CLINICAL RESEARCH STUDY

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Optimal Systolic Blood Pressure Target in Resistant and Non-Resistant Hypertension: A Pooled Analysis of Patient-Level Data from SPRINT and ACCORD

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ABSTRACT

BACKGROUND: Prior studies suggest benefits of blood pressure lowering on cardiovascular risk may be attenuated in patients with resistant hypertension compared with the general hypertensive population, but prospective data are lacking.

METHODS: We assessed intensive (<120 mm Hg) versus standard (<140 mm Hg) systolic blood pressure targets on adverse outcome risk according to baseline resistant hypertension status, using Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Systolic Blood Pressure Intervention Trial (SPRINT) patient-level data. Patients were categorized as having baseline apparent resistant hypertension (blood pressure ≥130/80 mm Hg while using 3 antihypertensive drugs or use of ≥4 drugs regardless of blood pressure) or non-resistant hypertension (all others). Cox regression was used to assess effects of treatment assignment, resistant hypertension status, their interaction, and other covariates, on first occurrence of 2 outcomes: myocardial infarction, stroke, cardiovascular death ± heart failure, and the same outcomes plus all-cause death, individually.

RESULTS: Among 14,094 patients, 2710 (19.2%) had baseline apparent resistant hypertension. In adjusted models, an intensive target reduced risk of both outcomes (myocardial infarction/stroke/cardiovascular death: hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.71-0.93; myocardial infarction/stroke/heart failure/cardiovascular death: HR 0.78; 95% CI, 0.69-0.88) as well as stroke (HR 0.72; 95% CI, 0.55-0.94) and heart failure (HR 0.73; 95% CI, 0.59-0.91). An intensive target also appeared to reduce myocardial infarction, cardiovascular death, and all-cause death risk. Benefits were observed irrespective of baseline resistant hypertension status.

CONCLUSIONS: Our findings provide the first evidence to support guidance to treat resistant hypertension to the same blood pressure goal as non-resistant hypertension.

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KEYWORDS: ACCORD; Antihypertensive agents; Blood pressure; Hypertension; Resistant hypertension; SPRINT

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Over 1 billion individuals worldwide have hypertension, the leading reversible risk factor for major adverse cardiovascular outcomes and death.[1,2] Of these individuals, 10% to 20% are thought to have resistant hypertension, a high-risk phenotype defined by uncontrolled blood pressure despite treatment with ≥3 antihypertensive drugs, or need for ≥4 antihypertensive drugs regardless of blood pressure.[3] Prior studies, defining uncontrolled blood pressure as ≥140/90 mm Hg, have consistently documented excess risk of adverse cardiovascular outcomes and death,[4-10] and impaired quality of life,[11,12] comparing resistant versus non-resistant hypertension.

Although management of the general hypertensive population has been extensively studied, remarkably little evidence guides treatment in resistant hypertension. In particular, prospective studies are lacking on the most appropriate blood pressure target in this population. Absent such data, recommendations for the general hypertensive population are extrapolated to resistant hypertension.[13] However, empiric evidence suggests that benefits of blood pressure lowering on cardiovascular outcomes in the general population may not extend fully to resistant hypertension.[4,5,10,14,15] For example, prior studies have observed no difference in outcomes comparing controlled (blood pressure <140/90 mm Hg) with uncontrolled resistant hypertension,[5] that achieving blood pressure <140/90 mm Hg reduces cardiovascular risk by half as much in resistant hypertension compared to non-resistant hypertension,[14] and that greater blood pressure control portends worse renal outcomes in resistant versus non-resistant hypertension.[15] Additionally, more intensive therapy is associated with greater rates of cardiovascular events[4] and lower quality of life[12] in resistant hypertension. Nevertheless, all prior studies have examined the relationship between blood pressure and outcomes in observational cohorts, or randomized controlled trials treated as observational cohorts, and it remains unclear to what extent these findings impact patient care.

Therefore, we investigated the relationship between resistant hypertension, systolic blood pressure target, and adverse outcomes, pooling patient-level data from the Systolic Blood Pressure Intervention Trial (SPRINT)[16] and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[17] both of which prospectively tested intensive (<120 mm Hg) versus standard (<140 mm Hg) systolic blood pressure targets among diverse high-risk hypertensive populations. We hypothesized that intensive systolic blood pressure lowering would confer similar benefits on cardiovascular outcomes and death in resistant and non-resistant hypertension.

CLINICAL SIGNIFICANCE

- Data regarding the optimal blood pressure target in treatment-resistant hypertension are sparse and inconsistent, and current recommendations are extrapolated from the general hypertensive population.
- Among 14,094 SPRINT and ACCORD-BP participants, 19.2% had baseline apparent treatment-resistant hypertension using the revised 2017 hypertension guideline definition.
- A systolic blood pressure target <120 mm Hg, compared to a target <140 mm Hg, reduced risk of most major cardiovascular outcomes and death, irrespective of baseline treatment-resistant hypertension status.

METHODS

The design and principal findings of SPRINT[16,18] and the ACCORD blood pressure trial (ACCORD-BP)[17,19] are published. Briefly, SPRINT was a prospective, randomized, open-label, blinded-endpoint (PROBE) trial enrolling 9361 hypertensive individuals with elevated cardiovascular risk, but without diabetes or stroke. Participants were assigned to a target systolic blood pressure <120 mm Hg ("intensive") or <140 mm Hg ("standard"). They were aged ≥50 years, with hypertension and ≥1 additional cardiovascular risk factor. SPRINT follow-up was terminated early due to a clear benefit with the intensive systolic BP target.[16] ACCORD was also a PROBE-design trial enrolling 10,251 high-risk individuals with diabetes from the United States and Canada. The design included a 2 × 2 factorial to assess glycemic control in all participants and of these, 4733 were simultaneously enrolled in ACCORD-BP, testing the same blood pressure targets used in SPRINT. Major inclusion criteria were type 2 diabetes mellitus and age ≥40 years with cardiovascular disease or ≥55 years without cardiovascular disease. The Supplement (available online) contains additional eligibility criteria for both trials.

Cohort Assembly

Patient-level data were acquired from the National Heart, Lung, and Blood Institute pursuant to a data use agreement after institutional review board approval. Complete ACCORD-BP data were available, whereas only data presented in the primary outcome paper[16] were available from SPRINT, including baseline measures, follow-up blood pressure and antihypertensive use (number only, not specific drugs/classes), and outcomes.

Prior to pooling both trials, we tested study by treatment assignment interactions for all outcomes to assess heterogeneity. Thereafter, data were pooled and harmonized. Because the available data from SPRINT did not include information on specific drug use, dosing, or adherence, we categorized patients as having apparent resistant hypertension (denoting an inability to exclude pseudoresistance) or non-resistant hypertension at baseline. Apparent resistant hypertension was defined per prevailing guidelines[13] as using ≥3 antihypertensive drugs with blood pressure ≥130 mm Hg systolic or ≥80 mm Hg diastolic, or use of

≥ 4 antihypertensives regardless of blood pressure. For both trials, blood pressures represented the average of 3 clinic measurements via automated Omron 907 monitors (Omron Healthcare, Kyoto, Japan) with patients seated after 5 minutes of quiet rest. Patients not meeting apparent resistant hypertension criteria were considered to have non-resistant hypertension.

To assess possible influence of misclassifying pseudoresistant hypertension as resistant hypertension, we also performed sensitivity analyses by categorizing resistant hypertension status at the 6-month visit (or immediate prior visit if 6-month data were unavailable) rather than the baseline visit, under the assumption that in-trial blood pressure measurement and antihypertensive medication prescribing would have greater standardization per study protocols and that patients would have greater in-trial adherence. Patients with an event before the 6-month visit were excluded from these analyses.

Outcomes

The SPRINT primary outcome was first occurrence of nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, heart failure, or acute coronary syndrome, whereas the ACCORD-BP primary outcome was first occurrence of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death; heart failure was a secondary outcome and acute coronary syndrome was not. Therefore, we created 2 composite measures for all patients using data available in both datasets: the ACCORD-BP primary outcome (PO_{ACCORD}) and a hybrid primary outcome defined as first occurrence of myocardial infarction, stroke, heart failure, or cardiovascular death (PO_{hybrid}). We also assessed individual outcomes of myocardial infarction, stroke, heart failure, cardiovascular death, and all-cause death.

