Received: 25 February 2019 | Revised: 1 April 2019 | Accepted: 11 April 2019

DOI: 10.1111/jch.13550

ORIGINAL PAPER

WILEY

Incidence, prevalence, and predictors of treatment-resistant hypertension with intensive blood pressure lowering

Steven M. Smith PharmD, MPH[1] | Matthew J. Gurka PhD[2] | Almut G. Winterstein PhD[3] | Carl J. Pepine MD[4] | Rhonda M. Cooper-DeHoff PharmD, MS[1,4]

[1]Department of Pharmacotherapy & Translational Research, College of Pharmacy, Gainesville, Florida

[2]Department of Health Outcomes & Biomedical Informatics, College of Medicine, Gainesville, Florida

[3]Department of Pharmaceutical Outcomes & Policy, College of Pharmacy, Gainesville, Florida

[4]Division of Cardiovascular Medicine, Department of Medicine, College of Medicine, University of Florida, Gainesville, Florida

Correspondence
Steven M. Smith, PharmD, MPH, Department of Pharmacotherapy & Translational Research, PO Box 100486, Gainesville, FL.
Email: ssmith@cop.ufl.edu

Funding information
Dr Smith is funded by the National Heart, Lung, and Blood Institute (K01 HL138172). Dr Pepine is also funded by the National Heart, Lung, and Blood Institute (R01 HL132448 and R01 HL033610).

Abstract

Recent guidelines call for more intensive blood pressure (BP)-lowering and a less-stringent treatment-resistant hypertension (TRH) definition, both of which may increase the occurrence of this high-risk phenotype. We performed a post hoc analysis of 11 784 SPRINT and ACCORD-BP participants without baseline TRH, who were randomized to an intensive (<120 mm Hg) or standard (<140 mm Hg) systolic BP target. Incidence, prevalence, and predictors of TRH were compared using the updated definition (requiring ≥4 drugs to achieve BP < 130/80 mm Hg) during intensive treatment, vs the former definition (requiring ≥4 drugs to achieve BP < 140/90 mm Hg) during standard treatment. Incidence/prevalence of apparent refractory hypertension (RFH; uncontrolled BP despite ≥5 drugs) was similarly compared. Overall, 5702 and 6082 patients were included in the intensive and standard treatment cohorts, respectively. Crude TRH incidence using the updated definition under intensive treatment was 30.3 (95% CI, 29.3-31.4) per 100 patient-years, compared with 9.7 (95% CI, 9.2-10.2) using the prior definition under standard treatment. Point prevalence using the prior TRH definition at 1-year was 7.5% in SPRINT and 14% in ACCORD vs 22% and 36%, respectively, with the updated TRH definition. Significant predictors of incident TRH included number of baseline antihypertensive drugs, having diabetes, baseline systolic BP, and Black race. Incidence of apparent RFH was also significantly greater using the updated vs prior definition (4.5 vs 1.0 per 100 person-years). Implementation of the 2017 hypertension guideline, including lower BP goals for most individuals, is expected to substantially increase treatment burden and incident TRH among the hypertensive population.

1 | INTRODUCTION

Cases of difficult-to-control blood pressure (BP) despite treatment with multi-drug regimens—so called "treatment-resistant hypertension" (TRH)—have been recognized for over half a century. This phenotype is known to portend worse outcomes, both in terms of higher risk of adverse cardiovascular outcomes including death,[1-3] and diminished health-related quality of life, compared to non-resistant hypertension.[4] In the 1970s, TRH was considered to be rare and diminishing,[5] particularly at a time when increasingly effective and safer antihypertensive agents were entering the market. However, research over the last decade has shown that, far from being rare, TRH appears to be present in a sizeable proportion of the overall treated hypertensive population. For example, a recent meta-analysis of observational and interventional studies suggests an overall TRH prevalence between 11% and 21% of patients with treated

Trial Registrations: SPRINT (ClinicalTrials.gov number, NCT01206062); ACCORD-BP (ClinicalTrials.gov number, NCT00000620)

hypertension.[6] Furthermore, data from the National Health and Nutrition Examination Survey (NHANES) suggest the prevalence of TRH has more than doubled over the past 25 years.[7]

All prior studies used a TRH definition of requiring ≥3 antihypertensive medications to achieve a BP < 140/90 mm Hg (including use of ≥4 antihypertensive drugs, regardless of BP).[8] However, in 2017, the American College of Cardiology/American Heart Association hypertension guidelines revised the definition for TRH as requiring ≥4 antihypertensive medications to achieve a BP < 130/80 mm Hg.[9] These less-stringent criteria, combined with a lowering of the BP goal in the overall hypertensive population, are anticipated to result in greater antihypertensive use[10] and a corresponding rise in the incidence and overall prevalence of TRH among treated hypertensive patients, but empiric data are lacking. Accordingly, we assessed the incidence, prevalence, and predictors of TRH using the revised definition during treatment to an intensive systolic BP target, vs the prior TRH definition during treatment to a standard systolic BP target (ie, <140 mm Hg), for comparison. We used pooled, patient-level data pooled from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Systolic Blood Pressure Intervention Trial (SPRINT) studies to emulate a randomized comparison of TRH development within the context of current guideline-recommended practice patterns to TRH development during prior hypertension guidance and practice patterns.

2 | METHODS

Details of the design and principal findings of SPRINT[11,12] and ACCORD-BP[13,14] have been published. Briefly, SPRINT was a prospective, randomized, open-label, blinded-endpoint (PROBE) design trial enrolling hypertensive individuals with elevated cardiovascular (CV) risk from across the US, with random assignment to a systolic BP target < 120 mm Hg ("intensive") or <140 mm Hg ("standard"). Participants were aged ≥50 years, with a baseline systolic BP 130 to 180 mm Hg, and ≥1 additional CV risk factor (see Supplement for detailed eligibility criteria). Major exclusion criteria were diabetes or prior stroke. Due to superior benefits of intensive treatment, SPRINT was stopped early.[11]

ACCORD-BP was a PROBE design trial, enrolling patients with type 2 diabetes mellitus, an A1c ≥ 7.5%, age ≥40 years with CV disease or ≥55 years without CV disease, and evidence of elevated CV risk (see additional detail in Supplement). Patients were also required to have a baseline systolic BP between 130 and 180 mm Hg. Major exclusion criteria were BMI ≥ 45 kg/m^2, serum creatinine ≥1.5 mg/dL, 24-hour protein excretion rate ≥1.0 g, ≥2+ on dipstick protein in a spot urine test, ≥700 mg/g protein/creatinine ratio in a spot urine test, or other serious illness.

