Original articles

Prognostic value of combined echocardiography and ambulatory blood pressure monitoring in hypertensive patients at low or medium cardiovascular risk

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Blood pressure; Cardiovascular diseases; Echocardiography; Hypertension; Hypertrophy; Prognosis.

Background. **The clinical value of echocardiography and ambulatory blood pressure monitoring (ABPM) in hypertensive patients at low immediate risk of cardiovascular disease is still unknown.**

Methods. **Echocardiography and ABPM were performed in 715 untreated subjects with essential hypertension World Health Organization/International Society of Hypertension stage I or II and low or medium cardiovascular risk defined by the absence of diabetes, previous cardiovascular events, left ventricular (LV) hypertrophy at electrocardiography, proteinuria, stages III-IV retinopathy and creatinine levels > 106.08 mmol/l (1.2 mg/dl) and the presence of one or two traditional risk factors.**

Results. **The LV mass was increased in 26.5% of these subjects. Subjects with a limited blood pressure reduction from day to night (non-dippers) were 11.3%. Over 1-13 years of follow-up, 31 subjects developed a first major cardiovascular event. The event rate (per 100 person-years) was 0.60 in the subgroup with a normal LV mass vs 1.63 in that with an increased LV mass ($p < 0.017$), and 0.74 in dippers vs 3.75 in non-dippers ($p < 0.001$). On multivariate analysis, the relative risk of cardiovascular events was 1.70 (95% confidence interval-CI 1.23-2.36) for each 11 g/m$^{2.7}$ increment in LV mass ($p < 0.01$), and 2.77 (95% CI 1.12-6.83) in non-dippers vs dippers ($p < 0.05$). Overall, on the basis of results of combined echocardiography and ABPM, 33% of subjects were at increased risk of future cardiovascular events.**

Conclusions. **At standard first-line work-up performed on hypertensive subjects at low or medium cardiovascular risk, combined echocardiography and ABPM identify an increase in the risk of subsequent cardiovascular disease in one third of subjects.**

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Introduction

The demonstration that left ventricular (LV) mass at echocardiography is an independent predictor of cardiovascular risk in hypertension[1-9] and the initial clues that serial changes in LV mass contribute to the refinement of risk stratification[10-12] do not imply that echocardiography is indicated in all subjects with hypertension[13,14]. There is no evidence that patient management guided by results of echocardiography or ambulatory blood pressure monitoring (ABPM) is superior to that without these procedures for the prevention of the cardiovascular complications of hypertension. Therefore, both the World Health Organization/International Society of Hypertension (WHO/ISH)[13] and the Joint National Committee (JNC VI)[14] do not recommend echocardiography in all hypertensive patients, but recognize its potential value in uncomplicated mild hypertension, for which a period of observation without drug treatment is advised[13,14]. It has been noted[15,16] that results of echocardiography could change the risk category in a number of patients and therefore force the therapeutic decisions by orienting the physician towards a more aggressive strategy with elimination of the observation period without drugs in case of detection of an increased LV mass.

Similarly, ABPM is a diagnostic procedure that is increasingly being used in clin-

ical practice, though no specific indication exists in the current guidelines[13,14,17]. There is growing evidence that results of ABPM contribute to the refinement of cardiovascular risk stratification in subjects with essential hypertension[17].

In this context of uncertainty about the use of procedures that would make the work-up for arterial hypertension substantially more expensive, no outcome-based study of the prognostic value of echocardiography and ABPM has yet been completed in the specific setting of mildly hypertensive patients at low or medium risk of cardiovascular events, for whom, according to the WHO/ISH classification[13] it is suggested that no treatment be prescribed for a variable period of time. Appropriate cardiovascular risk stratification is of critical importance in these subjects[13,14] and both echocardiography and ABPM might be useful in improving our ability to discriminate. However, the low incidence of cardiovascular morbid events in this specific subset of patients may limit the completion of outcome-based studies.

We take advantage of the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) database, a long-term prospective registry of morbidity and mortality in initially untreated subjects with essential hypertension, in order to investigate the prognostic value of echocardiographically diagnosed LV hypertrophy and of ABPM in patients with stage I or II essential hypertension and a low or medium cardiovascular risk according to the WHO/ISH guidelines[13].

