines, echocardiography modifies the risk classification in 29% of the cases, identifying a need for immediate drug treatment. In low-risk untreated hypertensive individuals, echocardiography commonly alters risk stratification based on the initial WHO–ISH work-up.** ***J Hypertens*** **20:1519–1525 © 2002 Lippincott Williams & Wilkins.**

Journal of Hypertension 2002, 20:1519–1525

Keywords: arterial hypertension, hypertrophy, cardiovascular risk, evaluation, management

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Sponsorship: Supported in part by grants from Associazione Umbra Cuore e Ipertensione, Perugia, Italy.

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Received 22 October 2001 **Revised** 9 April 2002
Accepted 18 April 2002

Introduction

The goal of antihypertensive treatment is to prevent cardiovascular events. As the percent reduction in cardiovascular complications conferred by antihypertensive treatment is relatively constant over a wide range of absolute risk levels, the main determinant of the absolute benefit of treatment is the absolute pretreatment cardiovascular risk [1,2]. Accordingly, the decision to start treatment in a given patient with mildly increased blood pressure is driven by the total cardiovascular risk, which is determined not only by blood pressure values, but also by the presence, severity and number of associated cardiovascular risk factors and by the degree of preclinical [3] and overt clinical cardiovascular disease. Recent guideline committees, including the Joint National Committee (Sixth Report, JNC VI) [4] and the World Health Organization–International Society of Hypertension (WHO–ISH) Guidelines Subcommittee [5], have taken into account total cardiovascular risk rather than blood pressure alone as the key criterion for initiation of treatment. According to the WHO–ISH guidelines, immediate drug treatment is recommended only for those defined as being at high or very high risk, whereas a period of observation up to 1 year is suggested for those at low or medium risk. Moreover, drug treatment may be avoided in low-risk individuals with only borderline increases in blood pressure (systolic blood pressure (SBP) 140–149 mmHg, or diastolic blood pressure (DBP) 90–94 mmHg, or both) [5]. Similarly, JNC VI

recommends a period of observation up to 1 year for individuals with stage 1 hypertension (SBP 140–159 mmHg, or DBP 90–99 mmHg, or both) who are at low (group A) or medium (group B) cardiovascular risk. The above risk stratifications include assessment of left ventricular hypertrophy using electrocardiography. A major limitation of this approach is that the sensitivity of electrocardiography for identification of prognostically adverse left ventricular hypertrophy, even using the most accurate methods [6,7], is considerably lower than that of echocardiography [8]. Echocardiographic left ventricular mass is a powerful independent predictor of cardiovascular risk [9,10], and its treatment-induced reduction is associated with improved prognosis [11,12]. Despite the above evidence, because of the additional cost of this procedure, there is still uncertainty regarding the use of echocardiography as a routine diagnostic procedure in patients with hypertension. Although the presence or absence of echocardiographic left ventricular hypertrophy is not expected to influence therapeutic decisions in high- or very-high-risk patients, it could modify clinical decision-making in those at low and medium risk, because left ventricular hypertrophy identified through the sensitive tool of echocardiography is a marker of increased risk in these patients, thus identifying a need for immediate drug treatment [13].

Accordingly, the present study was undertaken to assess the impact of echocardiography on cardiovascular risk stratification in a large untreated hypertensive population at low or medium cardiovascular risk.

Methods

The present analysis involved 1322 patients with untreated essential hypertension who had been consecutively enrolled, between May 1988 and December 1999, in the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study. This study is a prospective observational survey of initially untreated adult individuals with essential hypertension, referred to three participating centres (Perugia, Città della Pieve and Castiglione del Lago) for baseline evaluation by a group of general practitioners practising in Umbria, central Italy [14]. All the participants had office blood pressure $\geq$ 140/90 mmHg on at least three visits at 1-week intervals, no previous or current treatment for hypertension, and no clinical or laboratory evidence of heart failure, coronary heart disease, previous stroke, valvular defects, secondary causes of hypertension or important concomitant disease. All gave informed consent to inclusion in the study.