2.1 | Cohort assembly and outcome ascertainment

Patient-level data from both trials were acquired from the National Heart, Lung, and Blood Institute pursuant to a data use agreement after local Institutional Review Board approval. Complete data were available from ACCORD-BP, whereas only baseline measures, follow-up BP and antihypertensive use (number only, not specific drugs/classes), and outcomes were available from SPRINT.

Data from both trials were pooled, with an indicator for original study, and harmonized. Patients were divided into two cohorts according to random treatment assignment (systolic BP target < 140 mm Hg [standard] or <120 mm Hg [intensive]) and categorized according to TRH status at baseline using treatment arm-specific definitions. For patients assigned the intensive systolic BP target, TRH (referred to hereafter as $TRH_{updated}$) was defined per the 2017 ACC/AHA hypertension guidelines[9] as use of ≥3 antihypertensive drugs with systolic BP ≥ 130 or diastolic BP ≥ 80 mm Hg, or use of ≥4 antihypertensive drugs regardless of BP. For patients assigned to the standard systolic BP target, TRH (referred to hereafter as TRH_{prior}) was defined per the 2008 AHA TRH scientific statement[8] as use of ≥3 antihypertensive drugs with a systolic BP ≥ 140 or diastolic BP ≥ 90 mm Hg, or use of ≥4 antihypertensive drugs regardless of BP. Additional details regarding the rationale and operationalization of these definitions are contained in the Supplement. A thiazide diuretic was not required for either definition in the primary analysis because data on specific antihypertensive drug use were not available from SPRINT. However, inclusion of a diuretic was considered in sensitivity analyses using ACCORD-BP data only. We also performed sensitivity analyses using a more conservative $TRH_{updated}$ definition that considered individuals with controlled systolic BP (<130 mm Hg) while taking 4 antihypertensive drugs as not having TRH, because some of these patients were titrated to the fourth drug per trial protocols even though they would not meet the 2017 hypertension guideline definition for TRH. Patients meeting, at baseline, the definition of $TRH_{updated}$ (intensive arm) or TRH_{prior} (standard arm) were excluded from primary analyses. We then categorized patient-level TRH status at each follow-up visit, using the aforementioned cohort-specific definitions.

We also compared occurrence of apparent refractory hypertension (RFH), using a definition modified from the 2017 hypertension guidelines,[9] as uncontrolled BP despite use of ≥5 antihypertensive drugs, where uncontrolled BP was defined as ≥130/80 mm Hg for the intensive group ($RFH_{updated}$) and ≥140/90 mm Hg for the standard group (RFH_{prior}). Neither aldosterone antagonists nor thiazide diuretic use were required for these definitions because the ACCORD dataset did not explicitly record aldosterone antagonist use, and available SPRINT data did not include patient-level data on specific drugs used.

For assessment of incidence, we identified first occurrence of the outcome (eg, TRH, RFH). For those developing an outcome, timing of the event was determined by the timing of the first visit at which the patient met criteria because actual visit dates were unavailable. For example, a patient first meeting TRH criteria at the 12-month visit was assumed to have developed TRH at exactly 12 months, although the 12-month study visit could have occurred within a pre-specified window around 12 months after randomization. Follow-up in those not developing an outcome was censored

at the time of the last visit at which BP and antihypertensive medication log data were available. The main comparison of interest was incidence (first occurrence) of $TRH_{updated}$ under intensive systolic BP-lowering vs TRH_{prior} under standard systolic BP-lowering. To account for potential variation in TRH status over time, we also assessed incidence of persistent TRH, defined as first occurrence of 2 and 3 consecutive visits with TRH, in sensitivity analyses. We also compared point prevalence of $TRH_{updated}$ and TRH_{prior}, as well as $RFH_{updated}$ and RFH_{prior} at each protocol-mandated visit. Sensitivity analysis was performed on TRH point prevalence by including individuals with baseline TRH. Patients with baseline RFH were largely excluded from both trials; thus, no similar sensitivity analysis was performed on RFH.

Because nonadherence is thought to be a significant contributor to pseudoresistance, we performed sensitivity analyses for TRH incidence and point prevalence that incorporated self-reported medication adherence data from ACCORD-BP (adherence unavailable in SPRINT data). These sensitivity analyses operationalized the TRH definitions as above, but with the additional requirement that adherence for each drug be documented in the medication log as "All or almost all (≥80% of the time)," or "Greater than prescribed (>100% of the time)."

2.2 | Statistical analysis

Crude incidence rates and 95% confidence intervals (CIs) were calculated via Poisson regression and expressed per 100 patient-years. Cumulative incidence curves were created for each outcome. Point prevalences were calculated by dividing the total number of patients meeting TRH (or RFH) criteria by the total number of patients with BP and antihypertensive medication use data at each visit. Because visit timing differed between trials, point prevalence data were calculated separately for each trial.

