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Diagnostics

Impact of Baseline Echocardiography on Treatment Outcome in Primary Care Patients With Newly Detected Arterial Hypertension: A Randomized Trial

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Background: The objective of this study was to test whether baseline echocardiography in newly detected hypertension improves left ventricular mass index and blood pressure control. This is a randomized trial with primary care patients.

Methods: After routine clinical work-up 177 consecutive patients with newly detected hypertension were randomized according to result of their echocardiogram (echo group and control group). Treating physicians were encouraged to prescribe angiotensin II receptor antagonist therapy for patients with evidence of hypertensive target organ damage. Mean blood pressure (BP) and echocardiographic left ventricular mass index were measured at baseline and after 6 months of therapy in both groups.

Results: More patients with hypertensive target organ damage were identified in the echo group as compared to the control group (58 of 91 [64%] *v* 42 of 86 [49%] patients (difference 15%, 95% CI 1%–29%). In the echo group, 41 patients (45%) received angiotensin II receptor antagonist therapy as compared to 27 patients (31%) in the control group (difference 14%, 95% CI 0–28%). After 6 months, there were no differences in mean left ventricular mass index, mean diastolic 24-h ambulatory BP monitoring, or mean systolic and diastolic office BP between the two groups.

Conclusions: In patients with newly detected hypertension, baseline echocardiography detects more patients with hypertensive target organ damage, but does not lead to a reduction in left ventricular mass index or improved BP control after 6 months of therapy. Am J Hypertens 2006; 19:1150–1155 © 2006 American Journal of Hypertension, Ltd.

Key Words: Echocardiography, target organ damage, arterial hypertension.

Left ventricular hypertrophy (LVH) is a hypertensive target organ damage and an independent cardiovascular risk factor.[1–3] Importantly, LVH occurs not only in severe but also in mild hypertension.[4–7] In outpatients with mild definite hypertension LVH is encountered in up to 38% of patients.[1]

Most outpatients with newly diagnosed hypertension have mild hypertension. Identifying hypertensive target organ damage is important for early treatment stratification. According to current guidelines,[8–10] patients with mild hypertension and LVH should receive immediate drug treatment. Antihypertensive drug treatment reduces left ventricular mass (LVM),[11–16] and regression of LVH is associated with reduced cardiovascular risk.[11,13] Angiotensin II receptor antagonist therapy is more effective in reducing LVM than β-adrenergic receptor therapy.[12] The Losartan Intervention for Endpoint (LIFE) Reduction in Hypertension Study trial demonstrated the superiority of the angiotensin II receptor antagonist losartan compared to atenolol in reducing cardiovascular end points in hypertensive patients with electrocardiographic[13] and echocardiographic LVH.[17]

Although the value of baseline echocardiography for LVH detection[4–7,18,19] and risk stratification[4,7,18,19] in hypertensive patients has clearly been demonstrated, performing baseline echocardiography for detection of LVH in patients with newly detected hypertension is not recommended in current guidelines.[8–10] Thus, the presence of

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LVH might be missed in patients with mild hypertension.[4,7,18,19]

To our knowledge there are no randomized outcome studies evaluating the impact of baseline echocardiography on treatment outcomes in primary care patients with newly detected essential hypertension. In this prospective randomized trial, we evaluated the impact of baseline echocardiography on LVM index and blood pressure (BP) control in consecutive general medical outpatients from an unselected primary care population with never-treated essential hypertension.

Methods

Consecutive adult general medical outpatients (2615) were screened for office hypertension.

All patients with elevated sitting office BP were deemed eligible for the study (after 5 min of rest, mean of two BP measurements ≥140/90 mm Hg at two different visits, according to standard guidelines).[8] Exclusion criteria were pretreated hypertension, missing study participation consent, severe concomitant illness with the exception of diabetes mellitus, and accepted indications for echocardiography (eg, pericarditis, heart failure, or the presence of a heart murmur suggesting valvular heart disease). The study protocol had been approved by the local ethics committee.