Study population

For the purpose of the present study, we included all never-treated individuals from the PIUMA cohort for whom the routine clinical and laboratory data required for risk stratification by WHO–ISH [5] and JNC VI [4] guidelines were complete. According to WHO–ISH guidelines [5], delay or avoidance of antihypertensive drug treatment is suggested in individuals at low or medium cardiovascular risk. Hypertensive individuals were classified as at low WHO–ISH risk if they had grade 1 hypertension, no diabetes, no clinical cardiovascular disease, no target-organ damage (serum creatinine $\geq$ 106 μmol/l, proteinuria, left ventricular hypertrophy on the electrocardiogram), and no concomitant cardiovascular risk factors (age $\geq$ 55 years for men and $\geq$ 65 years for women; total cholesterol $>$ 6.46 mmol/l, smoker, family history of premature cardiovascular disease). Individuals were defined as at medium risk if they had no target-organ damage, no clinical cardiovascular disease, no diabetes, and either grade 1 hypertension with 1 or 2 risk factors or grade 2 hypertension with 0–2 risk factors. In the presence of grade 3 hypertension, at least three concomitant risk factors, diabetes, target-organ damage, or clinical cardiovascular disease, individuals were considered to be at high or very high risk [5]. According to JNC VI guidelines [4], those at low risk (stage 1 hypertension in the absence of diabetes, target-organ damage, or clinical cardiovascular disease) are candidates for a period of up to 1 year without drug treatment. For the purpose of JNC VI risk stratification, we defined dyslipidaemia as a cholesterol concentration $\geq$ 6.21 mmol/l, and renal disease as overt proteinuria, or serum creatinine $\geq$ 136 μmol/l in men and $\geq$ 120 μmol/l in women [15].

Office blood pressure was measured by a physician in the hospital outpatient clinic using a mercury sphygmomanometer, with the patient sitting for at least 10 min. The average of six measurements was considered for the analysis. Left ventricular hypertrophy on the electrocardiogram was defined according to the Perugia criterion ($S_{V3} + R_{aVL} > 2.4$ mV in men, > 2.0 mV in women, or typical left ventricular strain, or Romhilt–Estes score $\geq$ 5) [6]. Compared with several traditional criteria, this criterion showed a greater sensitivity at acceptable levels of specificity for the detection of echocardiographic left ventricular hypertrophy [6], and its accuracy was independent of obesity [16]. Moreover, the Perugia criterion exhibited a greater attributable risk for cardiovascular morbidity and mortality than do other criteria [17]. Retinal changes were graded according to the Keith–Wagener–Barker classification [18]; advanced (grade 3 or 4) retinopathy was considered to be a sign of clinical cardiovascular disease [5]. Grade 1 and 2 retinopathy are considered to be unspecific findings [19] and their prognostic impact is currently unsettled; therefore, it has been suggested that grade 1 and 2 retinopathy should not be included among the criteria for risk stratification in hypertension [19]. In the present study, data were analysed after both exclusion

and inclusion of grade 1 and 2 retinopathy among the criteria for risk stratification.

Echocardiography

Quantitative M-mode echocardiography of the left ventricle was performed under two-dimensional control, using standard methods [12]. Measurements were taken according to the American Society of Echocardiography recommendations [20], as previously reported in detail elsewhere [10,12]. Intra-observer and intrapatient variabilities in our laboratory have been reported elsewhere [21,22]. Left ventricular mass was calculated according to Devereux *et al.* [23], and normalized both by body surface area and by height$^{2.7}$ [24], to account for the effect of overweight. Left ventricular hypertrophy was defined as left ventricular mass index ≥ 50 g/m$^{2.7}$ in men or ≥ 47 g/m$^{2.7}$ in women [24], and an individual's risk was re-classified if their echocardiographic left ventricular mass was greater than these cut-off values. Relative wall thickness was calculated as posterior wall thickness/left ventricular internal radius.

