Intensive Blood Pressure Lowering Improves Left Ventricular Hypertrophy in Older Patients with Hypertension: The STEP Trial

Introduction

- Hypertension: the leading risk factor for CVD
- Primary target of EOD: Left ventricle
- Long term increase in afterload: LVE and LVH and cardiac remodeling
- Initially beneficial, with long term decrease in cardiac function
- LVH often develops in patients with standard BP control
- Changes in cardiac structure happens in patients with high normal BP (120-139 , 80-89 mmHg)

Introduction, cont’d

- Remodeling secondary to HTN is less significant in Asian populations
- role in the context of intensive SBP lowering is still not well understood and whether LVH mediates the cardiovascular benefits associated with intensive SBP deserves further interrogation
- examine the effect of intensive SBP lowering on LVH assessed by ECG[17] and the clinical prognostic value of LVH beyond intensive SBP reduction in older patients with hypertension

Methods- Population

Inclusion criteria:

- age 60 to 80 years
- Han ethnicity
- SBP 140 to 190 mmHg or on antihypertensive medication

Exclusion Criteria:

- previous stroke
- mental impairment
- Uncontrolled diabetes
- serious life-limiting condition

LVH Assessment

- 12-lead ECG at baseline, year 3 and year 4
- LVH: defined by sex-specific Peguero-LoPresti criteria
  - summing the deepest S wave amplitude of any lead and the S wave amplitude of lead V4
  - cutoff point of ≥2300 μV for women and ≥2800 μV for men.

Follow-Up and interventions

- antihypertensive medication: olmesartan, amlodipine, and hydrochlorothiazide (if needed)
- Sitting brachial BP was measured in the upper right arm using an appropriately sized cuff after 5 min of rest and calculated as the average of 3 readings obtained at 1-minute intervals
- Patients were scheduled for follow-up visits at 1, 2, and 3 months and every 3 months thereafter

- To examine whether the impact of intensive treatment on the primary outcome could be explained by its impact on LVH, we examined the magnitude of attenuation of the association between intensive treatment and standard treatment with the primary outcome of STEP after adjusting for LVH or the Peguero-Lo Presti index value as a time-varying covariate
- major intraventricular conduction delay as a result of complete left or right bundle branch block, Wolf-Parkinson-White syndrome, placement of a ventricular pacemaker, and major nonspecific conduction delay (all with a QRS duration ≥120 ms)

Results

- a total of 7141 patients from the STEP trial were included in this analysis (intensive group, n=3578; standard group, n=3563)
- Baseline BP and fasting serum glucose were both significantly higher ($P<0.05$) in patients with LVH at baseline than in those without LVH.
- Body mass index and the 10-year Framingham risk score were numerically higher in patients with LVH at baseline
- median follow-up of 3.24 years

Characteristics	Intensive treatment (N = 3578)	Standard treatment (N = 3563)	*P* value
Age, y	66.1±4.8	66.2±4.8	0.286
Age ≥70 y, n (%)	842 (23.5)	849 (23.8)	0.769
Male, n (%)	1670 (46.7)	1640 (46.0)	0.601
Body mass index, kg/m^2	25.6±3.1	25.7±3.2	0.434
Baseline blood pressure, mm Hg			
Systolic	146.5±16.7	146.3±16.7	0.713
Diastolic	82.8±10.7	82.4±10.6	0.123
Distribution of systolic blood pressure, n (%)*			0.725
≤138 mm Hg	1160 (32.4)	1183 (33.2)	
139–151 mm Hg	1161 (32.4)	1156 (32.4)	
≥152 mm Hg	1257 (35.1)	1224 (34.3)	
Fasting serum glucose, mmol/L	6.1±1.6	6.2±1.6	0.012
eGFR<60 mL/(min·1.73m^2), n (%)	51 (1.4)	59 (1.6)	0.429