Methods

The PIUMA study. The PIUMA study is a prospective registry of morbidity and mortality in subjects with essential hypertension whose off-therapy initial diagnostic work-up includes 24-hour non-invasive ABPM according to a standardized protocol. Details of the PIUMA registry have been reported elsewhere[5,12]. Admission criteria included office systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on three or more visits performed at 1-week intervals, no previous treatment for hypertension or withdrawal from antihypertensive drugs ≥ 4 weeks prior to the study and no clinical or laboratory evidence of heart failure, renal failure, coronary artery disease, valvular defects or secondary causes of hypertension. The office blood pressure was measured using a standard mercury sphygmomanometer after the subject had been seated for ≥ 10 min. The heart rate was determined immediately thereafter.

Ambulatory blood pressure was recorded using the SpaceLabs units 90202 and 90207 (SpaceLabs, Redmond, Washington, DC, USA) set to take a reading every 15 min throughout the 24 hours. Normal daily activities were allowed, and patients were recommended to keep their non-dominant arm still and relaxed to the side during measurements. The spontaneous day-to-day variability of ambulatory blood pressure was assessed in some of these patients[18]. Day and night were defined using the so-called "narrow fixed-clock intervals" (day from 10.00 a.m. to 8 p.m.; night from midnight to 6 a.m.)[19]. Non-dippers were defined by a less than 10% reduction in systolic and diastolic blood pressure from day to night[5] whereas the remaining subjects were scored as dippers. White-coat hypertension was defined by an average daytime systolic blood pressure < 130 mmHg and diastolic blood pressure < 80 mmHg[20].

Echocardiography was performed according to standard laboratory procedures under cross-sectional control and using commercially available machines[5,12]. Examinations were performed by two operators (PV, GS) in the three hospital centers participating in the PIUMA registry. At the time of the echocardiographic examination, all involved investigators were unaware of patients' clinical data including office and ambulatory blood pressure. The linear LV measurements were obtained using the American Society of Echocardiography leading edge to leading edge criteria[21] and LV mass was estimated using the equation validated by Devereux et al.[22]: $0.80 \times \{1.04 \times [(\text{septum thickness} + \text{LV internal diameter} + \text{posterior wall thickness})^3 - (\text{LV internal diameter})^3]\} + 0.6$ g, and normalized by the height in meters and elevated to the power of 2.7. Intra- and interobserver coefficients of variability for LV mass in our laboratory have been reported elsewhere[12].

Definition of the study population. The selection procedure of the study population is outlined in figure 1. The original database included subjects with essential hypertension consecutively enrolled in the PIUMA registry