Statistical analysis

SPSS statistical package, release 10.0 (SPSS Inc., Chicago, Illinois, USA), was used to perform analyses. Data are reported as mean ± SD. Standard descriptive and comparative analyses were undertaken. The differences in clinical variables among groups of hypertensive individuals at different cardiovascular risk [5] were assessed by one-way analysis of variance (3 degrees of freedom) followed by linear contrasts in comparison with the normotensive group, with no assumption of equal variances. Analysis of categorical data was carried out using the χ^2 test, or Fisher's exact test when appropriate. A two-tailed $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the main characteristics of the study population, stratified according to the WHO–ISH classification of cardiovascular risk. The proportion of individuals at low risk was 16.6% ($n = 220$), and that of individuals at medium risk was 43.3% ($n = 572$).

Of 1322 hypertensive individuals meeting inclusion criteria, 1181 (89%) had M-mode echocardiographic tracings of good technical quality. Compared with individuals with good-quality tracings, those with readings of insufficient quality were older (56 ± 11 years compared with 47 ± 11 years, $P < 0.0001$), were more frequently men (63% compared with 56%, $P = 0.04$), and had a greater body mass index (27.8 ± 3 kg/m^2 compared with 26.6 ± 4 kg/m^2, $P < 0.0001$) and SBP (158 ± 16 mmHg compared with 153 ± 17 mmHg, $P < 0.001$). The proportion of individuals with echocardiograms of insufficient quality increased progressively across risk groups (5, 9, 15 and 12% in those at low, medium, high and very high risk, respectively; $P < 0.002$).

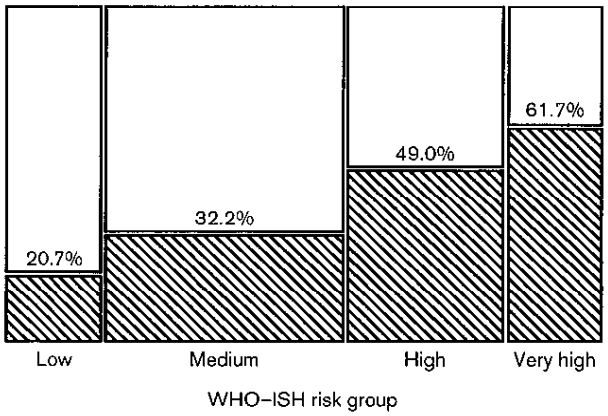
Echocardiographic data are presented in Table 1. Echocardiographic left ventricular hypertrophy was present in 452 (38.3%) of 1181 hypertensive individuals with good-quality echocardiographic readings. The prevalence of left ventricular hypertrophy was 20.7, 32.2, 49.0 and 61.7% in hypertensive groups at WHO–ISH low, medium, high and very high risk, respectively (Fig. 1; $P < 0.001$ for trend). Among the hypertensive individuals without indication for immediate treatment according to WHO–ISH criteria (low and medium risk combined), the prevalence of left ventricular hypertrophy was 28.9%. Because relatively few low- and medium-risk patients had unreadable echocardiograms, the overall prevalence of left ventricular hypertrophy in

Table 1 Selected clinical characteristics of the study population, and echocardiographic findings in individuals with good-quality echocardiographic tracings

