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Incremental effects of antihypertensive drugs: instrumental variable analysis

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ABSTRACT

OBJECTIVES

To assess the incremental effects of adding extra antihypertensive drugs from a new class to a patient's regimen.

DESIGN

Instrumental variable analysis of data from SPRINT (Systolic Blood Pressure Intervention Trial). To account for confounding by indication—when treatments seem less effective if they are administered to sicker patients—randomization status was used as the instrumental variable. Patients' randomization status was either intensive (systolic blood pressure target <120 mm Hg) or standard (systolic blood pressure target <140 mm Hg) treatment. Results from instrumental variable models were compared with those from standard multivariable models.

SETTING

Secondary data analysis of a randomized clinical trial conducted at 102 sites in 2010-15.

PARTICIPANTS

9092 SPRINT participants with hypertension and increased cardiovascular risk but no history of diabetes or stroke.

MAIN OUTCOMES MEASURES

Systolic blood pressure, major cardiovascular events, and serious adverse events.

RESULTS

In standard multivariable models not adjusted for confounding by indication, addition of an antihypertensive drug from a new class was associated with modestly lower systolic blood pressure (−1.3 mm Hg, 95% confidence interval −1.6 to −1.0) and no change in major cardiovascular events (absolute risk of events per 1000 patient years, 0.5, 95% confidence interval −1.5 to 2.3). In instrumental variable models, the addition of an antihypertensive

drug from a new class led to clinically important reductions in systolic blood pressure (−14.4 mm Hg, −15.6 to −13.3) and fewer major cardiovascular events (absolute risk −6.2, −10.9 to −1.3). Incremental reductions in systolic blood pressure remained large and similar in magnitude for patients already taking drugs from zero, one, two, or three or more drug classes. This finding was consistent across all subgroups of patients. The addition of another antihypertensive drug class was not associated with adverse events in either standard or instrumental variable models.

CONCLUSIONS

After adjustment for confounding by indication, the addition of a new antihypertensive drug class led to large reductions in systolic blood pressure and major cardiovascular events among patients at high risk for cardiovascular events but without diabetes. Effects on systolic blood pressure persisted across all levels of baseline drug use and all subgroups of patients.

Introduction

Hypertension is a pervasive and growing threat to global health. The number of adults with hypertension has nearly doubled from 442 million to 874 million worldwide in the past 25 years.¹ Among those with hypertension, many take antihypertensive drugs from multiple classes (such as thiazide-type diuretics and angiotensin converting enzyme (ACE) inhibitors) to control their blood pressure and reduce cardiovascular risk.² Although the addition of a second (or third) class of antihypertensive drug to a patient's hypertension treatment regimen is done routinely in clinical practice, the incremental benefits and risks of each additional drug class remain controversial. It is commonly believed that the addition of a new drug class to a patient's regimen will result in progressively smaller reductions in blood pressure while increasing the risk of adverse events.³⁻⁵ Because of physiologic limitations or drug-drug interactions, escalation of the number of antihypertensive drugs has been postulated to produce diminishing benefits and increasing harms.⁶ Such concerns are particularly pronounced for older patients^{7,8} or those for whom some drugs might prove less effective, such as patients with resistant hypertension⁹⁻¹¹ or black patients.^{12,13} Others have argued that adding a drug from a new class that targets a distinct and complementary mechanism, however, could reduce blood pressure at lower doses of each drug, improving therapeutic benefit and lowering side effects.^{14,15}

Evidence to support diminishing benefits and increasing harms of adding antihypertensive drugs

WHAT IS ALREADY KNOWN ON THIS TOPIC

Patients with hypertension often require multiple antihypertensive drugs

Observational studies suggest that benefits diminish when additional antihypertensive drugs are prescribed

These results could be caused by confounding by indication—when treatments seem less effective if used in sicker patients

WHAT THIS STUDY ADDS

Addition of antihypertensive drugs from a new drug class results in large reductions in blood pressure that are similar in magnitude for patients already taking antihypertensive drugs from zero, one, two, or three or more drug classes

These results challenge the view that the effects of antihypertensive drugs will diminish with each added drug class

is problematic. Observational studies suggest that incremental improvements to hypertension control diminish across successively greater numbers of drugs^{16 17} and that beyond a certain point such gains might be accompanied by an increased risk of adverse events (such as injurious fall) and cardiovascular events (such as myocardial infarction).^{8 9 18 19} Yet these results could be confounded by indication. This occurs when a treatment seems harmful or less effective because it is used in sicker patients. Meta-analyses of randomized trials have relied largely on studies of monotherapy compared with dual combination therapy, with mixed conclusions regarding whether addition of a second drug class produces additive^{15 20} or diminishing²¹ incremental effects on systolic blood pressure. As a result, data are lacking on the incremental effects of successively higher numbers of antihypertensive drugs, particularly when the use of three or more drug classes is considered.⁵

The Systolic Blood Pressure Intervention Trial (SPRINT) presents a unique opportunity to study this question.²² The trial compared intensive blood pressure treatment (systolic blood pressure target <120 mm Hg) versus standard treatment (target <140 mm Hg). The trial was terminated early after it was found that intensive treatment substantially lowered the risk of major cardiovascular events and mortality. Nonetheless, concerns have been raised regarding an increased risk of some serious adverse events.²³ Understanding how these benefits and risks vary with an increasing number of antihypertensive drugs is critical to guide clinical practice. We conducted a secondary analysis of SPRINT data to evaluate the incremental effects of antihypertensive drugs. To account for confounding by indication, we performed an instrumental variable analysis, with random assignment to intensive versus standard treatment independently increasing the probability of another antihypertensive drug class being added to a patient's regimen.

