Clinical outcomes of modifying hypertension treatment in older adults treated to low blood pressure

Carole E. Aubert, MD,[1,2,3,4] Jin-Kyung Ha, PhD,[5] Hyungjin Myra Kim ScD,[6,7] Nicolas Rodondi, MD, MAS, [1,2] Eve A. Kerr, MD, MPH,[3,4,8] Timothy P. Hofer, MD, MSc ,[3,4,8] Lillian Min, MD, MSHS[3,4,5,9]

[1] Department of General Internal Medicine, Bern University Hospital, University of Bern, Bern, Switzerland;
[2] Institute of Primary Health Care (BIHAM), University of Bern, Switzerland;
[3] Center for Clinical Management Research, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, MI, USA;
[4] Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, MI, USA;
[5] Division of Geriatric and Palliative Medicine, Department of Medicine, University of Michigan, Ann Arbor, MI, USA;
[6] Consulting for Statistics, Computing & Analytics Research (CSCAR), University of Michigan, Ann Arbor;
[7] Department of Biostatistics, University of Michigan Medical School;
[8] Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA;
[9] VA Ann Arbor Medical Center VA Geriatric Research, Education, and Clinical Center (GRECC), Ann Arbor, MI, USA.

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E-mail addresses: caroleelodie.aubert@insel.ch; jinha@med.umich.edu; myrakim@umich.edu; nicolas.rodondi@insel.ch; ekerr@umich.edu; thofer@umich.edu; lmin@med.umich.edu

Corresponding author: Carole E. Aubert, MD, Department of General Internal Medicine, Bern University Hospital, Freiburgstrasse, 3010 Bern; +41 31 632 21 11; caroleelodie.aubert@insel.ch; @aubert_carole

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KEY POINTS BOX

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- Deintensifying antihypertensive medication in older adults with systolic blood pressure (SBP) <130 mmHg was not associated with better outcomes, except when baseline SBP was <95 mmHg.

- It is possible that some patients deintensifying treatment at low SBP were addressing unobservable symptoms related to falling, thus confounding our observational study. Therefore, a trial is needed.

WHY DOES THIS MATTER?

Benefits and harms of deintensifying antihypertensive medication in older adults with low SBP is uncertain.

ABSTRACT

Background/Objectives: Hypertension treatment reduces cardiovascular events. However, uncertainty remains about benefits and harms of deintensification or further intensification of antihypertensive medication when systolic blood pressure (SBP) is tightly controlled in older multimorbid patients, because of their frequent exclusion in trials. We assessed the association of hypertension treatment deintensification or intensification with clinical outcomes in older adults with tightly-controlled SBP.

Design: Longitudinal cohort study (2011-2013) with nine-month follow-up.

Setting: US-nationwide primary care Veteran Health Administration healthcare system.

Participants: Veterans ≥65 years with baseline SBP <130 mmHg and ≥1 antihypertensive medication during ≥2 consecutive visits (N=228,753).

Exposure: Deintensification or intensification, compared to stable treatment.

Main Outcomes and Measures: Cardiovascular events, syncope, or fall injury, as composite and distinct outcomes, within nine months after exposure. Adjusted logistic regression and inverse probability of treatment weighting (IPTW, sensitivity analysis).

Results: Among 228,753 patients (mean age 75 [SD 7.5] years), the composite outcome occurred in 11,982/93,793 (12.8%) patients with stable treatment, 14,768/72,672 (20.3%) with deintensification, and 11,821/62,288 (19.0%) with intensification. Adjusted absolute outcome risk (95%CI) was higher for deintensification (18.3% [18.1 to 18.6%]) and intensification (18.7% [18.4 to 19.0%]), compared to stable treatment (14.8% [14.6 to 15.0%]), $P<.001$ for both effects in the multivariable model). Deintensification was associated with fewer cardiovascular events than intensification. At baseline SBP <95 mmHg, cardiovascular event risk was similar for deintensification and stable treatment, and fall risk lower for deintensification than intensification. IPTW yielded similar results. Mean follow-up SBP was 124.1 mmHg for stable treatment, 125.1 mmHg after deintensification ($P<.001$), and 124.0 mmHg after intensification ($P<.001$).

Conclusion: Antihypertensive treatment deintensification in older patients with tightly-controlled SBP was associated with worse outcomes than continuing same treatment intensity. Given higher mortality among patients with treatment modification, confounding by indication may not have been fully corrected by advanced statistical methods for observational data analysis.