	Low risk	Medium risk	High risk	Very high risk	ANOVA (*P* value)
	($n = 220$)	($n = 572$)	($n = 356$)	($n = 174$)	
Age (years)	44 ± 10	47 ± 11	50 ± 12	52 ± 13	< 0.0001
Men/women (%)	47/53	53/47	63/37	59/41	< 0.001
Body mass index (kg/m^2)	26.0 ± 3	26.5 ± 4	27.2 ± 4	27.0 ± 4	< 0.0001
Family history of premature CVD (%)	0	10	8	8	< 0.0001
Current smokers (%)	–	37	22	42	< 0.0001
Diabetes (%)	–	–	11	7	< 0.0001
Serum creatinine (μmol/l)	81 ± 12	82 ± 13	94 ± 19	95 ± 34	< 0.0001
Total cholesterol (mmol/l)	5.10 ± 0.8	5.63 ± 1.0	5.61 ± 1.1	5.70 ± 1.1	< 0.0001
LV hypertrophy at ECG (%)	–	–	35	29	< 0.0001
Office SBP (mmHg)	141 ± 8	151 ± 13	154 ± 15	178 ± 19	< 0.0001
Office DBP (mmHg)	92 ± 4	96 ± 7	97 ± 10	106 ± 13	< 0.0001
	($n = 208$)	($n = 519$)	($n = 301$)	($n = 153$)	
LV mass/body surface area (g/m^2)	92 ± 18	100 ± 22	110 ± 19	119 ± 31	< 0.0001
LV mass/height$^{2.7}$ (g/m$^{2.7}$)	41.3 ± 8	45.3 ± 11	50.3 ± 14	54.4 ± 15	< 0.0001
Relative wall thickness	0.39 ± 0.06	0.41 ± 0.08	0.42 ± 0.08	0.45 ± 0.09	< 0.0001

Values are mean ± SD. *n*, number of individuals. ANOVA, analysis of variance; CVD, cardiovascular disease; LV, left ventricular; ECG, electrocardiography; DBP, SBP, diastolic and systolic blood pressures.

Fig. 1

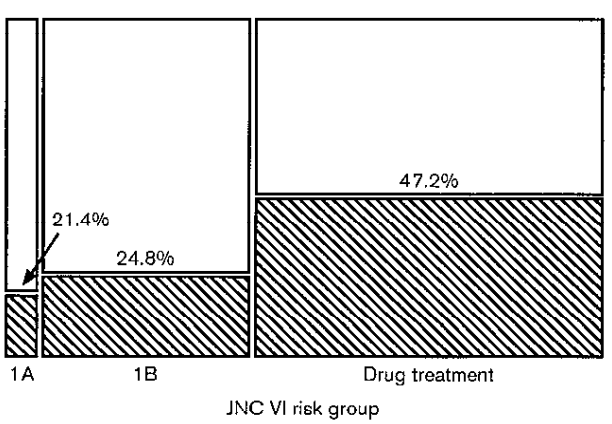


Bar diagram illustrating the prevalence of left ventricular hypertrophy at echocardiography (cross-hatched areas) in hypertensive individuals ranked by WHO–ISH risk category [5]. The width of the bars represents the proportion of individuals belonging to each risk group.

these groups, including also those without echocardiographic readings of sufficient quality, decreased only slightly, to 26.5%. The progressive increase in left ventricular mass across risk groups was accompanied by a progressively more concentric geometry ($P < 0.0001$ for relative wall thickness).

The proportion of individuals in whom treatment was not immediately indicated by JNC VI guidelines was 37.9% (Fig. 2). The suggested period of observation was up to 1 year in 4.4% ($n = 58$; stage 1, group A), and up to 6 months in 33.5% ($n = 443$; stage 1, group B). The proportion of individuals with left ventricular hypertrophy among those with good-quality echocardiographic tracings was 21.4% in stage 1, group A, and 24.8% in stage 1, group B. The proportion was 47.2% in the remaining individuals, in whom immediate treatment was suggested. Among all hypertensive individuals without indication for immediate treatment (stage 1, groups A and B combined), the prevalence of left ventricular hypertrophy was 24.3%. The prevalence was 22.4% when those without echocardiographic left ventricular mass readings were included.

Fig. 2



Bar diagram illustrating the prevalence of left ventricular hypertrophy at echocardiography (cross-hatched areas) in hypertensive individuals ranked by JNC VI risk category [4]. The width of the bars represents the proportion of individuals belonging to each risk group. 1A, stage 1, group A; 1B, stage 1, group B.