Statistical Analysis

Baseline characteristics were summarized by hypertension status and treatment assignment, with between-treatment comparisons (intensive vs standard) performed using student *t* tests and chi-squared test. Cumulative incidence curves were created for each outcome, comparing intensive vs standard arms, by hypertension status. Cox proportional hazards models were fit for each outcome in 2 stages: 1) simple models testing treatment assignment, hypertension status (apparent resistant vs non-resistant hypertension), and their interaction; and 2) full models for each outcome. Treatment assignment, hypertension status, and study cohort (SPRINT vs ACCORD-BP; also, a proxy for no diabetes [SPRINT] or diabetes [ACCORD-BP]) were forced into all full models. We used stepwise selection ($P < .2$ for entry; $P < .1$ to remain), examining the following predetermined covariates: age, sex, race/ethnicity, baseline statin and aspirin use, clinical cardiovascular disease history, smoking status, baseline systolic and diastolic blood pressure, Framingham 10-year cardiovascular risk, baseline body mass index, estimated glomerular filtration rate and glucose, and assignment to the intensive glycemia vs standard glycemia arm (all SPRINT patients considered as receiving standard glycemia treatment). The proportional hazards assumption was confirmed for treatment assignment and hypertension status in all models. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Excluding one ACCORD-BP patient with missing baseline data, 14,093 participants were pooled in the analysis: 9,361 (66.4%) from SPRINT and 4,733 (33.6%) from ACCORD-BP (Supplemental Figure S1, available online). Of these, 2,710 (19.2%) met apparent resistant hypertension criteria and 11,383 (80.8%) had non-resistant hypertension at baseline, with approximately equal proportions assigned to the intensive or standard arms in each cohort (Table 1). Baseline characteristics were well-balanced between treatment groups within each hypertension cohort, whereas substantial differences existed comparing patients with apparent resistant versus non-resistant hypertension.

Blood Pressure and Antihypertensive Use

Most patients had baseline blood pressure ≥ 130/80 mmHg, including 94% of those with apparent resistant hypertension and 76% of those with non-resistant hypertension. Mean systolic blood pressure diverged rapidly between treatment arms in the first 6 months in both hypertension cohorts (Figure 1). Among those with baseline apparent resistant hypertension, mean ± SD systolic blood pressure was reduced to 124 ± 16 mmHg in the intensive arm and 136 ± 15 mmHg in the standard arm at the 1-year visit. Blood pressure was moderately lower at 1-year in both treatment groups in the non-resistant hypertension cohort, though with a similar absolute difference between treatment arms (intensive, 121 ± 14 mmHg, vs. standard, 134 ± 13 mmHg). Diastolic blood pressure is displayed in Supplemental Figure S2, available online. Among those with uncontrolled (≥ 130/80 mmHg) apparent resistant hypertension assigned to the intensive arm, 64% achieved blood pressure <130/80 mmHg at 1 year, compared to 70% of those with initially uncontrolled non-resistant hypertension in the intensive arm ($P < .001$).

At the 1-year visit, significant differences were observed in number of antihypertensives used comparing apparent resistant hypertension (mean ± SD, 3.36 ± 1.09) versus non-resistant hypertension (2.11 ± 1.16; $P<.001$). Among those with apparent resistant hypertension, antihypertensive use averaged 3.81 ± 1.00 medications in the intensive arm versus 2.91 ± 0.99 in the standard arm ($P < .001$). Corresponding use in persons with non-resistant hypertension was 2.64 ± 1.07 (intensive) and 1.58 ± 0.99 (standard) medications ($P < .001$). Antihypertensive regimen adjustments during the initial year are summarized in Supplemental Figures S3 (SPRINT) and S4 (ACCORD-BP), available online.

Table 1 Baseline Characteristics of Pooled Study Participants by Resistant Hypertension Status and Treatment Assignment*

	Apparent Resistant Hypertension			Non-Resistant Hypertension		
Characteristic	Intensive (n = 1337)	Standard (n = 1373)	*P*	Intensive (n = 5702)	Standard (n = 5681)	*P*
Study			.77			.98
SPRINT	996 (74.5%)	1016 (74.0%)		3682 (64.6%)	3667 (64.6%)	
ACCORD-BP	341 (25.5%)	357 (26.0%)		2020 (35.4%)	2014 (35.5%)	
Intensive glycemia arm†	157 (46.0%)	165 (46.2%)	.96	1020 (50.5%)	1028 (51.0%)	.73
Age	67.5 ± 9.0	67.4 ± 9.2	.78	65.9 ± 8.8	65.9 ± 8.9	.95
Female sex	565 (42.3%)	564 (41.1%)	.53	2247 (39.4%)	2214 (39.0%)	.63
Race/ethnicity			.75			.50
White	734 (53.5%)	734 (53.5%)		3401 (59.7%)	3335 (58.7%)	
Black	482 (35.1%)	482 (35.1%)		1458 (25.6%)	1521 (26.8%)	
Other	43 (3.1%)	43 (3.1%)		304 (5.3%)	288 (5.1%)	
Hispanic	114 (8.3%)	114 (8.3%)		539 (9.5%)	537 (9.5%)	
History of clinical CVD	351 (26.3%)	377 (27.5%)	.48	1232 (21.6%)	1195 (21.0%)	.46
Framingham risk score, %	37.4% ± 24.7%	37.7% ± 24.2%	.50	38.5% ± 25.0%	38.3% ± 24.9%	.55
Smoking status			.086			.48
Never	583 (43.6%)	637 (46.4%)		2519 (44.2%)	2504 (44.1%)	
Past	605 (45.3%)	577 (42.0%)		2363 (41.4%)	2408 (42.4%)	
Current	106 (7.9%)	128 (9.3%)		552 (9.7%)	496 (8.7%)	
Unknown	43 (3.2%)	31 (2.3%)		268 (4.7%)	273 (4.8%)	
Statin use	719 (54.1%)	790 (58.1%)	.041	2767 (48.8%)	2842 (50.4%)	.086
Aspirin use	774 (58.0%)	817 (59.6%)	.41	2896 (51.0%)	2742 (48.5%)	.008
No. of antihypertensives			.64			.51
0 drugs	0	0		981 (17.2%)	1006 (17.7%)	
1 drug	0	0		2079 (36.5%)	2089 (36.8%)	
2 drugs	0	0		2325 (40.8%)	2303 (40.5%)	
3 drugs	1033 (77.3%)	1076 (78.4%)		317 (5.56%)	283 (4.98%)	
4 drugs	292 (21.8%)	284 (20.7%)		0	0	
5 or 6 drugs	12 (0.89%)	13 (0.95%)		0	0	
Mean ± SD	3.27 ± 0.46	3.25 ± 0.46	.65	1.45 ± 0.78	1.43 ± 0.78	.19
Lab values						
TC, mg/dL	186 ± 41.2	184 ± 39.6	.101	192.8 ± 43.0	192.2 ± 42.5	.46
HDL, mg/dL	49.9 ± 14.3	50.0 ± 13.6	.81	50.8 ± 14.3	50.8 ± 15.0	.99
LDL, mg/dL	108 ± 34.4	106 ± 34.2	.063	113 ± 36.0	112 ± 36.8	.26
Trig, mg/dL	145 ± 120	142 ± 94	.43	150 ± 143.7	149 ± 130.9	.64
Glucose, mg/dL	118 ± 43.6	119 ± 45.0	.69	125 ± 52.1	124 ± 50.7	.16
eGFR, mL/min	72.1 ± 23.2	71.9 ± 24.5	.76	80 ± 26.5	80 ± 24.6	.83
UACR, mg/g	79.3 ± 247	99.3 ± 328	.081	53.8 ± 216	53.3 ± 236	.89
SCr, mg/dL	1.19 ± 0.38	1.11 ± 0.41	.29	0.99 ± 0.31	0.99 ± 0.29	.65
Baseline BP						
Systolic, mm Hg	143 ± 14.1	144 ± 14.0	.27	139 ± 16.2	139 ± 15.6	.88
Diastolic, mm Hg	77 ± 11.7	77 ± 11.8	.36	77 ± 11.5	77 ± 11.4	.90
BMI, kg/m^2	31.7 ± 6.1	31.3 ± 6.0	.069	30.4 ± 5.8	30.4 ± 5.6	.83

ACCORD = Action to Control Cardiovascular Risk in Diabetes; BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SCr = serum creatinine; SPRINT = Systolic Blood Pressure Intervention Trial; TC = total cholesterol; TRH = treatment-resistant hypertension; UACR = urinary albumin-to-creatinine ratio.

*Data represent mean ± SD or No. (%). *P*-values are for comparisons between treatment assignment.

†Row percents are calculated using the ACCORD-BP sample sizes (in the row directly above) as the denominator.

