Clinical outcomes of modifying medication intensity in older adults treated to low blood pressure

ONLINE SUPPLEMENTAL MATERIAL

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Supplemental File 1. Details on the study methods.

Population and setting

Ongoing primary care at the Veteran Health Administrations was defined as at least two visits during 7/1/2009-6/30/2012. Hypertension diagnosis was defined as any International Classification of Diseases (ICD)-9 401.x diagnosis code. The two consecutive visits used to define eligibility in the cohort were during 7/1/2009-6/30/2012. The last of the two consecutive visits, defining baseline, was during 7/1/2011-6/30/2012.

Statistical analyses

Systolic blood pressure (SBP) was modeled as a quadratic variable because of a non-linear effect. of baseline SBP. Since outcomes of treatment modification may vary by baseline SBP, we included an interaction term between the treatment indicator and baseline SBP. Since proximity to death may lead to deintensification, particularly for preventive medications (rather than death being the result of deintensification), we did not include death as outcome, and the analytic cohort included only those who were observed for the outcome or alive until end of follow-up; this corresponded to 96.4% of all identified patients. To account for a potential bias from missing outcome data in patients lost due to early death, we weighted the analyses by the inverse probability of remaining in the analytic cohort, which was estimated by separate logistic regression predicting the probability of missing outcome due to death, using all baseline covariates. Based on the model, we obtained marginal risk estimates by the three treatment strategies, which provide estimates under each treatment strategy if all identified patients were to be alive until the end of the study follow-up.

For the inverse probability of treatment weighting (IPTW) by propensity score (PS) analysis, we simplified the three-level as a two-level treatment strategy, and compared deintensification with stable treatment and with intensification, respectively, in two separate analyses. PS were estimated by multivariable logistic regression with deintensification as outcome, and baseline covariates (age, chronic conditions, SBP, and antihypertensive medication dose and medication count) as independent variables. Weights were computed as 1/PS for patients with deintensification, and 1/(1-PS) for those with stable treatment or intensification, respectively. We assessed PS and covariates' balance with density graphs and absolute standardized differences (<10% indicating sufficient balance).[1]

Supplemental Table 1. Definition of chronic conditions.

Conditions	International Classification of Diseases-9 codes
General medical condition	
Anemia	280.0-285.9
Arrhythmia	427.31, 427.32, 427.81
Cardiac or peripheral vascular disorder	410.0-414.9, 427.5, 429.2, 440.0-442.9, 443.1-445.89, 557.0, 557.1, 557.9, 996.03, V45.81, V45.82
Cerebrovascular disorder	433.0-438.9, 997.02, V12.54
Heart failure / valve disorder	394.0-398.99, 402.XX, 404.XX, 416.0-416.9, 424.XX, 425.XX, 428.XX, 429.3, 429.4, 429.81-429.89, 746.XX, V42.1, V42.2, V43.2-V43.22, V43.3
Chronic kidney disease	249.4X, 250.4X, 271.4, 274.10, 403.XX, 404.XX, 572.4, 582.XX, 583.6, 585-590.01
Lung disorder	491.0-505, 506.4, 508.1, 512.83, 515, 516.XX, 517.2, 518.83, 518.84
Malignancy	140.0-172.9, 174.0-209.79, 789.51
Peptic or liver disorder	070.2-070.33, 070.44, 070.54, 070.7X, 456.0X, 456.1X, 530.0-530.6, 530.85, 531.40-531.91, 532.40-532.91, 533.4X, 536.3, 571.0-573.9, 787.2X
Substance abuse disorder	291.0-292.9, 303.00-305.93
Cardiovascular risk factors	
Diabetes mellitus	249.XX, 250.XX, 357.2, 362.01-362.07, V58.67
Obesity or overweight	278.0X, V85.30-V85.45
Geriatric conditions	
Arthritis or joint pain	712.XX, 714.XX, 715.XX, 719.4X, 721.0-721.3, 721.90, 721.91, 724.1, 724.2, 724.5
Cognitive disorder	290.XX, 292.8X, 294.XX, 330.XX, 331.XX, 438.0, 780.93, 780.97, 797.XX, 799.59, V40.31
Defecation disorder	560.32, 560.39, 564.0X, 564.1, 564.5, 787.6X
Fall risk	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
Hearing impairment	388-389.9X, V41.2, V53.2
Mood and sleep disorder	290.13, 290.21, 290.43, 291.82, 292.84, 292.85, 293.83, 293.84, 296.XX, 300.01, 300.02, 300.4, 307.4X, 309.1, 311.XX, 327.XX, 780.5X, V69.4
Nutrition deficiency	260-269.9, 783.0, 783.2-783.3, 799.4, V85.0
Osteoporosis	733.00-733.19, 733.93-733.98, V56.68
Psychotic disorder	290.12, 290.20, 290.42, 290.8, 290.9, 291.XX, 295.XX, 297.XX, 298.XX
Severe vision impairment	360.21, 360.41, 360.42, 365.73, 369.XX
Skin ulceration	707.XX, 440.23, 440.24, 454.0, 454.2, 459.11, 459.13
Urination and prostate disorder	788.2X, 788.20, 788.21, 788.29, 788.3X, 788.6, 788.61-788.65, 788.69, 788.8, 788.9, 788.91, 788.92, 595.1, 595.2, 596.0, 596.4, 596.5, 596-596.55, 596.59, 600.XX, 601.1X

Legend: Two additional chronic conditions were not defined using International Classification of Diseases-9 codes. Current smoking was defined retrieving information from the Corporate Data Warehouse and Medicare diagnosis files. Hyperlipidemia was defined using laboratory data, as cholesterol LDL >1.60 mg/dl, or total cholesterol/HDL cholesterol ratio >4.