The Medical Outpatient Department of the University Hospital Basel, Switzerland, provides primary care for general medical walk-in patients. Approximately 20% are referred by general practitioners for second opinion or for interdisciplinary ambulatory care. All patients are routinely seen by three- or four-year residents. They are supervised by an attending physician in General Internal Medicine.

Patients with newly detected office hypertension received routine clinical work-up, according to standard guidelines[8] (ie, history, physical examination, routine blood tests, electrocardiogram [ECG] and urinalysis, and 24h ambulatory BP monitoring [24-h ABPM] with validated devices [Spacelabs, Diessenhofen, Switzerland, and Mobilograph, Stolberg, Germany]). Normal mean 24-h ABPM values were defined as <130/80 mm Hg.

After having obtained informed written consent and having ruled out white coat hypertension, patients with definite hypertension were randomized by computer as to make the result of the echocardiogram available to their treating physician (echo group) or to withhold it (control group).

Then all study patients underwent transthoracic echocardiography with a HP 5500 system (Hewlett Packard, Andover, MA) performed by one of two experienced cardiologists who were instructed not to inform patients about the echo findings. Both cardiologists were blinded to the patients' group allocation during the course of the study. Only residents treating patients randomized to the echo group, but not of patients randomized to the control group, obtained a written report about the findings of baseline echocardiography. Results of target organ damage other than LVH were available for the treating physicians of both groups.

Left ventricular mass index was calculated according to the formula: $0.8 \times (1.04 \times [\text{Interventricular septal thickness} + \text{posterior wall thickness} + \text{enddiastolic diameter (EDD)}]^3 - \text{EDD}^3) + 0.6)/\text{m}^2$ body surface area. The LVH was defined conservatively as LVM index >136 g/m^2 for men and >110 g/m– for women, with sufficient sensitivity to diagnose the more severe cases of LVH that are more likely to change the routine treatment decision.

Area-based methods perform as well as height-based methods for normalization of LVM mass for body size[20] in populations with a low rate of obesity such as ours (24%).

Treating residents received a written Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) VI guideline summary as a general recommendation for antihypertensive treatment decision. They based their treatment decision on the presence of hypertensive cardiac or renal target organ damage. Specifically, renal target organ damage was defined as microalbuminuria (albumin-to-creatinine ratio >2.26 mg/mmol) or proteinuria (protein-to-creatinine ratio >11 mg/mmol), cardiac target organ damage as having electrocardiographic signs of LVH (Sokolow-Lyon index >3.5 mV or Cornell product >2440 mV × msec), or an elevated LVM index in echocardiography (>136 g/m^2 for men and >110 g/m^2 for women). When hypertensive target organ damage was identified (LVH shown by ECG or echocardiography, microalbuminuria, proteinuria, diabetes mellitus, history of cardiovascular events), drug treatment with angiotensin II receptor antagonist therapy (particularly valsartan) was strongly encouraged. In the course of the study, treating resident physicians were free to adjust treatment if necessary. End of study examinations including BP measurements and echocardiography were performed after 6 months.

The primary outcome was the difference in mean LVM index between the two groups. Secondary outcomes were the comparison of mean differences in LVM index, office and 24-h ABPM between the two groups, and the proportion of patients with elevated LVM index in the two groups after 6 months of therapy.

Descriptive statistics were calculated using two sample test of proportions. We conducted analyses of covariance to evaluate between group differences in LVM index at the end of follow-up using baseline LVM index as a covariate, and BP values at the end of follow-up using baseline BP as a covariate. Primary analyses were performed on an intention-to-treat basis. We used the last value carried-forward method for missing values. In addition, we conducted per protocol analyses for the primary outcomes (LVM index and BP values after 6 months of follow-up) to minimize potential masking of changes from baseline that might occur with an intention-to-treat analysis. The

predefined level of significance was $P = .05$ (two-sided). Statistical analyses were performed using Excel 5.0 (Microsoft, Redmond, WA) and Stata 8.0 (Stata Corporation, College Station, TX) software.

The prevalence of echocardiographic LVH in mild-to-moderate hypertensive patients is about 30%, whereas the prevalence of electrocardiographic LVH is about 10%.[1,18] In addition to the patients qualifying for angiotensin II receptor antagonist therapy identified by echocardiography and electrocardiography, we expected to identify an additional 10% of patients with microalbuminuria, therefore a total of 40% of patients in the echo group and a total of 20% of patients in the control group would be prescribed angiotensin II receptor antagonist therapy. Based on expected differences in regression of LVM index from a randomized controlled trial comparing the effects of valsartan and atenolol,[15] and taking into consideration the expected differences in prescription rates of angiotensin II receptor antagonist therapy in both groups, the estimated sample size of 91 patients in each group allowed us to detect a difference in LVM index of 2 g/m^2 between the two groups after 6 months of therapy (power 0.8, two-sided α 0.05).

Results

Five hundred eighty of 2615 unselected consecutive medical outpatients screened had an elevated first office BP value; 207 had treated hypertension, 98 patients refused participation, 48 patients were early dropouts or had normal second office BP values. A total of 227 patients with newly detected office hypertension (according to JNC VI definition) were included. Of the 227 patients examined, 50 (22%) had white coat hypertension and consequently were not eligible for randomization. The remaining 177 (78%) patients had definite hypertension (defined as mean 24-h ABPM values ≥130/80 mm Hg) and were randomized into the echo group ($n = 91$) and control group ($n = 86$). Of these 177 patients, 43 (24%) were obese, 9 had diabetes mellitus, and 6 had a history of cardiovascular disease. Echocardiographic imaging quality was very good. Fewer than 10% of examinations had limited image quality. However, even in these patients, standard M-mode dimensions for LVM could still be sufficiently determined.

Prevalence of Hypertensive Target Organ Damage

The overall prevalence of echocardiographic LVH in both groups was 29%. Seven patients (4%) had isolated microalbuminuria, and 67 patients (38%) had proteinuria. Hypertensive target organ damage was diagnosed in 58 of 91 (64%) patients in the echo group and in 42 of 86 (49%) patients in the control group, based on results of baseline diagnostic tests made available to the treating physician ($P = .04$). An additional 5 patients (6%) in the control group had LVH on echocardiography only, and thus were missed as patients at higher risk for cardiovascular complications. Baseline characteristics, as well as data on LVM and geometry are given in Table 1.

Proportion of Patients Receiving Angiotensin II Receptor Antagonist Therapy

In the echo group, 41 of 91 patients (45%) received angiotensin II receptor antagonist therapy, compared to 27 of 86 patients (31%) in the control group (difference 14%, 95% CI 0–28%).

Ten of 91 patients (11%) in the echo group had echocardiographic LVH without any other signs of hypertensive target organ damage. Nine of these 10 patients were prescribed angiotensin II receptor antagonist therapy. The treatment allocation for angiotensin II receptor antagonist

Table 1. Baseline characteristics of patients with definite hypertension ($n = 177$)

	Echo group $n = 91$	Control group $n = 86$	P
Mean age (y ± SD)	51 (13)	52 (14)	.6
Male	51 (56)	55 (64)	.7
Mean BMI (kg/m^2 ± SD)	28.0 (5)	26.9 (5)	.14
Mean office blood pressure (mm Hg ± SD)	164(16)/101(9)	161(12)/101(9)	.16/1.0
Mean 24-h ambulatory blood pressure (mm Hg ± SD)	138(8)/87(7)	139(10)/85(6)	.5/0.04
Mean LVM index (g/m^2 ± SD)	111.3 (28)	112.4 (27)	.8
Sokolow/Cornell index/product positive* (%)	18 (20)	12 (14)	.3
Elevated LVM index† (%)	29 (32)	22 (26)	.4
Relative wall thickness‡ (mean ± SD)	0.49 (0.09)	0.50 (0.09)	.56
Prevalent concentric geometry§ (%)	47	54	.17
Isolated microalbuminuria (%)	3 (3)	4 (4)	.6
Proteinuria (%)	36 (40)	31 (36)	.6
Patients with target organ damage at baseline (%)	58 (64)	47 (55)‖	.22

* Sokolow index positive: >35 mV or Cornell product positive >2440 mV × msec; † >136 g/m^2 for men and >110 g/m^2 for women; ‡ 2x end-diastolic posterior wall thickness/end-diastolic LV internal diameter; § Relative wall thickness ≥0.43; ‖ Including five patients with echocardiographic LVH whose echocardiographic results were not communicated to the treating physician.

Table 2. Treatment allocation at baseline

	Echo group *n* = 91	Control group *n* = 86	*P*
Angiotensin II antagonists (%)	41 (45)	27 (31)	.06
Nondrug treatment only (%)	32 (35)	39 (45)	.17
β-blockers (%)	6 (7)	6 (7)	.9
Calcium antagonists (%)	3 (3)	2 (2)	.7
Diuretics (%)	9 (10)	11 (13)	.5
ACE inhibitor	0	1	1.0

therapy and other types of antihypertensive drugs in both groups is shown in Table 2.

Physicians' Compliance With Recommendation to Prescribe Angiotensin II Receptor Antagonist Therapy in the Presence of Target Organ Damage

In the echo group, 18 of 58 patients (31%) did not receive angiotensin II receptor antagonist therapy according to guidelines in the presence of target organ damage as compared to 23 of 42 patients (55%) in the control group (difference 24%, 95% CI 5%–43%).

Of the 18 patients in the echo group not receiving treatment according to guidelines with an angiotensin II receptor antagonist, 9 had pathologic urine analysis, 6 had electrocardiographic LVH, and 3 had echocardiographic LVH with pathologic urine analysis. Hence, 3 of 29 patients with echocardiographic LVH in the echo group did not receive angiotensin II receptor antagonist therapy. All of them had mild hypertension and borderline elevation of LVM index (mean 5 g/m^2 above cutoff), and were prescribed nondrug treatment. Thus, treatment allocation to angiotensin II receptor antagonist therapy in the presence of echocardiographic LVH was 90% (26 of 29 patients with echocardiographic LVH).

Of the 23 patients in the control group not receiving recommended treatment with an angiotensin II receptor antagonist, 16 had isolated pathologic urine analysis, 5 isolated electrocardiographic LVH, and 2 combined pathologic urine analysis and electrocardiographic LVH.

Six-Month Follow-Up Results

After 6 months, follow-up information was available for 74 patients in the echo group (81%) and from 71 patients in the control group (83%).

There was no difference in LVM index or relative wall thickness between the two groups (Table 3). Similarly, there was no difference in systolic and diastolic office BP between the two groups after 6 months of follow-up. Mean systolic 24-h ABPM was higher in the echo group than in the control group, whereas there was no statistically significant difference in mean diastolic 24-h ABPM between the two groups.

After 6 months of follow-up, 19 of 29 (66%) patients in the echo group compared to 14 of 22 patients (64%) in the control group had persistent elevated LVM index on echocardiography (difference 2%, 95% CI −2% to 3%).

Results of all analyses performed after a follow-up of 6 months were not different when repeated on a per protocol basis.

Discussion

In our trial, more newly detected hypertensive patients with target organ damage compared to a control group without the available information on baseline echocardiography were identified, but this was not associated with a reduction in LVM index or improved BP control.

The lack of difference in LVM index between the two groups may have several reasons. Mean systolic 24-h ABPM at the end of the trial was lower in the control group than in the echo group (130 ± 10 *v* 133 ± 10 mm Hg, $P = .05$). Blood pressure reduction by itself leads to a reduction in LVM, independent of the antihypertensive agent used. Therefore, the observed difference in mean systolic 24-h ABPM, in favor of the control group, may have masked a beneficial effect on LVM in the echo group. Furthermore, most patients with LVH had borderline elevated LVM index and therefore, any expected benefit on regression of LVM was smaller than in patients who have markedly elevated LVM.

Table 3. Left ventricular mass index (g/m^2), mean office, and 24-h ambulatory blood pressure (mm Hg) after 6 months

	Echo group	Control group	*P*
Left ventricular mass index	106 ± 21	106 ± 23	.9*
Prevalent concentric geometry‡ (%)	69	75	.25
Systolic office blood pressure (mm Hg)	141 ± 15	142 ± 16	.5†
Diastolic office blood pressure (mm Hg)	88 ± 10	89 ± 8	.3†
Mean 24-h systolic blood pressure (mm Hg)	133 ± 12	130 ± 10	.05†
Mean 24-h diastolic blood pressure (mm Hg)	83 ± 7	81 ± 8	.11†

* After adjustment for differences in baseline left ventricular mass index; † After adjustment for differences in baseline blood pressure; ‡ 2x end-diastolic posterior wall thickness/end-diastolic LV internal diameter ≥0.43.

We purposely assessed extracardiac target organ damage in both groups to evaluate the impact of echocardiographic evidence of LVH in addition to the impact of BP measurements, ECG and extracardiac evidence of target organ damage on treatment outcomes. To our knowledge, this is the first randomized trial to examine the effect of baseline echocardiography on antihypertensive treatment decision and treatment outcomes in newly detected hypertensive patients. We studied unselected primary care walk-in patients who were obviously more likely to have mild hypertension leading to an excellent generalizability for a primary care population. Physicians performing echocardiography on patients assigned to the control group were instructed not to inform patients about the results to keep the patients blinded as to the results. In addition, doctors performing 6-month follow-up examinations were fully blinded to the patients' group assignment to enhance the internal validity of this trial. Participating physicians complied well with the trial's recommendation to prescribe angiotensin II receptor antagonist therapy in case of echocardiographically documented LVH in the echo group (90% of patients with echocardiographic LVH were prescribed angiotensin II receptor antagonists, particularly valsartan).

The trial has several limitations. Results of 6-month follow-up examinations were available from only about 82% of the original trial population. Dropout rate was relatively high, because our patients were unselected younger walk-in outpatients with a high percentage of migration. By performing an intention-to-treat analysis using the last value carried-forward method for missing values, we might have introduced a bias in favor of the control group by underestimating potential treatment benefits on LVM index and BP in the echo group. However, the results of the analyses did not qualitatively change when repeated on per protocol analyses. There were no appreciable differences regarding age, gender, and baseline LVM between patients with complete follow-up compared to the entire study population.

Six months is a rather short period to evaluate treatment-induced LVM changes; however, first significant treatment-induced changes in LVM are observed after 6 months.[12]

We chose relatively high cutoff values to predefine LVH. Lower cutoff values for LVH might have yielded a higher LVH prevalence of predominantly borderline LVH with possibly more aggressive treatments and possibly a better outcome regarding LVM reduction.

The prevalence of target organ damage other than echocardiographic LV hypertrophy at baseline was higher in the echo group, although not significantly. As a result, theoretically, it could be expected that target organ damage is detected more often, leading to a bias in favor of the echo group. Significantly more patients in the control group compared to the echo group did not receive the recommended treatment with an angiotensin II receptor antagonist in the presence of target organ damage (55% *v* 31%, $P = .02$). This may lead to a bias in favor of the echo group. The absence of any therapeutic benefit in the echo group despite a significantly better adherence to the trial's recommendation to use angiotensin II receptor antagonists in the presence of target organ damage supports the trial's conclusion that baseline echocardiography does not improve LVM index or BP control in patients with newly detected hypertension.

The absence of any improvement of LVM index and BP control may be a consequence of recommending monotherapy with an angiotensin II receptor antagonist in the presence of target organ damage. It is still possible that the recommendation of combined angiotensin II receptor antagonist and diuretic therapy or other treatment, such as angiotensin-converting enzyme inhibitors with or without with diuretics, based on baseline echocardiographic information may yield more beneficial changes in LVM index and BP control.

The main outcomes examined in this trial are intermediate end points. The trial focused on the impact of echocardiography without specific hypertensiologic supervision of the treating physicians, and was not powered to look at cardiovascular complications. We can therefore not completely rule out a potential benefit of baseline echocardiography on cardiovascular outcomes. However, the absence of any reduction in LVM and the absence of any improved BP control in patients randomized to the echo group markedly reduces the likelihood of any cardiovascular benefit in this group.

We conclude that knowledge about baseline echocardiography leads to a higher rate of identification of hypertensive target organ damage, but is not necessarily associated with a reduction in LVM index or improved BP control.

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