Cardiovascular Outcomes and Death

Tests for heterogeneity of outcomes by treatment assignment and original study are summarized in Supplemental Figure S5 (available online). Outcome-specific numbers of events and crude incidence rates are summarized in Table 2. Major adverse events occurred at a consistently higher rate in those with apparent resistant versus non-resistant hypertension for all outcomes ($P < .05$ for myocardial infarction, all-cause death; $p < 0.005$ for all others). Among those with apparent resistant hypertension, crude incidence rates for all outcomes except myocardial infarction and stroke were significantly lower in the intensive vs standard arm. Among the non-resistant hypertension cohort, crude incidence rates of the hybrid primary outcome and stroke were significantly lower for patients in the intensive vs standard arm. Cumulative incidence curves for each outcome are displayed in Figures 2 and 3. No significant

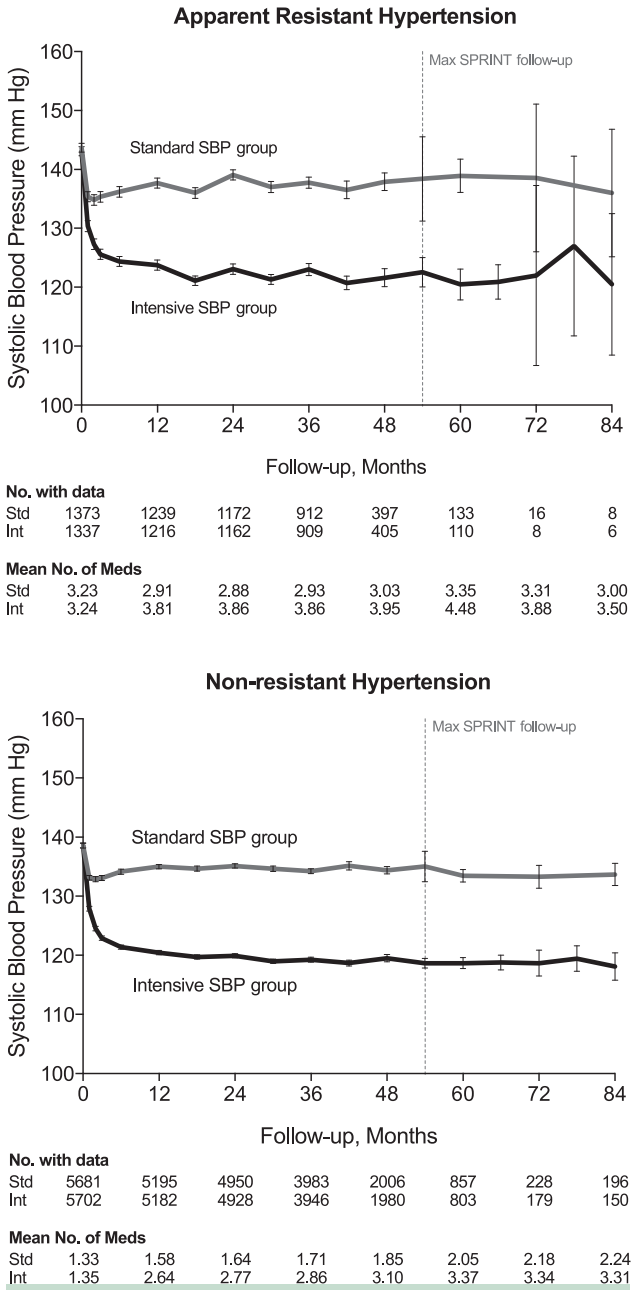


Figure 1 Systolic blood pressure by treatment assignment during follow-up. Bars indicate 95% confidence intervals.

interactions were observed between resistant hypertension status and treatment assignment for any outcome, suggesting that hypertension status did not influence the relative benefit (or lack thereof) of an intensive blood pressure target (Figure 4).

In full models adjusting for baseline hypertension status and other covariates, intensive treatment significantly reduced the risk of the ACCORD-BP primary outcome (hazard ratio [HR] 0.81; 95% confidence interval [CI], 0.71-0.93), hybrid primary outcome (HR, 0.78; 95% CI, 0.69-0.88), stroke (HR 0.72; 95% CI, 0.55-0.94), and heart failure (HR 0.73; 95% CI, 0.59-0.91). The intensive systolic target also appeared to reduce risk of myocardial infarction (HR 0.85; 95% CI, 0.71-1.02), cardiovascular death (HR 0.79; 95% CI, 0.60-1.03), and all-cause death (HR 0.87; 95% CI, 0.74-1.01), though in each case the confidence interval bounded 1. Apparent resistant hypertension also independently predicted increased risk of the hybrid primary outcome (HR 1.30; 95% CI 1.12-1.50) and heart failure (HR 1.89; 95% CI, 1.50-2.37), but not the ACCORD primary outcome, myocardial infarction, stroke, cardiovascular death, or all-cause death. Full model results for the composite and individual outcomes are displayed in Supplemental Figures S6 and S7 (available online), respectively. Similar results were observed in sensitivity analyses defining resistant hypertension status at 6 months (data not shown).

DISCUSSION

While we understand the importance of controlling blood pressure among patients with resistant hypertension, concrete information on blood pressure targets in this high-risk population remains sparse. To a large degree, our insight is hindered by hurdles related to extrapolation of data from studies of the general hypertensive population.[13,20,21] For the first time, we demonstrate that patients with apparent resistant hypertension benefit similarly from an intensive systolic blood pressure target, compared with those with non-resistant hypertension. Furthermore, we provide evidence to support that, regardless of the presence or absence of resistant hypertension, an intensive systolic target is beneficial for most major cardiovascular outcomes and death across a diverse population of hypertensive individuals, including those with normoglycemia, pre-diabetes, and diabetes, and in those with and without a history of stroke. Finally, we demonstrate that the updated definition for resistant hypertension proposed in the 2017 hypertension guidelines[13] identifies a higher-risk hypertensive subpopulation. To our knowledge, this is the first study of major outcomes using this updated definition.

Among those enrolled in the ACCORD and SPRINT trials, our findings indicate that an intensive systolic blood pressure target reduces the risk of most major adverse cardiovascular events and death, and that these benefits do not differ significantly among those with and without resistant hypertension. The greatest risk reduction appears to be for stroke and heart failure, although our results also suggest moderate reductions (12% to 21%) in myocardial infarction, cardiovascular death, and all-cause death risk. These results should provide confidence in the most recent guidance on treatment targets in the resistant hypertension population,[13] namely that they are likely to benefit, at least in terms of risk for cardiovascular outcomes and death, from blood pressure lowering to <130/80 mm Hg.

Prior studies have had mixed results with regard to the benefits of blood pressure-lowering or achieving control (to <140/90 mm Hg) in resistant hypertension. For example, among a hypertensive coronary artery disease population,

Table 2 Number of Events and Crude Incidence Rates (95% CIs) of Outcomes, by Resistant Hypertension Status Overall and by Treatment Assignment*

	Apparent Resistant Hypertension			Non-Resistant Hypertension		
Outcome	Overall (n = 2710)	Intensive (n = 1337)	Standard (n = 1373)	Overall (n = 11,383)	Intensive (n = 5702)	Standard (n = 5681)
PO_{ACCORD}						
No. events	195	76	119	644	302	342
Follow-up, y	9483	4674	4809	42,162	21,113	21,048
IR (95% CI)	20.6 (17.9-23.7)	16.3 (13.0-20.4)	24.7 (20.7-29.6)	15.3 (14.1-16.5)	14.3 (12.8-16.0)	16.2 (14.6-18.1)
PO_{HYBRID}						
No. events	269	108	161	782	357	425
Follow-up, y	9338	4611	4727	41,913	21,004	20,909
IR (95% CI)	28.8 (25.6-32.5)	23.4 (19.4-28.3)	34.1 (29.2-39.8)	18.7 (17.4-20.0)	16.9 (15.3-18.9)	20.3 (18.5-22.4)
MI						
No. events	107	43	64	378	180	198
Follow-up, y	9566	4717	4849	42,378	21,187	21,190
IR (95% CI)	11.2 (9.3-13.5)	9.1 (6.8-12.3)	13.2 (10.3-16.9)	8.9 (8.1-9.9)	8.5 (7.3-9.8)	9.3 (8.1-10.7)
Stroke						
No. events	59	30	29	171	68	103
Follow-up, y	9651	4741	4911	42,878	21,440	21,438
IR (95% CI)	6.1 (4.7-7.9)	6.3 (4.4-9.1)	5.9 (4.1-8.5)	4.0 (3.4-4.6)	3.2 (2.5-4.0)	4.8 (4.0-5.8)
Heart failure						
No. events	113	45	68	223	100	123
Follow-up, y	9568	4718	4850	42,773	21,376	21,397
IR (95% CI)	11.8 (9.8-14.2)	9.5 (7.1-12.8)	14.0 (11.1-17.8)	5.2 (4.6-5.9)	4.7 (3.8-5.7)	5.7 (4.8-6.9)
CV death						
No. events	58	19	39	162	78	84
Follow-up, y	9780	4806	4974	43,255	21,590	21,666
IR (95% CI)	5.9 (4.6-7.7)	4.0 (2.5-6.2)	7.8 (5.7-10.7)	3.7 (3.2-4.4)	3.6 (2.9-4.5)	3.9 (3.1-4.8)
All-cause death						
No. events	142	58	84	517	247	270
Follow-up, y	9855	4849	5006	43,676	21,784	21,892
IR (95% CI)	14.4 (12.2-17.0)	12.0 (9.2-15.5)	16.8 (13.5-20.8)	11.8 (10.9-12.9)	11.3 (10.0-12.8)	12.3 (10.9-13.9)

CI = confidence interval; CV = cardiovascular; IR = incidence rate; MI = myocardial infarction.