Lipid profile, mmol/L			
Total cholesterol	4.9±1.1	4.9±1.1	0.726
Triglycerides (IQR)	1.3 (1.0, 1.9)	1.3 (1.0, 1.9)	0.930
High-density lipoprotein cholesterol	1.3±0.3	1.3±0.3	0.883
Low-density lipoprotein cholesterol	2.7±0.9	2.7±0.9	0.756
Smoking, n (%)	571 (16.0)	567 (15.9)	0.959
Medical history, n (%)			
Diabetes mellitus	684 (19.1)	697 (19.6)	0.655
Hyperlipidemia	1329 (37.1)	1303 (36.6)	0.633
Cardiovascular diseases	224 (6.3)	233 (6.5)	0.426
The 10-year Framingham risk score ≥15%,† n (%)	2318/3564 (65.0)	2275/3550 (64.1)	0.400
Baseline ECG			
$S_{D,}$‡ μV	1205.9±448.6	1204.8±439.2	0.920
SV_4, μV	604.9±401.9	603.1±387.5	0.851
Peguero-Lo Presti index (S_D+$SV_{4)}$, μV	1810.7±763.8	1807.9±744.2	0.875
Peguero-Lo Presti-LVH,§ n (%)	593 (16.6)	588 (16.5)	0.936

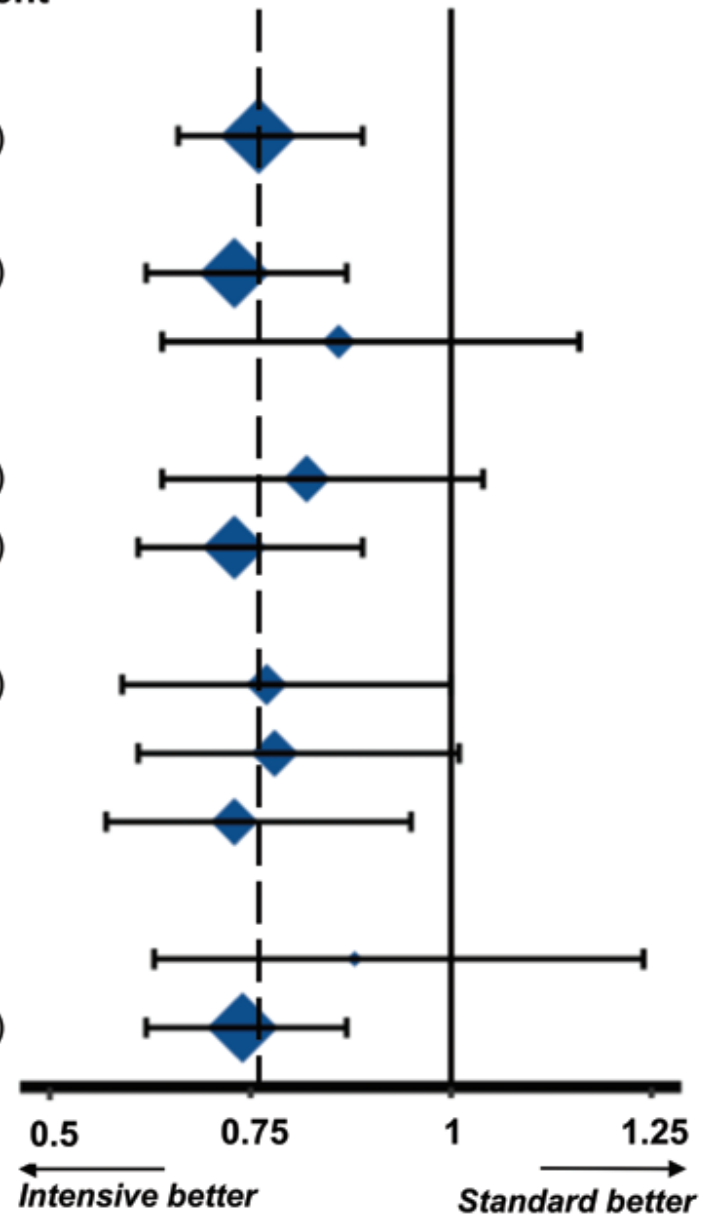
Results

- BP: 126.8/76.5 mmHg in the intensive treatment group and 136.2/79.3 mmHg in the standard treatment group
- 708 **new cases** of LVH (intensive group, n=305; standard group, n=403) occurred (hazard ratio [HR], 0.76 [95% CI, 0.66–0.89]; *P*<0.001)
- The number of cases of **regression** of LVH that had been present at baseline did not differ significantly between treatment groups (HR, 1.12 [95% CI, 0.94–1.33]; *P*=0.215)