The analysis was also performed after inclusion of retinal changes among the criteria for risk stratification, as suggested in the WHO–ISH guidelines [5]. Keith–Wagener–Barker grade 1 or 2 retinopathy [18] was considered as target-organ damage, and advanced (grade 3 or 4) retinopathy was considered as a sign of clinical cardiovascular disease [5]. In this analysis, the proportion of individuals at low risk was 10.8% ($n = 143$), and that of individuals at medium risk was 25.4% ($n = 336$). Among patients with good-quality echocardiographic readings, echocardiographic left ventricular hypertrophy was present in 17.0% of low-risk patients and in 31.3% of medium-risk patients.

Discussion

There is unequivocal evidence that drug treatment substantially reduces the risk of cardiovascular complications and death in hypertensive individuals over a wide range of blood pressure values [1]. In the presence of mildly increased blood pressure, however, as many as 86 hypertensive individuals need to be treated for an average of 5 years to prevent one event [25], and attempts are being made to target the use of antihypertensive drugs at those individuals who need them most. In fact, the expected gain of treatment is inevitably low in those hypertensive individuals in whom the absolute cardiovascular risk is below a given threshold. Thus the need for drug treatment in the single individual and the time interval before it should be instituted remain a matter of debate. The ultimate goal in selecting patients for antihypertensive treatment would be to treat only those who would otherwise develop cardiovascular events and to avoid treatment in all others. Unfortunately, the blood pressure alone is a weak predictor of absolute cardiovascular risk, and of benefit from treatment. In several recent sets of guidelines for the management of hypertension, the need for treatment is based on an estimation of the absolute risk of complications, which depends largely on factors other than blood pressure, such as sex, age, concomitant risk factors, target-organ damage and history of cardiovascular disease [4,5], and drug treatment may be avoided in those at very low cardiovascular risk [5,26]. Therefore, a few tests, including electrocardiogram,

urine analysis, fasting blood glucose, creatinine and total cholesterol, are currently recommended in all hypertensive individuals, to refine cardiovascular risk prediction [4,5].

Left ventricular hypertrophy, detected either by electrocardiography [17,27] or by echocardiography [9,10], is a powerful predictor of cardiovascular risk in hypertension, and the sensitivity of echocardiography in diagnosing left ventricular hypertrophy is much greater than that of electrocardiography, even when the most accurate electrocardiographic methods are used [6,7]. Moreover, echocardiographic left ventricular hypertrophy has been shown to predict mortality independently of electrocardiographic left ventricular hypertrophy [28]. However, the generalized use of echocardiography to detect left ventricular hypertrophy would double the cost of the initial work-up for arterial hypertension, a burden that needs to be proved useful in terms of clinical decision making. In some guidelines for the management of hypertension, echocardiography is indicated in those with 'suspected' left ventricular hypertrophy [5,25,29], whereas JNC VI [4] considered the need for echocardiography in untreated hypertensive individuals at low cardiovascular risk.

Two studies have opened the way to investigating the impact of echocardiography in hypertensive patients judged to be at relatively low risk on the basis of traditional clinical evaluation [19,30]. The study by Cuspidi *et al.* [19] showed that the use of two additional tests, namely echocardiography and carotid artery ultrasonography, modified cardiovascular risk stratification in 99 hypertensive patients classified as at low or medium risk according to the WHO–ISH guidelines. Abergel *et al.* [30] demonstrated that adherence to the 1993 WHO/ISH recommendations (i.e. without performing systematically echocardiograms) leaves untreated a proportion of patients with 'mild hypertension' who would have been treated if the decision had also been based on echocardiographic information on left ventricular geometry. Our analysis extends those findings to a larger sample, by highlighting the independent contribution of echocardiography to risk classification, and by operating a more rigid selection of low-to-medium risk patients, with both exclusion and inclusion of funduscopic examination in the WHO–ISH primary work-up. Our study demonstrates that 29% of individuals not requiring immediate treatment by the WHO–ISH guidelines [5], and 24% of those classified by the JNC guidelines [4], would be reclassified at high cardiovascular risk [4,5] after echocardiographic detection of left ventricular hypertrophy, as a result of which antihypertensive drug treatment would be started without delay.