Methods

Study data

We performed a secondary analysis of SPRINT data. SPRINT data are held by the National Heart, Lung, and Blood Institute (NHLBI) in a formal data repository intended to facilitate the sharing of data from clinical trials and observational studies (<https://biolincc.nhlbi.nih.gov/home/>).²⁵ Our research team had no relationship to the original trial. Data were made available to our research team through our participation in the *New England Journal of Medicine's* "SPRINT Data Analysis Challenge," a research competition intended to explore the benefits and challenges of sharing data from clinical trials.^{26 27} Data were made available on 1 November 2016, one year earlier than required by the NHLBI, participants of the challenge, who received institutional review board approval (or exemption) and signed a data use agreement. Our study was deemed exempt from review by the institutional review board of the University of Michigan. SPRINT

data are now available on the NHLBI repository to the public. Prior to analyzing SPRINT data, we created a study plan describing our overall study objectives and analytic strategy. We provide this study plan, as well as revisions we undertook on accessing and analyzing SPRINT data, in appendix 1 (source code available at github.com/adammarkovitz/sprint²⁸).

Study population

SPRINT included participants aged at least 50 with a systolic blood pressure of 130-180 mm Hg, no history of diabetes or stroke, and at least one cardiovascular risk factor (clinical or subclinical cardiovascular disease other than stroke or chronic kidney disease), a 10 year risk of cardiovascular disease of $\geq 15\%$ based on the Framingham risk score, or age 75 or older. We excluded any patients for whom we did not have at least one measure of the number of antihypertensive drugs used after baseline examination. We summarize these inclusion and exclusion criteria in appendix 2, as adapted from the original SPRINT analysis.²²

Outcomes

We followed SPRINT's protocol in selecting and defining our three primary study outcomes: systolic blood pressure; composite major cardiovascular events; and composite serious adverse events.²² Systolic blood pressure was defined as each patient's final recorded measurement. Major cardiovascular events were defined as a composite comprising myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes. Serious adverse events were defined as a composite comprising evaluations in an emergency department for hypotension, syncope, bradycardia, electrolyte imbalance, injurious fall, or hospital admissions for acute kidney injury or acute renal failure. Secondary outcomes included the individual components of composite major cardiovascular events, the individual components of composite serious adverse events, and diastolic blood pressure.

Exposure

Our exposure was the number of distinct antihypertensive classes of drugs prescribed at the final SPRINT visit. For example, a patient prescribed one thiazide-type diuretic and two β blockers would have been recorded as taking two drug classes. Conversely, a patient prescribed one thiazide-type diuretic, one β blocker, and one ACE inhibitor would have been recorded as taking three drug classes.

To account for confounding by indication, we performed an instrumental variable analysis to assess the incremental effects of antihypertensive drugs. We leveraged SPRINT's study design, in which a participant's random assignment to the intensive versus standard treatment arm independently increased the probability of another antihypertensive drug class being added. We then assessed if incremental effects varied with each added drug class by performing both

multivariable adjusted and instrumental variable analyses stratified by the number of antihypertensive drug classes at baseline.

Statistical analysis

We first analyzed associations between the number of distinct antihypertensive drug classes and outcomes using standard multivariable adjusted models. To account for observed differences across baseline antihypertensive drug use, we adjusted for a rich set of baseline characteristics including age, sex, race, body mass index (BMI), smoking, high density lipoprotein (HDL), serum creatinine, use of statin drugs, history of cardiovascular disease, and history of chronic kidney disease. We estimated ordinary least squares regression models for blood pressure analyses. We estimated Aalen additive hazards models for cardiovascular and adverse event analyses to account for the right censored nature of survival outcomes.²⁹ We specified robust standard errors with clustering at the trial site level.

We then performed instrumental variable models to deal with confounding by indication. We estimated two stage least squares models for our blood pressure analyses, estimating blood pressure as a function of predicted number of antihypertensive drug classes (because of randomization status) and covariates (described above). For our cardiovascular and adverse event models, we estimated a recently validated two stage additive hazards model.³⁰ We based statistical inferences from this model on 2000 non-parametric bootstrap samples to account for the combined statistical uncertainty of the first and second stage regressions (see appendix 3 for further details).

Next, we assessed if the incremental effects on blood pressure varied when a first, second, third, or fourth or more antihypertensive drug class was added to a patient's regimen. We conducted stratified analyses according to the baseline number of classes of antihypertensive drug and then compared whether these incremental effects differed across baseline strata (see appendix 3 for further details).

Finally, to confirm that our instrument (randomization status) met the three conditions for validity, we conducted analyses to verify that our instrument was highly correlated with the exposure (number of distinct classes of antihypertensive drug); was random (no confounding factor jointly affecting the instrument and outcome); and did not affect the outcome independent of the exposure. Because SPRINT patients and physicians were not blinded to randomization status (although study outcomes were adjudicated by blinded committee), we examined whether randomization led to differential exposure to other interventions (such as smoking cessation, dietary changes, more frequent blood pressure measurements) whose effects would be subsequently attributed to antihypertensive drugs. Specifically, we evaluated incremental effects among patients who were unlikely to receive behavioral interventions (namely—patients who at baseline were not obese or who had never smoked); incremental effects at times

we considered too early in the study period to be likely driven by behavioral interventions (namely—the three month visit); and incremental effects on total number of blood pressure measurements over the study period. We also tested the additive hazards model assumption that effects are additive and constant over time via non-parametric goodness of fit tests and plots of observed cumulative effect estimates (see appendix 3 for details).