To identify predictors of incident TRH, Cox proportional hazards models were fit for each treatment cohort separately. Models accounting for all-cause death (via censoring) as a competing risk did not appreciably alter results; thus, the final models did not consider death as a competing risk for simplicity. Study cohort (SPRINT vs ACCORD; also, a proxy for no history of diabetes [SPRINT] or history of diabetes [ACCORD] based on original study inclusion/exclusion criteria) was included as an independent variable in both models. We also examined the following covariates using backward elimination and requiring $P < 0.1$ to stay in the model: age, sex, race/ethnicity, baseline statin use, baseline aspirin use, history of clinical CV disease, smoking status, baseline systolic BP, baseline diastolic BP, Framingham 10-year cardiovascular risk score, body mass index (BMI), baseline estimated glomerular filtration rate (eGFR), baseline glucose, and assignment to an intensive glycemia vs standard glycemia arm; for the latter, all SPRINT patients were considered as receiving standard glycemia treatment. Pairwise interactions between age, sex, and race were also explored. For all models, ties were handled with the Efron method. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

A total of 14 094 patients were included in the pooled cohort: 9361 from SPRINT and 4733 from ACCORD-BP. After exclusion of those with TRH at baseline (n = 2310), 5702 patients remained in the intensive treatment cohort and 6082 in the standard treatment cohort (Figure 1). The modest imbalance in sample size between the treatment cohorts was due to the less restrictive TRH_{prior} definition in the standard treatment cohort, resulting in fewer exclusions for baseline TRH in this group. Pertinent baseline characteristics of each treatment cohort are summarized in Table 1. In general, the cohorts were similar, consistent with randomization employed in both trials. Baseline characteristics of excluded patients are summarized in Table S1.

3.1 | Incidence

Among patients assigned to the intensive systolic BP goal, 3256 (57.1%) developed $TRH_{updated}$ during 10 740 patient-years of follow-up, for an overall crude incidence rate of 30.3 (95% CI, 29.3-31.4) per 100 patient-years. Among patients assigned to the standard systolic BP goal, 1653 (27.2%) developed TRH_{prior} over 17 052 patient-years, for an overall crude incidence rate of 9.7 (95% CI, 9.2-10.2) per 100 patient-years. Figure 2 displays cumulative incidence curves for each TRH definition. TRH incidence was higher among ACCORD-BP compared with SPRINT participants (Figure S1). Sensitivity analyses considering individuals with controlled BP while taking 4 antihypertensives as not having TRH revealed only a modest reduction in incidence of $TRH_{updated}$ (27.9 per 100 patient-years; 95% CI, 27.0-28.9). Likewise, sensitivity analyses incorporating adherence into the TRH definitions revealed only modestly lower incidences (Figure S2). As shown in Figure S3, the incidence of persistent TRH (ie, requiring a patient to meet TRH criteria over consecutive visits) was lower, with both definitions, compared with the primary analysis (ie, requiring only a single visit where TRH criteria were met). However, incidence rate ratios (comparing incidence of $TRH_{updated}$ to TRH_{prior}) were modestly increased with persistent TRH definitions compared with the primary analysis, suggesting that the greater incidence of $TRH_{updated}$ was not markedly influenced by single visits meeting TRH criteria.

The incidence of TRH, regardless of the definition/treatment assignment, was associated with number of antihypertensive agents used at enrollment (Figure 3). Among those randomly assigned to the intensive systolic BP goal, $TRH_{updated}$ incidence was approximately 20 per 100 patient-years, whether treated with 0 or 1 antihypertensive drugs at baseline. In contrast, among persons taking 3 antihypertensive drugs at baseline who were assigned to intensive systolic BP goal, the $TRH_{updated}$ incidence rate was 85.1 (95% CI, 75.4-96.0) per 100 patient-years. Similar trends were observed with TRH_{prior}.

Incident RFH was considerably less common, compared with incident TRH. Cumulative incidence curves for apparent RFH are displayed in Figure 4. During a total of 22 094 person-years, 997 individuals in the intensive arm met $RFH_{updated}$ criteria, for a crude

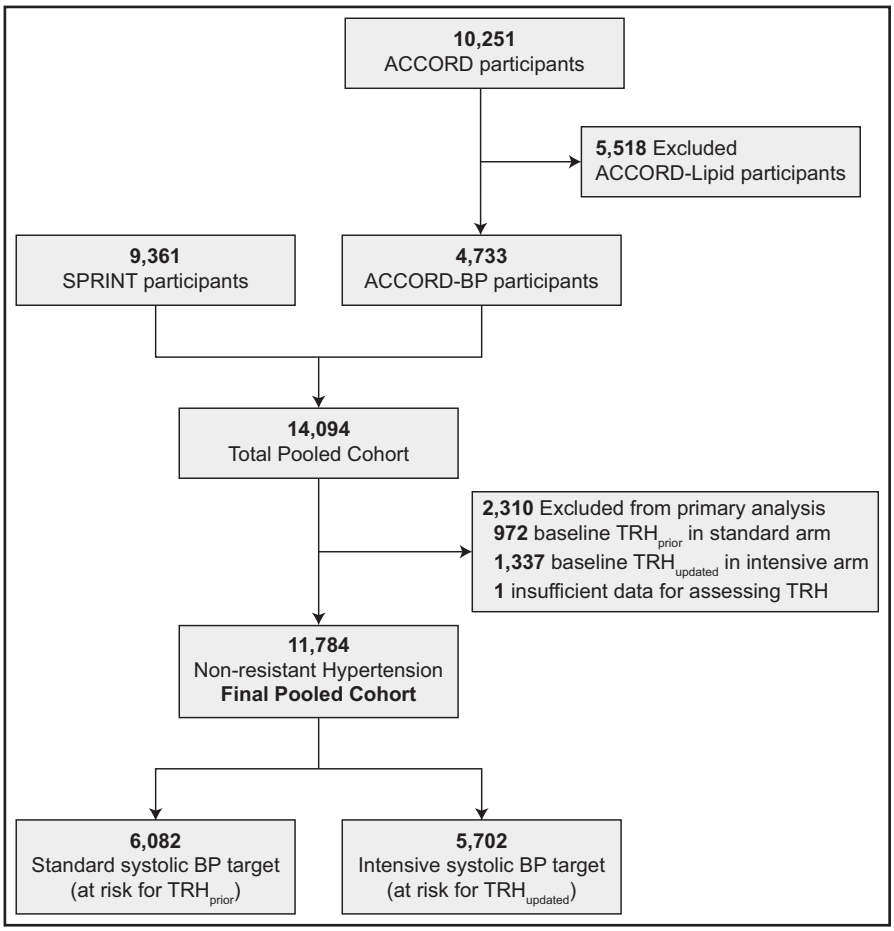

FIGURE 1 Flow diagram for cohort assembly for primary analysis. ACCORD, Action to Control Cardiovascular Risk in Diabetes; BP, blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial; TRH, treatment-resistant hypertension

incidence rate of 4.5 (95% CI, 4.2-4.8) per 100 person-years. Among those assigned to the standard arm, 231 met RFH_{prior} criteria during a total of 24 112 person-years, for a crude incidence rate of 1.0 (95% CI, 0.8-1.1) per 100 person-years.