*Incidence rates are per 1000 patient-years. PO_{ACCORD} is first occurrence of myocardial infarction, stroke, or cardiovascular death. PO_{HYBRID} is first occurrence of myocardial infarction, stroke, heart failure, or cardiovascular death.

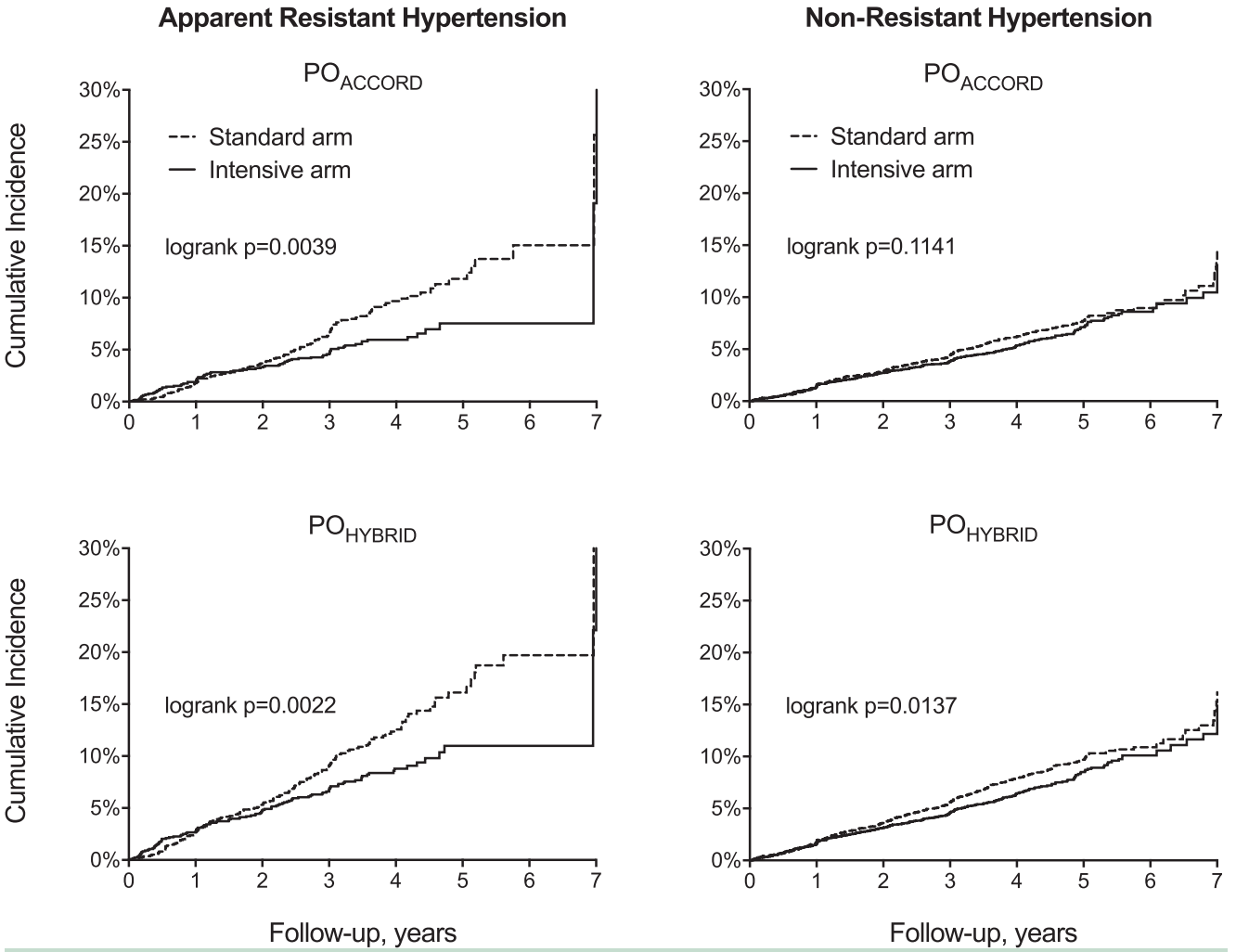


Figure 2 Cumulative incidence for each composite outcome, comparing treatment assignments. Data are stratified by baseline apparent resistant hypertension (left column) and non-resistant hypertension (right column).

no difference in outcomes was observed comparing controlled and uncontrolled resistant hypertension, despite a substantial differential in mean blood pressure (28/10 mm Hg).[5] Similar findings were observed in hypertensive diabetics, where controlled (vs uncontrolled) resistant hypertension was not associated with improved renal outcomes.[15] Others have shown attenuated benefits in those with controlled versus uncontrolled resistant hypertension,[14] or benefits only on certain outcomes.[8] However, these prior findings were largely from observational cohort studies testing associations between achieved blood pressure and outcomes, and such studies may suffer from issues of confounding or time-related biases inadvertently introduced by study design. The present analysis used prospective clinical trial data that tested random assignment to an intensive or standard systolic BP and therefore is less likely to suffer from some of the limitations inherent to observational research.

It is noteworthy that patients with apparent resistant hypertension, who by definition have more difficult-to-treat hypertension, achieved relatively rapid blood pressure lowering, resulting in a mean 1-year blood pressure of 124/68 mm Hg in the intensive arm with addition of approximately 1 antihypertensive drug. That blood pressure control improved from 6% at baseline to 64% at 12 months in this group, suggesting that significantly improved long-term blood pressure control, using updated blood pressure targets, is achievable in most patients with resistant hypertension. However, 2 important factors in these trials, which are not always present in real-world treatment settings, should be highlighted. First, both trials provided most antihypertensive drugs free of charge. Interestingly, data from SPRINT suggest only a minority of patients with resistant hypertension in the intensive arm (<20% during any year-1 visit) required addition of new drugs to achieve target blood pressure. Secondly, protocols for both studies included frequent early follow-up (5-6 visits at which medications could be adjusted), and guidance on antihypertensive regimen titration.[16,17] Prior work suggests frequent follow-up and appropriate antihypertensive medication titration are