These findings have important implications for clinical practice and public health. A significant proportion of cardiovascular events in low-risk hypertensive individuals might potentially be prevented if prompt institution of effective antihypertensive treatment reversed both the left ventricular hypertrophy and its associated clinical risk. In a preliminary prospective analysis of the present study, we found that detection of echocardiographic left ventricular hypertrophy is associated with a more than double risk of cardiovascular events in hypertensive individuals at low or medium risk by WHO–ISH clinical evaluation (data not shown). The potential benefits of a policy of inclusion of echocardiographic evaluation might be greater if a longer period of time were considered. Several clinical guidelines [5,26,31] recommend leaving untreated those individuals with very low 10-year risk of cardiovascular disease, because of their very low expected absolute benefit, which hardly justifies long-term drug treatment. In this context, knowledge of left ventricular hypertrophy may enable the clinician better to assess the absolute risk of an individual patient, and to make a better-informed decision regarding initiation of antihypertensive drug treatment. This policy might be of particular value in clinical settings, such as cases of borderline isolated systolic hypertension (SBP 140–159 mmHg and DBP < 90 mmHg), in which there is no current proof of prognostic benefits from treatment.

Some other points deserve comment. First, individuals at low and medium risk had no evidence of target-organ damage according to the work-up proposed by the WHO–ISH guidelines. In order to maximize the diagnostic sensitivity of electrocardiography, we used a criterion of which the sensitivity, accuracy and prognostic value are greater than those of several other more widely used standard criteria [6,17]. Thus the incremental contribution of the echocardiographic examination to risk stratification in our study was, conservatively, above that of the best current use of standard electrocardiography. Secondly, the proportion of individuals with poor-quality echocardiograms was greater in those at greater cardiovascular risk. Thus the yield of echocardiography appeared to be superior in low-risk individuals in whom further risk stratification could modify treatment decisions.

These results should be interpreted in the context of their possible limitations. The study population was referred by a group of general practitioners and might therefore not be fully representative of the general population. However, this cohort may represent the distribution of patients in a general practice, which is the context in which the first decision making about treatment most often occurs. In addition, individuals who were classified as at low or medium WHO–ISH risk or grade A or B/stage 1 JNC VI were accurately defined on the basis of a recognized complete diagnostic

work-up, and thus can be considered as well-characterized in their overall cardiovascular risk profile. The PIUMA study cohort is composed exclusively of white individuals and therefore these findings cannot be extrapolated to other ethnic groups. Examination of other populations and ethnic groups is needed before the present conclusions can be automatically extended to other racial groups.

Clinical implications

Despite limitations imposed by a number of approximations, the estimation of total cardiovascular risk is a cornerstone of the clinical evaluation of individuals with essential hypertension, the absolute baseline risk being the main determinant of the absolute benefit provided by treatment [1,2]. The uncertainty regarding the optimal management of hypertensive individuals with a low risk profile has been fostered by a recent analysis of the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study population [31]. In individuals with grade 1 hypertension and low overall cardiovascular risk (risk group A of the JNC VI [4]), the number-needed-to-treat for 10 years to prevent one cardiovascular death was as high as 394, whereas the numbers-needed-to-treat were much lower in individuals at greater risk [32]. Rational and cost-effective management of the large subgroup of hypertensive individuals at relatively low risk may be aided by accurate stratification of their cardiovascular risk. In low-risk hypertensive individuals, in whom JNC VI and WHO–ISH guidelines [4,5] recommend delaying or even avoiding drug treatment, echocardiography may be indicated to identify those with left ventricular hypertrophy who would have remained untreated after the standard work-up suggested by WHO–ISH and JNC VI. In these individuals, the increased risk of cardiovascular complications arising within the subsequent few years appears to warrant immediate treatment with antihypertensive drugs.

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