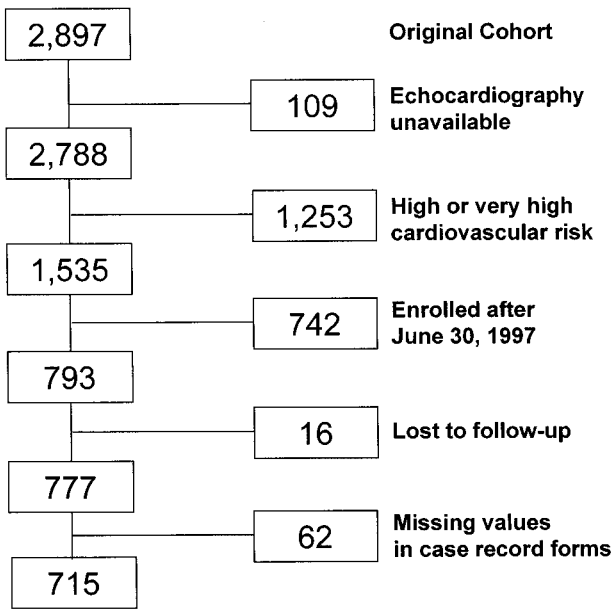

Figure 1. *Selection procedures.*

from June 12, 1986 to January 31, 2000. Subjects enrolled after June 30, 1997, were not included in the follow-up because of their limited observation time. The study sample included subjects with low or medium cardiovascular risk as defined by the WHO/ISH guidelines[13]. In particular, the systolic office blood pressure had to be < 180 mmHg and the diastolic blood pressure had to be < 110 mmHg. Besides, the patient's history had to be negative for diabetes mellitus, coronary or cerebrovascular morbid events, serum creatinine levels > 106.08 mmol/l (1.2 mg/dl), proteinuria, electrocardiographically diagnosed LV hypertrophy as defined by the Perugia score[23,24] and stage III or IV retinopathy. Previous morbid events were defined as myocardial infarction, angina, heart failure (the simultaneous presence of two or more major criteria or one major plus two minor criteria as reported in the Framingham Heart Study[25]), transient ischemic attack, stroke, renal failure requiring dialysis and occlusive peripheral arterial disease. Diabetes mellitus was defined by a fasting blood glucose level ≥ 140 mg/dl, a random non-fasting blood glucose level ≥ 200 mg/dl or the use of an oral hypoglycemic agent or insulin. The subjects with medium cardiovascular risk had to be characterized by the presence of one or two traditional risk factors (total cholesterol > 6.465 mmol/l - 250 mg/dl), cigarette smoking, age > 65 in men or > 55 in women, family history of premature death due to coronary heart disease (at age < 55 in the father or < 65 in the mother), obesity (body mass index > 30 kg/m^2).

Follow-up. Follow-up was mainly performed by the patient's family doctor, often in cooperation with the staff of the outpatient clinic of the referring hospital, with the aim of reducing the office blood pressure below 140/90 mmHg using standard lifestyle and pharmacological measures. There were periodical contacts with family doctors and telephone interviews with patients in order to ascertain the vital status and the occurrence of major cardiovascular complications. Interviews were conducted without knowledge of the patient's data.

Endpoint evaluation. Hospital record forms and other source documents of patients who suffered an endpoint event were reviewed in conference. Cardiovascular events considered in this study included myocardial infarction, unstable angina with concomitant ischemic electrocardiographic changes, stroke, transient cerebral ischemia, symptomatic aorto-iliac occlusive disease verified at angiography, congestive heart failure defined by the simultaneous presence of two or more major criteria or one major plus two minor criteria as reported in the Framingham Heart Study[25] and cardiac death. The international standard criteria used to diagnose outcome events in the PIUMA study have been described elsewhere[5,12,24].

Statistical analysis. Statistical analysis was performed using SPSS (SPSS Inc., Chicago, IL, USA), release 8.0.2. Parametric data are reported as mean ± SD. For the subjects who experienced multiple events, survival analysis was based on the first event. Survival curves were estimated using the Kaplan-Meier product-limit method[26] and compared by the Mantel (log-rank) test[27]. The effect of prognostic factors on survival was evaluated by the stepwise Cox model[28]. We tested the following variables: age (years), sex (women, men), serum cholesterol (mmol/l), serum creatinine (mmol/l), smoking habits (number of cigarettes smoked per day), body mass index (kg/m^2), LV mass (g/m$^{2.7}$), family history of premature death due to coronary heart disease (yes, no) and dipping pattern (dippers, non-dippers). Blood pressure was also tested as a continuous variable using the average 24-hour values of diastolic blood pressure and pulse pressure because their predictive value proved to be superior to the corresponding values of office blood pressure[29]. The LV mass was corrected for height in meters and elevated to the power of 2.7 in order to account for the effect of obesity[30]. In two-tailed tests, p values < 0.05 were considered statistically significant.

Results

Selection procedures of the study population from the original PIUMA cohort are reported in figure 1. All the original PIUMA subjects who fulfilled the inclusion criteria for this study were consecutively included. Out of 715 subjects meeting the inclusion criteria, 187 (26%) were classified in the low and 528 (74%) in the medium WHO/ISH risk cluster. The technical quality of the echocardiographic tracings was good in 648 (91%) subjects. The LV mass was increased (> 51 g/m$^{2.7}$) in 172 (26.5%) of these subjects. Table I shows the main characteristics of the study population. The group of subjects who experienced a cardiovascular event were older, less frequently women and more frequently heavy smokers as compared with the event-free group. Their baseline HDL cholesterol was lower (p = 0.003) and their total/HDL cholesterol ratio higher (p = 0.0001) than in patients without subsequent cardiovascular events. The increase in LV mass was higher in subjects experiencing adverse events during follow-up than in those with event-free survival. The same applied to the ambulatory blood pressure, particularly that during the night (0.02 < p < 0.0001). On the other hand, the office blood pressure did not differ between the two groups. The increase in LV mass in the subjects with subsequent cardiovascular events was accounted for by an increase in both the wall thickness and LV cavity dimensions. The prevalence of subjects with white-coat hypertension was 6.6% and that of subjects with a non-dipping pattern was 11.3%.

Table I. Clinical characteristics of the study population.