Sensitivity analyses

In accordance with SPRINT's protocol,²² we evaluated variation in the incremental effects of antihypertensive drugs by estimating models stratified by the following patient characteristics: age, sex, race, obesity, smoking, history of cardiovascular disease, and history of chronic kidney disease. We also evaluated incremental effects of adding another drug class for patients already taking drugs from four or more distinct drug classes. We also performed sensitivity analyses estimating instrumental variable models without further adjustment for patient covariates. Finally, we estimated reduced form models of the effect of randomization status on the number of distinct drug classes prescribed and associated changes in systolic blood pressure.

Statistical analyses were performed with Stata version 14.1 and the R *timereg* and *survival* packages.³¹

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no specific plans to disseminate the results of the research to study participants or the relevant patient community beyond the usual channels of publication.

Results

Patients' characteristics and use of antihypertensive drugs

We identified 9092 SPRINT patients who met our inclusion criteria (fig A in appendix 4 shows the CONSORT diagram). Median follow-up was 3.25 years. At baseline, 861 (9%) patients were not taking any antihypertensive drugs, 2662 (29%) were taking drugs from one drug class, 3201 (35%) were taking drugs from two distinct classes, and 2368 (26%) were taking drugs from three or more distinct classes (table 1). All patients' characteristics except smoking status varied across categories of baseline drug use. By the end of the study, 855 (19%) and 242 (5%) patients in the intensive treatment group were taking drugs from four and five distinct drug classes, respectively (online appendix table 2).

Instrument validity

We first confirmed that our instrumental variable analysis was necessary: standard multivariable adjusted models yielded biased estimates relative to those from instrumental variable models through

Table 1 | Baseline characteristics of SPRINT study participants by number of distinct antihypertensive drug classes at baseline. Figures are means (SD) unless stated otherwise

Characteristics	Total (n=9092)	Antihypertensive drug classes at baseline*				P value
		None (n=861)	One (n=2662)	Two (n=3201)	Three or more (n=2368)	
Age (years)	67.8 (9.4)	65.6 (9.5)	67.6 (9.3)	68.0 (9.5)	68.7 (9.2)	<0.001
No (%) of women	3217 (35.4)	226 (26.2)	942 (35.4)	1151 (36.0)	898 (37.9)	<0.001
No (%) black†	2856 (31.4)	216 (25.1)	759 (28.5)	1020 (31.9)	861 (36.4)	<0.001
BMI	29.9 (5.8)	29.0 (5.6)	29.1 (5.5)	30.0 (5.7)	30.9 (6.0)	<0.001
Fasting HDL cholesterol (mmol/L)	1.37 (0.38)	1.36 (0.36)	1.40 (0.39)	1.37(0.38)	1.33 (0.35)	<0.001
Serum creatinine (µmol/L)	97.24 (26.52)	88.4 (17.68)	88.4 (26.52)	97.24 (26.52)	106.08 (35.36)	<0.001
No (%) using statin	3970 (43.7)	175 (20.3)	1097 (41.2)	1497 (46.8)	1201 (50.7)	<0.001
No (%) of ever smokers	5096 (56.0)	497 (57.7)	1459 (54.8)	1790 (55.9)	1350 (57.0)	0.31
No (%) with history of cardiovascular disease	1524 (16.8)	72 (8.4)	335 (12.6)	604 (18.9)	513 (21.7)	<0.001
No (%) with history of chronic kidney disease‡	2572 (28.3)	115 (13.4)	617 (23.2)	937 (29.3)	903 (38.1)	<0.001
Baseline blood pressure (mm Hg):						
Systolic	139.7 (15.6)	145.1 (15.4)	139.9 (15.3)	138.7 (15.6)	138.8 (15.7)	<0.001
Diastolic	78.1 (11.9)	84.2 (11.9)	79.1 (11.2)	77.5 (11.8)	75.7 (12.1)	<0.001

BMI=body mass index; HDL=high density lipoprotein.

*Classes: thiazide diuretics; loop diuretics; potassium sparing diuretics, aldosterone receptor blockers, β blockers; β blockers with intrinsic sympathomimetic activity; combined α and β blockers; angiotensin converting enzyme (ACE) inhibitors; angiotensin II receptor blockers (ARB); non-dihydropyridine calcium channel blockers; dihydropyridine calcium channel blockers; α -1 blockers; central α -2 agonists or other centrally acting drugs; direct vasodilators, direct renin inhibitors.

†Self reported. Black race includes non-Hispanic and Hispanic black participants.

‡Participants with no history of chronic kidney disease includes some participants with unknown disease status at baseline.

the C or difference-in-Sargan test of endogeneity ($F_{1,101}=1547$; $P<0.001$).³² We next verified that our instrument met the three conditions for validity.