INTRODUCTION

Hypertension affects over 70% US adults after the age of 60 years.[1] While there is strong evidence that modest blood pressure (BP) control reduces cardiovascular risk in older adults, intensive control for those patients remains controversial. In the HYVET trial, a target systolic BP (SBP) <150 mmHg reduced cardiovascular event relative risk by 34% in patients ≥80 years.[2] In the SPRINT trial, a target SBP <120 mmHg reduced cardiovascular disease and mortality, even in patients aged ≥75 years, but adverse events were increased.[3,4] Following SPRINT, US hypertension guidelines were revised to lower BP targets,[5,6] although a meta-analysis (including SPRINT) found no reduction in mortality or major cardiovascular events in trials where patients with a baseline SBP <140 mmHg were treated to lower targets.[7] However, because older multimorbid patients were often excluded from trials (e.g., high-fall risk patients, such as patients with dementia or living in nursing home, were excluded in HYVET and SPRINT),[2,3] little is known about optimal BP goals for a real-world population that includes individuals at high risk of adverse events.[8]

In several observational studies, patients with SBP <130 mmHg had higher rates of cardiovascular events, mortality, and cognitive impairment, supporting a J-curve hypothesis, i.e., an increased risk of cardiovascular events not only for hypertensive blood pressure values, but also when blood pressure is very low.[9,10] Among Medicare patients with hypertension, patients taking antihypertensive medications were also found to have a higher risk of serious fall injuries compared to those not taking medication.[11] A study among 211,667 Veterans reported that almost 40% of treated older multimorbid adults have a SBP <120 mmHg, yet less than 20% of those with SBP <120 mmHg received deintensification.[12] Responding to these observations, some studies have looked for benefits of deintensification. The DANTE trial of 385 participants aged ≥75 years found no change in cardiovascular and cognitive outcomes 16 weeks after deintensification,[13] while two small studies reported lower fall risk after deintensification.[14,15] The OPTIMISE trial found that there was little difference in SBP after deintensification (569 patients, ≥80 years, baseline SBP <150 mmHg), but long-term clinical outcomes were not reported.[16]

Accordingly, there remains uncertainty about the potential benefits and harms of intensive BP control in older adults with multimorbidity. Given recent evidence, clinicians may fear that deintensification for older patients with low SBP will lead to an increased risk of cardiovascular events.[17,18] Yet, some older adults fear serious fall injuries as much as they fear cardiovascular events.[19] Nonetheless, the SPRINT trial, performance measures, and lower BP targets in guidelines will inevitably lead to more aggressive treatment of older patients, potentially including those at high risk for adverse events, to whom the guidelines may not explicitly apply. We therefore examined the association between change in hypertension treatment intensity and cardiovascular events, syncope, and fall injuries, among over 200,000 older patients with treated BP in

the Veterans Health Administration (VHA), the largest US integrated health system. We focused on those outcomes because they can significantly impact the functional status of older patients. We hypothesized that hypertension treatment deintensification would be associated with fewer syncope and fall injury events, without increasing cardiovascular event risk in older adults with tightly-controlled SBP.

METHODS

Data from the study are not openly available to other researchers due to protected patient information by the Veterans Health Administration (VHA). Statistical codes can be provided by the corresponding author upon request. The codes for the Hypertension Daily Dose (HDD, see below) and fall injury have been published in open source format. [20,21]

Overall approach

We used data from electronic health records from the national Veterans Affairs (VA) healthcare system from July 2011 through June 2013, linked to VA and Medicare pharmacy and outcome data. In all Veterans aged ≥65 years with tightly-controlled SBP, we first assessed whether modifying the intensity of hypertension treatment was associated with cardiovascular, syncope, and fall injury events. Second, we assessed the effect of treatment intensity modification on subsequent SBP.

Study population

The study included all patients ≥65 years with ongoing primary care at the VHA, a diagnosis of hypertension, and tightly-controlled SBP, defined as SBP <130 mmHg with ≥1 antihypertensive medication on ≥2 consecutive visits (**Figure 1**). The 130 mmHg threshold was chosen as being 10 mmHg below the recommended SBP target at the study time (2011-2013).[22] To increase precision, we used mean SBP of the two visits to define baseline SBP. This research was conducted under Human Subjects review (VA IRB 2015-286).

Variable construction and definition

Using ICD-9 codes, we classified comorbidities into chronic conditions, including general medical conditions, cardiovascular risk factors, and geriatric conditions (**Supplemental Table 1**), and defined multimorbidity as ≥1 chronic

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condition in addition to hypertension.[23] We selected all conditions potentially associated with our treatment and/or outcomes of interest, as well as markers of patient sickness or frailty. To capture antihypertensive treatment, we applied an algorithm that we previously validated in older Veterans, which uses Veterans Affairs and Medicare Part D pharmacy fills to determine the most likely antihypertensive medication on any day.[24] We standardized doses to Hypertension Daily Doses (HDDs), allowing comparison across medications.[20] We defined one HDD as half the maximum beneficial dose demonstrated in trials (**Supplemental Table 2**),[25-27] and aggregated the standardized doses to obtain total dose. For example, hydrochlorothiazide 50 mg (maximal beneficial dose: 2 HDDs) with candesartan 16 mg (half maximal beneficial dose: 1 HDD) would equal 3 total HDDs.