- the rate of **progression** of the Peguero-Lo Presti value was evidently **slower** in patients of the intensive treatment (-23.47 μV/y)\
- Each 1 SD (765.1 μV) increase in the mean Peguero-Lo Presti index value as a time-varying covariate was associated with a 15.6% increase in the risk of cardiovascular events (HR, 1.16 [95% CI, 1.02–1.31]; *P*=0.01
- intensive treatment was associated with a 25% lower risk (95% CI 0.58–0.96, *P*=0.0221)
  - 24% lower risk (95% CI 0.59–0.97, *P*=0.030) after adjusting for LVH as a time-varying covariate.
  - mediation analyses indicated little mediation by Peguero-Lo Presti value (2.7% [95% CI, 0.4%–16.2%]; *P*=0.1075) on the effect of intensive SBP lowering on cardiovascular events

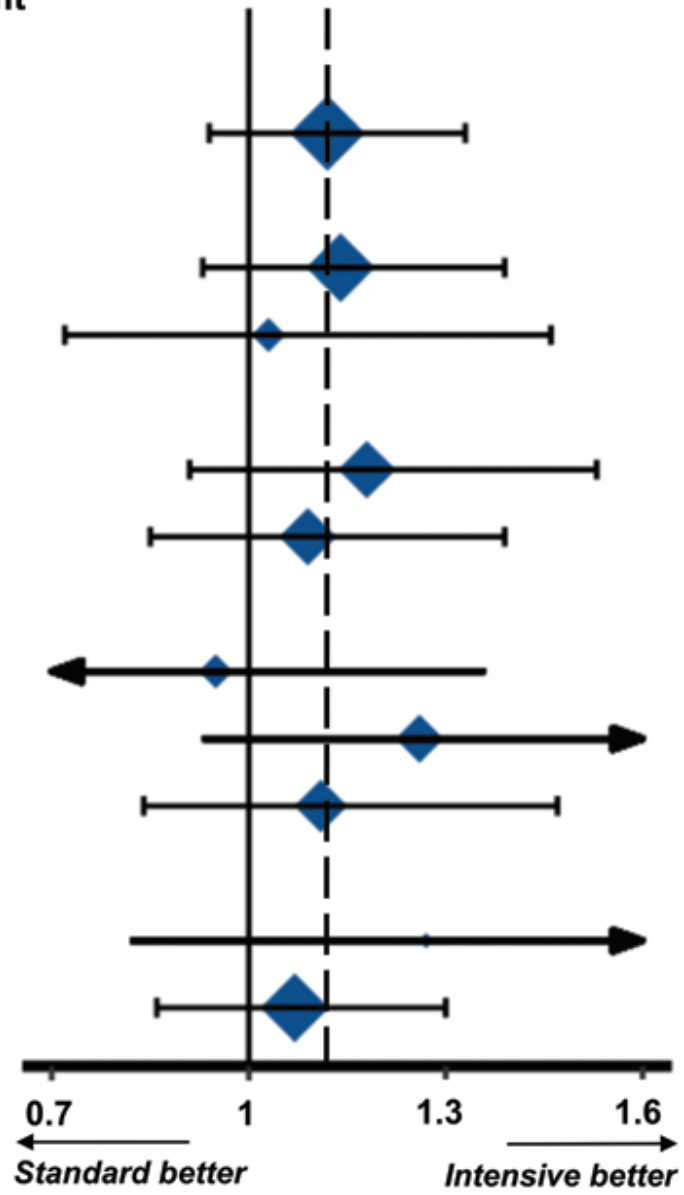
risk of new LVH

Subgroups	Intensive Treatment	Standard Treatment	Hazard ratio (95% CI)	*P* value	*P*-interaction
	No. of events/participant (% per year)				
Overall	305/2985 (3.35)	403/2975 (4.52)	0.76 (0.66–0.89)	0.000	-
Age (years)					0.345
60–69	227/2280 (3.19)	304/2259 (4.33)	0.73 (0.62–0.87)	0.000	
70–80	78/705 (3.59)	99/716 (4.47)	0.86 (0.64–1.16)	0.323	
Sex					0.464
Men	121/1398 (2.80)	147/1368 (3.46)	0.82 (0.64–1.04)	0.099	
Women	184/1587 (3.71)	256/1607 (5.15)	0.73 (0.61–0.89)	0.001	
SBP tertiles					0.602
≤138 mmHg	97/996 (3.16)	130/1025 (4.13)	0.77 (0.59–1.00)	0.054	
139–151 mmHg	107/1009 (3.43)	135/987 (4.42)	0.78 (0.61–1.01)	0.058	
≥152 mmHg	101/980 (3.26)	138/963 (4.57)	0.73 (0.57–0.95)	0.017	
Previous diabetes					0.266
Yes	61/564 (3.49)	75/579 (4.17)	0.88 (0.63–1.24)	0.479	
No	244/2421 (2.85)	328/2396 (4.42)	0.74 (0.62–0.87)	0.000	