Characteristic	All subjects (n=715)	Non-cardiovascular endpoints (n=684)	Cardiovascular endpoints (n=31)	p
Age (years)	48 ± 11	48 ± 11	57 ± 10	0.0001
Women (%)	50.5	51.3	32.3	0.029
Duration of hypertension (years)	3.5 ± 5	3.5 ± 5	4.9 ± 7	0.12
Body mass index (kg/m^2)	26.6 ± 4	26.6 ± 4	26.9 ± 4	0.54
Cigarette smoking (%)				0.005
0 cigarettes per day	77	78	68	
1-19 cigarettes per day	15	15	10	
≥ 20 cigarettes per day	8	7	22	
TC (mmol/l)	5.41 ± 0.99	5.40 ± 1.0	5.46 ± 0.81	0.75
HDL cholesterol (mmol/l)	1.26 ± 0.30	1.27 ± 0.30	1.07 ± 1.27	0.003
LDL cholesterol (mmol/l)	3.51 ± 0.91	3.51 ± 0.92	3.53 ± 0.74	0.91
TC/HDL cholesterol	4.52 ± 1.2	4.48 ± 1.2	5.42 ± 1.6	0.0001
Triglycerides (mmol/l)	1.49 ± 0.86	1.48 ± 0.88	1.67 ± 0.83	0.25
Creatinine (µmol/l)	81.4 ± 12	81.3 ± 12	84.1 ± 12	0.22
Glucose (mmol/l)	5.35 ± 0.66	5.34 ± 0.67	5.42 ± 0.50	0.55
Office BP (mmHg)				
Systolic/diastolic	150 ± 13/96 ± 7	150 ± 13/96 ± 7	154 ± 12/94 ± 6	0.11/0.09
Pulse	54 ± 13	54 ± 12	61 ± 12	0.015
Average 24-hour BP (mmHg)				
Systolic/diastolic	132 ± 11/84 ± 8	132 ± 11/84 ± 8	137 ± 11/86 ± 7	0.007/0.267
Pulse	48 ± 7	48 ± 7	51 ± 8	0.007
Average daytime BP (mmHg)				
Systolic/diastolic	139 ± 11/90 ± 9	138 ± 11/90 ± 9	141 ± 11/90 ± 8	0.26/0.94
Pulse	48 ± 8	48 ± 8	51 ± 8	0.02
Average nighttime BP (mmHg)				
Systolic/diastolic	119 ± 13/72 ± 9	119 ± 12/72 ± 9	129 ± 16/77 ± 9	0.0001/0.004
Pulse	47 ± 7	47 ± 7	51 ± 10	0.001
Interventricular septum (cm)*	1.07 ± 0.18	1.07 ± 0.19	1.18 ± 0.20	0.005
LV internal diameter (cm)*	4.88 ± 0.45	4.88 ± 0.45	5.09 ± 0.57	0.03
Posterior wall (cm)*	0.97 ± 0.16	0.97 ± 0.16	1.06 ± 0.19	0.004
LV mass (g/m$^{2.7}$)*	44.9 ± 10	45.3 ± 11	54.3 ± 15	0.0001

BP = blood pressure; LV = left ventricular; TC = total cholesterol. * echocardiographic parameters refer to 648 subjects with a good-quality echocardiogram, 23 of whom suffered an event.

Prognostic value of left ventricular mass. The subjects who developed a first cardiovascular event during follow-up were 31, 23 of whom in the subset with good-quality echocardiographic tracings. The subjects with technically inadequate echocardiographic tracings were not included in the prognostic analysis of the LV mass. Two subjects died suddenly, 9 subjects had stroke, 4 a cerebrovascular transient ischemic attack, 9 a non-fatal myocardial infarction, 3 new-onset unstable angina, 2 heart failure requiring hospitalization, and 2 peripheral arterial occlusive disease. The event rate (per 100 person-years) was higher among subjects with suboptimal echocardiographic tracings than in the other group [2.73 vs 0.89, p = 0.008 (log-rank test); unadjusted relative risk 2.93, 95% confidence interval 1.3-6.7], but such a difference did not hold (p = 0.33) after adjustment for age. In the subset with good-quality echocardiographic tracings, the event rate was 0.88 in the total population, 0.60 in the subset with a normal LV mass (< 51 g/m$^{2.7}$) and 1.63 in that with an increased LV mass (log-rank test p = 0.017). The event-free survival in the two groups is shown in figure 2.