Our primary exposure of interest was a three-level treatment strategy based on dose changes between baseline and +90 days (**Figure 1**): deintensification (any dose decrease), intensification (any dose increase), or stable treatment intensity (no dose change). The 90-day period was selected because it is the usual refill period. To interpret our results in light of prior studies that have historically reported the results of changes in medication count only,[13,14,28] we conducted sensitivity analyses that similarly defined treatment strategy by modification in medication count.

The primary outcome was a binary composite outcome of any inpatient (hospitalizations) or outpatient (emergency department visits) encounter for acute cardiovascular events, syncope, or fall injury, within nine months after treatment strategy assignment (i.e., 90-365 days after baseline, **Figure 1**). Cardiovascular events included only acute diagnoses of hemorrhagic and ischemic stroke, acute coronary syndrome, and decompensated heart failure. We used ICD-9 codes for cardiovascular events and syncope (**Supplemental Table 3**), and a validated algorithm for capturing comprehensive new fall injury events across inpatient and outpatient care.[21] We assessed cardiovascular events, syncope, and fall injury separately as secondary outcomes to avoid missing potential opposite associations, and because some patients may value avoiding one event more than the other.[19]

Statistical analyses

In order to estimate the association between treatment intensity modification and outcome, we used a logistic regression with categorical indicators for treatment strategy, adjusting for baseline covariates, which included age, chronic conditions, baseline SBP, and baseline antihypertensive medication dose. Since close proximity to death could directly result in a general deintensification of preventive medications, we did not include death as outcome, and the analytic cohort included only patients who were survived until end of follow-up (i.e., 365 days after baseline) (96.4% of all identified patients). To reduce potential bias resulting from deaths during the follow-up period, we weighted the analyses by the inverse probability of survival. This main model resulted in estimated marginal risk associated with the three treatment strategies as

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if the patients who died were included in the analysis and survived. Next, in order to reduce bias resulting from patient factors associated with deintensification (versus no deintensification), we conducted a sensitivity analysis using inverse probability of treatment weighting (IPTW) by propensity scores (PS). Models to derive both survival and treatment weights included all baseline covariates. Since patients with cardiovascular disease or heart failure may benefit from a lower SBP target, we conducted a sensitivity analysis assessing patients with and without cardiovascular disease or heart failure separately. All outcome models included two interaction terms, between age and baseline SBP (to account for and non-linear effect of SBP with increasing age) and between treatment strategy and baseline SBP (to account for effect modification that baseline SBP might have on treatment effect).

To assess the association between treatment strategy and follow-up SBP, we calculated the mean SBP across all visits during follow-up period, and compared changes in mean SBP between baseline and follow-up, according to treatment strategy and adjusting for baseline SBP. We compared proportions with ≥10 mmHg change in mean SBP using χ^2 tests.

Details of the statistical analyses are provided in **Supplemental File 1**. All analyses were performed with Stata/MP 15.1 (StataCorp), and SAS Enterprise Guide 7.1 (SAS Institute).

RESULTS

After excluding 8,461 (3.6%) patients with missing outcome data due to death before end of follow-up, 228,753 patients (mean age 75.2 [SD 7.5] years, 98.2% males) were included in the analytic cohort. Mean baseline SBP was 116.7 (SD 7.6) mmHg, and 183,436 (80.2%) patients had multimorbidity. Baseline characteristics according to treatment strategy are presented in **Table 1**. Deintensification was observed in 72,672 (31.8%) patients, and intensification in 62,288 (27.2%) patients. Patients with deintensification had the highest mortality rate (4.1%), followed by those with intensification (3.2%), and stable treatment (1.8%, p<0.001).

Association of deintensification and intensification with the composite outcome

The primary composite outcome occurred in 38,571 (16.9%) patients, including 25,601 cardiovascular events, 3,438 syncope episodes, and 20,282 fall injuries (**Supplemental Table 4**). The composite outcome occurred in 12.8% (11,982/93,793) of patients with stable treatment, 20.3% (14,768/72,672) with deintensification, and 19.0% (11,821/62,288) with intensification.

Adjusted absolute outcome risk (95%CI) was higher for deintensification (18.3% [18.1 to 18.6%]) and intensification (18.7% [18.4 to 19.0%]), compared to stable treatment (14.8% [14.6 to 15.0%]), *P*<.001) (**Table 2, Figure**

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2A). Although the overall composite outcome risk associated with deintensification was higher compared with stable treatment, the risks associated with these two treatment strategies were similar in those with low baseline SBP (<95 mmHg), while the risk associated with deintensification was higher than that associated with stable treatment with higher baseline SBP (**Figure 2A**). In the sensitivity analysis with treatment strategy defined using medication count change, adjusted outcome risk (95% CI) was 16.2% (16.0 to 16.3%; reference) for stable treatment, 19.8% (19.4 to 20.3%; *P*<.001) for deintensification, and 22.1% (21.5% to 22.7%; *P*<.001) for intensification (**Table 2, Supplemental Figure 1A**).

