

it is likely that these two conditions will remain difficult to separate, we plan further analyses to explore these possibilities. Withdrawal symptoms can only occur in the discontinuation group, but participants reported some new and worsening symptoms while continuing to take antidepressants. We found no evidence that the hazard ratio for relapse varied across the 12-month follow-up period, whereas one would expect withdrawal symptoms to cluster around the time after the medication was terminated. We found that the difference in withdrawal symptoms between the groups was largest at 12 weeks.

Kuschpel inquires about the severity of relapses in our trial. In addition to our prespecified definition of relapse, we used internationally agreed-upon International Classification of Diseases, version 10, criteria for relapse of depression and found similar results to those in our primary analysis (see Table S11 in the Supplementary Appendix, available with the full text of our article at NEJM.org). We recorded relapses that may have occurred at any time in the 3 months

preceding the assessment and may have resolved by the time the participant was assessed on our secondary outcomes, such as the PHQ-9. We therefore would have expected a smaller between-group difference regarding secondary outcomes because they only assessed how the participant was feeling at the time of the assessment. Our finding that people in the discontinuation group were more likely to guess their allocation could be due to the clinical effect of discontinuation and is not, in our view, an indication that our findings were invalid.

Gemma Lewis, Ph.D.
Louise Marston, Ph.D.
Glyn Lewis, Ph.D.

University College London
London, United Kingdom
gemma.lewis@ucl.ac.uk

for the ANTLER study team

Since publication of their article, the authors report no further potential conflict of interest.

DOI: 10.1056/NEJMc2117168

Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension

TO THE EDITOR: In a trial involving elderly patients with hypertension, Zhang et al. (Sept. 30 issue)¹ found that intensive treatment (systolic blood-pressure target, 110 to <130 mm Hg) resulted in a lower incidence of cardiovascular events and stroke than standard treatment (target, 130 to <150 mm Hg). However, the use of antihypertensive drugs was imbalanced between the two groups. For example, at 42 months, hydrochlorothiazide was used more in the intensive-treatment group (280 patients) than in the standard-treatment group (102 patients).

A recent systematic review² showed that use of calcium-channel blockers led to a higher risk of major cardiovascular events than use of diuretics (risk ratio, 1.05) but to a lower risk than use of beta-blockers (risk ratio, 0.84) or angiotensin-converting-enzyme inhibitors (risk ratio, 0.90). Use of calcium-channel blockers also led to a lower risk of myocardial infarction than use of angiotensin-receptor blockers (risk ratio, 0.82).

Given that several lines of evidence have shown that these drugs affect the cardiovascular system independent of blood pressure,^{3,4} the type of antihypertensive drug used can bias trial results. We wonder whether the authors could provide a subgroup analysis with the type of antihypertensive drug as a variable.

Shin Osawa, M.D.
Itabashi Chuo Medical Center
Tokyo, Japan
4.shin.sawa@gmail.com

Junichi Mori, M.D., Ph.D.
Jyoban Hospital
Fukushima, Japan

No potential conflict of interest relevant to this letter was reported.

1. Zhang W, Zhang S, Deng Y, et al. Trial of intensive blood-pressure control in older patients with hypertension. *N Engl J Med* 2021;385:1268-79.

2. Zhu J, Chen N, Zhou M, et al. Calcium channel blockers versus other classes of drugs for hypertension. *Cochrane Database Syst Rev* 2021;10:CD003654.

3. Re RN. Mechanisms of disease: local renin-angiotensin-aldosterone systems and the pathogenesis and treatment of cardiovascular disease. *Nat Clin Pract Cardiovasc Med* 2004;1:42-7.
4. Leonetti G, Egan CG. Use of carvedilol in hypertension: an update. *Vasc Health Risk Manag* 2012;8:307-22.