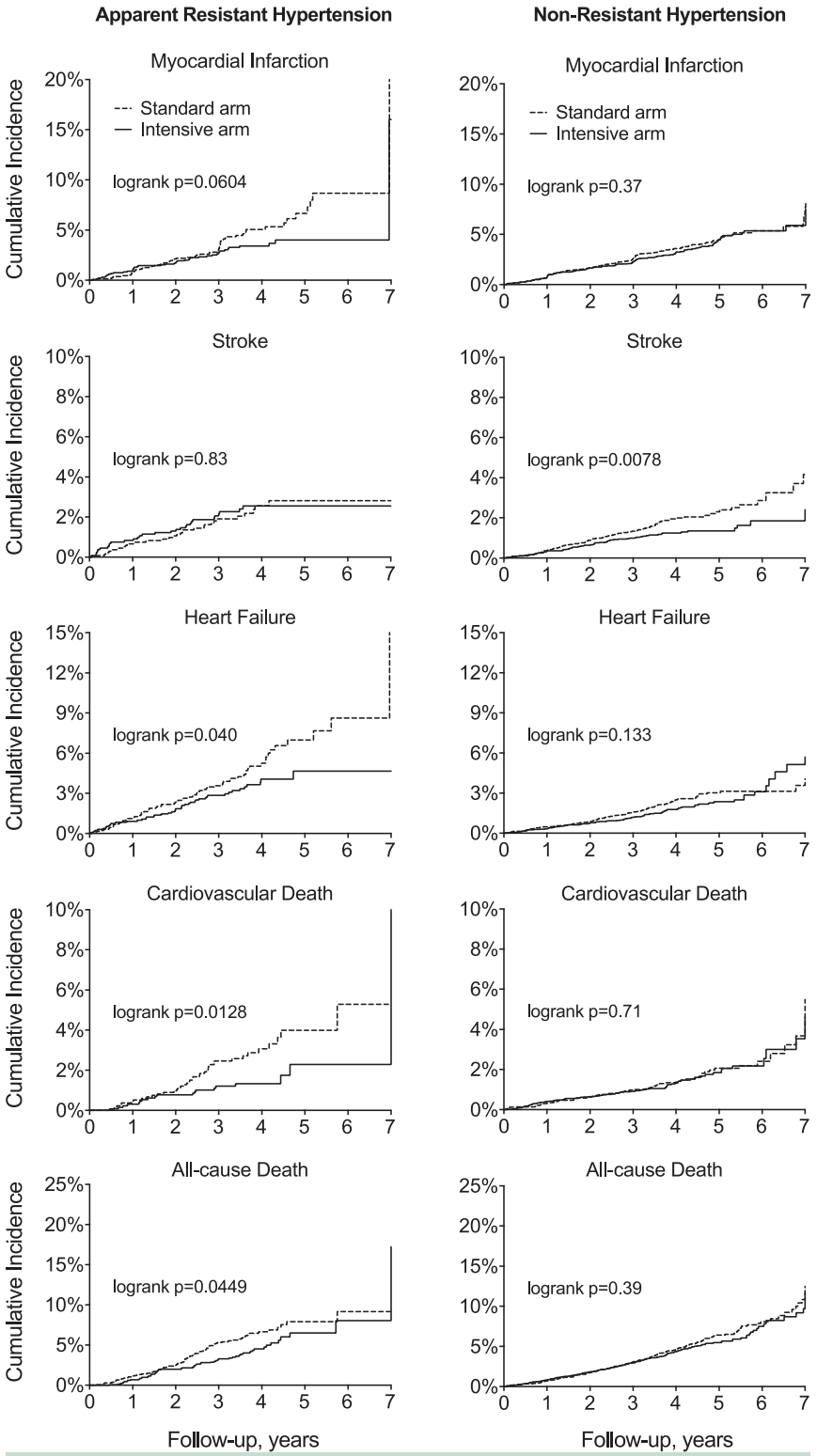


Figure 3 Cumulative incidence for each individual outcome, comparing treatment assignments. Data are stratified by baseline apparent resistant hypertension (left column) and non-resistant hypertension (right column).

effective in achieving rapid blood pressure control in this population.[22,23] Thus, there are at least 3 plausible explanations for our findings of rapid blood pressure target attainment. First, treatment adherence was suboptimal at enrollment and provision of free therapies improved adherence. Second, dose titrations contributed to rapid attainment

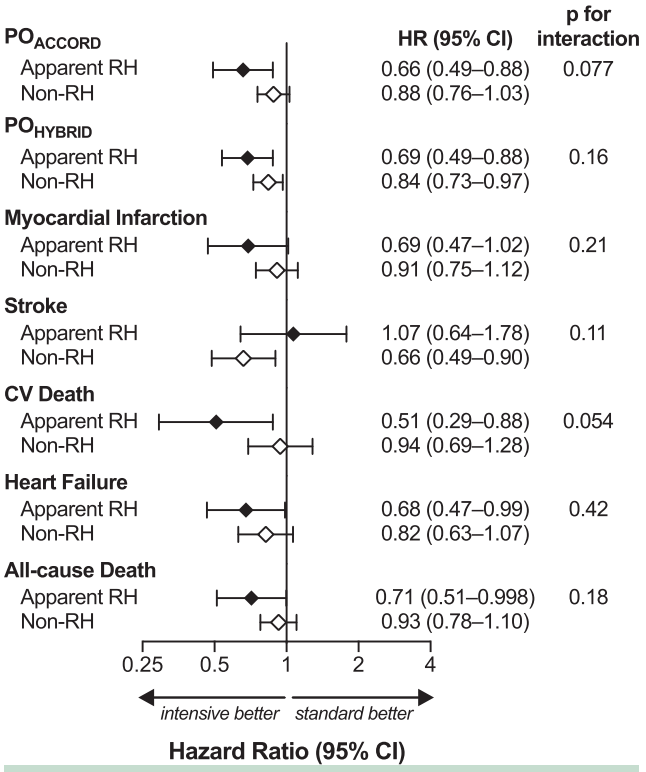


Figure 4 Tests for interactions between treatment assignment and baseline resistant hypertension status. PO_{ACCORD} is first occurrence of myocardial infarction, stroke, or cardiovascular death. PO_{HYBRID} is first occurrence of myocardial infarction, stroke, heart failure, or cardiovascular death. CV = cardiovascular; RH = resistant hypertension.

of blood pressure control, in which case patients may have had suboptimal dosing at baseline. Third, semi-protocolized treatment approaches and frequent follow-up visits, per se, were associated with substantial blood pressure reductions. Unfortunately, available SPRINT data did not allow for assessment of medication doses, titrations, or adherence.

Our study has notable strengths, including pooling of patient-level data from 2 large randomized trials encompassing a diverse high-risk hypertensive population. Both trials had remarkably similar protocols and pre-specified outcomes, resulting in a large cohort of patients with apparent resistant hypertension with up to 7 years follow-up, and adjudicated outcomes relevant to the hypertensive population and cardiovascular disease generally. Nevertheless, some limitations are worthy of comment. First, although benefits of randomization appear to have been conserved, strengthening the case for causal inference, we cannot be sure that unmeasured factors were equally distributed between treatment arms within the resistant hypertension group. Second, our definition for resistant hypertension was not inclusive of a thiazide because patient-level drug data were unavailable for SPRINT. However, prior studies have shown no difference in outcome risk comparing resistant hypertension definitions inclusive vs exclusive of thiazides.[5,24] Third, we were unable to exclude pseudoresistance: out-of-office blood pressure was not measured in most patients; adherence data were unavailable in SPRINT, although ACCORD-BP data suggest relatively few (<15%) with apparent resistant hypertension report nonadherence; and, secondary hypertension was not collected systematically, although SPRINT did exclude some patients with secondary hypertension. Thus, we cannot exclude the possibility that misclassifying pseudoresistant hypertension as resistant hypertension biased our results. However, any such bias would be expected to conservatively estimate intensive treatment benefits in resistant hypertension. And, our sensitivity analyses suggest that pseudoresistance did not substantially influence our results. Finally, both trials excluded refractory hypertension. Thus, we cannot say whether lower blood pressure benefits this group.

In conclusion, we provide evidence that an intensive systolic target reduces risk of adverse cardiovascular events including death in apparent resistant hypertension. These findings provide confidence in recently revised guidance to target lower blood pressure (<130/80 mm Hg) in this population.[13] Additional studies are needed to better understand optimal treatments to maximally reduce risk, as well as medication-related adverse effects with more intensive treatment in this population, because most patients will require second-line antihypertensives associated with more adverse effects and lower quality of life.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.amjmed.2018.08.005.

References

1. Muntner P, Carey RM, Gidding S, et al. Potential US population impact of the 2017 ACC/AHA High Blood Pressure Guideline. *Circulation*. 2018;137(2):109–118.
2. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005;365(9455):217–223.
3. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Hypertension*. 2008;51(6):1403–1419.
4. Kumbhani DJ, Steg PG, Cannon CP, et al. Resistant hypertension: a frequent and ominous finding among hypertensive patients with atherothrombosis. *Eur Heart J*. 2013;34(16):1204–1214.
5. Smith SM, Gong Y, Handberg E, et al. Predictors and outcomes of resistant hypertension among patients with coronary artery disease and hypertension. *J Hypertens*. 2014;32(3):635–643.
6. Smith SM, Huo T, Delia Johnson B, et al. Cardiovascular and mortality risk of apparent resistant hypertension in women with suspected myocardial ischemia: a report from the NHLBI-sponsored WISE Study. *J Am Heart Assoc*. 2014;3(1):e000660.
7. Smith SM, Huo T, Gong Y, et al. Mortality risk associated with resistant hypertension among women: Analysis from three prospective cohorts encompassing the spectrum of women's heart disease. *J Womens Health (Larchmt)*. 2016;25(10):996–1003.