Association of deintensification and intensification with cardiovascular events, syncope, and fall injuries as separate outcomes

The relationship between treatment modification and cardiovascular events was similar to the main analysis of the composite outcome, except for that for patients with baseline SBP <95 mmHg, there was no cardiovascular difference in risk associated with deintensification and stable treatment (**Figure 2B, Table 2, Supplemental Figure 1B, Supplemental Table 5**). Compared to intensification, cardiovascular event risk was 1.0% (95% CI -1.4 to -0.6%; *P*<.001) lower for dose deintensification, and 3.7% (95% CI -4.5 to -3.0%; *P*<.001) lower for medication count reduction. Both deintensification and intensification were associated with an increased syncope risk across all baseline SBP values, compared to stable treatment. Overall, deintensification was associated with a 1.5% (95% CI 1.1 to 1.9%; *P*<.001) greater risk of fall injury compared to stable treatment. However, at low baseline SBP (<95 mmHg), deintensification was associated with the lowest fall risk (**Figure 2D**).

Sensitivity analysis: Inverse probability weights to reduce bias of patient characteristic leading to different treatments

We found that IPTW was appropriate, improving balance in covariates between treatment groups from a maximum standardized difference of 36.9% to 4.2% (**Supplemental Figures 2-5**). After applying the IPTW, we found no differences with the main analyses (**Supplemental Table 5**).

Sensitivity analysis: patients with versus without cardiovascular disease or heart failure

Patients with cardiovascular disease or heart failure had an absolute outcome risk (95%CI) of 21.5% (21.1 to 22.0%) for stable treatment, 26.1% (25.6 to 26.5%) for deintensification, and 27.2% (26.7 to 27.7%) for intensification. Patients without cardiovascular disease or heart failure had an absolute outcome risk (95%CI) of 10.3% (10.1 to 10.6%) for stable treatment, 13.2 (12.9 to 13.5%) for deintensification, and 13.0 (12.7 to 13.4%) for intensification.

Follow-up SBP

Mean SBP at baseline was low and increased over the one-year follow-up in all treatment groups: from 117.5 to 124.1 mmHg for stable treatment, 115.7 to 125.1 mmHg for deintensification, and 117.0 to 124.0 mmHg for intensification; *P*<.001), consistent with regression to the mean (**Supplemental Table 6A**). A ≥10 mmHg decrease between mean baseline and follow-up SBP was less frequent after deintensification (5.7%; *P*<.001), and more frequent after intensification (7.5%; *P*<.001), compared to stable treatment (6.7%); a ≥10 mmHg increase was observed in 45.9% of patients with deintensification, 38.6% with intensification, and 37.0% with stable treatment (*P*<.001; **Supplemental Table 6B**). Similar findings were found using medication count instead of dose modification.

DISCUSSION

In this large-scale study of over 228,000 older adults with tightly-controlled SBP at baseline, we hypothesized, but did not find, that deintensification would be associated with a short-term reduction in injurious falls and syncope. The risk of cardiovascular events and fall injury increased when baseline SBP was low, while syncope risk varied little by baseline SBP. Deintensification was associated with fewer cardiovascular events than intensification, and there was a pattern for a lower risk of cardiovascular events and fall injury when baseline SBP was very low. Changes in SBP relative to baseline were small and did not vary by treatment strategy. Mean SBP remained <130 mmHg during follow-up for all treatment strategies.

We report our findings in the context of prior literature. Previous studies found that SBP <130 mmHg was associated with higher rates of cardiovascular events, mortality, and cognitive impairment,[9,10] and that antihypertensive medications were associated with a higher risk of serious fall injuries.[11] We observed a pattern for fewer fall injuries after deintensification compared to stable treatment only below baseline SBP 95 mmHg, which is consistent with a study reporting 11.4% lower fall risk after deintensification in nursing home patients with baseline 80-100 mmHg, but non-significant association at 101-120 mmHg.[14] Another study found a 0.35 hazard ratio for recurrent fall after withdrawing fall-risk increasing medications in 67 patients.[15] The results of those studies, compared to ours, may be explained by their focus on high fall-risk patients, intervention on several fall-risk increasing medications, or assessment of falls not leading to medical visit. While we observed an increased fall risk after deintensification at baseline SBP 95-130 mmHg, our findings may be related to unmeasured confounders (e.g., uncaptured higher fall risk in patients with treatment modification, treatment change related to other fall-risk increasing medications).