First, randomization status was highly correlated with the number of antihypertensive drugs from distinct classes ($F_{1,101}=1065$; $P<0.001$), where instruments with F statistics above 10 are considered strong (fig B and tables B and C in appendix 4).³³ Second, SPRINT's randomization of intensive versus standard treatment was successful, with patient characteristics balanced across the two groups (table D in appendix 4). Third, we verified that randomization did not seem to affect patient outcomes independent of antihypertensive drugs by confirming additive incremental effects held true for patient populations regardless of their propensity to receive behavioral interventions—that is, history of smoking versus no history of smoking, obese versus non-obese (figures C4 and C5 in appendix 4); similarly additive effects occurred at times too early to be driven largely by behavioral interventions—that is, the study's three month visit versus averaged over the entire study period (table E and fig D and E in appendix 4); and incremental changes in use of antihypertensive drugs did not affect the total number of blood pressure measurements, which could otherwise induce a spurious relation between changes in drug use and blood pressure (table F in appendix 4). Collectively, these results suggest that the effect of randomization status operated through changes in the use of antihypertensive drugs and not through non-pharmacologic changes. Additionally, we confirmed that our models did not violate the assumption that incremental effects of antihypertensive drugs and other covariates were constant and additive over time (table G and fig F in appendix 4).

Systolic blood pressure.

Figure 1 shows the incremental effects of adding antihypertensive drugs of another class on systolic

blood pressure. In standard multivariable models, addition of antihypertensive drugs was associated with modestly lowered systolic blood pressure (-1.33 mm Hg, 95% confidence intervals -1.63 to -1.03). These effects diminished with each additional drug class (interaction term $P<0.001$, table H in appendix 4). In instrumental variable models, we estimated a much larger effect of antihypertensive drugs on reductions of systolic blood pressure (-14.42 mm Hg, -15.57 to -13.27). These effects remained large and similar in magnitude when a drug from a new class was added for patients taking drugs from zero (-13.90 mm Hg, -16.29 to -11.50), one (-14.22 mm Hg, -16.00 to -12.43), two (-14.75 mm Hg, -16.41 to 13.08), or at least three (-15.11 mm Hg, -17.62 to -12.61) (fig 1 and table H in appendix 4). The pattern was similar for diastolic blood pressure: the addition of a new antihypertensive drug class was associated with small diminishing effects in standard multivariable models and with large approximately additive effects in instrumental variable models (table H and fig G in appendix 4).

Major cardiovascular events

Figure 2 shows the incremental effects of adding another antihypertensive drug class on major cardiovascular events. In standard multivariable models, antihypertensive drugs were not associated with differences in the risk of composite cardiovascular events (absolute risk 0.47 events per 1000 patient years; 95% confidence interval -1.45 to 2.27) or any component outcomes (fig H in appendix 4). Conversely, our instrumental variable models suggested that antihypertensive drugs caused a large reduction in risk of composite major cardiovascular events (-6.23 , -10.87 to -1.30 ; fig 2). These effects did not vary systematically across levels of baseline drug use. In these models, addition of a drug class also reduced risk of heart failure (-3.97 , -6.60 to -1.45), death from cardiovascular

Table 2 | Incremental effects (95% confidence interval) of antihypertensive drugs across clinical and demographic subgroups