Supplemental Table 2. Blood pressure medication classes, names, and doses, based on American College of Cardiology / American Heart Association (ACC/AHA), Joint National Committee (JNC) 7, and literature reviews.[2-12]

Class	Medication name	Dose (mg/day)		
		Geriatric starting dose	Dose for one HDD	Maximum dose
Angiotensin converting enzyme inhibitor and angiotensin receptor blocker	Benazepril	10	20	40
	Captopril	25	50	100
	Enalapril	5	20	40
	Fosinopril	10	20	40
	Lisinopril	10	20	40
	Moexipril	7.5	15	30
	Perindopril	4	8	16
	Quinapril	20	40	80
	Ramipril	2.5	10	20
	Trandolapril	1	2	4
	Azilsartan	20	40	80
	Candesartan	8	16	32
	Eprosartan	400	600	800
	Irbesartan	75	150	300
	Losartan	25	50	100
	Olmesartan	5	20	40
	Telmisartan	20	40	80
	Valsartan	80	160	320
Beta blocker	Acebutolol	200	400	800
	Atenolol	25	50	100
	Bisoprolol	2.5	5	10
	Carvedilol	12.5	25	50
	Labetalol	200	400	800
	Metoprolol	50	100	200
	Nadolol	40	80	120
	Nebivolol	5	20	40
	Penbutolol	10	20	40
	Pindolol	10	30	60
	Propranolol	40	80	160
	Sotalol	160	320	640
Calcium channel blocker	Amlodipine	2.5	5	10
	Diltiazem	120	240	420
	Felodipine	2.5	5	10
	Isradipine	2.5	5	10
	Nicardipine	60	90	120
	Nifedipine	30	60	90*
	Nisoldipine	8.5	17	34
	Verapamil	120	240	480
Centrally-acting alpha blocker	Clonidine (oral; patch)	0.2; 0.1	0.4; 0.2	0.8; 0.3
	Guanfacine	0.5	1	2
	Methyldopa	250	500	1000
	Reserpine	0.05	0.125	0.25
Thiazide-like diuretics	Chlorthalidone	12.5	12.5	25
	Hydrochlorothiazide	12.5	25	50
	Indapamide	1.25	2.5	5
	Metolazone	2.5	5	5*
	Polythiazide	2	2	4
Potassium-sparing diuretic	Amiloride	2.5	5	10
	Eplerenone	25	50	100
	Spironolactone	25	50	100
	Triamterene	25	50	100
Direct vasodilator	Minoxidil	5	20	80
Systemic vasodilator	Hydralazine	50	100	200
Direct renin blocker	Aliskiren	75	150	300

Alpha blocker	Doxazosin	4	8	16
	Prazosin	2	10	20
	Silodosin	4	4	8
	Terazosin	2	10	20
Loop diuretics	Bumetanide	0.5	1	2
	Furosemide	20	40	80
	Torsemide	2.5	5	10
	Bosentan	125	250	500
Nitrate	Isosorbide dinitrate (oral; patch)	30; 4.8	120; 9.6	480;19.2
	Isosorbide mononitrate	30	60	240

Abbreviation: HDD, Hypertension Daily Dose.

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

Outcome	International Classification of Diseases-9 codes
Stroke	430.X, 431.S, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 436
Acute coronary syndrome	410.00, 410.20, 410.30, 410.40, 410.50, 410.60, 410.70, 410.80, 410.90, 410.01, 410.21, 410.31, 410.41, 410.51, 410.61, 410.71, 410.81, 410.91, 411.1
Decompensated heart failure	428.X
Syncope	780.2

Supplemental Table 4. Outcome rates according to treatment strategy (N=228,753 patients).

Outcome	Treatment strategy, n (%)		
	Stable treatment (N=93,793)	**Dose decrease (N=72,672)**	**Dose increase (N=62,288)**
Composite outcome [b]	11,982 (12.8)	14,768 (20.3)	11,821 (19.0)
Decompensated heart failure	5,172 (5.5)	8,709 (12.0)	7,165 (11.5)
Acute coronary syndrome	1,728 (1.8)	2,115 (2.9)	1,650 (2.7)
Stroke	737 (0.8)	914 (1.3)	648 (1.0)
Syncope	1,106 (1.2)	1,324 (1.8)	1,008 (1.6)
Fall injury	7,112 (7.6)	7,487 (10.3)	5,683 (9.1)
	Stable treatment (N=183,926)	**Med count decrease (N=29,161)**	**Med count increase (N=15,666)**
Composite outcome [b]	28,203 (15.3)	6,776 (23.0)	3,675 (23.5)
Decompensated heart failure	14,484 (7.9)	4,085 (14.0)	2,477 (15.8)
Acute coronary syndrome	3,991 (2.2)	944 (3.2)	558 (3.6)
Stroke	1,683 (0.9)	432 (1.5)	184 (1.2)
Syncope	2,570 (1.4)	577 (2.0)	291 (1.9)
Fall injury	15,345 (8.3)	3,330 (11.4)	1,607 (10.3)

Abbreviations: Med, medication.

[a] Reference group, defined as no dose or medication count change, respectively.

[b] The total number of composite outcomes is lower than the addition of all outcomes because some patients had two different outcomes on the same day.

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

Treatment strategy	Adjusted marginal effect (95% CI), %			
	Composite outcome [a]	CV event	Syncope	Fall injury
Three-level treatment strategy				
Dose decrease vs. no change, RA	3.6 (3.2 to 3.9)	3.2 (2.9 to 3.5)	0.5 (0.3 to 0.6)	1.4 (1.1 to 1.7)
Dose increase vs. no change, RA	3.9 (3.5 to 4.3)	4.1 (3.8 to 4.4)	0.4 (0.2 to 0.5)	0.8 (0.5 to 1.1)
Med count decrease vs. no change, RA	3.7 (3.2 to 4.1)	2.9 (2.6 to 3.3)	0.4 (0.2 to 0.6)	1.5 (1.2 to 1.9)
Med count increase vs. no change, RA	5.9 (5.3 to 4.1)	6.2 (5.7 to 6.8)	0.4 (0.2 to 0.5)	1.2 (0.7 to 1.7)
Two-level treatment strategy				
Dose decrease vs. no change, RA	3.6 (3.2 to 3.9)	3.1 (2.8 to 3.4)	0.5 (0.3 to 0.6)	1.4 (1.1 to 1.7)
Dose decrease vs. no change, IPT	3.4 (3.0 to 3.8)	3.0 (2.6 to 3.2)	0.5 (0.3 to 0.6)	1.3 (1.0 to 1.6)
Dose decrease vs. increase, RA	-0.4 (-0.8 to 0.0)	-1.0 (-1.4 to -0.6)	0.1 (-0.1 to 0.2)	0.6 (0.2 to 0.9)
Dose decrease vs. increase, IPTW	-0.4 (-0.9 to 0.0)	-1.1 (-1.4 to -0.7)	0.1 (-0.1 to 0.2)	0.6 (0.2 to 0.8)
Med count decrease vs. no change, RA	3.6 (2.2 to 4.1)	2.9 (2.5 to 3.2)	0.3 (0.2 to 0.5)	1.5 (1.1 to 1.9)
Med count decrease vs. no change, IPT	3.8 (3.3 to 4.2)	3.0 (2.7 to 3.5)	0.4 (0.2 to 0.5)	1.6 (1.2 to 1.9)
Med count decrease vs. increase, RA	-2.5 (-3.3 to -1.7)	-3.7 (-4.5 to -3.0)	0.0 (-0.3 to 0.3)	0.4 (-0.3 to 1.0)
Med count decrease vs. increase, IPT	-2.6 (-3.4 to -1.7)	-3.9 (-4.7 to -3.1)	0.0 (-0.3 to 0.4)	0.4 (-0.3 to 1.0)

Abbreviations: IPT, inverse probability of treatment weighting by the propensity score; Med, medication; RA, regression adjustment.

Legend: Adjusted logistic regression analysis, and inverse probability of treatment weighting by the propensity score, both with inverse probability of censoring weighting. Results are presented as marginal risks in %, with 95% confidence interval. 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 (**Appendix Table 1**).

[a] Including cardiovascular event, syncope, and fall injury.

Supplemental Table 6A. Mean change in SBP between baseline and follow-up period according to treatment strategy and baseline SBP.

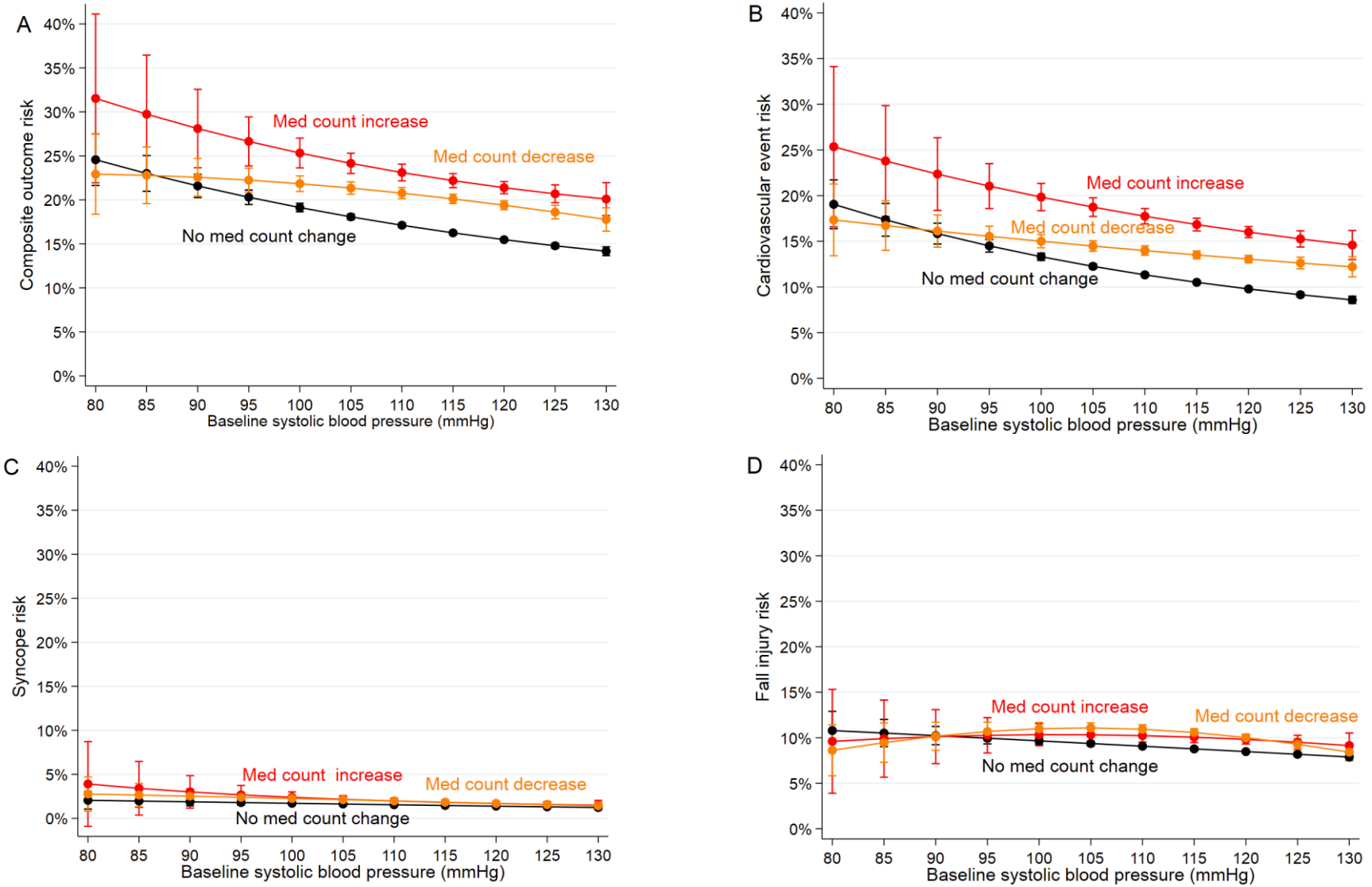
Treatment strategy	Mean (SD) change in mean SBP				
	Baseline SBP (mmHg)				
	≤90	90.5-100	100.5-110	110.5-120	100.5-130
All (N=205,395)	**31.9 (15.5)**	**21.5 (13.5)**	**14.4 (12.5)**	**7.6 (11.7)**	**1.8 (11.3)**
By dose change					
Stable treatment (N=84,714) [a]	*28.4 (14.4)*	*20.1 (12.7)*	*13.6 (11.8)*	*7.1 (11.2)*	*1.4 (10.8)*
Dose decrease (N=64,558)	33.9 (15.4)	23.1 (13.7)	15.9 (13.1)	8.7 (12.2)	2.7 (11.8)
Dose increase (N=56,123)	30.3 (15.8)	20.4 (13.6)	13.7 (12.5)	7.2 (12.0)	1.4 (11.6)
By medication count					
Stable treatment (N=166,032) [a]	*30.7 (15.0)*	*20.7 (13.1)*	*14.0 (12.1)*	*7.4 (11.5)*	*1.6 (11.1)*
Medication count decrease (N=25,166)	35.2 (16.0)	24.7 (13.9)	17.0 (13.8)	9.9 (12.7)	3.6 (12.4)
Medication count increase (N=14,197)	30.3 (16.1)	21.2 (14.5)	14.0 (13.3)	6.9 (12.7)	1.2 (12.3)

Supplemental Table 6B. Change in mean SBP ≥10 mmHg between baseline and follow-up period according to treatment strategy.

Treatment strategy	Change in mean SBP	
	≥10 mmHg decrease	≥10 mmHg increase
By dose change		
Stable treatment (N=84,714) [a]	*5,683 (6.7)*	*31,321 (37.0)*
Dose decrease (N=64,558)	3,676 (5.7) [b,c]	29,658 (45.9) [b,c]
Dose increase (N=56,123)	4,204 (7.5) [b]	21,656 (38.6) [b]
By medication count		
Stable treatment (N=166,032) [a]	*11,016 (6.6)*	*64,241 (38.7)*
Medication count decrease (N=25,166)	1,301 (5.2) [b,c]	12,857 (51.1) [b,c]
Medication count increase (N=14,197)	1,246 (8.8) [b]	5,537 (39.0) [d]

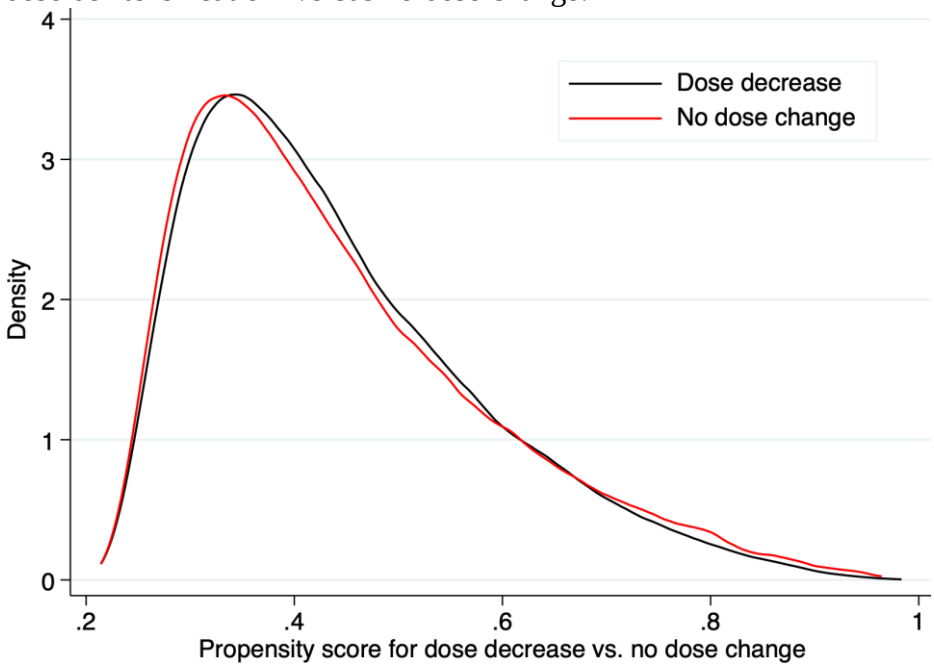
Abbreviations: SBP, systolic blood pressure; SD, standard deviation; N, number of patients.
Legend: Data are number with percentages. Of the 228,753 patients, 205,395 (89.8%) had ≥1 SBP measurement between treatment assignment (+90 days) and end of follow-up.
[a] Reference group, defined as no dose or medication count change, respectively; displayed in italic to facilitate reading.
[b] p <0.001 for comparison with stable treatment.
[c] p <0.001 for comparison with intensification.
[d] p=0.47 for comparison with stable treatment.

Supplemental Figure 1. Adjusted absolute risk for A) composite outcome, B) cardiovascular event, C) syncope, and D) fall injury, according to medication count change and baseline systolic blood pressure.

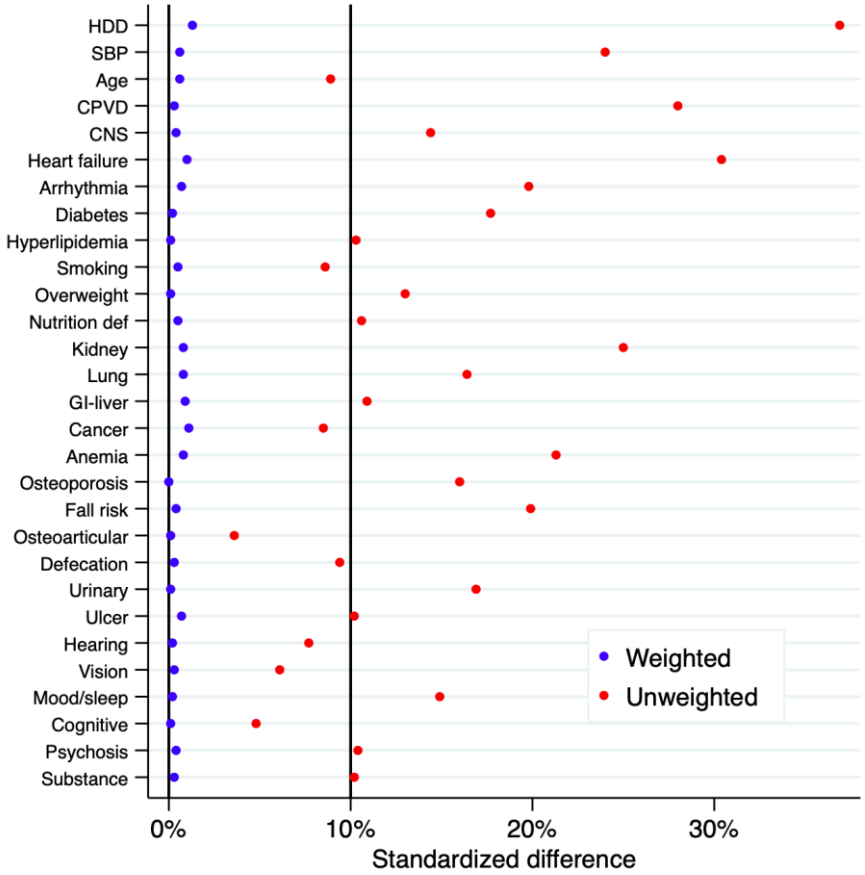


Legend: Based on logistic regression model weighted to account for missing outcome. The model included interaction terms between age and systolic blood pressure and between systolic blood pressure and treatment strategy, and was also adjusted for baseline antihypertensive medication dose and for chronic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

Supplemental Figure 2A. Density of the treatment propensity score for dose deintensification versus no dose change.

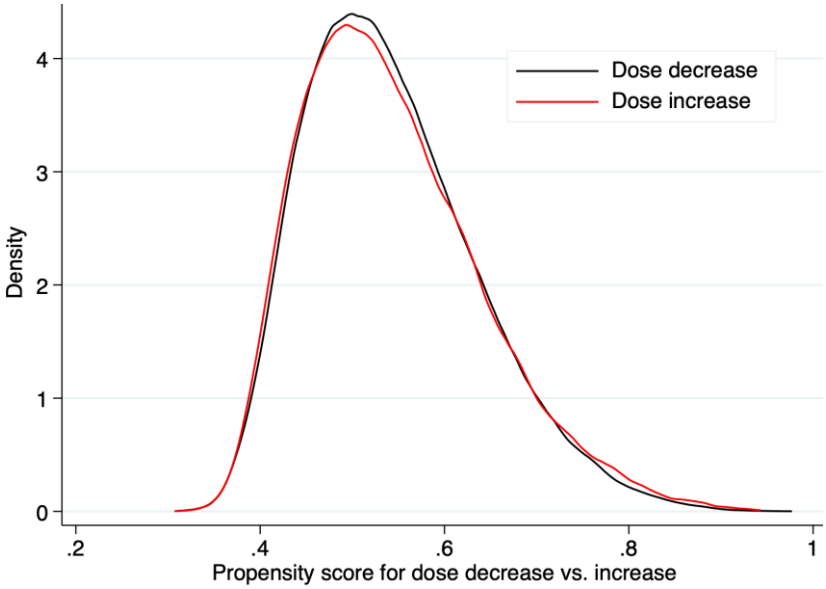


Supplemental Figure 2B. Absolute standardized differences for covariates of the treatment propensity score for dose deintensification versus no dose change, in the weighted and unweighted samples.

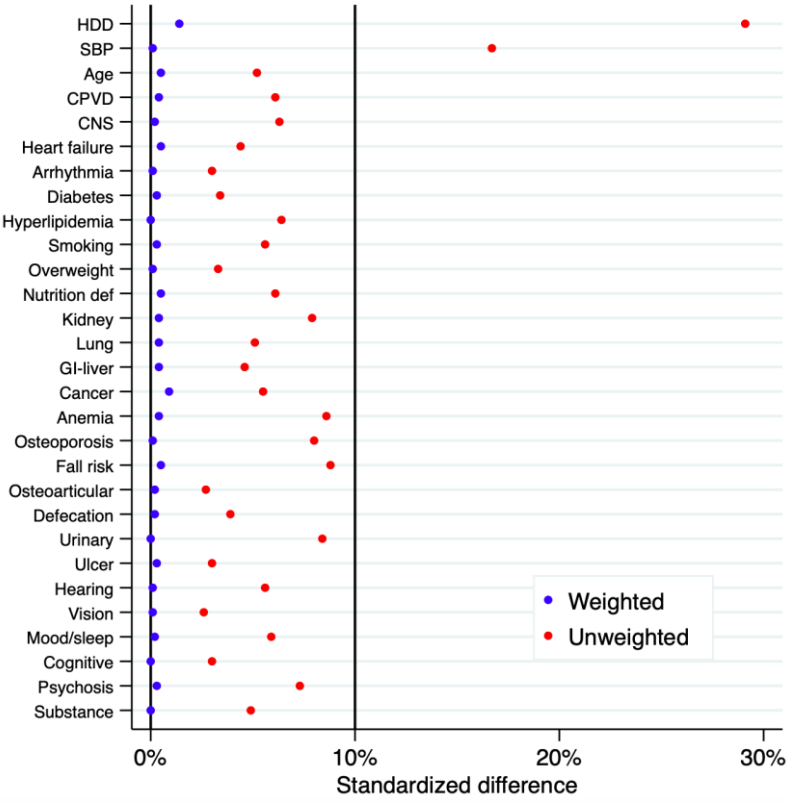


Legend: Enough balance is considered if the standardized difference is <10%.
Abbreviations: CNS, cerebrovascular disease; CPVD, cardiovascular and peripheral vascular disease; def, deficiency; GI, gastrointestinal; HDD, Hypertension Daily Dose; SBP, systolic blood pressure.

Supplemental Figure 3A. Density of the treatment propensity score for dose deintensification versus dose intensification.



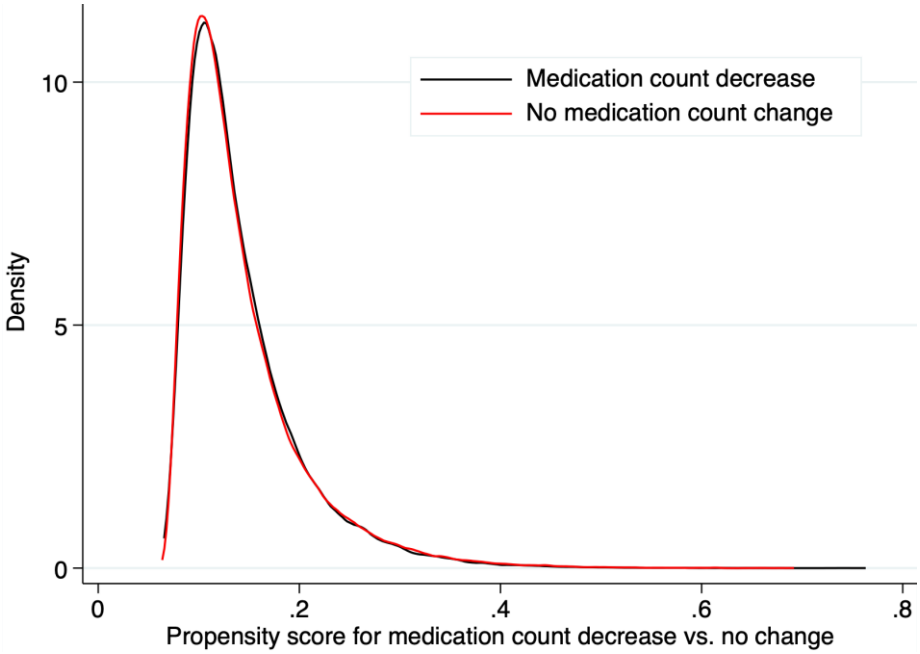
Supplemental Figure 3B. Absolute standardized differences for covariates of the treatment propensity score for dose deintensification versus dose intensification, in the weighted and unweighted samples.



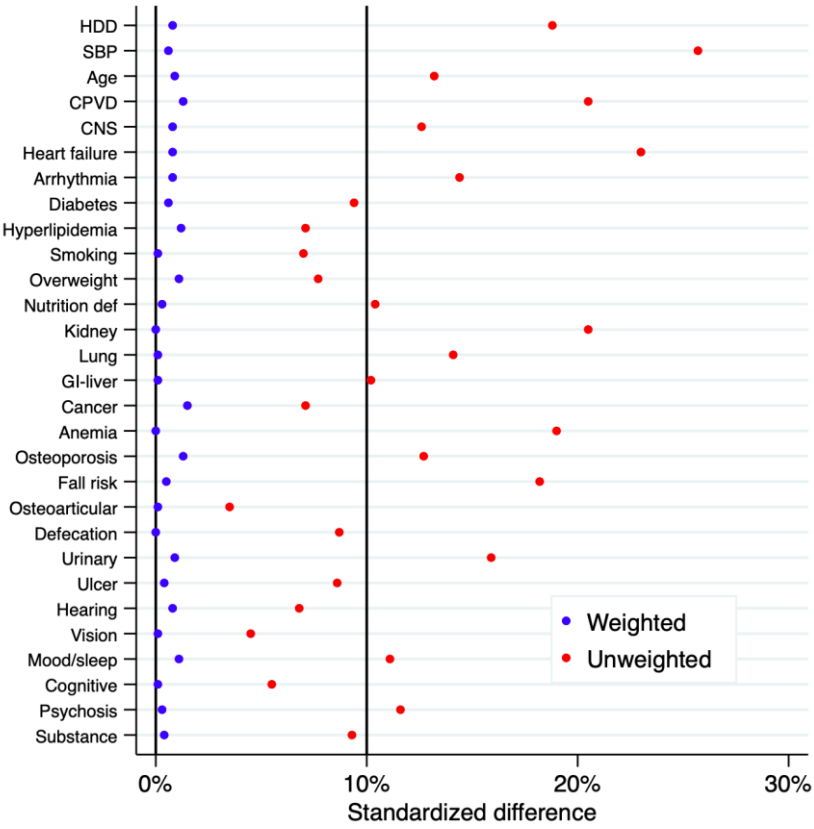
Legend: Enough balance is considered if the standardized difference is <10%.

Abbreviations: CNS, cerebrovascular disease; CPVD, cardiovascular and peripheral vascular disease; def, deficiency; GI, gastrointestinal; HDD, Hypertension Daily Dose; SBP, systolic blood pressure.

Supplemental Figure 4A. Density of the treatment propensity score for medication count deintensification versus no medication count change.

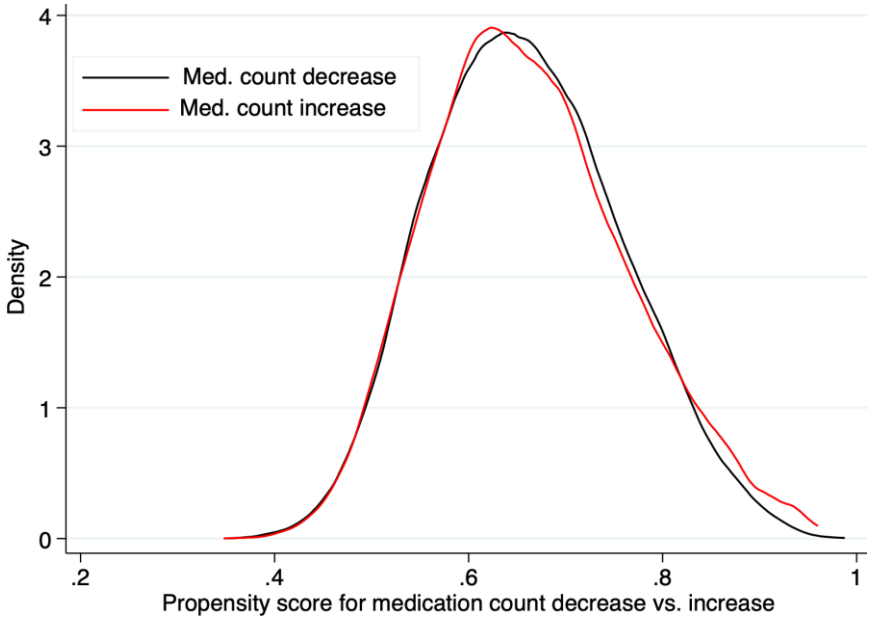


Supplemental Figure 4B. Absolute standardized differences for covariates of the treatment propensity score for medication count deintensification versus no medication count change, in the weighted and unweighted samples.

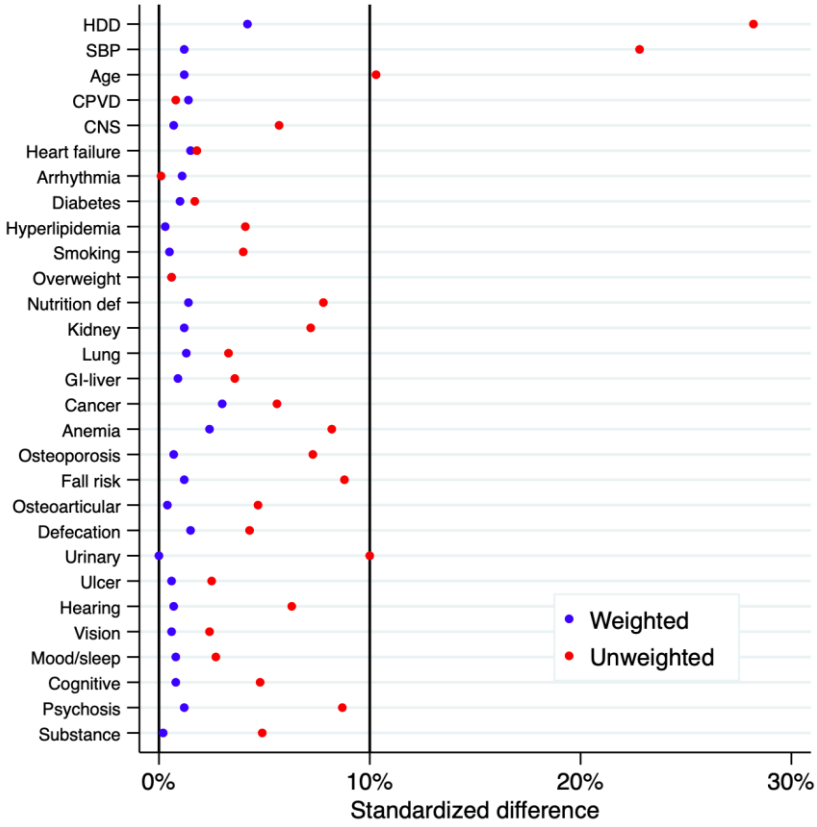


Legend: Enough balance is considered if the standardized difference is <10%.
Abbreviations: CNS, cerebrovascular disease; CPVD, cardiovascular and peripheral vascular disease; def, deficiency; GI, gastrointestinal; HDD, Hypertension Daily Dose; SBP, systolic blood pressure.

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



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



Legend: Enough balance is considered if the standardized difference is <10%.
Abbreviations: CNS, cerebrovascular disease; CPVD, cardiovascular and peripheral vascular disease; def, deficiency; GI, gastrointestinal; HDD, Hypertension Daily Dose; Med., medication; SBP, systolic blood pressure.

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