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In the DANTE trial, there was no difference in cardiovascular outcomes after deintensification, but patients with serious cardiovascular disease were excluded, mean baseline SBP was 148 mmHg, and follow-up was limited to 16 weeks.[13] In SPRINT, reducing SBP from a mean of 139.7 to 121.5 mmHg decreased cardiovascular events and mortality, even in patients aged ≥75 years.[3,4] However, none of the patients we studied would have been eligible for SPRINT, because their baseline SBP was already treated to <130 mmHg. Moreover, we included patients who were excluded in SPRINT (diabetes, stroke, heart failure, dementia, 65-74 years without cardiovascular history). In this population, we found that deintensification was associated with worse outcomes, compared to a strategy of maintaining antihypertensive treatment intensity, except when baseline SBP was very low.

Our hypothesis that deintensification would be associated with fewer syncope and fall injuries, without increasing cardiovascular event risk, was not confirmed. Although we used robust methods for observational data analysis, we could not control for all confounders. It is possible that continued unmeasured confounding and/or confounding by indication may have led to our results, despite these advanced methods. Baseline characteristics and death rates during follow-up indeed suggest that deintensified and intensified patients were sicker than those with stable treatment. One-year mortality was indeed more than twice as high within among patients who deintensified, compared to those with stable treatment. Furthermore, the association of treatment modification with adverse outcomes was greater in patients with cardiovascular disease or heart failure. This suggests that patients with treatment intensity modification had a higher baseline outcome risk. Greater outcome risk and more severe disease may have driven both treatment intensity modification and outcome occurrence. In addition, unlike a trial where patients would have been assigned to deintensification or intensification based on their baseline SBP in otherwise stable clinical conditions, we could not capture reasons other than SBP that may have led to treatment modification if they were not coded (e.g., change in control of heart failure or atrial fibrillation, end-of-life, medication adverse effects). These reasons could also have contributed to treatment intensification despite low baseline SBP. The outcomes may have been different in a randomized controlled trial than in this retrospective study using administrative data. Another possible explanation is that any change to a medication regimen is in itself a significant risk for older patients. Polypharmacy and age-related changes in medication metabolism and elimination can make multimorbid older patients more sensitive to medication adverse effects and interactions.[29] The relatively small differences in follow-up SBP across treatment groups themselves argue that the differences in outcomes observed for those with a change in their regimen vs. stable treatment was mediated through something else than the BP level alone.

Strengths and limitations

Our study has several strengths. First, we included a far larger number of patients than previous studies.[14,16] Second, we used the best-available real-world data that included clinical blood pressure measurements, and a near-universal data

source on medication fills from the largest US healthcare system and Medicare. Third, we simulated an experiment by assessing the association between treatment modification and events occurring *after* treatment modification, using advanced statistical methods to reduce the risk of confounding: in the multivariable regression, we adjusted for a broad range of variables, and we additionally conducted a sensitivity analysis using inverse probability of treatment weights to assure balance on average of all of that wide range of measured covariates. Furthermore, since proximity to death may lead to deintensification, we additionally weighted the sample by the inverse probability of survival. Fourth, unlike prior studies,[13,14,16,28] we quantified treatment intensity modification with two measures (standardized dose and medication count), averaged two consecutive SBP measurements to reduce measurement error in a key baseline covariate, and used two consecutive visits to define eligibility, according to both baseline SBP and medication, limiting the risk of including patients without tightly-controlled SBP. Finally, we assessed multiple clinical outcomes over nine months, while previous studies were limited to a few weeks, or did not have not yet reported clinical outcomes.[13-16]

We must acknowledge some limitations. First, we cannot exclude unmeasured confounding resulting from bias in distributing the treatment approach in observation studies. We addressed this bias with two different methods for causal inference in observational data (regression adjustment in the main analysis and an IPTW sensitivity analysis). The similar results of the IPTW, with good PS and covariate balance, add validity to our results. However, as discussed above, administrative data alone cannot provide enough data for us to control for confounding by indication, and the small difference in SBP suggests that the results were mediated through something else than BP alone. Second, pharmacy fill data do not ascertain medication consumption. However, there is no gold standard for medication consumption in outpatient care, and prior research have proposed fills as a reliable source of data.[30,31] Third, the use of administrative data precluded our ability to ascertain the clinical reasoning behind any dose modification event. Fourth, the study time frame (2011-2013) predates the newest guidelines (following the SPRINT trial), which lowered recommended SBP to <130 mmHg for most older adults.[5] However, SBP target used by most healthcare systems for performance measures was identical at the time of the study to current measures (<140 mmHg).[32-34] Fifth, because our overarching interest was on clinical events that can impact older adults' functional status, we focused on cardiovascular events, syncope and fall injuries. We cannot draw conclusions about other types of outcomes such as acute kidney injury or electrolyte abnormalities, events that were also increased by SPRINT intervention.[3] Finally, as all studies in older Veterans, the results may not be generalizable to older women. However, the great strengths for this dataset for studying health systems outweighs this limitation. No other national dataset exists and is compiled in a national repository that includes medications, blood pressures, comorbid conditions, and outcomes.