Subgroup	Systolic blood pressure (mm Hg)	Major cardiovascular events (per 1000 person years)	Serious adverse events (per 100 person years)	No of patients
Multivariable adjusted models*				
Overall	-1.3 (-1.6 to -1)	0.5 (-1.5 to 2.3)	4.9 (-2.1 to 12.1)	9092
Age (years):				
<75	-1.6 (-1.9 to -1.2)	0.5 (-1.2 to 2.2)	7.2 (0.2 to 14.2)	6535
≥75	-0.8 (-1.3 to -0.3)	0.7 (-4.7 to 5.9)	8.4 (-8.9 to 26.2)	2557
Sex:				
Women	-1.5 (-1.9 to -1.1)	0.3 (-2 to 2.7)	2.2 (-6.6 to 10.7)	5875
Men	-1.1 (-1.6 to -0.7)	0.8 (-1.9 to 3.7)	15.8 (4.5 to 27.4)	3217
Race:				
Black	-1.5 (-1.8 to -1.2)	1.4 (-1 to 3.9)	11.5 (3.5 to 20.4)	6236
Non-black	-1 (-1.4 to -0.5)	-1.4 (-4.2 to 1.4)	-1.8 (-13.2 to 9.2)	2856
Obesity:				
Non-obese	-1.4 (-1.8 to -1.1)	0.4 (-1.9 to 2.6)	6.5 (-0.7 to 13.6)	7582
Obese	-1.1 (-1.7 to -0.5)	1.2 (-2.2 to 4.7)	9.1 (-7 to 26.4)	1569
Smoking status:				
Never smoker	-1.1 (-1.5 to -0.7)	2.7 (0.1 to 5.6)	5 (-4.1 to 14.5)	3996
Ever smoker	-1.5 (-1.9 to -1.1)	-1.3 (-3.9 to 1.3)	8.9 (-1 to 18.7)	5096
History of cardiovascular disease:				
Yes	-1.5 (-1.8 to -1.1)	0.7 (-1.1 to 2.5)	8.9 (1.8 to 15.9)	7568
No	-0.7 (-1.4 to 0)	-0.9 (-8.2 to 6.4)	-4.1 (-29.6 to 22.2)	1524
History of chronic kidney disease:				
No	-1.7 (-2.1 to -1.4)	0.5 (-1.4 to 2.5)	4.8 (-2.6 to 12.2)	6520
Yes	-0.4 (-0.9 to 0.1)	-0.3 (-4.5 to 4)	11.4 (-4.9 to 28)	2572
Instrumental variable models*				
Overall	-14.4 (-15.6 to -13.3)	-6.2 (-10.9 to -1.3)	12.7 (-5.0 to 31.0)	9092
Age (years):				
<75	-14.7 (-16 to -13.4)	-3.4 (-7.9 to 1.1)	16.7 (-0.9 to 34.1)	6535
≥75	-13.7 (-15.7 to -11.7)	-15.6 (-30.9 to -1.4)	0.1 (-47.5 to 44.5)	2557
Sex:				
Female	-13.7 (-14.9 to -12.6)	-6.8 (-12.5 to -0.9)	4.9 (-15.4 to 25.3)	5875
Male	-15.8 (-17.8 to -13.8)	-4.9 (-13.4 to 3.5)	30.3 (-1.5 to 61.5)	3217
Race†:				
Black	-14.6 (-15.9 to -13.3)	-6.4 (-12.8 to -0.2)	19.5 (-2.4 to 41.2)	6236
Not black	-14.1 (-15.8 to -12.4)	-5.5 (-13 to 2.1)	-1.8 (-30.3 to 26.5)	2856
Obesity‡:				
Non-obese	-14.5 (-15.6 to -13.3)	-6.9 (-12.2 to -1.6)	12.2 (-7.1 to 31.1)	7582
Obese	-13.7 (-16.1 to -11.2)	-2 (-13.2 to 8.5)	14.1 (-27.2 to 58.9)	1569
Smoking status:				
Never smoker	-14.6 (-16.3 to -12.9)	-4.9 (-11.5 to 1.6)	17.4 (-5.8 to 43.3)	3996
Ever smoker	-14.3 (-15.5 to -13.0)	-7.3 (-14.1 to -0.3)	9.6 (-14.3 to 33.4)	5096
History of cardiovascular disease:				
Yes	-14.5 (-15.8 to -13.2)	-6.9 (-11.7 to -2.5)	11.8 (-5.5 to 28.9)	7568
No	-14.0 (-16.4 to -11.5)	-0.8 (-21.5 to 18.2)	22.2 (-42.2 to 89.9)	1524
History of chronic kidney disease§:				
No	-14.4 (-15.6 to -13.2)	-6.9 (-12 to -2.1)	17.7 (-0.3 to 35.4)	6520
Yes	-14.6 (-16.9 to -12.3)	-5 (-18.3 to 7.9)	-6.6 (-48.8 to 38.7)	2572

*All models included following covariates: age, sex, race, body mass index (BMI), smoking, high density lipoprotein (HDL) cholesterol, serum creatinine, use of statin drugs, history of cardiovascular disease, and history of chronic kidney disease. Covariates (such as BMI) were omitted from models stratified by dichotomized versions of respective covariate (such as obese versus non-obese).

†Self reported. Black race includes Hispanic black and black.

‡Defined as BMI ≥35.

§No history of chronic kidney disease includes some participants with unknown chronic kidney disease status at baseline.

causes (-1.85, -3.62 to -0.05), and death from any cause or a composite cardiovascular outcome (-6.93, -12.35 to -1.62) (fig H in appendix 4).

Serious adverse events

The addition of antihypertensive drugs from a new class was not associated with increased risk of composite serious adverse events in either standard multivariable models (absolute risk 4.89 events per 1000 patient years, 95% confidence interval -2.11 to 12.09) or instrumental variable models (12.66, -5.04 to 31.05; fig 3). Our instrumental variable models, however, suggested that addition of antihypertensive

drugs increased the risk of three component adverse events: hypotension (4.34, 1.44 to 7.28), electrolyte imbalance (5.51, 2.23 to 8.88), and acute kidney injury or renal failure (8.26, 4.46 to 12.30; fig H in appendix 4).

Sensitivity analyses

Table 2 shows the incremental effects of antihypertensive drugs stratified by prespecified clinical and demographic characteristics. We did not observe consistent heterogeneity in the effects on blood pressure, cardiovascular events, or adverse events. In analyses stratified by both baseline drug use

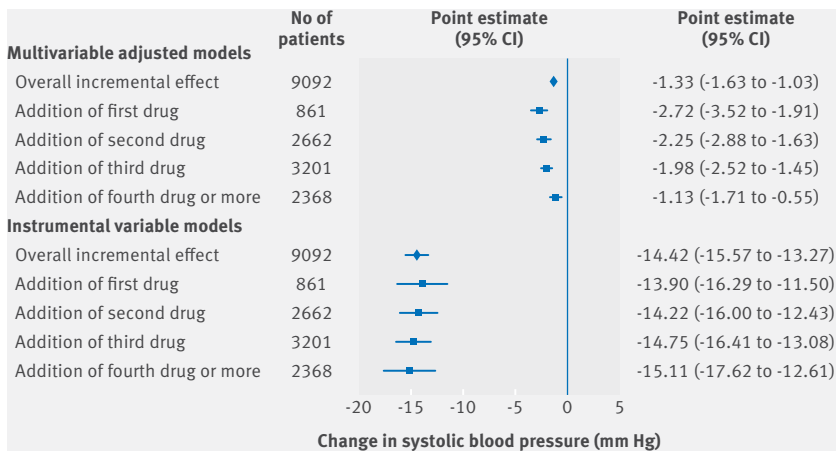


Fig 1 | Incremental effects of antihypertensive drug classes on systolic blood pressure. Diamonds represent point estimates from pooled models. Squares represent point estimates from models stratified by baseline number of drug classes. Systolic blood pressure was each patient's final recorded measurement. Antihypertensive drug classes are measured at baseline and at latest visit for which there was also recorded measurement of blood pressure. Multivariable adjusted models estimated with ordinary least squares regression. Instrumental variable models were estimated with two stage ordinary least squares regression

