

Change in Cardiac Geometry and Function in CKD Children During Strict BP Control: A Randomized Study

Maria Chiara Matteucci,* Marcello Chinali,[†] Gabriele Rinelli,[†] Elke Wühl,[‡] Aleksandra Zurowska,[§] Marina Charbit,^{||} Giacomo Pongiglione,[†] Franz Schaefer,[‡] and the ESCAPE Trial Group

Summary

Background and objectives Left ventricular hypertrophy (LVH) and abnormal systolic function are present in a high proportion of children with CKD. This study evaluated changes in left ventricular (LV) geometry and systolic function in children with mild to moderate CKD as an ancillary project of the Effect of Strict Blood Pressure Control and ACE Inhibition on Progression of Chronic Renal Failure in Pediatric Patients trial.

Design, setting, participants, & measurements Echocardiograms and ambulatory BP monitoring were performed at baseline and at 1- or 2-year follow-up in 84 patients with CKD and 24-hour mean BP above the 50th percentile and/or receiving fixed high-dose angiotensin converting enzyme inhibition and randomized to conventional or intensified BP control.

Results LVH prevalence decreased from 38% to 25% ($P < 0.05$). Changes in LV mass index (LVMI) were restricted to patients with LVH at baseline ($-7.9 \text{ g/m}^2.7$; $P < 0.02$). Changes in LVMI were independent of randomization, reduction in BP, hemoglobin, and estimated GFR. A significant increase in midwall fractional shortening was observed in the total cohort ($P < 0.05$), and was greater in the intensified group compared with the conventional BP control group ($12\% \pm 1.9\%$ versus $8\% \pm 1.5\%$; $P = 0.05$). In multivariate analysis, improvement in myocardial function was associated with reduction in BP ($r = -0.4$; $P < 0.05$), independently of LVMI reduction.

Conclusions In children with CKD, angiotensin converting enzyme inhibition with improved BP control, LVH regression, and improved systolic function was observed within 12 months. Lowering BP to the low-normal range led to a slightly more marked improvement in myocardial function but not in LVMI.

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Introduction

Abnormalities in cardiac geometric are highly prevalent in children with mild to moderate CKD (1,2). Concentric and eccentric left ventricular (LV) geometry are both represented, most likely resulting from the interaction between cardiac load and nonhemodynamic factors. Male sex, higher body mass index (BMI), anemia, fluid overload, and low-grade inflammation contribute to abnormalities in LV mass (LVM) and geometry, whereas the effect of hypertension appears to be less relevant (1,2). Although chamber function is generally preserved, LV myocardial function (measured at the level of the midwall) is often abnormal in patients with CKD (3). Abnormal systolic function has been found to be especially evident in CKD patients with LV concentric remodeling, also independently of clear-cut LV hypertrophy (LVH).

In adults, LVH predicts cardiovascular events, also independently of traditional risk factors (4–6). Patients with LVH and concentric geometry have the highest incidence of events, including death. In contrast, patients with eccentric LVH or isolated concentric geometry (*i.e.*, increase in cardiac wall thickness with normal LVM) have shown intermediate rates compared with

patients with normal LV geometry (5). Longitudinal studies in adult patients with high BP, either in the presence or absence of CKD (7–9), have reported that antihypertensive treatment induces reduction in LVH and improves prognosis. Thus, both the prevention and reversal of LVH have been shown to reduce incident cardiovascular events. However, because the incidence of CKD among children is low, few data are available on the effect of antihypertensive therapy on LV geometry in children with CKD (10–13).

An ancillary project of the Effect of Strict Blood Pressure Control and ACE Inhibition on Progression of Chronic Renal Failure in Pediatric Patients (ESCAPE) trial aims to evaluate the effect of intensified BP control in addition to fixed high-dose therapy with an angiotensin converting enzyme (ACE) inhibitor on cardiac geometry and systolic function in children with mild to moderate CKD (14,15).