Prognostic value of ambulatory blood pressure. There were 19 cardiovascular events among the 634 subjects showing an ambulatory blood pressure dipping pattern (3.0%) and 12 events (or 14.8%) in the non-dipper group (n = 81). The event rate (per 100 person-years) was 0.74 in dippers and 3.75 in non-dippers (p < 0.001, log-rank test). Figure 3 shows the event-free survival in the two groups. None of the 47 subjects with white-coat hypertension developed a cardiovascular event during follow-up.

Multivariate analysis. Results are reported in table II. After adjustment for age and cigarette smoking, the relative risk of cardiovascular events was 1.70 (95% confidence interval 1.23-2.36, p = 0.0014) for each 11 g/m$^{2.7}$ increment in LV mass, and 2.77 (95% confidence interval 1.12-6.83) in non-dippers compared to dippers. The insufficient number of subjects and the lack of cardiovascular events in the white-coat hypertension group precluded its statistical evaluation.

A total of 227 subjects (33% of total population), including 172 subjects with LV hypertrophy, 39 subjects

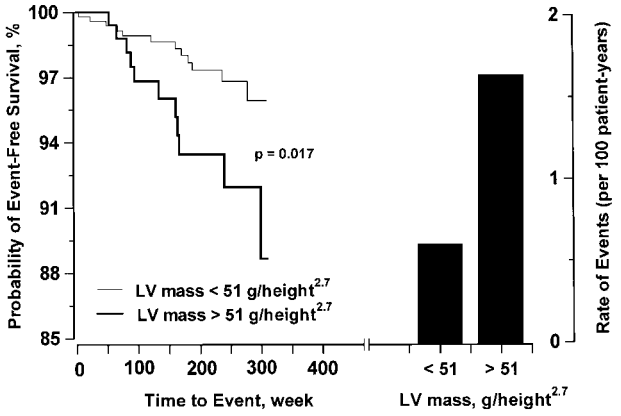

Figure 2. *Event-free survival and rate of events in subjects with and without left ventricular (LV) hypertrophy as detected at echocardiography.*

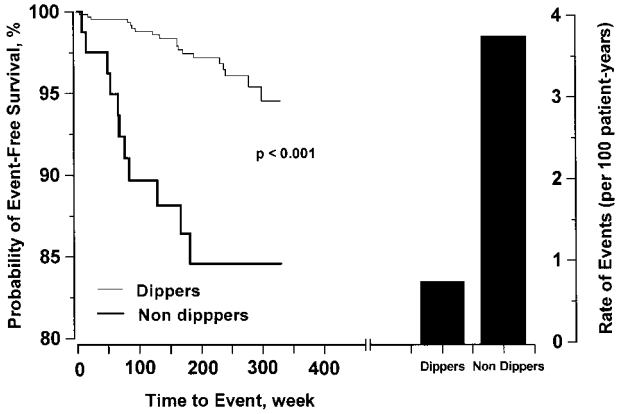

Figure 3. *Event-free survival and rate of events in dippers and non-dippers.*

with a non-dipping pattern and a normal LV mass and 16 subjects with a non-dipping pattern and a suboptimal quality echocardiogram were found, at echocardiography combined with ABPM, to be at increased risk of future cardiovascular events.

Discussion

Our findings demonstrate that combined echocardiography and ABPM considerably improve prognostic stratification in subjects with uncomplicated essential hypertension at a low or medium immediate risk of major cardiovascular events. According to current guidelines[13,14], these subjects have been identified by a systolic blood pressure < 180 mmHg and a diastolic blood pressure < 110 mmHg, by the absence of organ damage or previous cardiovascular disease and by the presence of one or two traditional risk factors. Since the average risk of cardiovascular disease is quite low in these subjects, both the WHO/ISH[13] and the JNC VI[14] guidelines recommend an observation period lasting up to 1 year and including lifestyle measures before starting drug treatment. Actually some of these subjects have a high risk of subsequent cardiovascular disease but they cannot be identified by the routine tests recommended for all subjects with hypertension[12,13]. Besides, a prolonged period of non-drug therapy would not be advisable in these subjects, who, because of their increased cardiovascular risk, probably require a more immediate and aggressive management.