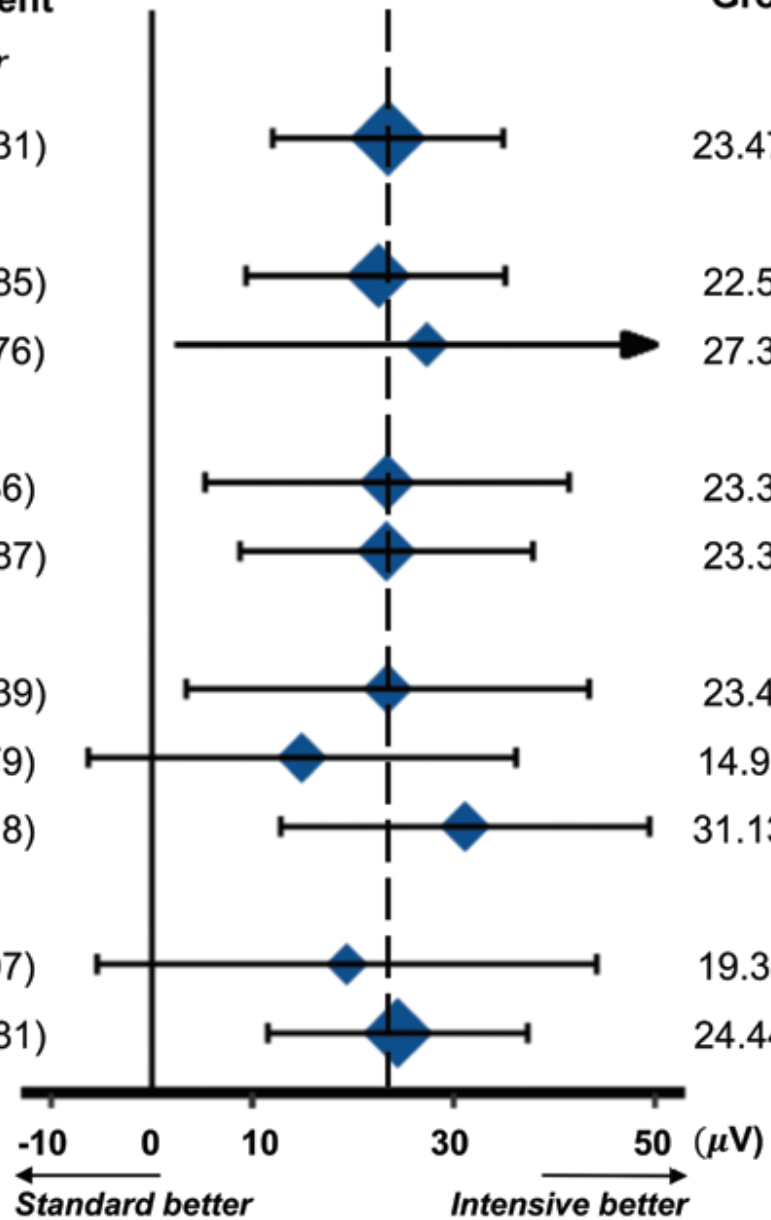
regression of existing LVH

Subgroups	Intensive Treatment	Standard Treatment	Hazard ratio (95% CI)	*P* value	*P*-interaction
	No. of events/participant (% per year)				
Overall	270/593 (15.5)	230/588 (13.5)	1.12 (0.94–1.33)	0.215	-
Age (years)					0.674
60–69	199/456 (14.0)	173/457 (12.2)	1.14 (0.93–1.39)	0.223	
70–80	71/137 (16.8)	57/131 (14.3)	1.03 (0.72–1.46)	0.884	
Sex					0.662
Men	127/272 (12.7)	127/272 (10.6)	1.18 (0.91–1.53)	0.208	
Women	143/321 (14.3)	122/316 (12.5)	1.09 (0.85–1.39)	0.501	
SBP tertiles					0.363
≤138 mmHg	62/164 (9.6)	63/158 (10.2)	0.95 (0.67–1.36)	0.789	
139–151 mmHg	91/184 (16.1)	78/202 (12.5)	1.26 (0.93–1.71)	0.131	
≥152 mmHg	117/245 (15.12)	89/228 (12.4)	1.11 (0.84–1.47)	0.449	
Previous diabetes					0.352
Yes	47/120 (12.5)	36/118 (9.7)	1.27 (0.82–1.96)	0.284	
No	223/473 (15.2)	194/470 (13.4)	1.07 (0.89–1.30)	0.467	



progression of Pegeuro-Lo Presti value

Subgroups	Intensive Treatment	Standard Treatment	Group difference (95% CI)	*P* value	*P*-interaction
	Progression of Peguero value per year				
Overall	1.56 (-6.36–9.47)	25.03 (16.74–33.31)	23.47 (12.01–34.93)	0.000	-
Age (years)					0.713
60–69	1.27 (-7.61–10.14)	23.53 (14.20–32.85)	22.53 (9.39–35.13)	0.001	
70–80	2.49 (-14.87–19.85)	29.81 (11.87–47.76)	27.32 (2.37–52.28)	0.032	
Sex					0.996
Men	-8.34 (-20.61–3.94)	15.04 (1.73–28.36)	23.38 (5.29–41.47)	0.011	
Women	10.22 (-0.02, 20.46)	33.54 (23.21–43.87)	23.32 (8.78–37.87)	0.002	
SBP tertiles					0.524
≤138 mmHg	7.93 (-5.25–21.1)	31.37 (16.35–46.39)	23.44 (3.44–43.44)	0.022	
139–151 mmHg	9.57 (-5.26–24.39)	24.48 (9.16–39.79)	14.91 (-6.29–36.21)	0.170	
≥152 mmHg	-11.72 (-24.85–1.42)	19.41 (6.64–32.18)	31.13 (12.81–49.45)	0.001	
Previous diabetes					0.733
Yes	8.05 (-9.45–25.55)	27.43 (9.79–45.07)	19.38 (-5.44–44.21)	0.126	
No	0.01 (-8.87–8.88)	24.44 (15.07–33.81)	24.44 (11.53–37.34)	0.000	