3.2 | Point prevalence

Point prevalence of TRH during follow-up, according to study (SPRINT vs ACCORD-BP), is summarized in Figure 5. At year 1, 22% of SPRINT and 36% of ACCORD-BP participants assigned to an intensive systolic BP target were classified as having $TRH_{updated}$. By year 4, the prevalence had modestly increased to 26% and 48%, respectively. In contrast, with a standard systolic BP target, the prevalence of TRH_{prior} at year 1 was 7.5% in SPRINT and 14% in ACCORD-BP. Thereafter, TRH_{prior} prevalence was essentially unchanged in SPRINT and increased only modestly in ACCORD-BP (17% at year 4; 25% at year 7). Sensitivity analyses using ACCORD-BP data only, and requiring minimum adherence levels or a diuretic in the definitions of TRH, revealed qualitatively similar findings (Figure S4). Similarly, sensitivity analyses using an alternative data source for medication use data in ACCORD-BP (see Supplement for additional details) revealed similar findings (data not shown). Inclusion of patients with TRH at baseline caused a modest upward shift in point prevalence estimates (Figure S5).

Similar to TRH prevalence, RFH prevalence was greater among ACCORD-BP than SPRINT participants. At year 1, 2.2% of SPRINT participants and 5.3% of ACCORD-BP participants met $RFH_{updated}$ criteria, compared with 0.4% and 1.2%, respectively, meeting RFH_{prior} criteria. Thereafter, prevalences for both RFH definitions remained essentially unchanged in SPRINT and increased only modestly in ACCORD-BP (Figure S6).

3.3 | Predictors of incident treatment-resistant hypertension

Table 2 summarizes results of the full models assessing predictors of incident TRH in each cohort. The predictors of incident TRH, regardless of the definition or cohort, were number of baseline antihypertensive agents, being an ACCORD-BP participant (also an indicator for having diabetes), baseline systolic BP, and Black race. Significant predictors were largely similar for each definition of TRH, except that female sex portended an 18% lower risk of developing $TRH_{updated}$, whereas sex was not a significant predictor for TRH_{prior}, and history of clinical cardiovascular disease was associated with a

TABLE 1 Baseline characteristics, by random treatment assignment, among patients with non-resistant hypertension at baseline

Characteristic	Intensive (n = 5702)	Standard (n = 6082)
Study		
SPRINT	3682 (64.6%)	3953 (65.0%)
ACCORD-BP	2020 (35.4%)	2129 (35.0%)
Intensive glycemia arm[a]	1020 (50.5%)	1087 (51.1%)
Age	65.9 ± 8.8	65.9 ± 8.9
Female sex	2247 (39.4%)	2365 (38.9%)
Race/Ethnicity		
White	3401 (59.7%)	3554 (58.4%)
Black	1458 (25.6%)	1644 (27.0%)
Other	304 (5.3%)	300 (4.9%)
Hispanic	539 (9.5%)	584 (9.6%)
History of clinical CVD	1232 (21.6%)	1313 (21.6%)
Framingham risk score, %	38.9% ± 25.4%	38.4% ± 25.1%
Smoking status		
Never	2519 (44.2%)	2692 (44.3%)
Past	2363 (41.5%)	2577 (42.4%)
Current	552 (9.7%)	529 (8.7%)
Unknown	264 (4.6%)	280 (4.6%)
Statin Use	2767 (48.8%)	3081 (51.0%)
Aspirin Use	2896 (51.0%)	2982 (49.3%)
Number of antihypertensives		
0 drugs	981 (17.2%)	1006 (16.5%)
1 drug	2079 (36.5%)	2089 (34.4%)
2 drugs	2325 (40.8%)	2303 (37.9%)
3 drugs	317 (5.6%)	684 (11.3%)
Mean ± SD	1.35 ± 0.83	1.44 ± 0.90
Laboratory values		
TC, mg/dL	193 ± 43	191 ± 43
HDL, mg/dL	51 ± 14	51 ± 15
LDL, mg/dL	113 ± 37	112 ± 36
Triglycerides, mg/dL	149 ± 131	150 ± 141
Glucose, mg/dL	126 ± 52	125 ± 51
eGFR, mL/min	80 ± 26	80 ± 25
UACR, mg/g	54 ± 216	53 ± 233
SCr, mg/dL	0.99 ± 0.31	1.00 ± 0.30
Baseline BP		
Systolic, mm Hg	139 ± 16	138 ± 15
Diastolic, mm Hg	77 ± 11	77 ± 11
BMI, kg/m^2	30.4 ± 5.8	30.5 ± 5.7

Note: Data represent mean ± SD or No. (%).
Abbreviations: 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; TC, total cholesterol; UACR, urinary albumin-to-creatinine ratio.
[a]Row percentages calculated using ACCORD-BP sample sizes (row directly above) as the denominator.