and patients' characteristics, we observed consistent additive reductions in systolic blood pressure within each patient subgroup, as defined by age, sex, race, obesity, smoking, history of cardiovascular disease, or history of chronic kidney disease (table I and fig C1-7 in appendix 4). Incremental effects were robust across our four alternative specifications: when the exposure was defined by the number of drug classes at the three month visit (table E and fig D in appendix 4);

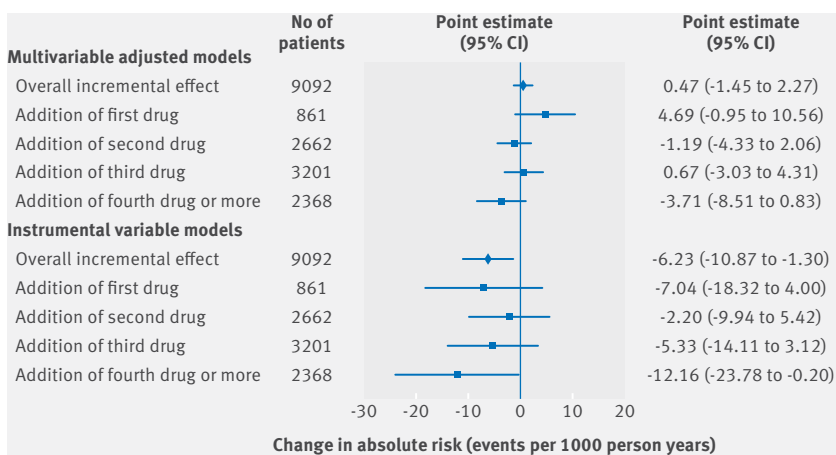


Fig 2 | Incremental effects of antihypertensive drug classes on major cardiovascular events. Diamonds represent point estimates from pooled models. Squares represent point estimates from models stratified by baseline number of drug classes. Major cardiovascular events defined as composite including myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes.²¹ Antihypertensive drug classes measured at baseline and at each patient's final visit. To minimize reverse causality, last recorded value of drug classes before incidence of event was used for patients who experienced a major cardiovascular event. For standard multivariable models, additive hazards models estimated to account for right censored nature of survival outcomes.²⁶ For instrumental variable models, recently validated two stage approach was implemented,²⁷ substituting predicted number of drug classes from first stage (function of randomization status and covariates) into additive hazards model

when the exposure was defined by the mean number of drug classes over the study period (table E and fig E in appendix 4); when no adjustment for patient covariates was made (fig J in appendix 4); and when a new drug class was given to patients already taking four or more distinct drug classes (fig K in appendix 4). In reduced form analyses, we found that randomization to the intensive group resulted in greater changes to both antihypertensive drug use and blood pressure among patients who were taking drugs from relatively fewer classes at baseline (table J in appendix 4). This likely reflects the fact that patients taking fewer drug classes at baseline had higher baseline blood pressure (table 1) and thus necessitated greater treatment intensification (and blood pressure reductions) to reach either the standard or intensive blood pressure targets.

Discussion

Principal findings

Our instrumental variable analysis of SPRINT data found that adding antihypertensive drugs from a new drug class to existing treatment led to clinically important reductions in systolic blood pressure and the risk of major cardiovascular events but no differences in serious adverse events. Incremental reductions in systolic blood pressure remained large and similar in magnitude with addition of drugs from a new class for patients already taking zero, one, two, or three or more distinct drug classes. This finding was consistent for each patient subpopulation tested. Collectively, these findings suggest that the incremental effects of antihypertensive drugs persist across clinically important subgroups and for up to four or more classes of drugs.

Comparison with other studies.

Physicians' belief that adding antihypertensive drug classes will result in progressively smaller reductions in blood pressure^{3-6 34} might decrease their likelihood of prescribing additional drugs to patients with hypertension. Investigators, however, have proposed two competing models: additive effects, in which the combined effect of antihypertensive drugs is equal to the sum of the drugs' individual effects,¹⁵ and synergistic effects, in which the rational addition of a drug class targeting a new complementary mechanism yields effects greater than the sum of the drugs' individual effects.³⁵ Meta-analyses of clinical trials comparing dual versus monotherapy have found either additive^{15 20} or diminishing effects,²¹ while safety and efficacy trials of some specific triple combination therapies have found short term effects that are less than additive.^{9 36-38}

Our study clarifies and extends these prior analyses, leveraging SPRINT's random assignment to evaluate longer run effects across a broad range of antihypertensive drug classes. We found large reductions in blood pressure that do not decrease as each extra drug class is added. Further, these additive effects were robust across a wide range of patient characteristics. Our findings are particularly relevant

