## Abstract

## Establishment of an optimal management strategy for older patients with hypertension

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It has been estimated that a quarter of the adults worldwide have hypertension and this rate is expected to go up with the increased risk of cardiovascular and cerebrovascular disease. In addition, with the world population aging, the prevalence of hypertension is expected to increase. There is a lot of evidence supporting the benefit of anti-hypertensive treatment among older adults, but the optimal target blood pressure for hypertension in older adults is uncertain, especially among patients with multimorbidity and frailty. This study conducted the 'HOW to Optimize eLDerly systolic Blood Pressure' (HOWOLD-BP) trial study. The aim of the trial was to evaluate whether an intensive treatment (systolic blood pressure ≤ 130 mmHq) provides more benefits in lowering cardiovascular events than a standard treatment (systolic blood pressure  $\leq$ 140 mmHg) in older hypertensive patients aged at 65 years and over. HOWOLD-BP was a multi-center, parallel-design, singleblinding randomized controlled trial aimed at eleven national hospitals throughout Korea that will be recruited participants and will be enrolled 3,176 older adults with hypertension into the trial. Eligible patients will be evaluated at baseline for sociodemographic status, personal and family history, orthostatic blood pressure, frailty status, physical and cognitive function, and quality of life. The patients will be measured every 3 months for the first year and every 6 months till 36 months. The primary outcome is a composite of the new development of cardiovascular disease (CVD), such as acute coronary syndrome, stroke, and heart failure; and the additional outcomes are death from CVD, hospitalization due to CVD, and quality of life. The HOWOLD-BP trial will provide evidence of the optimal target of blood pressure control for reducing cardiovascular disease among older Korean adults with hypertension. In addition, the trial's results will be helpful in developing a customized management model considering the characteristics of elderly hypertensive patients in Korea and improving the treatment guidelines.

Keywords: Older adults, Hypertension, Cardiovascular disease, Cognitive function, Physical function, Frailty





Table 1. S	Summary of	previous	anti-hypertensive	clinical studies
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	JATOS	SPRINT-SENIOR	VALISH	Wei et al.	FEVER	
Year	2008	2016	2010	2013	2005	
Participants	4,418	2,636	3,079	724	9,711	
Inclusion (year)	65-85	≥75	70-85	≥ 70	50-79	
Trial site	Japan	America	Japan	China	China	
Comparison	<140 vs 140−159	<120 vs <140	<140 vs 140−149	<140 vs 140−149	Felodipine vs placebo	
Median f/u (year)	2	3.1	3.1	4	3.7	
MACE	CVD (stroke, TIA, SAH) Cardiac / vascular (MI, angina need hospitalization, HF, sudden death, dissecting aneurysm, occlusive disease) Renal failure (doubling to 1.5 or higher)	Nonfatal MI, ACS not resulting MI, Nonfatal stroke, Nonfatal ADHF, Cadiovascular mortality	Sudden death, Stroke (fetal or nonfetal), MI (fetal or nonfatal), Unplanned hospitalization for CVD, Other CV death, renal dysfunction	Fatal / nonfatal stroke, AMI, CV mortality (sudden + HF)	Primary : stroke Secondary: 1st CV event / 1st cardiac event / death from any cause / death from cardiovascular disease	
Mean blood pressure difference (mmHg)	9.7/3.3	11.4/5.2	5.4/1.7	135.7/76.2 vs 149.7/82.1 (14/5.9)	4.2/2.0	
Outcome: 100 persons/year (%)						
MACE	2.26 vs 2.27	2.59 vs 3.85	3.04 vs 3.39	2.53 vs 4.68 (CV event)	HR 0.67 (0.48-0.91)	
CV death	0.08 vs 0.08	0.44 vs 0.71	0.71 vs 0.72	1.58 vs 3.49	HR 0.67 (0.48-0.91)	
MI	0.16 vs 0.16	0.92 vs 1.34	0.32 vs 0.26	0.57 vs 0.62		
Stroke	1.13 vs 1.00	0.67 vs 0.85	1.04 vs 1.50	1.33 vs 2.51	1.12 vs 1.59 (primary)	
HF	0.19 vs 0.19	0.86 vs 1.41		0.38 vs 1.12 (HF death)		

Table 2. The event rate of cardiovascular and cerebrovascular diseases from the national health insurance claim data (follow-up duration; 5 years)

[Age  $\geq$  65 years]

Month	Composite	Death	Stroke	Heart failure	IHD	Acute MI
12	1.8%	0.3%	0.6%	0.2%	0.8%	0.1%
24	11.2%	2.2%	3.8%	1.5%	5.1%	0.4%
36	19.8%	4.5%	7.1%	2.7%	8.9%	0.7%
48	27.3%	7.2%	9.9%	4.2%	12.3%	1.2%
60	33.8%	10.1%	12.4%	5.5%	15.1%	1.5%
71	39.1%	12.8%	14.4%	6.8%	17.4%	1.8%

## [Age $\geq$ 75 years]

Month	Composite	Death	Stroke	Heart failure	IHD	Acute MI
12	2.3%	0.6%	0.9%	0.3%	0.8%	0.2%
24	14.5%	4.0%	5.2%	2.2%	5.4%	0.7%
36	25.0%	8.4%	9.2%	3.9%	9.0%	1.1%
48	34.5%	13.6%	12.7%	6.0%	12.1%	1.7%
60	42.1%	18.9%	15.5%	7.6%	14.6%	2.1%
71	48.6%	24.0%	17.6%	9.2%	16.7%	2.5%

## Disease codes used in disease definitions

Event	KCD code
Death	Death for all causes
Stroke	160-164
Heart failure	150, 142, 1110, 1130, 1132, 1255, 1420
AMI	121
Hypertension	110-115 and antihypertensive medication
IHD	120, 121, 122, 123, 124, 125
Composite	Death or Stroke or Heart failure or Acute MI



Figure 2. Eleven centers participating in HOW to Optimize eLDly systolic Blood Pressure (HOWOLD-BP) clinical trials