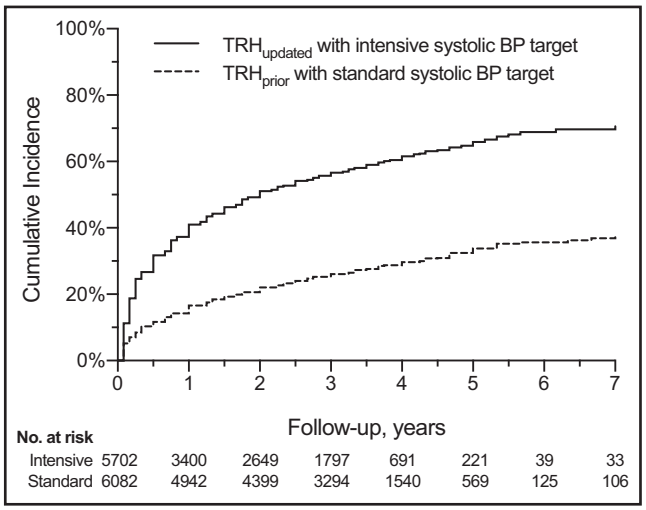

FIGURE 2 Cumulative incidence of treatment-resistant hypertension when targeting an intensive systolic vs standard systolic blood pressure. BP, blood pressure; TRH, treatment-resistant hypertension

20% greater risk of incident TRH$_{prior}$, but had no association with TRH$_{updated}$. However, confidence intervals for each risk factor comparison between the two TRH definitions overlapped and observed differences may be an artifact of statistical imprecision. In exploratory analyses, we also observed a significant interaction between sex and age on predicting TRH$_{updated}$, such that female sex was highly protective against incident TRH$_{updated}$ at younger ages, but not older ages (Figure S7).

4 | DISCUSSION

Data on the incidence of TRH are scarce, and no prior research has assessed the incidence of TRH using recently revised hypertension guidelines calling for more aggressive BP lowering and an expanded TRH definition. Accordingly, we assessed incident TRH following intensive antihypertensive treatment targeting lower BP goals and contrasted that with the incidence of TRH using the former definition, under treatment to a BP target < 140/90 mm Hg. Our results suggest a high rate of new-onset TRH may be expected among patients receiving antihypertensive therapy under current hypertension guidance in the US. Specifically, we observed an approximately 3-fold greater incidence of TRH comparing the recently updated definition to the prior definition. We found several clinical factors, including black race, baseline cardiovascular disease, and BMI (in addition to systolic BP and number of antihypertensive drugs) that portended increased risk for developing TRH, regardless of the definition, whereas female sex, higher diastolic BP, and higher eGFR were associated with lower risk. Finally, we also observed a 4.5-fold greater incidence of apparent RFH comparing the recently updated definition to the prior definition.

The authors of the 2017 AHA/ACC hypertension guidelines explicitly predicted that the revised TRH definition would likely

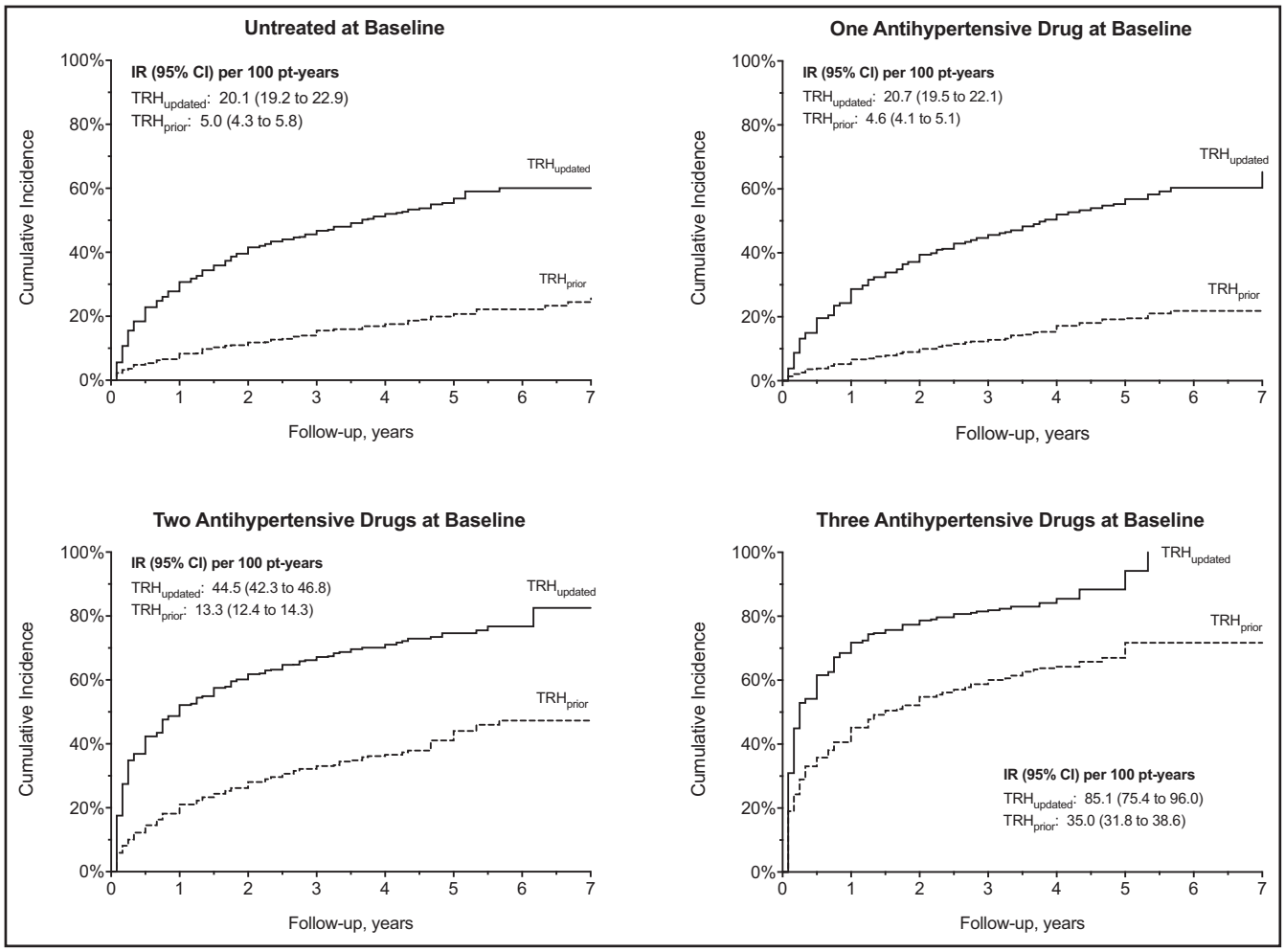

FIGURE 3 Treatment-resistant hypertension incidence stratified by number of antihypertensive agents prescribed at trial baseline. IR, incidence rate; TRH, treatment-resistant hypertension

increase prevalence by approximately 4%. The evidence base for this estimate is unclear, although it may stem from unpublished analyses of the number of individuals prescribed three drugs with a systolic BP between 130 and 139 mm Hg or diastolic BP between 80 and 89 mm Hg using NHANES data. A recent report using NHANES data from 2009 to 2014 observed a similarly small increase in prevalence of TRH comparing the updated definition (19.7% prevalence) vs the prior definition (17.7%).[15] However, these underlying data, collected prior to implementation of the new hypertension guidelines, do not account for the change in prescribing intensity stemming from the revised BP target for the general hypertensive population. In effect, the 2% increase may be thought of as the expected prevalence increase, only if clinical practice was to remain unchanged from 2014. We hypothesized that the increase in incidence and prevalence of TRH (using the recently updated definition[9]) with more intensive treatment targets would be markedly more elevated than 4%. Using the new TRH definition, we observed an overall crude incidence rate of 30.3 per 100 patient-years and a 1-year point prevalence between 22% and 36%, depending on the trial population, among patients without baseline TRH. By the end of follow-up, nearly 70% of patients had met the new criteria for TRH, and nearly one-in-four had met new criteria for apparent RFH, at some point during the trials. The same trends in TRH incidence and prevalence were observed for patients with untreated hypertension at baseline, who require substantial antihypertensive titration to meet TRH criteria, and those with 2 or 3 antihypertensive drugs at baseline, who may require minimal antihypertensive titration to meet TRH criteria. Regardless of the baseline number of antihypertensives used, TRH incidence with intensive treatment to meet lower BP targets, as compared to standard treatment, was approximately 3 to 4 times greater. These findings suggest that the proportion of patients who will be classified as having TRH under the recent ACC/AHA guidelines will rise substantially, contingent on incorporation of these treatment recommendations into real-world practice.

Compared to epidemiologic data such as offered by NHANES, we were able to emulate clinical practice where new BP targets were implemented, using two clinical trials that indeed employed lower targets. However, our results must also be interpreted with some caution. The systolic BP targeted in the intensive arms of SPRINT and ACCORD-BP (<120 mm Hg) is lower than the recently updated

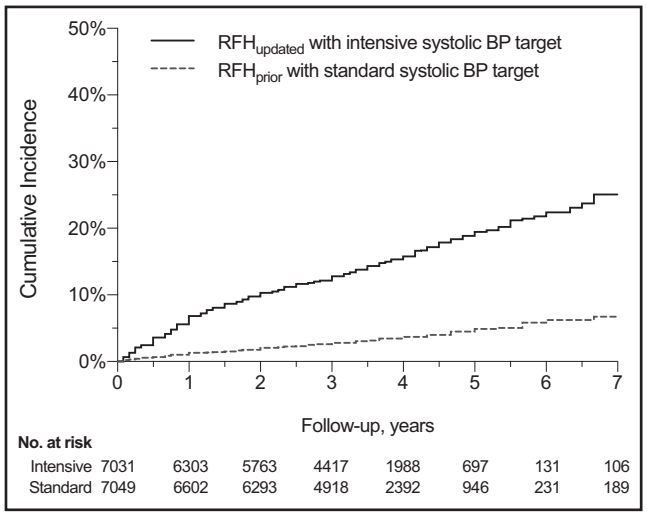

FIGURE 4 Cumulative incidence of apparent refractory hypertension, comparing definitions incorporating the updated blood pressure goal vs the prior blood pressure goal. Refractory hypertension was defined as uncontrolled blood pressure despite use of ≥5 antihypertensive drugs, where uncontrolled was defined as ≥130 mm Hg systolic or ≥80 mm Hg diastolic ($RFH_{updated}$), or ≥140 mm Hg systolic or ≥90 mm Hg diastolic (RFH_{prior}). RFH, refractory hypertension

TABLE 2 Hazard ratios and 95% confidence intervals from full models assessing predictors of incident treatment-resistant hypertension, by treatment cohort

Parameters	Intensive systolic BP cohort	Standard systolic BP cohort
Dependent variable	$TRH_{updated}$	TRH_{prior}
Independent variables[a]		
ACCORD-BP participant	1.60 (1.43-1.79)	1.21 (1.03-1.41)
Age (per decade)	0.99 (0.94-1.04)	1.02 (0.95-1.09)
Female sex	0.82 (0.76-0.88)	0.95 (0.85-1.05)
Black race	1.19 (1.10-1.29)	1.44 (1.28-1.61)
Smoking status		
Former vs never smoker	0.97 (0.90-1.05)	1.01 (0.91-1.13)
Current vs never smoker	1.12 (0.98-1.28)	1.02 (0.82-1.27)
Unknown vs never smoker	1.13 (0.96-1.33)	1.34 (1.07-1.66)
Clinical CV disease	1.08 (0.99-1.18)	1.20 (1.07-1.35)
Systolic BP (per 10 mm Hg)	1.36 (1.32-1.39)	1.50 (1.45-1.56)
Diastolic BP (per 10 mm Hg)	0.93 (0.89-0.97)	0.91 (0.86-0.96)
No. of antihypertensive drugs	1.89 (1.81-1.98)	2.45 (2.30-2.62)
BMI (per 5 kg/m^2)	1.08 (1.04-1.11)	1.09 (1.05-1.14)
eGFR (per 10 mL/min)	0.96 (0.94-0.98)	0.96 (0.93-0.98)
Glucose (per 10 mg/dL)	1.02 (1.01-1.02)	1.02 (1.01-1.03)

Note: Non-significant predictors included Hispanic ethnicity, Framingham risk score, statin use, aspirin use, cholesterol parameters, and randomization to the intensive glycemia arm (in ACCORD).
Abbreviations: BMI, body mass index; BP, blood pressure; CV, cardiovascular; eGFR, estimated glomerular filtration rate.
[a]Measured at study baseline visit.

systolic BP target (<130 mm Hg) in the guidelines.[9] Accordingly, in SPRINT and ACCORD, some patients with a systolic BP between 120 and 129, while using three drugs, were titrated to a fourth antihypertensive drug and, in our primary analysis, would have met the $TRH_{updated}$ definition, even though they would not meet the TRH definition in the updated guidelines. Nevertheless, in sensitivity analyses, we conservatively considered such individuals as not having TRH, which revealed only a modestly attenuated incidence of $TRH_{updated}$.

To our knowledge, only two prior studies have published data on TRH incidence, both of which used electronic health record (EHR) data from real-world treatment settings, and both assessed incidence of TRH using the former definition (with BP control as <140/90 mm Hg) under a BP target < 140/90 mm Hg.[16,17] In the first study, researchers assessed the incidence of TRH among 205 750 patients with incident treated hypertension in the Kaiser Permanente system.[16] After excluding patients with insufficient data or follow-up (9%) and poor adherence, they found that 1.9% of patients developed TRH over a median 1.5 years and observed a crude incidence rate of 0.7 per 100 patient-years. In the second study, researchers analyzed EHR data from 1.32 million primary care patients with treated hypertension contained in the UK Clinical Practice Research Datalink database for cases of TRH (again, using the prior US definition[8] and excluding patients for nonadherence).[17] From 1995 to 2015, they found a crude incidence rate ranging between 0.4 and 2.1 per 100 person-years, and point prevalences between 1.8% and 8.2%, depending on the year. In contrast, we observed a crude incidence rate of 9.4 per 100 person-years and a prevalence between 7.5% and 14% (among those with non-resistant hypertension at baseline) at year 1, using a similar TRH definition as in these studies and under mostly similar hypertension treatment guidance (excepting earlier years in the UK study). In our primary analysis, we did not require adherence to the antihypertensive regimen in the definition of TRH as in these prior studies. Our sensitivity analyses using ACCORD-BP data suggested very little reduction in the observed TRH incidence or prevalence when adherence requirements were added; however, whether self-reported adherence is an accurate measure in patients with TRH has been questioned.[18]

The significantly higher incidence and prevalence observed in our study likely stems from differences in clinical practice and patient populations. SPRINT and ACCORD-BP were randomized trials targeting specific BP thresholds, with frequent follow-up, encouraging rapid antihypertensive titration for uncontrolled BP, and providing most antihypertensives free of charge. In contrast, the observational studies likely reflect real-world clinical practice with less frequent provider visits and fewer opportunities to titrate medications, possible treatment inertia, and, for some patients, difficulty in attaining antihypertensive medications. Secondly, SPRINT and ACCORD-BP

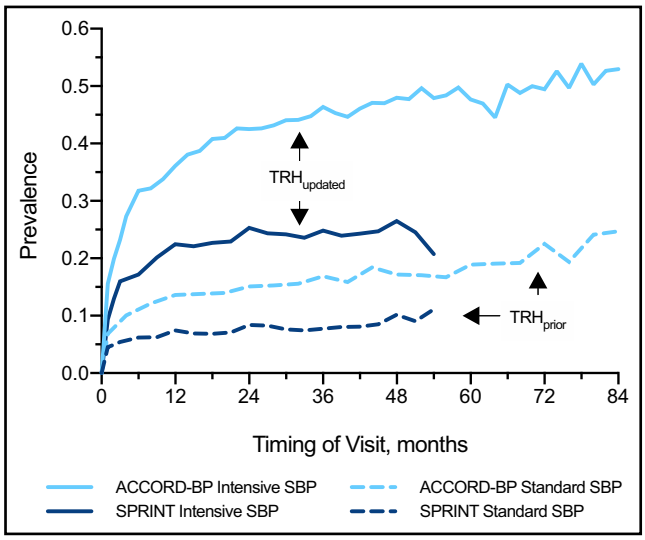

FIGURE 5 Point prevalence for treatment-resistant hypertension, by definition, study, and treatment cohort, during follow-up. SBP, systolic blood pressure, TRH, treatment-resistant hypertension

patients were, by design, a higher risk patient population than the general primary care population. Numerous cardiovascular co-morbidities have been associated with prevalent TRH, and it seems likely that our pooled patient population was at a higher baseline risk than these general primary care populations, even though SPRINT, in particular, enrolled a lower-risk population than planned.

Finally, we observed little difference between predictors, and the magnitude of their association, comparing the prior and updated TRH definitions. Consistent with prior research,[3,19-21] persons self-identifying as Black and those with greater BMI and poorer kidney function were at increased risk of developing TRH, regardless of the TRH definition. ACCORD-BP participants, compared with SPRINT participants, were also at a significantly greater risk. We suspect this finding serves as a proxy for diabetes status because all ACCORD-BP patients were diabetic, whereas such patients were excluded from SPRINT. Prior studies have shown diabetes to be a significant predictor of TRH,[3,20,21] and in our analysis, greater baseline glucose concentration predicted greater risk of TRH. Nevertheless, enrollment in ACCORD-BP and having a history of diabetes were inextricably linked; therefore, no strong conclusions can be made on this point. Interestingly, age was not significantly associated with TRH development, which contrasts with prior research. We explored interactions between age, sex, and race, and observed a significant interaction between age and sex, specifically that female sex was protective against $TRH_{updated}$ in younger persons, but not those aged ≥80 years. This finding accords with prior research showing that fewer women have HTN at ages <45 years, whereas the reverse is true in those aged ≥65 years, and women tend to require more antihypertensive agents, but are less likely to achieve BP control than age-matched men in older populations.[22-24]

The strengths of our study include pooling of data from trials with remarkably similar populations (excepting diabetes) and treatment protocols, resulting in a large cohort with non-resistant hypertension who were assigned treatment to standard or intensive systolic BP targets, with up to 7 years of follow-up. Nevertheless, there are noteworthy limitations. First, this was a post hoc analysis of randomized controlled trial data. Randomization appears to have been conserved in our restricted treatment cohorts, suggesting that the average patient at risk of TRH (or RFH) in each treatment cohort was similar. Nevertheless, we cannot be certain that unmeasured factors were similarly distributed between treatment arms within this subset of the overall trial populations; such factors could have impacted the observed incidence and prevalence. Second, our TRH and RFH definitions in the primary analysis did not require a thiazide diuretic because data on specific drug use were not available for SPRINT. However, sensitivity analyses with ACCORD-BP data revealed only a modest lowering of the incidence and prevalence when the TRH definition was inclusive of a diuretic. And, we[3] and others[25] have previously shown no appreciable difference in risk of outcomes whether a diuretic is included or not, and we are aware of no other contrary data. Similarly, we did not require "optimal" doses of antihypertensives, as sometimes specified in TRH definitions. However, it seems likely that most patients titrated per study algorithms to drug-specific dosing ranges would have been on optimal doses of antihypertensive therapy. Furthermore, any error in the estimation of incidence and prevalence due to not requiring a diuretic or optimal dosing would likely be similar for both treatment arms (and by extension, both definitions), and therefore unlikely to bias the relative difference (eg, the incidence rate ratio). Third, our analysis of predictors of TRH was somewhat restrained by the availability of baseline data from SPRINT, which at the time of this study, were limited to only data reported in the primary outcome paper.[11] Finally, women were underrepresented in these trials. Hypertension is highly prevalent among women in the age group enrolled, and they are at high risk for developing TRH and accompanying adverse outcomes.[26] Our results suggest that, had a greater proportion of women, particularly those aged 50-79 years, been enrolled in these trials, the observed incidence and prevalence of $TRH_{updated}$ may have been lower.

In conclusion, our findings document a high incidence and prevalence of TRH, using the recently revised criteria,[9] when patients are treated to a more intensive systolic BP target. These data suggest that recent guidance from the ACC/AHA hypertension guidelines, which lowered the target BP goal to <130/80 mm Hg for most patients, are likely to result in a substantially greater increase in the proportion of treated hypertensive patients who qualify as having TRH than previously thought. Future research will be needed to better understand TRH development under real-world treatment conditions as the new guidelines are implemented. Furthermore, additional research is needed to better understand the implications of the increased prevalence and incidence, including whether the updated TRH definition identifies patients at similarly high cardiovascular risk compared with the prior definition.

ACKNOWLEDGMENTS

This manuscript was prepared using ACCORD and SPRINT Research Materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the ACCORD and SPRINT investigators or the NHLBI.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Steven M. Smith: Study design, attainment of data, statistical analyses, drafting of the manuscript. Matthew J. Gurka: Study design, statistical analyses, critical review of the manuscript. Almut G. Winterstein: Study design, statistical analyses, critical review of the manuscript. Carl J. Pepine: Study design, critical review of the manuscript. Rhonda M. Cooper-DeHoff: Study design, critical review of the manuscript.

ORCID

Steven M. Smith https://orcid.org/0000-0002-0201-839X

REFERENCES

1. Irvin MR, Booth JN, 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.
2. 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.
3. 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.
4. 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.
5. Gifford RW, Tarazi RC. Resistant hypertension: diagnosis and management. *Ann Intern Med*. 1978;88(5):661-665.
6. Achelrod D, Wenzel U, Frey S. Systematic review and meta-analysis of the prevalence of resistant hypertension in treated hypertensive populations. *Am J Hypertens*. 2015;28(3):355-361.
7. Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. *Circulation*. 2011;124(9):1046-1058.
8. 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.
9. 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(6):e13-e115.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. Carey RM, Sakhuja S, Calhoun DA, Whelton PK, Muntner P. Prevalence of apparent treatment-resistant hypertension in the United States: comparison of the 2008 and 2018 American heart association scientific statements on resistant hypertension. *Hypertension*. 2019;73:424-431.
16. Daugherty SL, Powers JD, Magid DJ, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation*. 2012;125(13):1635-1642.
17. Sinnott SJ, Smeeth L, Williamson E, Douglas IJ. Trends for prevalence and incidence of resistant hypertension: population based cohort study in the UK 1995–2015. *BMJ*. 2017;358:j3984.
18. Pandey A, Raza F, Velasco A, et al. Comparison of morisky medication adherence scale with therapeutic drug monitoring in apparent treatment-resistant hypertension. *J Am Soc Hypertens*. 2015;9(6):420-426.e422.
19. Bangalore S, Fayyad R, Laskey R, et al. Prevalence, predictors, and outcomes in treatment-resistant hypertension in patients with coronary disease. *Am J Med*. 2014;127(1):71-81.e71.
20. Gupta AK, Nasothimiou EG, Chang CL, Sever PS, Dahlöf B, Poulter NR. Baseline predictors of resistant hypertension in the anglo-scandinavian cardiac outcome trial (ASCOT): a risk score to identify those at high-risk. *J Hypertens*. 2011;29(10):2004-2013.
21. Cushman WC, Ford CE, Cutler JA, et al. Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *J Clin Hypertens (Greenwich)*. 2002;4(6):393-404.
22. Gu Q, Burt VL, Paulose-Ram R, Dillon CF. Gender differences in hypertension treatment, drug utilization patterns, and blood pressure control among US adults with hypertension: data from the national health and nutrition examination survey 1999–2004. *Am J Hypertens*. 2008;21(7):789-798.
23. Gu Q, Burt VL, Dillon CF, Yoon S. Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the national health and nutrition examination survey, 2001 to 2010. *Circulation*. 2012;126(17):2105-2114.
24. Daugherty SL, Masoudi FA, Ellis JL, et al. Age-dependent gender differences in hypertension management. *J Hypertens*. 2011;29(5):1005-1011.
25. 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.e439.
26. 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.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Smith SM, Gurka MJ, Winterstein AG, Pepine CJ, Cooper-DeHoff RM. Incidence, prevalence, and predictors of treatment-resistant hypertension with intensive blood pressure lowering. *J Clin Hypertens*. 2019;21:825–834. https://doi.org/10.1111/jch.13550