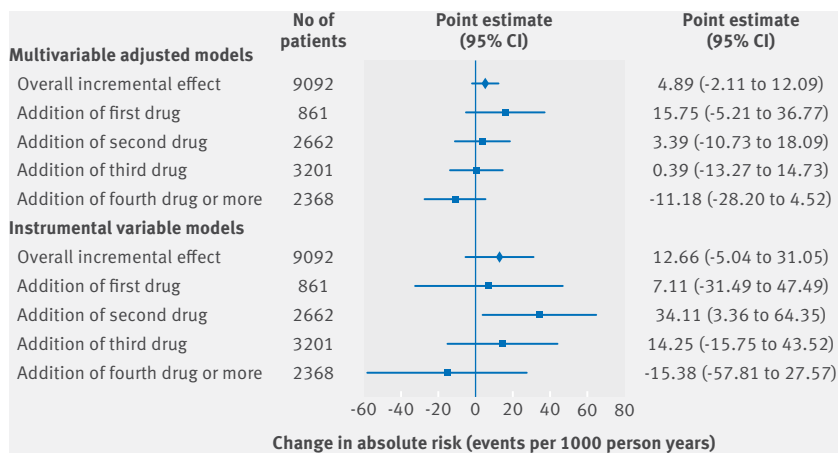


Fig 3 | Incremental effects of antihypertensive drug classes on serious adverse events. Diamonds represent point estimates from pooled models. Squares represent point estimates from models stratified by baseline number of drug classes. Serious adverse events defined as composite including emergency department evaluations for hypotension, syncope, bradycardia, electrolyte imbalance, injurious fall, or admissions for acute kidney injury or acute renal failure.²¹ Antihypertensive drug classes measured at baseline and at each patient's final visit. To minimize reverse causality, last recorded value of drug classes before incidence of event was used for those patient who experienced serious adverse event. For standard multivariable models, additive hazards models were estimated to account for right censored nature of survival outcomes.²⁶ For instrumental variable models, recently validated two stage approach was implemented,²⁷ substituting predicted number of drug classes from first stage (function of randomization status and covariates) into additive hazards model

given longstanding concerns about patients who might have fewer effective treatment options, including black patients (because of decreased responses to ACE inhibitors) and older patients (because of increased resistant hypertension).^{10 39 40} The large additive reductions in systolic blood pressure we observed in patients aged over 75 could also help to explain the strong mortality benefits previously reported in older SPRINT patients.⁴¹ This last observation is particularly important given the rising proportion of adults now using at least three classes of antihypertensive drugs.⁴²

There is a paucity of direct evidence on the incremental effects of antihypertensive drugs on risk of cardiovascular events and serious adverse events.¹⁵ Safety and efficacy trials of triple combination therapy have found diminishing short term (eight to 12 weeks) effects on risk of adverse events.^{9 36-38} Our study adds new evidence on the longer run effects of antihypertensive drugs, with the median follow-up of 3.25 years in SPRINT. Similar to the original SPRINT study, we found that the addition of an antihypertensive drug reduces the risk of composite major cardiovascular events (driven by decreased risk of heart failure) while increasing the risk of hypotension, electrolyte imbalance, and acute kidney injury or renal failure. More recently, a SPRINT subgroup analysis of patients without chronic kidney disease at baseline found that intensive blood pressure management was associated with increased incidence of chronic kidney disease.⁴³ This risk, however, was outweighed by benefits to cardiovascular risk and all cause mortality.⁴³ In stratified analyses, we found

that the incremental effects on cardiovascular risk and risk of adverse events, though estimated with less precision, did not systematically differ across levels of baseline drug use.

Strengths and limitations of study

The key strength of this study is its use of randomization from a clinical trial to examine a question critical to clinical practice but typically confounded by indication: what are the incremental effects of adding antihypertensive drugs from a new drug class to a patient's current regimen? By performing an instrumental variable analysis in the context of a clinical trial, we harnessed a particularly strong instrument—randomization status itself—to assess the effects of otherwise non-random changes in prescribing behavior. SPRINT's study design also allowed us to examine these incremental effects across a wider range of baseline drug use, with a more diverse set of drug classes, and over a longer period of follow-up than is typically assessed in trials of combination drug therapy. In addition, the excellent data capture in the SPRINT trial limits bias from non-random samples attrition.

We performed an instrumental variable analysis of SPRINT instead of an intention to treat analysis because it would not have allowed us to estimate the incremental effect of antihypertensive drugs. This is because the "treatment" to which SPRINT randomized patients was not antihypertensive drugs per se—it was a more intensive target systolic blood pressure (<120 mm Hg). Thus, a stratified intention to treat analysis answers an important but different question: does the effect of randomization to an intensive versus standard blood pressure goal vary across baseline number of drug classes? Conversely, by performing an instrumental variable analysis, we instead used randomization as an instrument to answer a related but clinically distinct question: does the effect of adding an extra drug class vary with each added drug?