Conclusion

In this large national healthcare sample with robust administrative, medication and vital signs data, deintensifying antihypertensive treatment in older patients with tightly-controlled SBP (baseline treated SBP <130 mmHg) was not associated with a lower risk of fall injury or syncope. Given higher mortality and more severe baseline cardiovascular disease severity among patients with deintensification, it is likely that patients' declining clinical state, which was inadequately recognized in the administrative data, may have both prompted attempts at deintensification and led to adverse events. Trial research will be needed to overcome these limitations of observational data, before we can conclude that treatment can be safely deintensified in older multimorbid adults without leading to adverse clinical outcomes.

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FIGURES LEGENDS

Figure 1. Study design.
Legend: Eligibility was defined as 2 consecutive visits with systolic blood pressure <130 mmHg and ≥1 antihypertensive medication within a 2-year period. Treatment assignment was defined by calculating the difference (Δ) in dose and medication count between day 0 (baseline) and day 90. The follow-up was between 90 days and 1 year after baseline.

Figure 2. Adjusted absolute risk for A) composite outcome, B) cardiovascular event, C) syncope, and D) fall injury, according to dose change and baseline systolic blood pressure.
Legend: Based on logistic regression model weighted to account for missing outcome. The model included interaction terms between age and systolic blood pressure and between systolic blood pressure and treatment strategy, and was also adjusted for baseline antihypertensive medication dose and for chronic conditions (**Supplemental Table 1**).

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Supplemental File S1. Details on the study methods.

Supplemental Table 1. Definition of chronic conditions.

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Supplemental Table 3. International Classification of Diseases-9 codes for cardiovascular events and syncope.

Supplemental Table 4. Outcome rates according to treatment strategy.

Supplemental Table 5. Adjusted marginal effects of treatment strategy on composite and secondary outcomes.

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Supplemental Figure 5A. Density of the treatment propensity score for medication count deintensification vs. medication count intensification.

Supplemental Figure 5B. Absolute standardized differences for covariates of the treatment propensity score for medication count deintensification vs. medication count intensification in the weighted and unweighted samples.

Table 1. Baseline characteristics according to treatment strategy.

Characteristic (No.=228,753)	No dose change (No.=93,793)	Dose decrease (No.=72,672)	Dose increase (No.=62,288)
Age, mean (SD), years	74.9 (7.4)	75.6 (7.6)	75.2 (7.5)
Male	92,051 (98.1)	71,380 (98.2)	61,242 (98.3)
Baseline SBP, mean (SD), mmHg	117.5 (7.1)	115.6 (8.3)	116.9 (7.5)
≤110.0 mmHg	14,775 (15.7)	17,202 (23.7)	11,329 (18.2)
110.5-120.0 mmHg	41,238 (44.0)	31,225 (43.0)	27,113 (43.5)
120.5-129.0 mmHg	37,780 (40.3)	24,245 (33.3)	23,846 (38.3)
Chronic conditions			
Number, mean (SD)	3.0 (3.1)	4.3 (3.6)	3.7 (3.5)
Multimorbidity [a]	70,850 (75.5)	62,013 (85.3)	50,573 (81.2)
Vascular disorder [b]	25,602 (27.3)	29,503 (40.6)	23,091 (37.1)
Heart failure or valve disorder	11,500 (12.3)	17,295 (23.8)	13,681 (22.0)
Diabetes mellitus	29,341 (31.3)	28,859 (39.7)	23,689 (38.0)
Fall risk [c]	15,788 (16.8)	18,089 (24.9)	13,196 (21.2)
Antihypertensive medication			
Total dose, mean (SD), HDD	2.2 (1.8)	2.9 (2.2)	2.3 (1.9)
Medication count, mean (SD)	2.2 (1.1)	2.8 (1.3)	2.6 (1.2)

Abbreviations: HDD, Hypertension Daily Dose; No., number.
Legend: Dichotomous variables are presented as N (%), and continuous variables as mean with standard deviation.
[a] Hypertension with ≥1 additional chronic condition.
[b] Cardiac, peripheral, and/or cerebral vascular disorder.
[c] Fall risk included Parkinson's disease, peripheral neuropathy, ataxia, vertigo/dizziness, orthostatic hypotension, walking difficulty/gait abnormality/lack of coordination, muscle weakness, syncope, history of fall (ICD-9 codes: 340-342.91, 356.XX, 357.XX, 386.XX, 438.2-438.22, 438.40-438.42, 438.84, 438.85, 458.0, 719.7, 728.87, 780.2, 780.4, 781.1, 781.2, 781.3, V15.88).

Table 2. Adjusted outcome risks according to treatment strategy (No. = 228,753 patients).

Outcomes	Adjusted absolute risks (95%CI), % [a]	
	Dose change	Medication count change
Composite outcome		
- Stable treatment [b]	*14.8 (14.6 to 15.0)*	*16.2 (16.0 to 16.3)*
- Deintensification	18.3 (18.1 to 18.6)	19.8 (19.4 to 20.3)
- Intensification	18.7 (18.4 to 19.0)	22.1 (21.5 to 22.7)
Cardiovascular event		
- Stable treatment [b]	*9.1 (8.9 to 9.2)*	*10.5 (10.4 to 10.6)*
- Deintensification	12.3 (12.0 to 12.5)	13.4 (13.1 to 13.8)
- Intensification	13.2 (12.9 to 13.4)	16.7 (16.2 to 17.3)
Syncope		
- Stable treatment [b]	*1.3 (1.2 to 1.3)*	*1.4 (1.4 to 1.5)*
- Deintensification	1.7 (1.6 to 1.8)	1.8 (1.6 to 1.9)
- Intensification	1.6 (1.5 to 1.7)	1.8 (1.6 to 2.0)
Fall injury		
- Stable treatment [b]	*8.3 (8.1 to 8.5)*	*8.7 (8.6 to 8.8)*
- Deintensification	9.7 (9.5 to 9.9)	10.2 (9.9 to 10.5)
- Intensification	9.1 (8.9 to 9.4)	9.9 (9.4 to 10.4)

Abbreviations: CI, confidence interval

[a] Based on logistic regression model weighted to account for missing outcome. The model included interaction terms between age and systolic blood pressure and between systolic blood pressure and treatment strategy, and was also adjusted for baseline antihypertensive medication dose and for chronic conditions (**Supplemental Table 1**).

[b] Reference group, defined as no dose or medication count change, respectively, is displayed in italic to facilitate reading.

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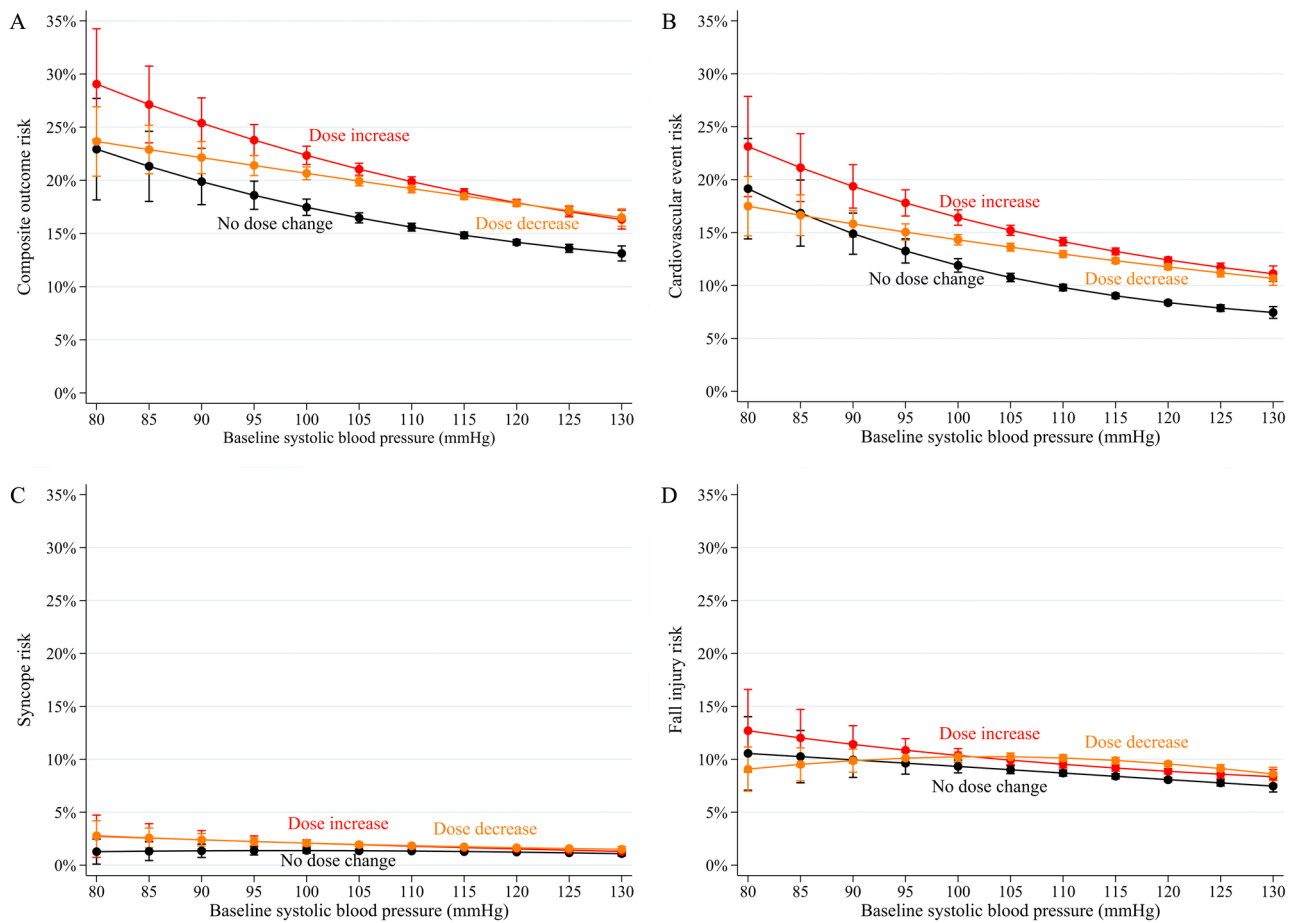| Component(s) in Article	Charge(s)	Quantity	Estimated Charge(s) (in USD)
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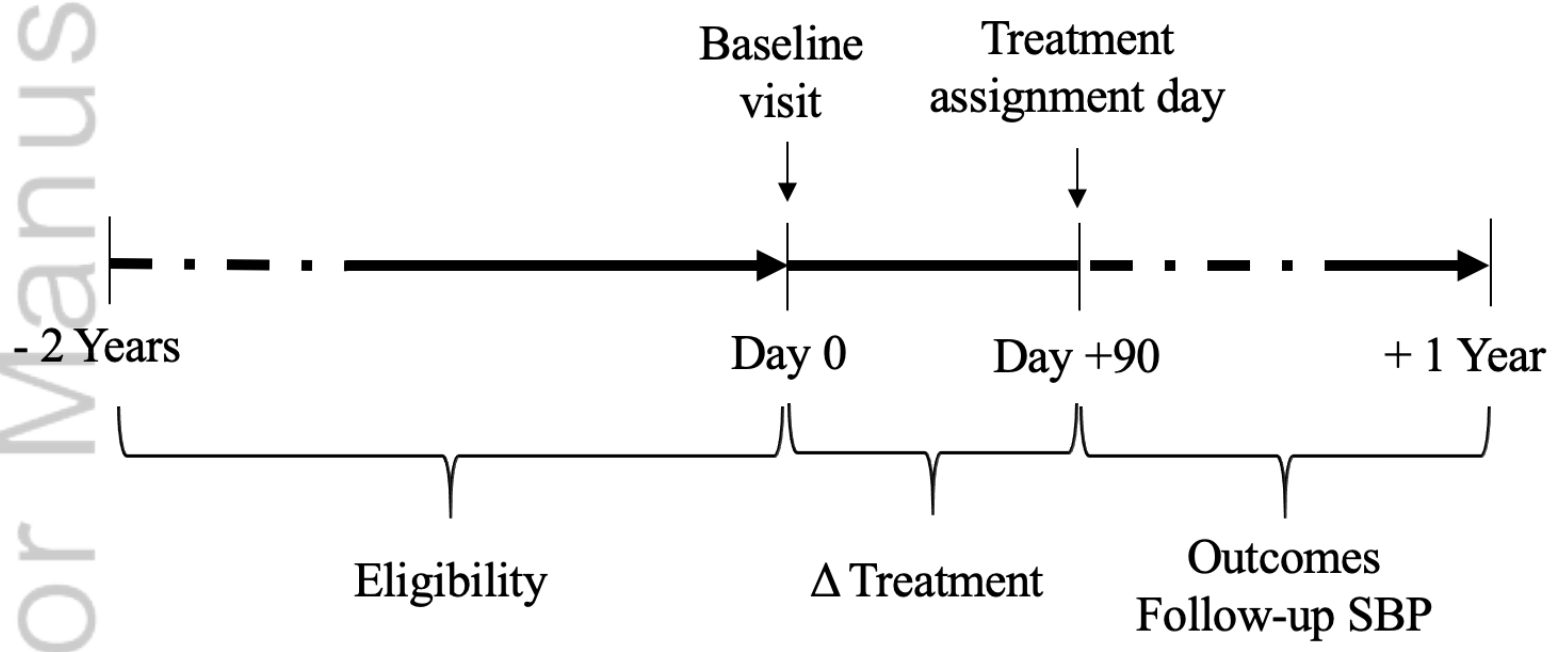Email Address: caroleelodie.aubert@insel.ch

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Treatment
assignment day

- 2 Years

Day 0

Day +90

+ 1 Year

Eligibility

Δ Treatment

Outcomes
Follow-up SBP

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