Materials and Methods

Study Protocol

Echocardiograms and 24-hour ambulatory BP monitoring (ABPM) profiles were obtained at baseline and

Departments of
*Pediatric Nephrology and Urology and
†Pediatric Cardiology and Cardiac Surgery, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy;
‡Division of Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, University of Heidelberg, Heidelberg, Germany;
§Department Pediatric and Adolescent Nephrology and Hypertension, Medical University of Gdansk, Gdansk, Poland; and
||Department of Pediatric Nephrology, Hopital Necker, Paris, France

Correspondence:

Dr. Maria Chiara Matteucci, Department of Pediatric Nephrology and Urology, Bambino Gesù Children's Hospital, Piazza Sant'Onofrio 4, 00153, Rome, Italy. Email: mchiara.matteucci@opbg.net

after either 1 or 2 years of treatment in children participating in the ESCAPE study (15). Only patients with baseline and at least one follow-up echocardiographic examination were included in the present subanalysis. The ESCAPE study is a randomized clinical trial (ClinicalTrials.gov number NCT00221845) in which we enrolled 468 patients from April 1998 through December 2001. The participants were aged 3–18 years with stage 2–4 CKD (*i.e.*, a GFR of 15–80 ml/min per 1.73 m² of body surface area), and their 24-hour mean arterial pressure was either elevated (*i.e.*, above the 95th percentile) or controlled by antihypertensive medication. Patients were excluded if they had renal-artery stenosis, had undergone kidney transplantation, were in an unstable clinical condition, were receiving immunosuppressive treatment including glucocorticoids, or had major primary cardiac, hepatic, or gastrointestinal disorders. Patients received a fixed dose of the ACE inhibitor ramipril (6 mg/m² body surface area once daily in the morning). Patients were randomized according to BP targets, to either conventional (50th–95th BP percentile reference value of 24-hour mean arterial pressure (MAP) for height and sex) (16,17) or intensified BP targets (MAP below the 50th percentile). In patients with previous treatment with ACE inhibitors, therapy was discontinued for at least 2 months before the run-in period. Details on the study design and focus were previously reported (2,3,15).

During study follow-up, echocardiograms were performed every 12 months and office BP and ABPM were measured every 6 months. Adjustment of antihypertensive treatment, to reach randomized BP targets, started after 6 months of therapy with the first ABPM profile. If necessary, therapy was modified every 6 months. To reach BP targets, diuretics, calcium channel blockers, and β blockers were used.

Echocardiography

Echocardiograms were obtained locally with available ultrasound machines. Studies were repeated every 12 months. Echocardiograms were blinded locally and sent to the reading center in Rome, Italy. Echocardiograms were examined offline, after digital acquisition with commercially available workstations (MediMatic, Genova, Italy). Quantification of interventricular septal thickness, posterior wall thickness, and internal LV diameter in both systole and diastole were performed on three to five cardiac cycles, according to the joint American Society of Echocardiography/European Association of Echocardiography recommendations (18), using digital calipers on M-mode stop-frames, from perfectly oriented short-axis or long-axis parasternal view. Measurements were obtained from two-dimensional parasternal long-axis view, when M-mode imaging was suboptimal (19). This first reading was validated by a second, senior reader (MC). The few disagreements were resolved by joint examination of the stop-frame.

For this analysis, data from the latest echocardiographic examination available for each patient were analyzed and compared with baseline examination.

LVM was computed applying a necropsy validated formula, the reliability of which has been determined in test–retest analyses (20). LVM was normalized for height in meters raised to the allometric power 2.7, in order to

linearize the relation between LVM and height (21), and expressed in g/m^{2.7} (LVMI). For consistency with our previous reports (2,3), LVH was defined as LVMI above the 95th percentile of the healthy control participants (38 g/m^{2.7}) for both boys and girls. However, because most recently reported definitions of LVH are suggested to improve the ability to identify abnormalities in LV geometry, analyses were also performed applying most recent age- and sex-specific partition values for LVH (22).

Relative wall thickness (RWT), a measure of LV concentric adaptation, was calculated as the mean thickness of the septal and posterior wall divided by LV end-diastolic dimension. To identify cardiac concentricity, a RWT partition value of 0.375 (95th percentile of control participants) was used (23). LV concentric remodeling was defined as elevated RWT with normal LVMI. Because no significant valve regurgitation was detected, stroke volume could be calculated by linear measures of LV dimensions (24) and cardiac output obtained by stroke volume multiplied by heart rate.

To measure LV systolic function, minor axis shortening was measured both at the endocardial (endocardial shortening [eS]) and the midwall level (mS) (25–28). As previously reported, systolic dysfunction was defined as mS <15.7% (3). Myocardial afterload was measured by circumferential end-systolic wall stress (σ), as previously reported (3). Both eS and mS were also evaluated as percentage of the age-adjusted value predicted by σ , representing measures of LV chamber and LV myocardial contractility, respectively (3).

BP Monitoring

ABPM was performed with a Spacelabs 90207 automatic cuff-oscillometric device (Issaquah, WA). Upper arm circumference was measured to adjust cuff size. ABPM measurements were performed according to a standardized protocol (15).

Mean values of 24-hour MAP, systolic BP, and diastolic BP were calculated and compared with published reference data (17). In addition to ABPM, office BP measurements were obtained at the time of the echocardiography after sitting for 5 minutes in a relaxed position, using either auscultatory or oscillometric techniques.

Laboratory Assessments

In each center, a full biochemical profile was locally obtained using standard laboratory techniques. Serum creatinine was measured centrally by the modified Jaffé method. GFR was estimated from serum creatinine and height using the pediatric equation of Schwartz *et al.* (29).

Statistical Analyses

ABPM data were analyzed using the Spacelabs ABPM Report Management System. The ABPM SD score (SDS) was calculated using German reference data (17). Swiss reference data were used to calculate the height SDS (30) and German reference data to calculate the BMI SDS (31).

All results are expressed as the mean \pm SD. Statistical analysis was performed using SPSS 15.0 software (SPSS Inc, Chicago, IL). All variables were assessed for normal distribution by Kolmogorov–Smirnov testing, and non-normally distributed parameters were log-transformed for parametric testing.

Comparison between baseline and follow-up echocardiographic variables (obtained from the latest echocardiogram available) was performed using paired *t* test and by analysis of covariance, correcting for age, sex, time to follow-up, and changes over time in heart rate and systolic BP. Multiple stepwise linear regression analysis was performed to assess potential independent clinical correlates of changes in geometric and functional parameters. The chi-squared test or Fisher's exact test was used to investigate changes in proportions of categorical variables. A *P* value <0.05 was considered statistically significant.

Results

Concomitant echocardiograms and 24-hour ABPM profiles at baseline and months 12 and/or 24 were obtained. Data from the last echocardiographic examination available (*i.e.*, 24 months when performed or 12 months otherwise) were compared with the baseline examination to evaluate changes in both cardiac geometry and systolic function. Overall, 84 patients had available baseline and at least one follow-up echocardiogram and comprised the population of this study. Of the 84 patients with an available follow-up examination, 56 patients had echocardiograms performed also at 24 months, whereas 28 patients had a follow-up echocardiogram performed at 12 months only. Compared with the complete ESCAPE study population, no differences could be found in the included study sample in regard to mean age, sex distribution, underlying kidney disorder prevalence, estimated GFR, BMI, BP values, heart rate, and/or blood hemoglobin.

Renal hypoplasia/dysplasia was the underlying kidney disorder in 76.2% of patients, acquired glomerulopathies in 7.1%, and hereditary or other kidney diseases in 16.7%. Our results also showed that 65% of patients had no antihypertensive medication at baseline, whereas 18% were taking antihypertensive monotherapy and 17% were taking two or more antihypertensive drugs, including calcium channel blockers (25%), β blockers (20%), or α -adrenergic blockers (7%), diuretics (14%), and centrally active agents (2%). We randomly assigned 45 patients to intensified BP control and 39 patients to conventional BP control. The groups did not differ significantly with respect to baseline characteristics except for age ($P<0.02$) and estimated GFR ($P<0.03$) (Table 1).

Clinical Characteristics

Significant reduction in BP was observed on mean 24-hour MAP (Figure 1), which decreased from 88.1 ± 8.2 mmHg (1.28 ± 1.43 SDS) to 80.3 ± 7.6 mmHg (-0.09 ± 1.34 SDS) at 12 months ($P<0.001$ versus baseline) and to 79.0 ± 6.6 mmHg (-0.37 ± 0.99) at 24 months ($P<0.001$ versus baseline).

The BP-lowering effect of the intervention was similar for systolic and diastolic BP values and for daytime and nighttime values (data not shown).

Patients with baseline MAP above the 95th percentile ($n=29$) had a significantly higher reduction in BP values at follow-up (-2.17 ± 1.32 SDS) compared with patients with baseline MAP below the 95th percentile ($n=55$; -1.03 ± 1.01 SDS; $P<0.001$). Anthropometric measures (height SDS, BMI SDS) did not change significantly over time (Table 2).

LVM and Geometry

Patients with baseline LVH did not differ in regard to prevalence of obesity (4.5% versus 5.5% in non-LVH; $P=0.32$) and hypertension compared with non-LVH children (25% versus 24%; $P=0.64$).

At follow-up, a mean significant reduction in LVMI was observed in the whole study sample (-2.6 g/m^{2.7}; range, $+2.3$ to -5.6 g/m^{2.7}; $P<0.05$ compared with baseline), with no significant differences between treatment arms. Reduction in LVMI was the consequence of a significant reduction in both LV internal diameter and wall thickness, resulting in no significant change in their ratio (*i.e.*, RWT; from 0.32 to 0.32; $P=0.93$). No significant differences were found when the reduction in LVMI at 12 months was compared with the reduction in LVMI observed at 24 months (Figure 2). This applies to overall and between the conventional and intensified groups.

Regardless of the follow-up time, reduction in LVMI was significantly higher in patients with LVH at baseline compared with patients without baseline LVH. Overall, patients with increased LVMI at baseline showed a mean reduction of 7.9 g/m^{2.7} (range, $+2.9$ to -19.7 g/m^{2.7}; $P<0.02$), whereas patients with normal baseline LVMI showed no significant change in LVM over time (mean change -0.9 g/m^{2.7}; $P=0.72$). Accordingly, LVMI reduction was significantly different in patients with baseline LVH compared with patients without LVH ($P<0.01$) (Figure 2).

Prevalence of LVH was slightly lower using a previously reported cutoff value (*i.e.*, 38 g/m^{2.7}) compared with the most recent published data (31% versus 38%; $P<0.05$). At follow-up, LVH reduced significantly by both definitions, from 31% to 23% ($P<0.01$) and from 38% to 25% ($P<0.01$) (Figure 3).

Comparing patients with LVH, using cutoffs by Khoury *et al.* (22) according to randomization class, we found that reduction in LVMI was only slightly higher in the presence of intensified BP control compared with the standard target (-8.9 g/m^{2.7} versus -5.9 g/m^{2.7}), without reaching statistical significance ($P=0.20$).

When applying traditional partition values for LVH, eccentric hypertrophy was the most common abnormal geometric pattern (22%) at baseline, whereas 6% had concentric LVH, 9% had concentric LV remodeling, and 63% had normal LV geometry. As shown in Table 3, no differences were found between the randomization arms either at baseline or at follow-up. Overall, the prevalence of normal geometry increased from 63% to 71% at follow-up, whereas the prevalence of eccentric LVH decreased from 22% to 15% (both $P<0.05$).

More than 75% (77.3%) of patients with normal geometry at baseline remained with normal geometry after 1 year of treatment. Prevalence of concentric LV remodeling remained constant throughout follow-up, whereas prevalence of concentric hypertrophy was only marginally reduced from 9% to 8%.

In multivariate analysis, we found that reduction in LVMI was independent of randomization arm and achieved BP (24-hour MAP, systolic BP, diastolic BP) reduction, estimated GFR, and hemoglobin (Table 4). These results were confirmed also when limiting the analysis to patients with LVH.

Table 1. Baseline characteristics of the 84 study patients according to randomization class

	Randomized to Intensified BP target	Randomized to Conventional BP Target	<i>P</i>
Patients (<i>n</i>)	45	39	
Sex (% boys)	48	71	0.06
Age (yr)	11.4±4.3	13.6±3.8	0.02
Height (cm)	131±21	141±24	0.06
Body mass index (kg/m ²)	17.3±3.6	18.1±3.3	0.31
Casual systolic BP (mmHg)	118±18	116±10	0.67
Casual diastolic BP (mmHg)	70±12	71±6	0.88
Heart rate (beats/min)	82±18	87±19	0.29
24-h MAP SDS	1.28±1.6	1.08±1.2	0.57
Estimated GFR (ml/min per 1.73 m ²)	47±17	56±17	0.03
Blood hemoglobin (g/dl)	12.2±1.2	12.6±1.4	0.20

Conventional BP target aims for the 50th–95th BP percentile reference value of 24-hour MAP for height and sex. Intensified BP target aims for MAP below the 50th BP percentile reference value of 24-hour MAP for height and sex. MAP, mean arterial pressure; SDS, SD score.

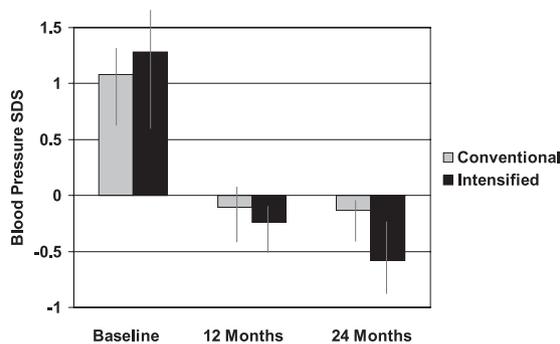


Figure 1. | Reduction in 24-hour MAP SDS during the study period, according to randomization class. Significant reduction in BP was observed on mean 24-hour MAP at 12 months ($P<0.001$ versus baseline) and at 24 months ($P<0.001$ versus baseline). Conventional BP target aims for the 50th–95th BP percentile reference value of 24-hour MAP for height and sex. Intensified BP target aims for MAP below the 50th percentile BP reference value of 24-hour MAP for height and sex. MAP, mean arterial pressure; SDS, SD score.

LV Systolic Performance

No change in endocardial shortening was observed over time. In contrast, a significant increase in midwall fractional shortening was found in the cohort as a whole, from 17.8% to 18.8% ($P<0.05$). Age and stress-corrected midwall shortening increased by a mean of 8% ($P<0.01$) from $93\% \pm 15\%$ to $101\% \pm 13\%$ ($P<0.01$). Accordingly, presence of clear-cut systolic dysfunction decreased from 20% to 9.1% ($P=0.05$). Comparing patients according to randomization arm, the increase in systolic function parameters was higher in the presence of intensified BP targets compared with standard BP targets ($12\% \pm 1.9\%$ versus $8\% \pm 1.5\%$; $P=0.05$).

In multivariate analysis, improvement of myocardial function was significantly associated with reduction in BP ($r=-0.41$; $P<0.05$), with no independent effect for LVM reduction. Because of insufficient sample size, improvement in LV systolic function was not analyzed in relation to baseline LV geometry.

Discussion

This study suggests that by achieving good overall BP control with high-dose ACE inhibition in children with CKD, LVMI regression and an improvement in myocardial function are achieved within 12–24 months. In contrast to previously published reports on BP intervention in hypertensive adults (32–36), the ESCAPE echocardiography substudy has been conceived (15) to assess the prevalence and severity of LV abnormalities (2) and the possible effects of antihypertensive treatment on echocardiographic LV geometry and mechanics in children with mild to moderate CKD. We previously showed in the same population sample that hypertension is only one of several factors in the pathogenesis of LVH. Here we noted that although antihypertensive treatment was associated with reduced LV mass and increased LV systolic function, intensified BP control targeting the low-normal range did not further enhance the reduction in LVMI but had an additional effect on indices of systolic function.

In our study, LVM reduction was not related to the extent of reduction in systolic and diastolic BP, thereby suggesting the hypothesis of a possible direct pharmacologic cardiac benefit on LV remodeling. This observation is partially different from that observed in adult hypertensive patients (36), in which LVM reduction was tightly related to systolic BP reduction (37–39).

In our study, over one in five children with abnormal LV geometry at baseline showed normal geometry at follow-up. Detailed analysis of BP characteristics by ABPM did not demonstrate any relationship between the reduction in BP and the regression in LVH, because the multivariate analysis suggests that the degree of BP reduction was not associated with change in LVM mass in children with CKD treated with ramipril. This finding suggests the intriguing hypothesis that the reduction observed in LVM may be also related to the direct influence of therapy on nonhemodynamic-mediated stimuli (2). However, the lack of a significant difference between groups might also be related to the relatively small number of participants in each subgroup. Previous studies have demonstrated that the increased regression in echocardiographic LVH induced

Table 2. Changes in BP and left ventricular parameters, according to follow-up time and randomization group

	Baseline	Conventional 12 mo	Intensified 12 mo	Conventional 24 mo	Intensified 24 mo	Conventional Overall Follow-up	Intensified Overall Follow-up
Patients (n)	84	15	13	24	32	39	45
24-h MAP (mmHg)	88.6	83.4 ^a	81.2 ^{a,b}	82.4	79.1 ^b	80.9 ^c	80.3 ^c
24-h mean SBP (mmHg)	115.3	109.0 ^a	107.4 ^{a,b}	108.2	106.8 ^b	108.9 ^c	107.7 ^c
24-h mean DBP (mmHg)	72.4	66.1 ^a	63.6 ^{a,b}	63.1 ^d	62.5 ^b	64.6 ^c	63.3 ^c
Heart rate (min ⁻¹)	82.1	81.0	80.2	81.2	79.8	81.2	79.5
BMI (kg/m ²)	18.0	17.8	18.2	17.9	18.5	17.8	18.4
LV mass/height ^{2.7} (g/m ^{2.7})	33.9	32.6	31.7	31.6	30.8	32.0 ^c	31.0 ^c
LV internal diameter (cm)	4.22	4.18	4.04 ^{a,b}	4.12 ^d	4.05	4.14 ^c	4.05 ^c
Relative wall thickness	0.32	0.32	0.31	0.32	0.32	0.32	0.32

Conventional BP target aims for the 50th–95th BP percentile reference value of 24-hour MAP for height and sex. Intensified BP target aims for MAP below the 50th BP percentile reference value of 24-hour MAP for height and sex. MAP, mean arterial pressure; SBP, systolic BP; DBP, diastolic BP; BMI, body mass index; LV, left ventricular.

^aP<0.05 comparing baseline versus 12 months.
^bP<0.05 comparing conventional versus intensified BP target.
^cP<0.05 comparing baseline versus overall follow-up.
^dP<0.05 comparing 12 versus 24 months.

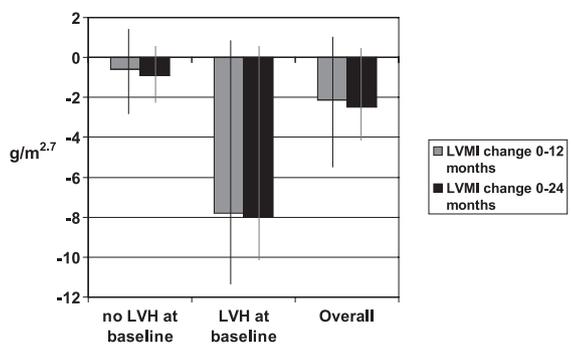


Figure 2. | Reduction in LVMI during follow-up. Gray bars refer to mean change in LVMI between baseline and 12-month follow-up, and black bars refer to mean change in LVMI between baseline and 24-month follow-up (no differences could be observed in LVMI change according to follow-up time; all P>0.05). Bars are grouped according to no LVH at baseline (left bars), LVH at baseline (center bars), and overall study population (right bars). LVMI, left ventricular mass index; LVH, left ventricular hypertrophy.

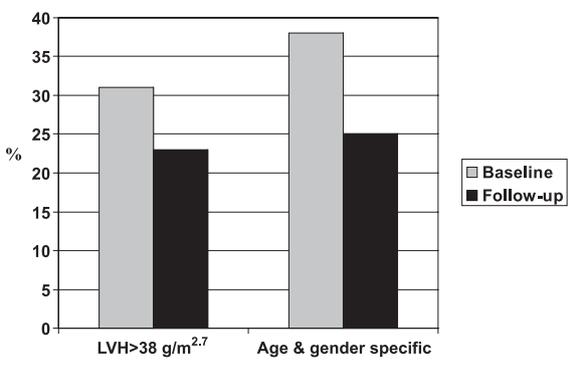


Figure 3. | Reduction in the prevalence of LVH at follow-up, according to LVH definitions. Prevalence of LVH was slightly lower using a previously reported cutoff value (i.e., 38 g/m^{2.7}) compared with the most recent published data (P<0.05). At follow-up, LVH reduced significantly by both definitions (P<0.01). LVH, left ventricular hypertrophy.

by ACE inhibition is independent of BP reduction (40), supporting the hypothesis of nonhemodynamic contribution of the renin-angiotensin system to LVH (41). Furthermore, studies performed in the neonatal renin transgenic rat (42) provide direct support for a BP-independent role of the angiotensin II receptor on LV hypertrophy.

A single administration of retroviral vector containing angiotensin II type I receptor antisense caused a long-term expression of the antisense transgene in the heart resulting in a significant attenuation of cardiac hypertrophy compared with viral vector-treated rats (42). In a previous study (2), we reported that an overactivation of the renin-angiotensin-aldosterone system provided a plausible

Table 3. Changes in LV geometric pattern at follow-up according to traditional definition of LVH

	Conventional Baseline	Intensified Baseline	Overall Baseline	Conventional Follow-up	Intensified Follow-up	Overall Follow-up
Normal LV geometry	62	64	63	68 ^a	73 ^a	71 ^a
Concentric remodeling	7	6	6	6	6	6
Eccentric LVH	21	22	22	17 ^a	14 ^a	15 ^a
Concentric LVH	10	8	9	9	7	8

Data are given in percentages. No differences were found between treatment groups at baseline or at follow-up. LV, left ventricular; LVH, left ventricular hypertrophy.
^aP<0.05 comparing baseline versus follow-up.

Table 4. Multivariate analysis for change in LVMI over time

	Mean LVMI Change (g/m ^{2.7})	95% CI	P
Δ Mean BP (mmHg)	-0.09	-0.55, 0.38	0.81
Δ Systolic BP (mmHg)	-0.25	-0.32, 0.06	0.24
Δ Diastolic BP (mmHg)	-0.05	-0.85, 0.15	0.86
Δ Estimated GFR (ml/min per 1.73 m ²)	-0.06	-0.31, 0.19	0.66
Δ Hemoglobin (g/L)	0.20	-1.99, 2.40	0.15
Randomization group (conventional versus intensified)	0.05	-2.64, 2.76	0.72

LVMI, left ventricular mass index; CI, confidence interval.

explanation for the increase in circulating volume in early CKD patients (43).

An additional, novel finding of our study is that, along with the reduction in BP and LVMI, a significant increase in myocardial systolic function appears to occur over time. In fact, BP reduction and the randomization to intensified BP control was significantly associated with increased myocardial function, although no independent effect on LVH regression could be observed. Because all patients in the ESCAPE trial received ACE inhibition at a single standardized dose, no untreated control group was available for the major effect on BP achieved by this first intervention and, although highly unlikely, we could not investigate the effect of ACE on regression of LVM and we cannot formally rule out the possibility that this effect occurred by chance. However, the difference observed with respect to myocardial function in the randomized phase of the trial strongly indicates a direct effect of BP control on myocardial function.

In conclusion, our study shows a regression of LVMI in patients with baseline LVH, paired with a significant improvement in LV systolic function. Forced BP lowering to the 50th percentile or lower did not achieve additional benefit in LVM but slightly affected LV function.

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Disclosures

None.

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