DOI: 10.1056/NEJMc2117463

TO THE EDITOR: The STEP (Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients) trial by Zhang et al. showed that intensive blood-pressure control with a systolic blood-pressure target of 110 to less than 130 mm Hg contributed to a lower incidence of cardiovascular events than standard treatment with a systolic blood-pressure target of 130 to less than 150 mm Hg in older patients with hypertension in the Han Chinese population. The Results and Discussion both note that most of the secondary outcomes favored intensive treatment. However, this statement is misleading, since only half the secondary outcomes differed meaningfully between the groups.

Moreover, the authors emphasize in the Discussion that patients with diabetes mellitus were included, but they did not discuss results in this subgroup of patients in detail. According to Figure S7 in the Supplementary Appendix (available with the full text of their article at NEJM.org), patients with diabetes mellitus did not seem to benefit significantly from intensive blood-pressure control — a finding that is supported by the results of the ACCORD BP trial¹ but that has been debated.² The interaction between blood-pressure treatment and glycemic control might play a significant role and warrants further investigation.³ Currently, less-intensive individualized blood-pressure targets are still recommended for older patients with hypertension, diabetes mellitus, and other coexisting conditions.⁴

Po-Jui Chu, M.D.

Chung Shan Medical University Hospital
Taichung, Taiwan
s0501055@gm.csmu.edu.tw

No potential conflict of interest relevant to this letter was reported.

1. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575-85.
2. Buckley LF, Dixon DL, Wohlford GF IV, Wijesinghe DS, Baker WL, Van Tassel BW. Intensive versus standard blood pressure control in SPRINT-eligible participants of ACCORD-BP. *Diabetes Care* 2017;40:1733-8.
3. Tsujimoto T, Kajio H. Benefits of intensive blood pressure

treatment in patients with type 2 diabetes mellitus receiving standard but not intensive glycemic control. *Hypertension* 2018;72:323-30.

4. de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:1273-84.

DOI: 10.1056/NEJMc2117463

TO THE EDITOR: At first sight, the results of the STEP trial seem to confirm the findings from the Systolic Blood Pressure Intervention Trial (SPRINT),¹ — that is, aiming at lower blood-pressure goals reduces the incidence of cardiovascular events and death, seemingly putting to rest the long-standing discussion about meaningful differences between observed and unattended office blood-pressure measurements. Although the authors obtained home blood-pressure readings from more than 95% of the trial participants, it is exactly these data that arouse questions about the validity of their final conclusions. According to Figure S5, the mean systolic home blood-pressure values in patients in the standard-treatment group increased continuously and crossed the threshold suggested in the European Society of Cardiology and the European Society of Hypertension guidelines² for the diagnosis of hypertension for approximately half the trial period. Thus, the observed lower incidence of cardiovascular events in the intensive-treatment group than in the standard-treatment group may simply be the consequence of masked uncontrolled hypertension, with the inherent unfavorable prognosis³ in a large proportion of patients receiving the standard treatment. In addition, there seems to be a graphical error in the alignment of the temperature and blood-pressure data, because the latter is inversely related to the ambient temperature.⁴

Hans-Michael Steffen, M.D.

University of Cologne
Cologne, Germany
hans-michael.steffen@uk-koeln.de

Gerd Bönner, M.D.

University of Freiburg
Freiburg, Germany

Martin Middeke, M.D.

Hypertoniezentrum München
Munich, Germany

No potential conflict of interest relevant to this letter was reported.

1. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;373:2103-16.
2. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39:3021-104.
3. Zhang DY, Guo QH, An DW, Li Y, Wang JG. A comparative meta-analysis of prospective observational studies on masked hypertension and masked uncontrolled hypertension defined by ambulatory and home blood pressure. *J Hypertens* 2019;37:1775-85.
4. Yang L, Li L, Lewington S, et al. Outdoor temperature, blood pressure, and cardiovascular disease mortality among 23000 individuals with diagnosed cardiovascular diseases from China. *Eur Heart J* 2015;36:1178-85.

DOI: 10.1056/NEJMc2117463

TO THE EDITOR: With regard to the trial conducted by Zhang et al., we think that several issues limit the generalizability of these findings.¹ The mean age of the patients was 66 years (with only 24% of the patients having an age of 70 to 80 years), and persons with dementia, cancer, sustained atrial fibrillation, and uncontrolled diabetes were excluded. Only 6.5% of the patients had cardiovascular disease and 2.5% had kidney failure; well-recognized comprehensive measures of health in older people² were not reported. The results are commendable and not unexpected in this “fit” population of patients younger than 70 years of age but are difficult to translate in older patients with multiple coexisting conditions. Such persons are almost invariably excluded from clinical trials, even though their conditions represent the most compelling challenge in clinical practice.³ In keeping with experts, we would advise a more cautious approach with regard to suggesting such an aggressive blood-pressure target in elderly patients.⁴

Guido S.G. Maggiani, M.D.

Mario Bo, M.D., Ph.D.

University of Turin Città della Salute e della Scienza
Turin, Italy
guidomaggiani@yahoo.it

No potential conflict of interest relevant to this letter was reported.

1. Sheppard JP, Lown M, Burt J, et al. Generalizability of blood pressure lowering trials to older patients: cross-sectional analysis. *J Am Geriatr Soc* 2020;68:2508-15.
2. Beard JR, Officer A, de Carvalho IA, et al. The world report on ageing and health: a policy framework for healthy ageing. *Lancet* 2016;387:2145-54.
3. He J, Morales DR, Guthrie B. Exclusion rates in randomized controlled trials of treatments for physical conditions: a systematic review. *Trials* 2020;21:228.
4. Lüscher TF, Kjeldsen SE, Mancia G, Papademetriou V. From

‘essential’ hypertension to intensive blood pressure lowering: the pros and cons of lower target values. *Eur Heart J* 2017;38:3258-71.

DOI: 10.1056/NEJMc2117463

THE AUTHORS AND A COLLEAGUE REPLY: In response to Osawa and Mori: A previous meta-analysis has shown that blood-pressure lowering is the predominant factor in reducing the risk of cardiovascular events, rather than the use of specific antihypertensive agents, although these agents may present subtle superiority among general drug classes.¹ In the STEP trial, the overall distribution of drug classes was similar in the two treatment groups, with the exception of an inevitably higher proportion of patients using combined antihypertensive therapy in the intensive-treatment group. With adjustment for drug classes at the 6-month visit (the stipulated time point for blood-pressure control), the observed cardiovascular benefits with intensive treatment were not noticeably affected (adjusted hazard ratio vs. standard treatment, 0.72; 95% confidence interval, 0.57 to 0.90). Detailed comparisons of the effects of various antihypertensive drug classes are under way.

A subgroup analysis of the STEP trial showed a consistently beneficial, albeit nonsignificant, effect of intensive treatment in patients with diabetes mellitus. Of note, the statistics were underpowered, as in the ACCORD BP trial. Thus far, robust evidence is scant, which prevents concrete conclusions from being drawn regarding an appropriate blood-pressure target in patients with diabetes mellitus. An ongoing randomized, controlled trial (Blood Pressure Control Target in Diabetes [BPROAD]; ClinicalTrials.gov number, NCT03808311) and our current analysis of combined individual-level data from patients with diabetes mellitus in the STEP trial and the ACCORD BP trial may be of value regarding Chu’s concern.

Steffen et al. question whether the conclusions of the STEP trial may be heavily biased by the inclusion of patients with masked uncontrolled hypertension in the standard-treatment group. Indeed, the initially overt difference between home and office blood-pressure measurements diminished gradually over time and nearly disappeared by the 30-month visit in the STEP trial. We considered this finding to be related to

a relief from white-coat hypertension, since patients became familiar with the same clinical setting and trial staff as the trial progressed.² This observed time-varying difference between home and office blood-pressure values indicated that time-stratified cutoff values remain important for evaluation. Figure S5 has been updated in the Supplementary Appendix to show the variation in home blood pressure over periods of calendar months.

As in most other trials, patients with severe frailty or limited life expectancy were excluded from the STEP trial. We agree with Maggiani and Bo that the extrapolation of our conclusions to such patients warrants more caution. Nevertheless, a population of persons with diverse coexisting conditions was enrolled in our trial, and the trial results are relevant to the majority of older Chinese people with hypertension. Meta-analyses have consistently shown additional cardiovascular benefits with a reduction in systolic blood pressure to less than 130 mm Hg, regardless of age.^{3,4}

Yue Deng, Ph.D.
Jingjing Bai, M.S.
Jun Cai, M.D., Ph.D.

FuWai Hospital
Beijing, China
caijun@fuwaihospital.org

Ms. Bai reports no potential conflict of interest relevant to this letter. Since publication of their article, Drs. Deng and Cai report no further potential conflict of interest.

1. Zanchetti A, Thomopoulos C, Parati G. Randomized controlled trials of blood pressure lowering in hypertension: a critical reappraisal. *Circ Res* 2015;116:1058-73.
2. Lüscher TF. Unanswered questions in hypertension: prematurity and long-term trajectories, masked and white coat hypertension. *Eur Heart J* 2020;41:1527-30.
3. Blood Pressure Lowering Treatment Trialists' Collaboration. Age-stratified and blood-pressure-stratified effects of blood-pressure-lowering pharmacotherapy for the prevention of cardiovascular disease and death: an individual participant-level data meta-analysis. *Lancet* 2021;398:1053-64.
4. Bundy JD, Li C, Stuchlik P, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. *JAMA Cardiol* 2017;2:775-81.

DOI: 10.1056/NEJMc2117463

Placement of a Double-Lumen Endotracheal Tube

TO THE EDITOR: In their video, Hao et al. (Oct. 14 issue)¹ clearly describe the techniques of the placement of a double-lumen endotracheal tube. The authors state that selection of such a tube is most often guided by the patient's sex and height. However, this recommendation may not be appropriate for all patients, especially for Asian women, who are generally smaller than their non-Asian counterparts. An inappropriate double-lumen endotracheal tube is frequently selected when the traditional method is used owing to the poor correlation between the patient's height and the airway size.² In fact, a combination of the patient's imaging data (such as computed tomography [CT] or chest radiography) and clinical characteristics (sex and height) has been proven to be a more effective method to predict the proper tube size in clinical practice.^{3,4} This combined method not only helps in the selection of the appropriate tube size but also helps in the evaluation of abnormal tracheobronchial anatomy, especially for placement of right-sided tubes.⁵ Therefore, we suggest that the patient's imag-

ing data (such as CT or chest radiography) be reviewed before selection of the appropriate tube size.

Bailong Hu, M.D.
Haiyan Zhou, M.D.
Xiaohua Zou, M.D.

Affiliated Hospital of Guizhou Medical University
Guiyang, China
zouxiaohuazxh@163.com

No potential conflict of interest relevant to this letter was reported.

1. Hao D, Saddawi-Konefka D, Low S, Alfille P, Baker K. Placement of a double-lumen endotracheal tube. *N Engl J Med* 2021;385(16):e52.
2. Kim D, Son J-S, Ko S, Jeong W, Lim H. Measurements of the length and diameter of main bronchi on three-dimensional images in Asian adult patients in comparison with the height of patients. *J Cardiothorac Vasc Anesth* 2014;28:890-5.
3. Brodsky JB, Lemmens HJM. Tracheal width and left double-lumen tube size: a formula to estimate left-bronchial width. *J Clin Anesth* 2005;17:267-70.
4. Shiqing L, Wenxu Q, Yuqiang M, Youjing D. Predicting the size of a left double-lumen tube for Asian women based on the combination of the diameters of the cricoid ring and left main bronchus: a randomized, prospective, controlled trial. *Anesth Analg* 2020;130:762-8.