

DATA REPORT

Redefining Resistant Hypertension

A Comparison of Cardiovascular Risk Associated With the 2018 Versus 2008 American Heart Association Definitions for Resistant Hypertension

Prior US and most current other hypertension guidelines define treatment-resistant hypertension (TRH) as requiring ≥ 4 antihypertensive drugs to achieve blood pressure (BP) $< 140/90$ mm Hg, and this phenotype has been consistently linked with increased risk of major adverse cardiovascular outcomes, relative to nonresistant hypertension.^{1,2} In 2017, US hypertension guidelines updated the TRH definition to requiring ≥ 4 antihypertensive drugs to achieve BP $< 130/80$ mm Hg, consistent with the BP target promulgated for most hypertensive individuals.^{1,3} This expanded definition and recommendations for more intensive treatment, generally, are expected to significantly increase TRH incidence and prevalence by now including individuals with presumably lower-risk profiles, that is, people taking 3 antihypertensives with a systolic BP between 130 and 139 or diastolic BP between 80 and 89 mm Hg.⁴ Yet, whether these revised TRH criteria identify a population with poor prognosis, similar to that observed with the prior US definition, is unknown. Therefore, we sought to compare updated and prior TRH definitions on risk of adverse cardiovascular events using patient-level data from the SPRINT (Systolic Blood Pressure Intervention Trial) and ACCORD (Action to Control Cardiovascular Risk in Diabetes) trials.

METHODS AND RESULTS

All data supporting the findings of this study are available from the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center, accessible at <https://biolincc.nhlbi.nih.gov/home/>. The design and results of SPRINT and ACCORD have been published previously.^{5,6} Briefly, both were prospective, randomized, open-label, blinded-end point trials comparing an intensive (< 120 mm Hg) versus standard (< 140 mm Hg) systolic BP target among high-risk individuals with hypertension and diabetes mellitus (ACCORD) or hypertension without diabetes mellitus (SPRINT) at baseline (see additional detail in the [Data Supplement](#)). Patient-level data from both trials were pooled and harmonized (Figure S1 in the [Data Supplement](#)); specific data elements included baseline demographics and clinical characteristics (detailed below), clinic BP measurements at each visit, medication use at each visit, and outcomes. Daily BP values between study visits were estimated using linear interpolation. Medication use and adherence were determined via detailed study medication logs, which included information on specific medications but not doses. Using these data, we determined apparent TRH (aTRH) status for each patient throughout the trial, taking advantage of treatment arm-specific BP targets that allowed definition of aTRH according to previous and updated guidelines. The term aTRH is used to signify the fact that data constraints (eg, lack of antihypertensive dosing information and out-of-office BP) did not allow for exclusion of pseudoresistance. For patients assigned the intensive target, aTRH (hereafter, aTRH_{updated}) was defined per the 2018 TRH scientific statement¹ as a systolic BP ≥ 130 or diastolic BP ≥ 80 mm Hg with adherent use of ≥ 3 antihypertensive drugs from different classes, including a diuretic; or, adherent use of ≥ 4 antihypertensive drugs from different classes, including a diuretic, regardless of BP. For patients assigned the standard target, aTRH (hereafter, aTRH_{prior}) was defined per the 2008 TRH scientific statement⁷ as having a

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systolic BP ≥ 140 or diastolic BP ≥ 90 mm Hg with adherent use of ≥ 3 antihypertensive drugs, including a diuretic, or adherent use of ≥ 4 antihypertensive drugs, including a diuretic, regardless of BP. To minimize misclassification following therapy adjustments, we required BP to remain uncontrolled for >7 days following the addition of a third antihypertensive agent before a patient could meet aTRH criteria (aTRH_{prior} in standard arm; aTRH_{updated} in intensive arm). For patients beginning a fourth antihypertensive drug, aTRH was considered to occur beginning on the date the fourth drug was added, with no lag period. Using daily aTRH status, we then calculated cumulative aTRH exposure, updated throughout follow-up. Patients meeting aTRH criteria at baseline were excluded from the analysis because prior duration of aTRH was unknown.

