**SUPPLEMENTAL MATERIAL**

# Redefining Resistant Hypertension: A Comparison of Cardiovascular Risk Associated with the 2018 versus 2008 American Heart Association Definitions for Resistant Hypertension

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## SUPPLEMENTAL METHODS

### Data Ascertainment

Patient-level data from both trials were acquired from the National Heart, Lung, and Blood Institute pursuant to a data use agreement after Institutional Review Board approval.

### Study Eligibility Criteria

*SPRINT*

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) ≥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 BP and number of antihypertensive drugs used at baseline. Specifically, patients were eligible if they had a systolic BP 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/1.73$m^2$ or end-stage renal disease; cardiovascular event or procedure (as defined above for clinical cardiovascular disease), or hospitalization for unstable angina within the prior 3 months; symptomatic heart failure within the past 6 months or left ventricular ejection fraction <35%; indication for a specific BP-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 BP <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 limiting survival to <3 years.

*ACCORD-BP*

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 ≥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 BP ≥140 mm Hg or diastolic BP ≥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 BP and number of antihypertensive drugs used at baseline. As in SPRINT, additional inclusion criteria were placed around systolic BP and number of antihypertensive drugs. Specifically, patients could be included if they had a systolic BP 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, ≥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.

**Rationale for Differing Treatment-Resistant Hypertension Criteria in each Treatment Cohort**

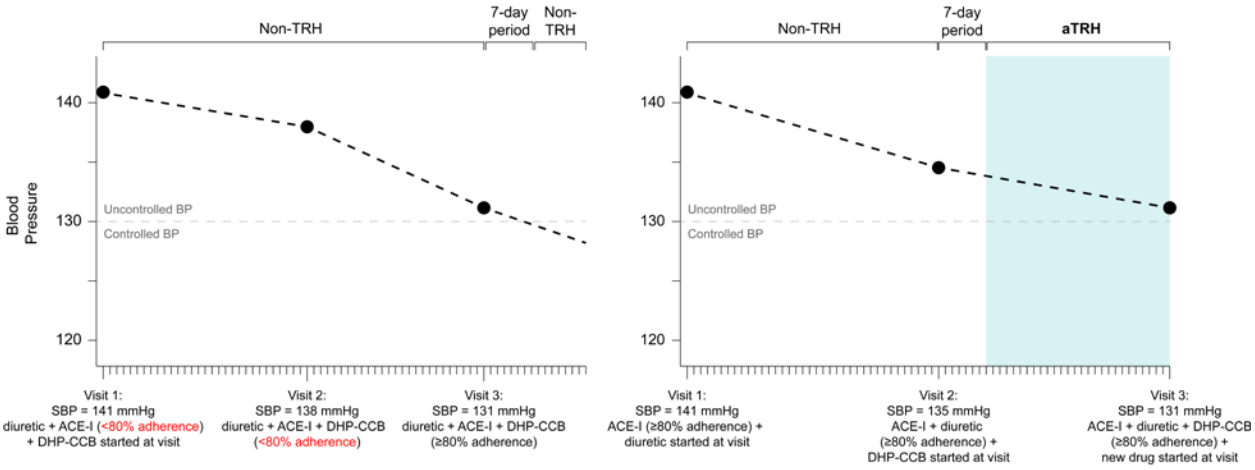
The primary purpose of this study was to assess cardiovascular risk, using adjudicated cardiovascular events, of the updated apparent treatment-resistant hypertension (aTRH) definition (using a BP threshold of <130/80 mm Hg to define control).[1] We further aimed to contrast these risk associations with those using the prior aTRH definition,[2] which is known from prior literature to be associated with excess cardiovascular risk relative to non-resistant hypertension, in the same study population. In reality, the new aTRH definition would be used only in the context of intensified treatment guidance, i.e., targeting a BP <130/80 mm Hg, and likewise, the prior aTRH definition used only in the context of previously standard treatment guidance, i.e., targeting a BP <140/90 mm Hg. Therefore, we created treatment arm-specific definitions to assess the risks associated with aTRH in these contexts to minimize misclassification of exposure (aTRH) during follow-up. Specifically, the updated aTRH definition could only be met in patients assigned to the intensive systolic BP arm, and the prior aTRH definition could only be met in patients assigned to the standard systolic BP arm.

**Classification of Treatment-Resistant Hypertension Status**

Available patient-level data from the NHLBI BioLINCC included the full clinical trial datasets, containing clinic BP at baseline and each follow-up visit, as well as specific antihypertensive agents prescribed at baseline and each follow-up visit. Data on medication doses were obscured (completely for SPRINT; partially for ACCORD) by NHLBI and thus unavailable for this analysis. Medication adherence data were available from patient report for both trials. In SPRINT, medication adherence was instantiated as a percentage of doses taken (in 10% increments) for the entire antihypertensive regimen at each visit. In the absence of drug-specific adherence data, we applied the overall regimen adherence level to each individual drug. In ACCORD, medication adherence was reported categorically as none (0%), some (1% to 79%), all or almost all (80% to 100%), or greater than prescribed (>100%) for each drug. For the purpose of this analysis, we assumed patients were adherent to a drug between two visits if they reported ≥80% adherence to that drug at the first of the two visits or if the drug was newly started.

Using these data, we determined aTRH status each day from baseline through the end of follow-up. First, we estimated clinic BP during each day of follow-up using linear interpolation for days between visits.

We then combined the daily BP (measured or interpolated) with the number of antihypertensives used (and adhered to) during each day of follow-up. For a patient to be considered as having aTRH, they had to either: 1) have uncontrolled BP (arm-specific, as above) while taking 3 antihypertensive agents from different classes for >1 week; or, 2) be taking ≥4 antihypertensive agents, regardless of BP control. Furthermore, to be considered aTRH, we required a diuretic be included in the regimen, and that adherence was high (≥80%) to each medication, including the diuretic. Any drug for which adherence was <80% was ignored in the calculation of number of drugs taken concurrently by a patient. If the diuretic was not adhered to, the patient was not considered to meet aTRH criteria during that period. Example patient scenarios in the intensive arm are provided in the figure below for illustrative purposes:




On the left panel, at visit 1, a patient is taking 2 drugs, including a diuretic, and begins a third drug, but because adherence is <80%, aTRH criteria are never met in the period between visits 1 and 2. Likewise, at visit 2, the same patient is taking 3 drugs, including a diuretic, and has uncontrolled BP, but reports <80% adherence with one or more drugs, thus does not meet aTRH criteria during the period between visits 2 and 3. At visit 3, the same patient meets criteria, but BP is controlled within 7 days of becoming adherent, thus does not accumulate aTRH exposure between visits 3 and 4. In the right panel, a patient has uncontrolled BP while taking 2 antihypertensives, including a diuretic, both of which are adhered to, and starts a third antihypertensive at that visit. As detailed above, we assume the patient to be adherent to this newly started third drug. After 7 days, BP remains uncontrolled, thus aTRH exposure begins to accumulate on the 8$^{th}$ day after visit 2.

**Outcomes**

The SPRINT trial primary outcome was first occurrence of MI, other acute coronary syndromes, stroke, heart failure, or cardiovascular death. The ACCORD trial primary outcome was first occurrence of MI, stroke, or cardiovascular death. ACCORD also adjudicated HF outcomes, although it was not a component of the composite primary outcome for ACCORD. For the present analysis, we created a hybrid primary outcome, similar to the SPRINT primary outcome, but excluding other acute coronary syndromes, which were not adjudicated in ACCORD.

**Statistical Analysis**

We used Cox regression to analyze the relationship between aTRH exposure and risk of adverse cardiovascular outcomes. Unadjusted models were created, regressing the outcome on time-varying aTRH exposure, which was categorized as none (reference), <4 months, 4 months to <1.5 years, and ≥1.5 years. These categorical thresholds were derived from the tertile boundaries of exposure times among all

aTRH-exposed patients. Separate models were developed for each exposure category-outcome comparison (3 exposure category comparisons [<4 months vs. none, 4 months to <1.5 years vs. none, ≥1.5 years vs. none] x 5 outcomes; 15 models in total stratified on treatment arm), using the following steps:

1. For each outcome, we created a counting-process dataset, where each observation represented a aTRH exposure period, such that an individual may have up to 4 periods of person-time representing no exposure, up to 4 months of exposure, 4 months to <1.5 years exposure, and ≥1.5 years exposure.
2. We then subsetted each of these datasets for the individual exposure-time comparisons, including only person-time relevant for the comparison (e.g., all person-time with no exposure or ≥1.5 years exposure before primary outcome occurrence or censoring); the reference group (person-time without aTRH exposure) was exactly the same across all datasets
3. Within each subset of data, we then regressed the outcome on the time-updated aTRH exposure variable (exposed vs. unexposed), stratifying by treatment arm (intensive vs. standard target)

Adjusted analyses were performed using the same approach as above, but also including a propensity score, summarizing baseline characteristics that were potential confounders, focusing particularly on those believed to be more strongly associated with the outcomes. These propensity scores were developed separately for each exposure category-outcome model, by first fitting a logit model, with the aTRH exposure category at last follow-up in the dataset as the outcome and the baseline characteristics as covariates. The output of these models was the predicted probability of aTRH exposure, conditioning on the baseline factors, i.e., the propensity score. After checking propensity score assumptions, we performed modeling, as described above, with the inclusion of the propensity score as a covariate.

**Supplemental Table S1. Baseline characteristics according to treatment arm and never/ever exposure to apparent treatment-resistant hypertension.**

| Characteristic | Intensive Systolic BP (<120 mmHg) Target | | Standard Systolic BP (<140 mmHg) Target | |
|---|---|---|---|---|
| | Never $aTRH_{updated}$ (n=2,378) | Ever $aTRH_{updated}$ (n=3,723) | Never $aTRH_{prior}$ (n=4,307) | Ever $aTRH_{prior}$ (n=1,984) |
| Study | | | | |
| SPRINT | 1,847 (77.7%) | 2,281 (61.3%) | 3,029 (70.3%) | 1,169 (60.3%) |
| ACCORD-BP | 531 (22.3%) | 1,442 (38.7%) | 1,278 (29.7%) | 788 (39.7%) |
| Intensive glycemia arm* | 274 (51.6%) | 717 (49.7%) | 683 (53.4%) | 374 (47.5%) |
| Age | 66.5 ± 9.3 | 65.9 ± 8.7 | 65.9 ± 9.0 | 66.2 ± 8.9 |
| Female sex | 934 (39.3%) | 1,447 (38.9%) | 1,603 (37.2%) | 805 (40.6%) |
| Race/Ethnicity | | | | |
| White | 1,418 (59.6%) | 2,170 (58.3%) | 2,568 (59.6%) | 1,087 (54.8%) |
| Black | 577 (24.3%) | 1,035 (27.8%) | 1,080 (25.1%) | 658 (33.2%) |
| Other | 114 (4.8%) | 189 (5.1%) | 208 (4.8%) | 84 (4.2%) |
| Hispanic | 269 (11.3%) | 329 (8.8%) | 451 (10.5%) | 155 (7.8%) |
| History of clinical CVD | 415 (17.5%) | 908 (24.4%) | 793 (18.4%) | 559 (28.2%) |
| Framingham Risk score, % | 31.0% ± 20.9% | 41.8% ± 25.7% | 34.8% ± 23.1% | 43.0% ± 26.3% |
| Smoking status | | | | |
| Never | 1,103 (46.4%) | 1,605 (43.1%) | 1,907 (44.3%) | 877 (44.2%) |
| Past | 944 (39.7%) | 1,589 (42.7%) | 1,837 (42.7%) | 827 (41.7%) |
| Current | 263 (11.1%) | 333 (8.9%) | 393 (9.1%) | 178 (9.0%) |
| Unknown | 68 (2.9%) | 196 (5.3%) | 170 (4.0%) | 102 (5.1%) |
| Statin Use | 1,069 (45.0%) | 1,915 (51.4%) | 2,095 (48.6%) | 1,099 (55.4%) |
| Aspirin Use | 1,189 (50.0%) | 1,968 (52.9%) | 2,100 (48.8%) | 1,047 (52.8%) |
| No. antihypertensives prescribed at randomization visit† | | | | |
| 0 drugs | 283 (11.9%) | 239 (6.4%) | 573 (13.3%) | 72 (3.6%) |
| 1 drug | 915 (38.5%) | 833 (22.4%) | 1,692 (39.3%) | 316 (15.9%) |
| 2 drugs | 907 (38.1%) | 1,538 (41.3%) | 1,535 (35.6%) | 821 (41.4%) |
| 3 drugs | 178 (7.5%) | 933 (25.1%) | 438 (10.2%) | 650 (32.8%) |
| ≥4 drugs | 95 (4.0%) | 180 (4.8%) | 68 (1.6%) | 125 (6.3%) |
| Mean ± SD | 1.5 ± 1.0 | 2.0 ± 1.0 | 1.5 ± 0.9 | 2.2 ± 0.9 |
| Lab values | | | | |
| TC, mg/dL | 192 ± 41 | 192 ± 44 | 192 ± 42 | 188 ± 43 |
| HDL, mg/dL | 52 ± 14 | 50 ± 14 | 51 ± 15 | 50 ± 14 |
| LDL, mg/dL | 114 ± 36 | 112 ± 37 | 112 ± 35 | 108 ± 36 |
| Triglycerides, mg/dL | 135 ± 113 | 155 ± 137 | 145 ± 133 | 155 ± 150 |
| Glucose, mg/dL | 114 ± 42 | 130 ± 54 | 120 ± 47 | 129 ± 55 |
| eGFR, mL/min | 79 ± 23 | 79 ± 25 | 79 ± 24 | 78 ± 27 |
| UACR, mg/g | 35 ± 140 | 68 ± 249 | 38 ± 151 | 97 ± 341 |
| SCr, mg/dL | 0.99 ± 0.29 | 1.02 ± 0.33 | 1.00 ± 0.29 | 1.04 ± 0.35 |
| Baseline BP | | | | |
| Systolic, mm Hg | 135 ± 15 | 142 ± 16 | 136 ± 14 | 144 ± 16 |
| Diastolic, mm Hg | 77 ± 11 | 78 ± 12 | 77 ± 11 | 78 ± 13 |
| BMI, $kg/m^2$ | 29.8 ± 5.8 | 30.9 ± 5.8 | 30.1 ± 5.6 | 31.2 ± 5.8 |

Ever aTRH groups indicate those who met the arm-specific aTRH criteria at ≥1 visit prior to the primary outcome or censoring. Data represent mean ± standard deviation or No. (%).

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

†Prescribed drugs that were not adhered to were not counted towards aTRH criteria; thus some patients with ≥4 prescribed drugs never met aTRH criteria because of nonadherence (or because a diuretic was not included in the regimen).
ACCORD, Action to Control Cardiovascular Risk in Diabetes; aTRH, apparent treatment-resistant hypertension; 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; UACR, urinary albumin-to-creatinine ratio.

**Supplemental Table S2. Crude incidence of cardiovascular outcomes by time-updated apparent treatment-resistant hypertension (using the updated definition) category for individuals assigned to the intensive treatment arm.**

| Outcome | Cumulative Exposure with $aTRH_{updated}$ | | | |
|---|---|---|---|---|
| | **None** | **<4 mo** | **4 mo to <1.5 y** | **≥1.5 y** |
| **First occurrence: MI, stroke, HF, CV death** | | | | |
| No. of events | 188 | 89 | 91 | 78 |
| Follow-up, person-years | 11,749 | 5,392 | 4,164 | 3,228 |
| Incidence* (95% CI) | 16 (13.9–18.5) | 16.5 (13.4–20.3) | 21.9 (17.8–26.8) | 24.2 (19.4–30.2) |
| IRR (95% CI) | Referent | 1.03 (0.80–1.33) | 1.37 (1.06–1.75) | 1.51 (1.16–1.97) |
| **Myocardial Infarction** | | | | |
| No. of events | 93 | 41 | 34 | 36 |
| Follow-up, person-years | 11,828 | 5,435 | 4,239 | 3,324 |
| Incidence* (95% CI) | 7.9 (6.4–9.6) | 7.5 (5.6–10.2) | 8.0 (5.7–11.2) | 10.8 (7.8–15.0) |
| IRR (95% CI) | Referent | 0.96 (0.66–1.39) | 1.02 (0.69–1.51) | 1.38 (0.94–2.02) |
| **Stroke** | | | | |
| No. of events | 39 | 20 | 27 | 12 |
| Follow-up, person-years | 11,921 | 5,494 | 4,286 | 3,390 |
| Incidence* (95% CI) | 3.3 (2.4–4.5) | 3.6 (2.3–5.6) | 6.3 (4.3–9.2) | 3.5 (2.0–6.2) |
| IRR (95% CI) | Referent | 1.11 (0.65–1.91) | 1.93 (1.18–3.14) | 1.08 (0.57–2.07) |
| **Heart Failure** | | | | |
| No. of events | 52 | 24 | 32 | 38 |
| Follow-up, person-years | 11,926 | 5,491 | 4,274 | 3,342 |
| Incidence* (95% CI) | 4.4 (3.3–5.7) | 4.4 (2.9–6.5) | 7.5 (5.3–10.6) | 11.4 (8.3–15.6) |
| IRR (95% CI) | Referent | 1.00 (0.62–1.63) | 1.72 (1.11–2.67) | 2.61 (1.72–3.96) |
| **Cardiovascular Death** | | | | |
| No. of events | 34 | 21 | 17 | 23 |
| Follow-up, person-years | 11,996 | 5,532 | 4,335 | 3,432 |
| Incidence* (95% CI) | 2.8 (2.0–4.0) | 3.8 (2.5–5.8) | 3.9 (2.4–6.3) | 6.7 (4.5–10.1) |
| IRR (95% CI) | Referent | 1.34 (0.78–2.31) | 1.38 (0.77–2.48) | 2.36 (1.39–4.01) |

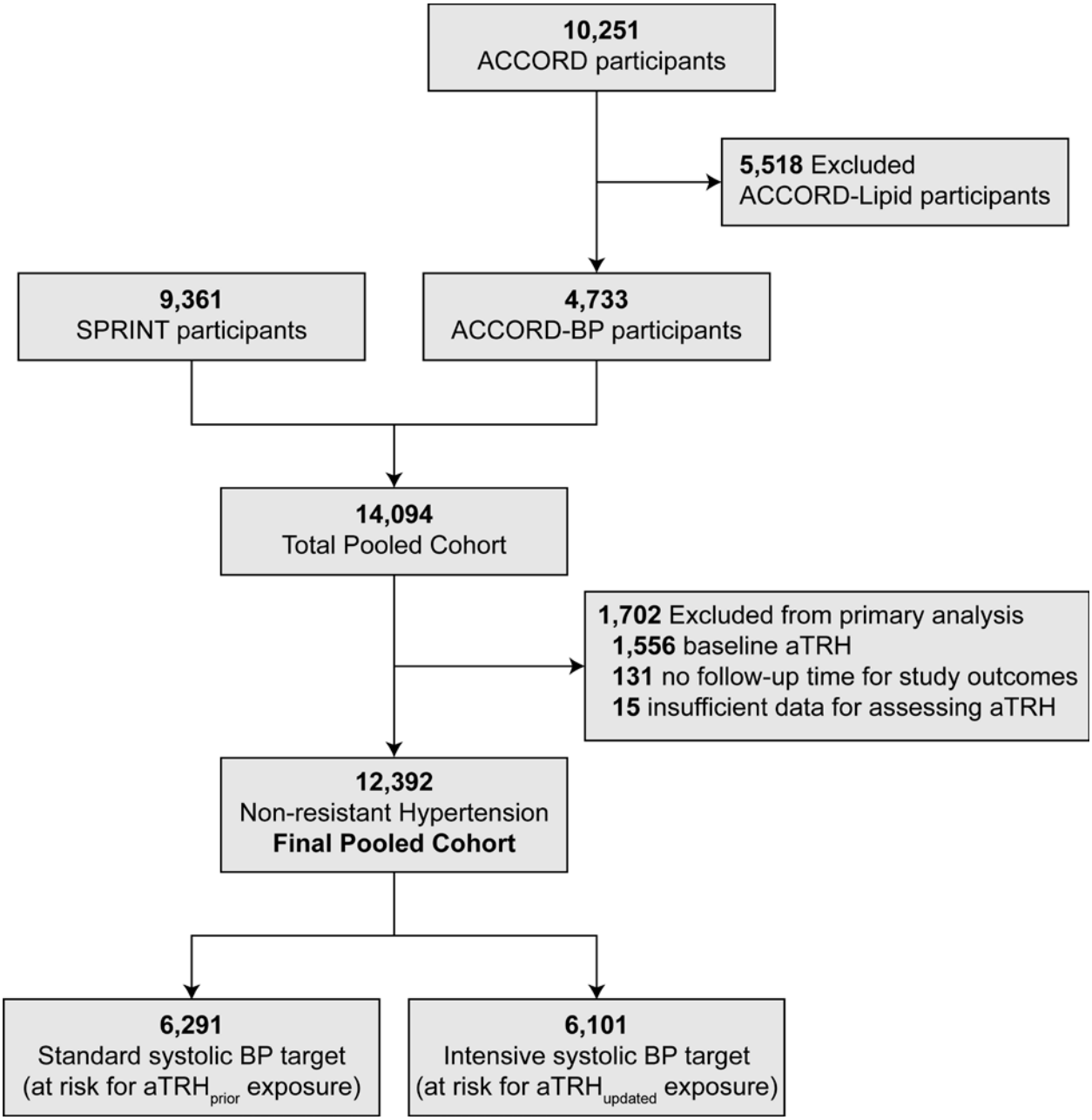
*Presented per 1,000 person-years. aTRH, apparent treatment-resistant hypertension; CI, confidence interval; CV, cardiovascular; HF, heart failure; IRR, incidence rate ratio; MI, myocardial infarction.

**Supplemental Table S3. Crude incidence of cardiovascular outcomes by time-updated apparent treatment-resistant hypertension (using the prior definition) category for individuals assigned to the standard treatment arm.**

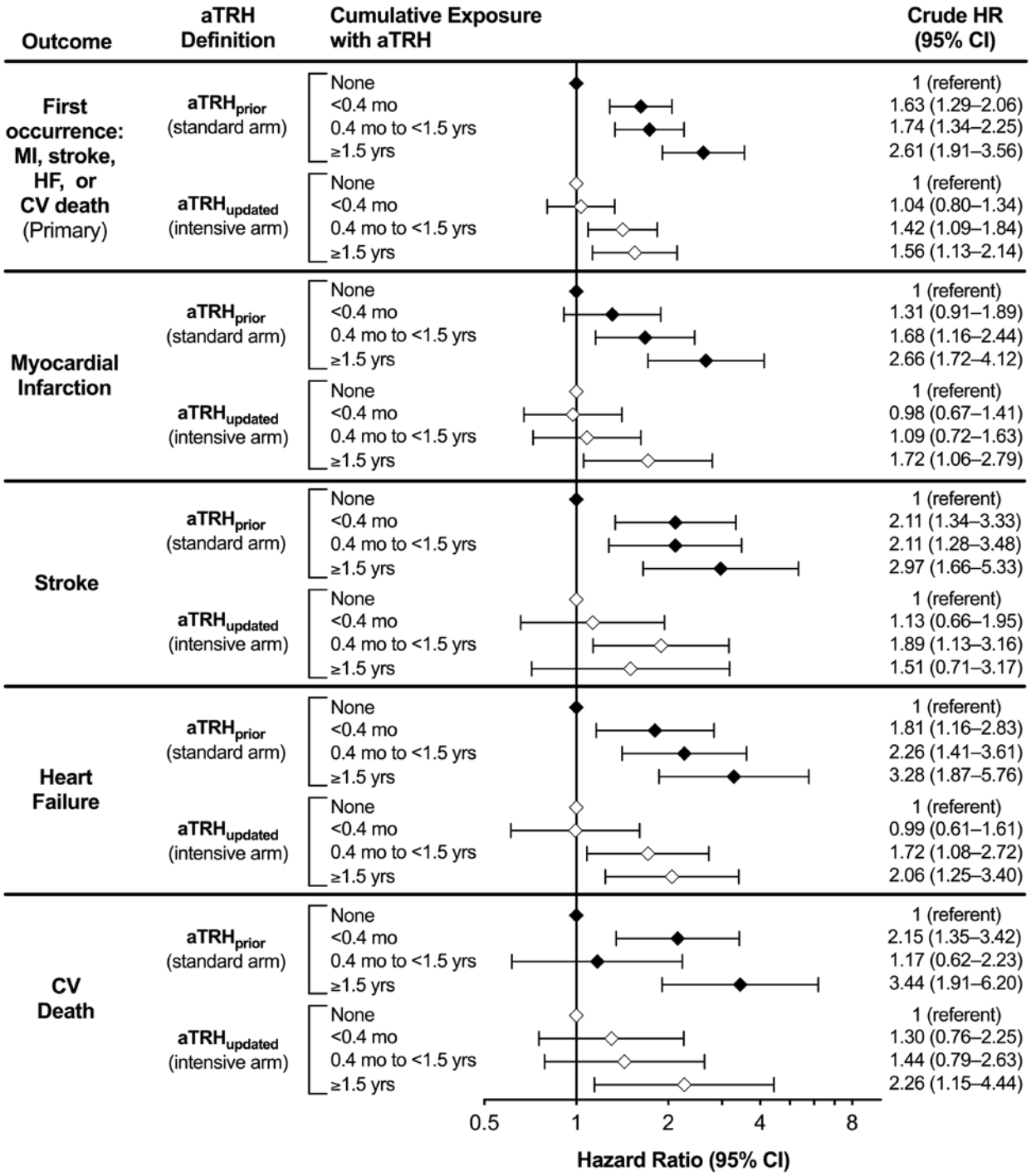
| Outcome | Cumulative Exposure with $aTRH_{prior}$ | | | |
|---|---|---|---|---|
| | **None** | **<4 mo** | **4 mo to <1.5 y** | **≥1.5 y** |
| **First occurrence: MI, stroke, HF, CV death** | | | | |
| No. of events | 348 | 89 | 71 | 53 |
| Follow-up, person-years | 19,199 | 2,964 | 2,165 | 1,012 |
| Incidence* (95% CI) | 18.1 (16.3–20.1) | 30 (24.4–37) | 32.3 (25.6–40.8) | 52.4 (40.1–68.5) |
| IRR (95% CI) | Referent | 1.66 (1.31–2.09) | 1.78 (1.38–2.3) | 2.89 (2.17–3.86) |
| **Myocardial Infarction** | | | | |
| No. of events | 168 | 35 | 35 | 27 |
| Follow-up, person-years | 19,368 | 3,025 | 2,254 | 1,076 |
| Incidence* (95% CI) | 8.7 (7.5–10.1) | 11.6 (8.3–16.1) | 15.1 (10.8–21.1) | 25.1 (17.2–36.6) |
| IRR (95% CI) | Referent | 1.33 (0.93–1.92) | 1.74 (1.2–2.51) | 2.89 (1.93–4.34) |
| **Stroke** | | | | |
| No. of events | 74 | 25 | 20 | 16 |
| Follow-up, person-years | 19,543 | 3,066 | 2,318 | 1,100 |
| Incidence* (95% CI) | 3.8 (3–4.8) | 8.2 (5.5–12.1) | 8.6 (5.6–13.4) | 14.6 (8.9–23.7) |
| IRR (95% CI) | Referent | 2.15 (1.37–3.39) | 2.28 (1.39–3.73) | 3.84 (2.24–6.58) |
| **Heart Failure** | | | | |
| No. of events | 88 | 26 | 23 | 17 |
| Follow-up, person-years | 19,546 | 3,041 | 2,287 | 1,112 |
| Incidence* (95% CI) | 4.5 (3.7–5.5) | 8.6 (5.8–12.5) | 10.1 (6.7–15.1) | 15.3 (9.5–24.6) |
| IRR (95% CI) | Referent | 1.9 (1.23–2.94) | 2.23 (1.41–3.53) | 3.4 (2.02–5.71) |
| **Cardiovascular Death** | | | | |
| No. of events | 71 | 24 | 11 | 17 |
| Follow-up, person-years | 19,699 | 3,103 | 2,364 | 1,150 |
| Incidence* (95% CI) | 3.6 (2.9–4.5) | 7.7 (5.2–11.5) | 4.7 (2.6–8.4) | 14.8 (9.2–23.8) |
| IRR (95% CI) | Referent | 2.15 (1.35–3.4) | 1.29 (0.69–2.43) | 4.1 (2.42–6.97) |

*Presented per 1,000 person-years. aTRH, apparent treatment-resistant hypertension; CI, confidence interval; CV, cardiovascular; HF, heart failure; IRR, incidence rate ratio; MI, myocardial infarction.

**Supplemental Figure S1. