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). 


**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, 303.00-303.93                                                                                                                                                    |
| **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                    | 260-269.7, 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, 596.5-596.55, 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 |
|                                            | Methyl dopa | 250 | 500 | 1000 |
|                                            | Reserpine | 0.05 | 0.125 | 0.25 |
| Thiazide-like diuretics                    | Chlorthalidone | 12.5 | 25 | 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 |
| Drug           | Dose 0.5 | Dose 1   | Dose 2   |
|----------------|---------|---------|---------|
| **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**    |         |         |         |
| Isosorbidedinitrate (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              |                           | 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)   |                           | 28,203 (15.3)               | 6,776 (23.0)             | 3,675 (23.5)            |
| Med count decrease (N=29,161)  |                           | 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.

* Reference group, defined as no dose or medication count change, respectively.

* 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 | Composite outcome | CV event       | Syncope       | Fall injury   |
|--------------------|------------------|----------------|---------------|--------------|
| Three-level 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 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*).

* 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 between baseline and follow-up period (mmHg) | 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)* | 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)* | 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 increase | ≥10 mmHg increase |
|-------------------|--------------------------------------|-------------------|
| By dose change    |                                       |                   |
| Stable treatment (N=84,714)* | 5,683 (6.7)                | 31,321 (37.0)     |
| Dose decrease (N=64,558) | 3,676 (5.7)                     | 29,658 (45.9)     |
| Dose increase (N=56,123) | 4,204 (7.5)                     | 21,656 (38.6)     |
| By medication count |                                       |                   |
| Stable treatment (N=166,032)* | 11,016 (6.6)                | 64,241 (38.7)     |
| Medication count decrease (N=25,166) | 1,301 (5.2)                 | 12,857 (51.1)     |
| Medication count increase (N=14,197) | 1,246 (8.8)                 | 5,337 (39.0)      |

**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.

* Reference group, defined as no dose or medication count change, respectively; displayed in italic to facilitate reading.

* p <0.001 for comparison with intensification.

* 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%.

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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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