8. Irvin MR, Booth J.N. 3rd, Shimbo D, et al. Apparent treatment-resistant hypertension and risk for stroke, coronary heart disease, and all-cause mortality. *J Am Soc Hypertens*. 2014;8(6):405–413.
9. Daugherty SL, Powers JD, Magid DJ, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation*. 2012;125(13):1635–1642.
10. Muntner P, Davis BR, Cushman WC, et al. Treatment-resistant hypertension and the incidence of cardiovascular disease and end-stage renal disease: results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Hypertension*. 2014;64(5):1012–1021.
11. Carris NW, Ghushchyan V, Libby AM, Smith SM. Health-related quality of life in persons with apparent treatment-resistant hypertension on at least four antihypertensives. *J Hum Hypertens*. 2016;30(3):191–196.
12. Zygmuntowicz M, Owczarek A, Elibol A, Olszanecka-Glinianowicz M, Chudek J. Blood pressure for optimal health-related quality of life in hypertensive patients. *J Hypertens*. 2013;31(4):830–839.
13. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:e13–e115.
14. Egan BM, Kai B, Wagner CS, Henderson JH, Chandler AH, Sinopoli A. Blood pressure control provides less cardiovascular protection in adults with than without apparent treatment-resistant hypertension. *J Clin Hypertens (Greenwich)*. 2016;18(8):817–824.
15. Viazzi F, Piscitelli P, Ceriello A, et al. Resistant hypertension, time-updated blood pressure values and renal outcome in type 2 diabetes mellitus. *J Am Heart Assoc*. 2017;6:e006745.
16. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373(22):2103–2116.
17. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362(17):1575–1585.
18. Ambrosius WT, Sink KM, Foy CG, et al. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). *Clin Trials*. 2014;11(5):532–546.
19. Buse JB, Bigger JT, Byington RP, et al. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. *Am J Cardiol*. 2007;99(12a):21i–33i.
20. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34(28):2159–2219.
21. National Institute for Health and Care Excellence. Hypertension: The Clinical Management of Primary Hypertension in Adults: *Update of Clinical Guidelines 18 and 34*. London: National Clinical Guideline Centre; 2016.
22. Acelajado MC, Pisoni R, Dudenbostel T, et al. Refractory hypertension: definition, prevalence, and patient characteristics. *J Clin Hypertens (Greenwich)*. 2012;14(1):7–12.
23. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet*. 2015;386(10008):2059–2068.
24. Bangalore S, Davis BR, Cushman WC, et al. Treatment-resistant hypertension and outcomes based on randomized treatment group in ALLHAT. *Am J Med*. 2017;130(4):439–448.

SUPPLEMENTAL METHODS

SPRINT eligibility criteria

Inclusion criteria for the SPRINT trial were age ≥ 50 years, with hypertension and ≥ 1 additional cardiovascular risk factor: clinical or subclinical cardiovascular disease other than stroke; chronic kidney disease, excluding polycystic kidney disease, with an estimated glomerular filtration rate (eGFR) between 20 and 59 mL/min/1.73 m^2 of body-surface area, calculated via the four-variable Modification of Diet in Renal Disease equation; a 10-year Framingham risk (for cardiovascular disease) $\geq 15\%$; or, age ≥ 75 years. Clinical cardiovascular disease was defined as: prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, carotid endarterectomy, or carotid stenting; peripheral artery disease with revascularization; acute coronary syndrome with or without resting electrocardiogram change, electrocardiogram change on graded exercise test, or positive cardiac imaging study; at least a 50% diameter stenosis of a coronary, carotid, or lower extremity artery; or, abdominal aortic aneurysm ≥ 5 cm with or without repair. Subclinical cardiovascular disease was defined as: coronary artery calcium score ≥ 400 Agatston units within the prior 2 years; ankle brachial index ≤ 0.90 within the prior 2 years; or, left ventricular hypertrophy within the prior 2 years. Inclusion was also dependent on tiered criteria for systolic blood pressure and number of antihypertensive drugs used at baseline. Specifically, patients were eligible if they had a systolic blood pressure between 130 and 180 mm Hg while taking ≤ 1 antihypertensive drug, between 130 and 170 mm Hg while taking 2 antihypertensive drugs, between 130 and 160 mm Hg while taking 3 antihypertensive drugs, or between 130 and 150 mm Hg while taking 4 antihypertensive drugs.

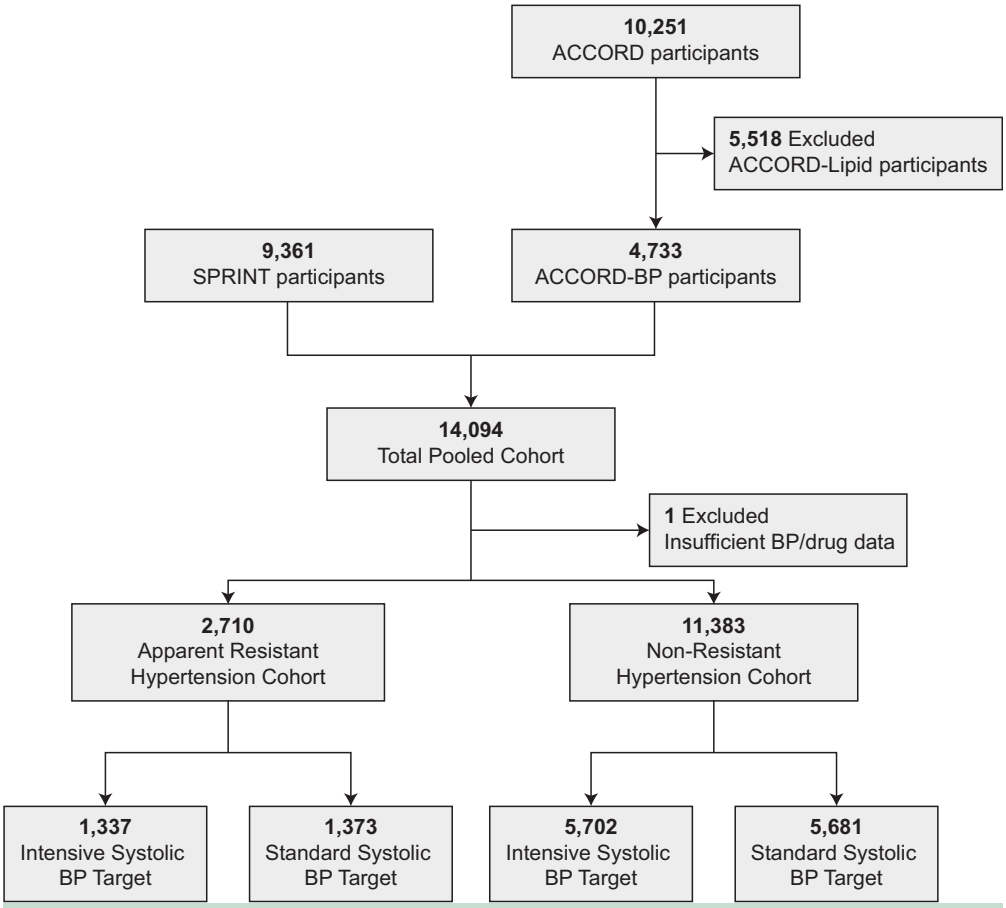
Major exclusion criteria were: diabetes mellitus; history of stroke; polycystic kidney disease; glomerulonephritis treated with immunosuppressive therapy; eGFR <20 mL/min/1.73m^2 or end-stage renal disease; cardiovascular event or procedure (as defined above for clinical cardiovascular disease), or hospitalization for unstable angina within prior 3 months; symptomatic heart failure within the past 6 months or left ventricular ejection fraction $<35\%$; indication for a specific blood pressure-lowering medication (e.g., β-blocker following acute myocardial infarction) that the person was not taking and where intolerance to that medication had not been documented; known secondary hypertension that caused concern regarding safety of the protocol; one minute standing systolic blood pressure <110 mm Hg; documented proteinuria in the past 6 months; arm circumference outside the range for accurate measurement with devices available in the clinic; any organ transplant; unintentional weight loss $>10\%$ in last 6 months; pregnancy or of child-bearing potential and not using birth control; and, any medical condition estimated to limit survival to <3 years.

ACCORD-BP Eligibility Criteria

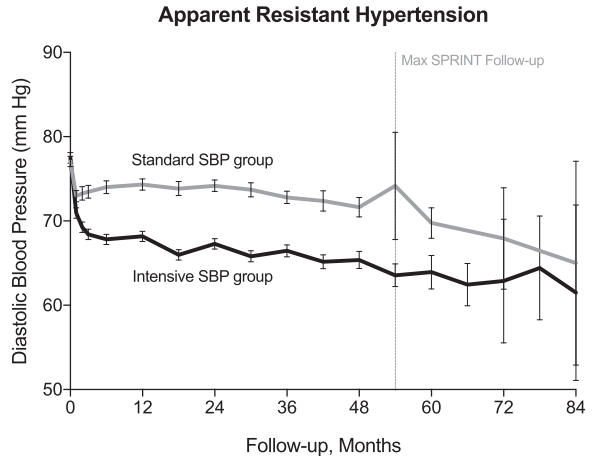
Inclusion criteria for the ACCORD trial were: type 2 diabetes with a duration and stable treatment >3 months; a hemoglobin A1c between 7.5% and 9% or 11%, with the upper range determined by use of insulin (and dose) or other oral agents; age 40 to 79 years with a history of clinical cardiovascular disease or age 55 to 79 years without a history of clinical cardiovascular disease; and, high cardiovascular event risk. The latter criteria was defined as presence of clinical cardiovascular disease (prior myocardial infarction, stroke, coronary revascularization, carotid or peripheral revascularization, angina with ischemic changes, electrocardiogram changes on a graded exercise test, or positive cardiac imaging study), evidence suggesting high likelihood of cardiovascular disease (microalbuminuria, ankle brachial index <0.9, left ventricular hypertrophy, or $\geq 50\%$ stenosis of coronary, carotid, or lower extremity artery), or presence of ≥ 2 cardiovascular risk factors (untreated low-density lipoprotein cholesterol >130 mg/dL or taking lipid-lowering therapy, high-density lipoprotein cholesterol <40 mg/dL for men or <50 mg/dL for women, untreated systolic blood pressure ≥ 140 Hg or diastolic blood pressure ≥ 95 mm Hg or taking antihypertensive therapy, current cigarette smoking, or body mass index >32 kg/m^2). In both trials, inclusion was dependent on tiered criteria for systolic blood pressure and number of antihypertensive drugs used at baseline. As in SPRINT, additional inclusion criteria were placed around systolic blood pressure and number of antihypertensive drugs. Specifically, patients could be included if they had a systolic blood pressure between 130 and 180 mm Hg while taking ≤ 1 antihypertensive drug, between 130 and 170 mm Hg while taking 2 antihypertensive drugs, or between 130 and 160 mm Hg while taking 3 antihypertensive drugs.