Discussion, key findings

- compared with standard treatment, intensive treatment resulted in a significantly reduced risk of new LVH in patients without LVH at baseline
- the PegueroLo Presti index value progressed evidently more slowly on intensive treatment than on standard treatment
- the favorable effect of intensive SBP lowering on LVH **did not** explain most of the reduction in cardiovascular events

Previous literature

- Controllo della Pressione Arteriosa Sistolica trial: lowering of SBP to <130 mmHg (versus to <140 mmHg) decreased the risk of ECG evidence of LVH by 39% in patients without diabetes
- Action to Control Cardiovascular Risk in Diabetes-Blood Pressure trial, intensive SBP therapy (targeting <120 mmHg) resulted in a similar 39% reduction in risk of LVH in patients with diabetes
- The SPRINT : intensive SBP lowering (to <120 mmHg) was associated with a 46% lower risk of developing new LVH in patients with high cardiovascular risk but without diabetes

aggressive antihypertensive management should be instigated as soon as possible for optimal control of BP and to prevent target organ damage, given that when hypertensive target organ damage is advanced, reversal of progression may be difficult, especially in the real-world setting

Limitations and strengths

- open-label design could lead to bias in the identification of certain end points
- STEP trial examined the effect of different SBP targets rather than the effect of specific drugs
- the possibility of variability in ECG measurements across sites can not be fully excluded
- unmeasured mediators that influence cardiac hypertrophy (eg, activity of the renin-angiotensin and sympathetic nervous systems, abnormalities of lipid metabolism, inflammation) may have confounded our findings
- large sample size, diverse population with inclusion of both sexes and patients with diabetes


Thank you
For your
Attention