The primary outcome was first occurrence of myocardial infarction, stroke, heart failure, or cardiovascular death, a hybrid of the SPRINT and ACCORD primary outcomes (see additional details in the [Data Supplement](#)). These same events were considered individually as secondary outcomes. Cox proportional hazards models were fit, regressing the outcome on time-updated cumulative aTRH exposure as a 4-level categorical variable (none [referent]; <4 months; 4 months to <1.5 years; and ≥ 1.5 year); these category thresholds were determined using approximate tertile boundaries for cumulative exposure-time among exposed. Separate models were fit for each exposure-outcome comparison, within each treatment cohort stratum (intensive, standard). Adjusted models were fit for each exposure-outcome comparison as above but with a propensity score summarizing information on original study cohort (SPRINT versus ACCORD), and potential confounders including baseline age, sex, history of clinical cardiovascular disease, smoking status, estimated glomerular filtration rate, total cholesterol, high-density lipoprotein cholesterol, glucose, and assignment to the intensive glycemia versus standard glycemia arm in ACCORD; all SPRINT patients were considered as receiving standard glycemia treatment. Finally, in pooled analysis of all patients, we regressed each outcome on time-varying aTRH status, type of aTRH definition (prior versus updated) and their interaction to determine whether risk differences between aTRH_{updated} and aTRH_{prior} were significant. Analyses were performed with SAS 9.4 (SAS Institute, Cary, NC). This research was approved by the University of Florida Institutional Review Board.

Among 14 094 individuals enrolled, 12 392 ($n=8353$ from SPRINT; $n=4039$ from ACCORD) had no evidence of aTRH at baseline and are included here. Of these, 5707 (46.1%) met aTRH criteria at some point during follow-up, including 61% of those assigned to the intensive target meeting aTRH_{updated} criteria, and 32% assigned the standard target meeting aTRH_{prior} criteria. Baseline characteristics are summarized in Table S1 in the [Data Supplement](#).

During 49 873 person-years of follow-up, 1007 patients (8.1%) experienced the primary outcome (myocardial infarction, stroke, heart failure, or cardiovascular death). Crude incidences appear in Tables S2 and S3 in the [Data Supplement](#). In unadjusted analyses, aTRH_{prior} was associated with increased risk for all outcomes. Likewise, aTRH_{updated} was associated with excess risk of the primary outcome and most individual outcomes but only with longer exposure periods (Figure S2 in the [Data Supplement](#)). In propensity score-adjusted analyses, aTRH_{prior} exposure was associated with greater risk of the primary outcome, ranging from 51% increased risk for

<4 months exposure versus no exposure (hazard ratio [HR], 1.51 [95% CI, 1.20–1.92]) to more than doubling the risk for ≥ 1.5 years exposure versus no exposure (HR, 2.33 [95% CI, 1.70–3.19]). Similar findings were observed for individual outcomes, where the longest exposure-times were associated with the highest point estimates, although the relationship between exposure-time and outcomes was not uniform and CIs overlapped to some degree in all cases (Figure). Conversely, aTRH_{updated} exposure was associated with more modestly elevated risk of the primary outcome, but only at longer exposure-times (HR, 1.28 [95% CI, 0.98–1.67] for 0.4 months to <1.5 years versus no exposure; and HR, 1.41 [95% CI, 1.02–1.95] for ≥ 1.5 years versus no exposure). Likewise, aTRH_{updated} exposure ≥ 1.5 years (versus none) was associated with greater risk of heart failure (HR, 1.93 [95% CI, 1.15–3.22]) and cardiovascular death (HR, 1.98 [95% CI, 1.00–3.95]). In pooled models, including an interaction term between aTRH definition and time-varying aTRH status, we found no evidence of significant risk differences among aTRH definitions (all interaction $P>0.1$).

COMMENT

The 2017 US hypertension guidelines redefined TRH to be consistent with the threshold for uncontrolled BP in the general population, but without empirical assessment of whether this new definition still identifies high-risk individuals who may benefit from closer follow-up and additional therapeutic intervention. We compared this new US aTRH definition, now employed under more intensive treatment recommendations, with the prior US aTRH definition employed under prior treatment norms, in terms of cardiovascular outcome risk. We found that the new US definition appears to effectively discriminate a higher-risk population, for most cardiovascular outcomes studied, when aTRH persists long-term. Although we observed no significant difference in risk comparing the 2 definitions, the generally lower hazard ratio point estimates for aTRH_{updated} versus aTRH_{prior} are consistent with prior findings of a benefit with intensive treatment among people with aTRH using the updated definition.⁸

Major strengths of this analysis are that we used pooled clinical trial data with similar standardized treatment algorithms and adjudicated outcomes. And, we compared the aTRH definitions approximating the treatment context within which they would be used, that is, the updated definition under more intensive BP targets, and the prior definition under previously standard targets. However, it must be noted that our estimates of risk with the new aTRH definition were derived under a systolic BP goal <120 mm Hg as employed in SPRINT/ACCORD, whereas the new US systolic BP goal is <130 mm Hg.

In sum, our data suggest that the current US definition of TRH will significantly broaden the population now classified as having TRH and that such patients remain at elevated risk of cardiovascular outcomes rela-

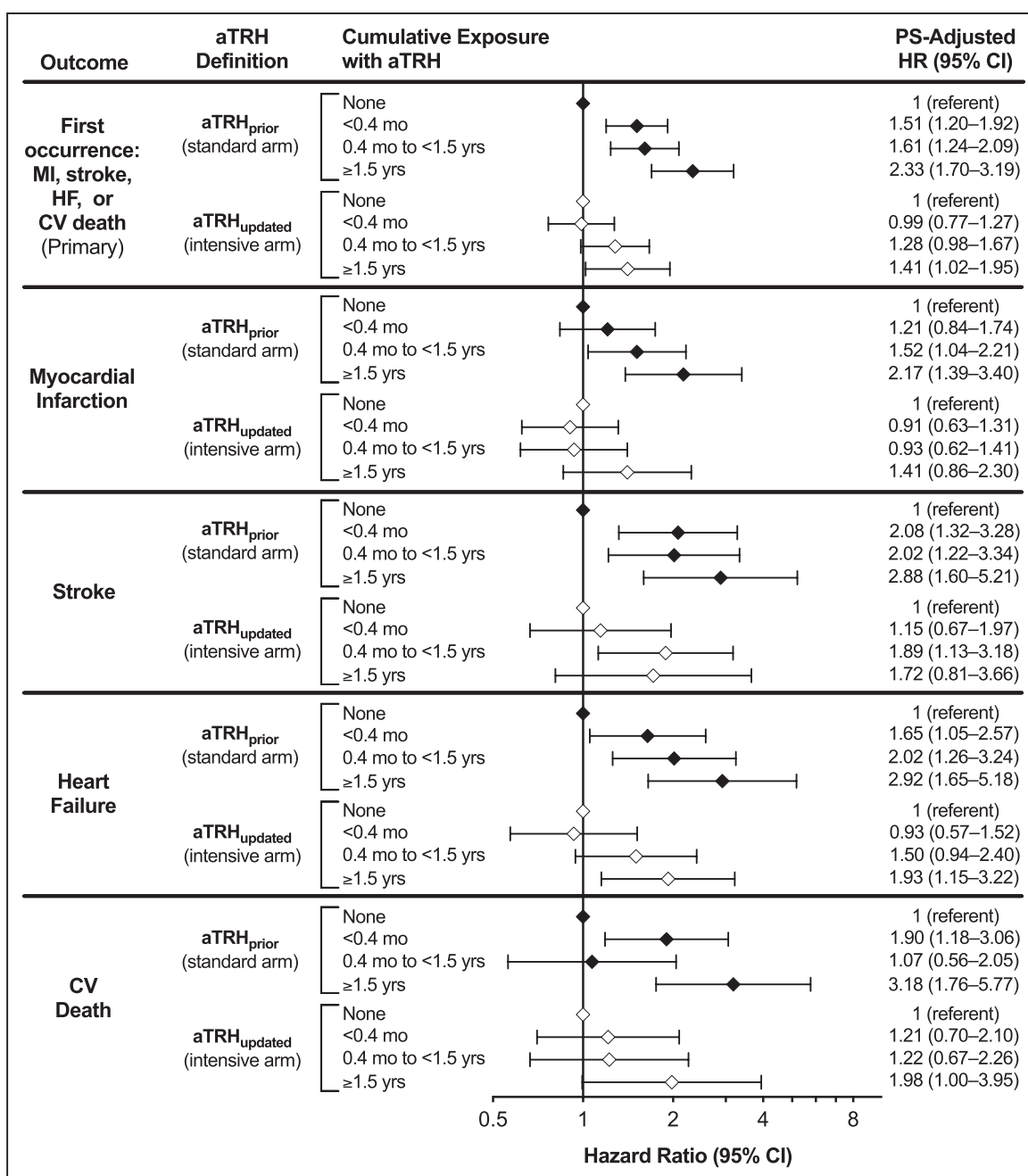


Figure. Adjusted hazard ratios and 95% CIs stratified by apparent treatment-resistant hypertension definition and cumulative exposure category. Cumulative exposure is modeled as a time-dependent categorical variable. The model is further adjusted for a propensity score incorporating study cohort (SPRINT [Systolic Blood Pressure Intervention Trial] vs ACCORD [Action to Control Cardiovascular Risk in Diabetes]), age, sex, history of clinical cardiovascular disease, smoking status, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, glucose, estimated glomerular filtration rate, and assignment to intensive vs standard glycemia treatment. aTRH indicates apparent treatment-resistant hypertension; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; and PS, propensity score.

tive to those with nonresistant hypertension. Future research, using real-world data subsequent to implementation of the 2017 US hypertension guidelines, is needed to further assess risk-benefit.

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Disclosures

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