Major exclusion criteria were history of hypoglycemic coma/seizure within prior year; hypoglycemia requiring assistance in prior 3 months and with concomitant glucose <60 mg/dL; history of type 1 diabetes; unwillingness to self-monitor blood glucose or inject insulin; body mass index ≥ 45 kg/m^2; serum creatinine >1.5 mg/dL in the prior 2 months, 24-hour protein excretion rate ≥ 1.0 g, $\geq 2+$ on dipstick protein in a spot urine test, or ≥ 700 mg/g protein/creatinine ratio in a spot urine test; transaminase >2 times upper limit of normal or active liver disease; ongoing medical therapy with known adverse interactions with glycemic interventions; cardiovascular event or procedure (defined as above) or hospitalization for unstable angina within prior 3 months; current symptomatic heart failure; history of New York Heart Association class III or IV heart failure at any time, or ejection fraction $<25\%$; any

organ transplant; weight loss >10% in prior 6 months; pregnancy or of child-bearing potential and not taking birth control; recurrent requirement for phlebotomy or transfusion of red blood cells; or, any medical condition estimated to limit survival to <3 years or likely to limit adherence to interventions.



Supplementary Figure S1 Flow diagram for cohort development from SPRINT and ACCORD-BP trials.
ACCORD, Action to Control Cardiovascular Risk in Diabetes; BP = blood pressure; SPRINT = Systolic Blood Pressure Intervention Trial.

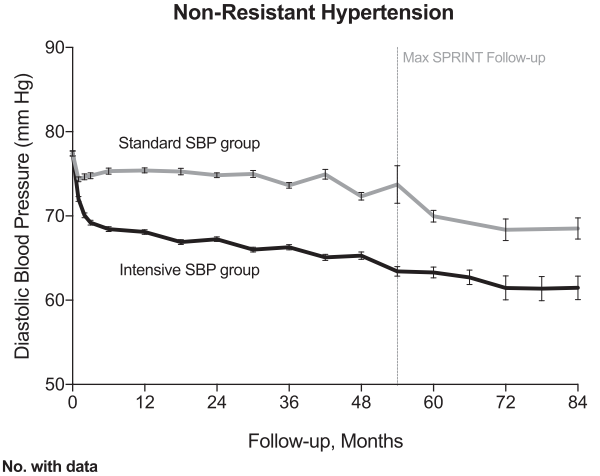


No. with data

Std	1373	1239	1172	912	397	133	16	8
Int	1337	1216	1162	909	405	110	8	6

Mean No. of Meds

Std	3.23	2.91	2.88	2.93	3.03	3.35	3.31	3.00
Int	3.24	3.81	3.86	3.86	3.95	4.48	3.88	3.50



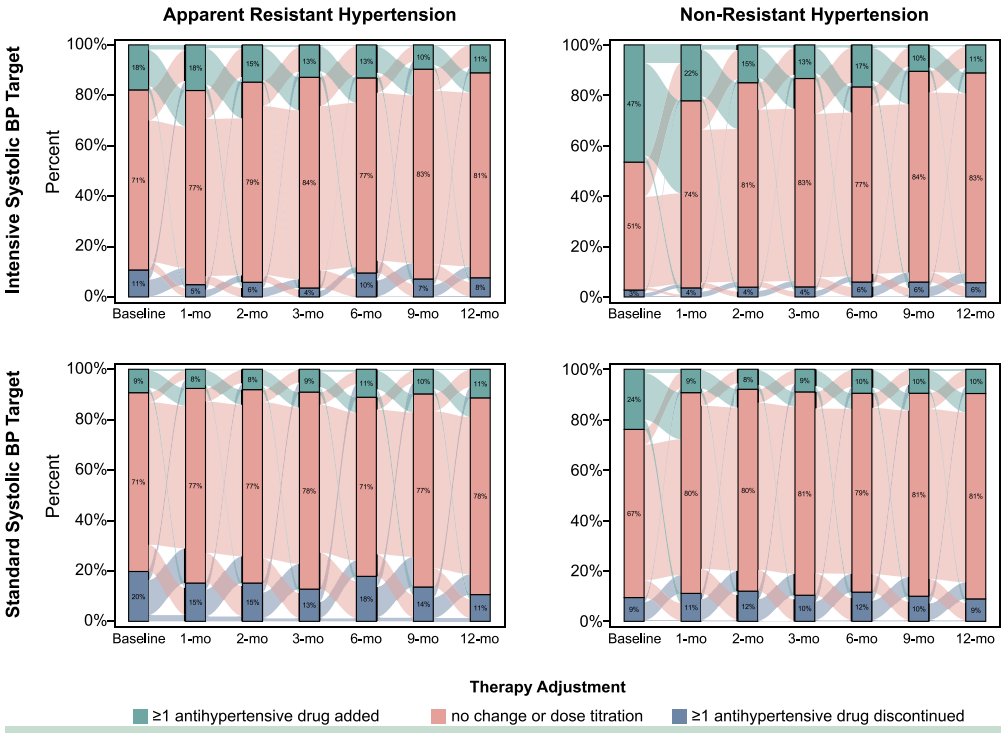
No. with data

Std	5681	5195	4950	3983	2006	857	228	196
Int	5702	5182	4928	3946	1980	803	179	150

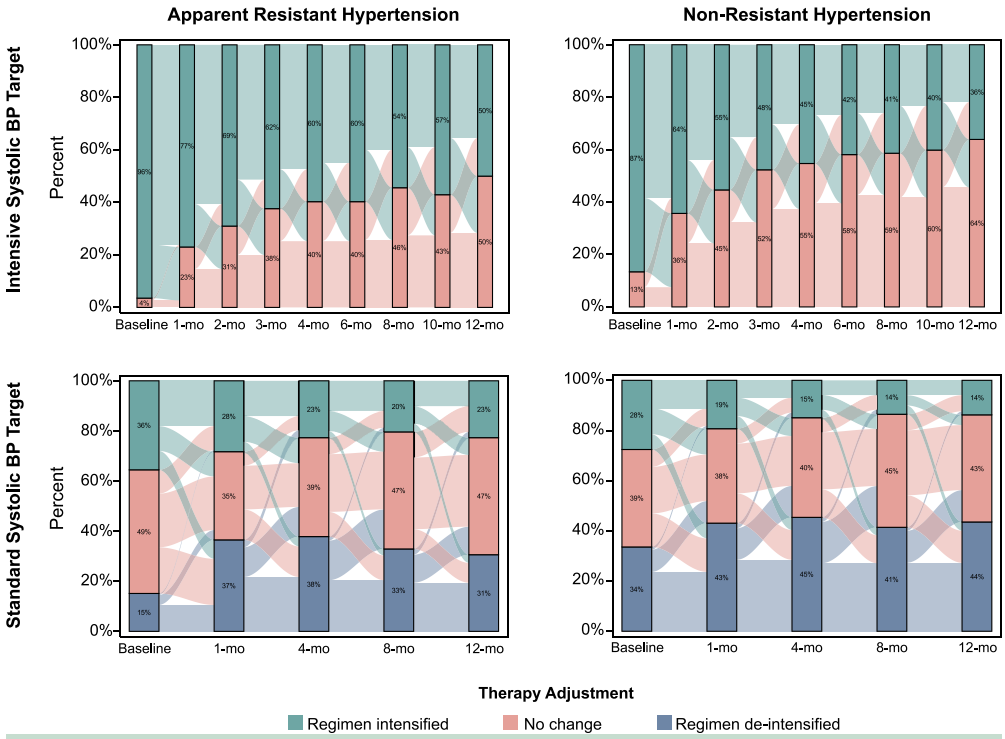
Mean No. of Meds

Std	1.33	1.58	1.64	1.71	1.85	2.05	2.18	2.24
Int	1.35	2.64	2.77	2.86	3.10	3.37	3.34	3.31