Echocardiography. Our findings indicate that the use of echocardiography for LV mass estimation is a valuable procedure in these subjects because it allows detection of a sizable subset with LV hypertrophy and increased cardiovascular risk that otherwise would remain undetected and erroneously classified as low risk. Several previous studies had shown that LV mass as determined at echocardiography provides independent prognostic information in a variety of clinical conditions[1-12], but none of these studies specifically examined low-risk subjects with essential hypertension. In a smaller study carried out in a population quite comparable to that of the present study, Abergel et al.[31] found that rigorous application of the WHO/ISH guidelines would leave a proportion of mildly hypertensive subjects with abnormalities of LV geometry detected at echocardiography untreated. Thus, lack of echocardiographic information would deprive the physician of clues which are essential for the isolation of high-risk subjects from the context of a population at a low average risk of cardiovascular complications.

Ambulatory blood pressure monitoring. Several event-based studies have shown that ABPM improves cardiovascular risk stratification over and beyond tra-

Table II. Multivariate survival analysis.

Variable	Comparison	RR (95% CI)	p
Age	10 years	1.87 (1.22-2.87)	0.0041
Cigarette smoking	Smokers vs non smokers	2.58 (1.05-6.31)	0.0381
LV mass/height$^{2.7}$*	11 g/m$^{2.7}$	1.70 (1.23-2.36)	0.0014
Dipping pattern	Non-dippers vs dippers	2.77 (1.12-6.83)	0.0263

CI = confidence interval; LV = left ventricular; RR = relative risk. * 11 g/m$^{2.7}$ is 1 SD around the mean.

ditional risk markers[5,29,32-38]. These studies have been conducted in initially untreated subjects with essential hypertension[5,29,32,34,35,38], in subjects with hypertension poorly controlled by treatment[37], subjects with diabetes[36] or in the general population[33], but none of these studies specifically addressed mildly hypertensive subjects at low or medium cardiovascular risk. Similarly to echocardiography, ABPM could be clinically useful to identify subjects at increased cardiovascular risk who need a more aggressive management. White-coat hypertension vs ambulatory hypertension[5,38] and dippers vs non-dippers[5,33-35] are two widely used operational, although arbitrary, classifications. In this study, a non-dipping pattern detected during ABPM identified subjects at increased risk of events (3.75 cardiovascular events per 100 person-years).

The reproducibility of the dippers/non-dippers classification is generally considered poor. However, the use of the so-called "narrow fixed-clock intervals"[19] may lead to a more appropriate definition of the daytime and nighttime sub-periods, with resulting improved reproducibility of the classification. In one study, about 86% of hypertensive subjects remained classified in the same category (dippers or non-dippers) over two ABPM sessions held at an interval of 1 month and in the absence of treatment[39]. Such a reproducibility figure is not dissimilar to that of other widely used biological measures including, for example, LV mass at echocardiography[40]. In a previous reproducibility study from the PIUMA database, 74% of subjects remained classified as dippers or non-dippers in two consecutive sessions held at an interval of a few days[18].

Of note, LV hypertrophy and a non-dipping pattern were independent predictors of cardiovascular risk and their adverse prognostic value remained significant even after adjustment for age and cigarette smoking. Our findings also suggest that the cardiovascular risk is lower in subjects with white-coat hypertension than in those with ambulatory hypertension[5,38]. However, because of the lack of cardiovascular events in the small group of subjects with white-coat hypertension, its favorable prognostic potential could not be evaluated statistically.

Limitations of the study. A limitation of the study was the inclusion, among the outcome events, of two quite "soft" endpoints, namely unstable angina and transient ischemic attack. However, in the pre-definition of these events, the PIUMA protocol outlined the need of the concomitant presence of typical ischemic electrocardiographic changes for angina and of a certified diagnosis, in the presence of neurological deficit, for transient ischemic attacks. Another limitation of the study was the lack of data on blood pressure control during follow-up. Since these data were available in only 30% of the population, results could not be analyzed. Thus, our study cannot clarify whether the degree of long-term blood pressure control is a potential confounder in the evaluation of the prognostic value of the baseline LV mass and of the circadian blood pressure rhythm.

In conclusion, in initially untreated hypertensive subjects at a low or medium risk of cardiovascular events, echocardiography and ABPM are valuable procedures which allow identification of an increased risk of subsequent cardiovascular events in a sizable proportion of subjects (33%), who otherwise would remain undetected and possibly left untreated. Echocardiography and ABPM appear to be valuable procedures in hypertensive patients who, according to the first-line work-up suggested by the WHO/ISH guidelines would be classified at low or medium cardiovascular risk.

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