In comparing results from our instrumental variable models with those from standard multivariable regression models, we shed light on a pervasive source of bias in observational medical studies—confounding by indication. This confounding dramatically changed estimates in our study, biasing our estimates to such an extent that antihypertensive drugs seem to have almost no effect on blood pressure (from -1.3 mm Hg in standard models to -14.4 mm Hg in instrumental variable models) and increase the risk of major cardiovascular events (from 0.5 per 1000 patient years in standard models to -6.2 events per 1000 patient years in instrumental variable models). Importantly, this bias persists after adjustment for a rich set of baseline clinical covariates that are not always available to researchers, including BMI, smoking status, high density lipoprotein cholesterol, serum creatinine, statin use, and history of cardiovascular and chronic kidney disease. The nature of confounding by indication in our study predicts the direction of this bias: because the omitted variable (more severe

hypertension, increased cardiovascular risk) is positively related to both the exposure (number of antihypertensive drug classes) and the outcome (blood pressure, incidence of cardiovascular events), failure to account for the confounder will positively bias estimates of the true effect (described by the “omitted variable bias formula”⁴⁴). Conversely, in instrumental variable models that are robust to confounding by indication, we find that adding antihypertensive drug classes leads to large decreases in blood pressure and risk of cardiovascular events.

Several important limitations to our study also merit discussion. First, because we observed only the number of prescribed classes of drug and not drug dose or adherence, we cannot exclude the possibility that randomization led to differential changes in drug dose or adherence whose effects would be subsequently attributed to changes in the number of drug classes. It is unclear, however, whether randomization to the intensive group and subsequent addition of a new drug class would be accompanied by a clinician increasing the dose of the first drug to lower blood pressure further (negatively biasing estimates away from zero by attributing this dose change to the addition of a new drug class) or lowering the dose of either the first or added drug class to take advantage of complementary mechanisms and widening therapeutic windows (positively biasing estimates toward zero). Thus, the net effect in our study remains uncertain. These data limitations also precluded our ability to analyze whether certain drug combinations or intensification sequences were more successful than others. Nonetheless, supplemental analysis suggests that the effects of antihypertensive drugs on blood pressure do not attenuate for patients already taking drugs from at least four or more distinct drug classes (fig K in appendix 4). Moreover, the original SPRINT analysis reported a diverse range of prescribed drug classes: along with first line agents such as thiazide-type diuretics (67% of patients by the study’s end), calcium channel blockers (57%), and ACE inhibitors/angiotensin II receptor blockers (77%), SPRINT patients were also prescribed β blockers (41%), aldosterone receptor blocker diuretics (9%), and direct vasodilators (7%), among others.²² Given that 19% and 5% of patients in the intensive group were taking four and five drug classes, respectively, by the end of the study, these data suggest that the additive effects we observed were not attributable to first line agents.

Second, we could not ascertain whether patients in the intensive group were differentially exposed to behavioral interventions such as dietary changes or smoking cessation. Nonetheless, sensitivity analyses showed similar effects among those patients who were unlikely to receive such behavioral interventions (namely—those who were not obese and were non-smokers at baseline) and at times too early to be likely driven by non-pharmacologic means (namely—at the three month visit). Third, our results might not generalize to several high risk populations excluded from SPRINT, including those with diabetes or prior

stroke.^{45 46} Similarly, because SPRINT patients were screened for non-adherence, incremental effects might be smaller in real world settings where adherence is lower.^{5 47} While our estimate of systolic blood pressure is larger than those previously reported for a “standard dose” (reductions of 14.8 v 9.1 mm Hg,²⁰ respectively), our results parallel SPRINT’s finding that the intensive treatment arm achieved a 14.8 mm Hg greater reduction than the standard treatment arm and that doing so, on average, required prescription of one more drug class.²² Fourth, because our instrumental variable analysis relied on randomization to target systolic blood pressures for causal inference, we could not assess whether incremental effects of a defined blood pressure change varied according to the level of a patient’s achieved blood pressure (for example, 120 v 130 mm Hg). Finally, our analyses of cardiovascular and adverse events might have had insufficient power to detect variation in incremental effects across levels of baseline drug use. We did not, however, see a clear pattern of evidence suggestive of effect modification by baseline drug use.

Conclusions and policy implications.

These limitations notwithstanding, our findings provide important new evidence on the incremental effects of antihypertensive drugs. Our results challenge the view that adding antihypertensive drugs will result in progressively diminishing effects on blood pressure and cardiovascular events. Our findings provide patients and clinicians with more rigorous nuanced insight into optimal management of hypertension. For clinical and health services researchers, we have shown the importance of accounting for confounding by indication and the value of using randomization from clinical trials to understand important causal pathways. For policymakers, our results inform efforts to model and improve cost effective treatment for hypertension, a condition with annual costs exceeding \$370bn globally.⁴⁸ Evidence on the incremental effects of combinations of three or more antihypertensive drugs is particularly critical for evaluating the cost effectiveness of widespread treat to target recommendations and the polypharmacy that such policies require.⁵

Collectively, these findings suggest that antihypertensive drugs can be used to lower blood pressure effectively with the addition of a first, second, third, or fourth class of drug or more to a patient’s regimen. Future research on this issue should focus on developing experimental evidence on how the strong additive reductions in blood pressure observed in our study could translate to patient benefit and harm.

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Ethical approval: Not required.

Data sharing: SPRINT data are available on the NHLBI repository (<https://biolincc.nhlbi.nih.gov/home/>). Source code for replicating this analysis is available at <https://github.com/adammarkovitz/sprint>.⁴⁸

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Appendix 1: Study plan

Appendix 2: Inclusion and exclusion criteria

Appendix 3: Supplementary methods

Appendix 4: Supplementary figures and tables