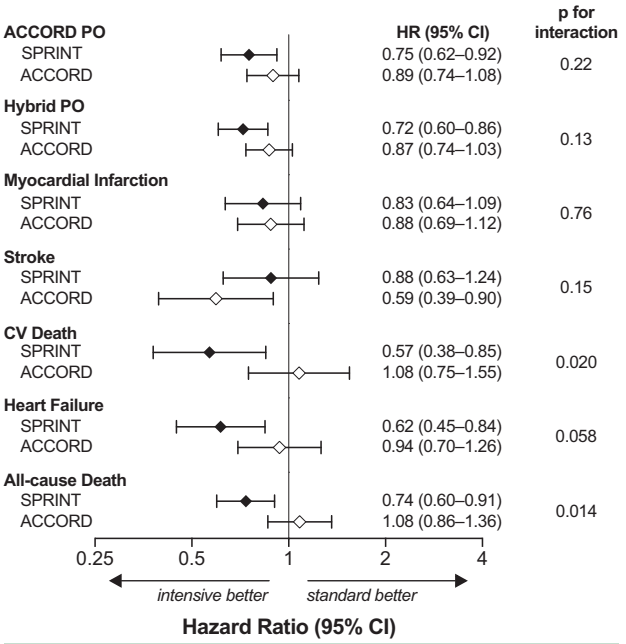
Supplementary Figure S2 Diastolic blood pressure, by treatment assignment, during follow-up for patients with apparent treatment-resistant hypertension (top panel) and non-resistant hypertension (bottom panel). Bars indicate 95% confidence intervals.



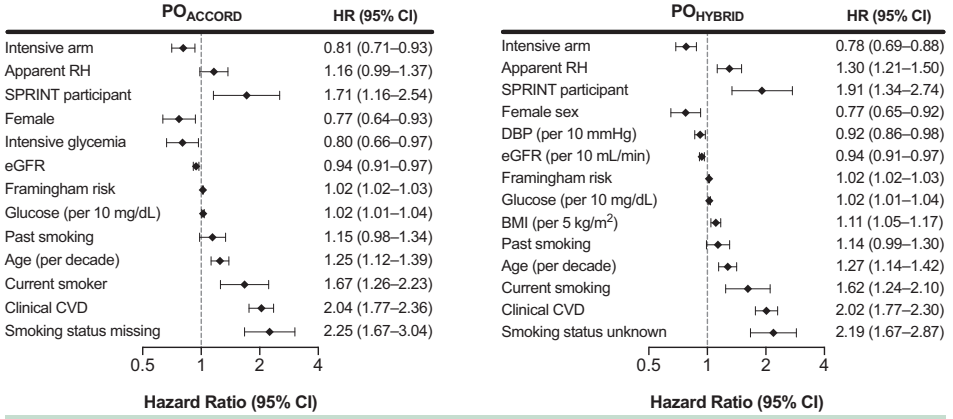
Supplementary Figure S3 Therapy adjustment by visit during the first year of follow-up, according to apparent resistant hypertension status and randomized assignment in SPRINT. Stacked columns represent proportion of all patients having therapy intensified, unchanged, or de-intensified. Lighter bands between columns represent flow of patients from category to category at each visit. SPRINT data include only addition or discontinuation of medications, not dose titrations.



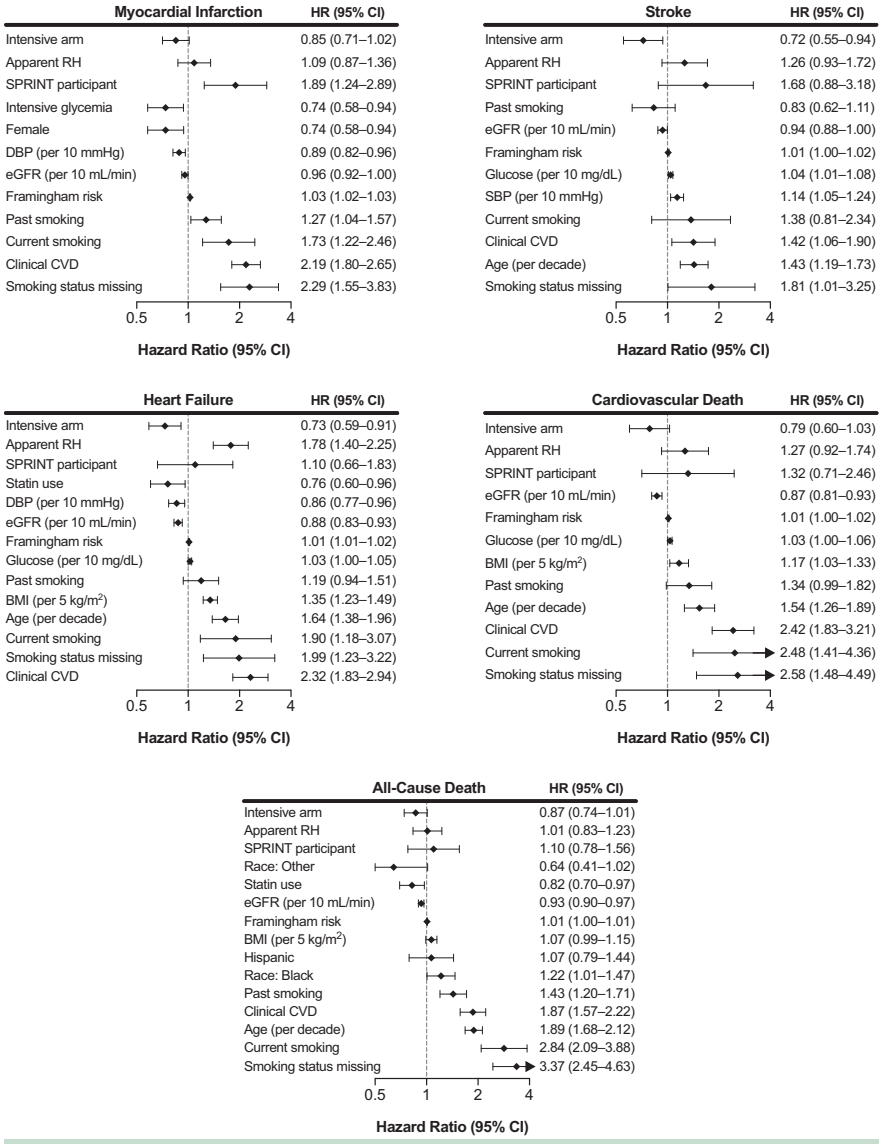
Supplementary Figure S4 Therapy adjustment by visit during the first year of follow-up, according to apparent resistant hypertension status and randomized assignment in ACCORD-BP. Stacked columns represent proportion of all patients having therapy intensified, unchanged, or de-intensified. Lighter bands between columns represent flow of patients from category to category at each visit. ACCORD-BP data include a dose increase or addition of a new drug (intensified), or drug discontinuation or dose decrease (De-intensified). Data shown are for protocol-specified visits in year 1, during which time ACCORD-BP patients assigned to the intensive systolic blood pressure target had more frequent protocol-specified follow-up than those assigned to the standard systolic blood pressure. De-intensification of therapy was not recorded for individuals in the intensive systolic blood pressure arm.



Supplementary Figure S5 Interaction tests for the association between treatment assignment and outcomes. Hazard ratios and 95% confidence intervals are derived from proportional hazards models testing treatment assignment, original study cohort (SPRINT or ACCORD) and their interaction on each outcome separately.



Supplementary Figure S6 Hazard ratios (95% confidence intervals) for the full Cox proportional hazards models for both primary composite outcomes. ACCORD-BP primary outcome: first occurrence of myocardial infarction, stroke, or cardiovascular death. Hybrid primary outcome: first occurrence of myocardial infarction, stroke, heart failure, or cardiovascular death. Referents are: non-resistant hypertension (for apparent resistant hypertension); standard arm (for intensive arm); standard glycemia target (for intensive glycemia); never smoked (for all smoking categories); ACCORD-BP participant (for SPRINT participant). BMI = body mass index; CVD = cardiovascular disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; RH = resistant hypertension.



Supplementary Figure S7 Hazard ratios (95% confidence intervals) for the full Cox proportional hazards models for individual outcomes. Referents are: standard systolic blood pressure target arm (for intensive arm); non-resistant hypertension (for apparent resistant hypertension); ACCORD-BP participant (for SPRINT participant); standard glycemia target (for intensive glycemia); never smoked (for all smoking categories); white race (for all race categories). BMI = body mass index; CVD = cardiovascular disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; RH = resistant hypertension; SBP = systolic blood pressure.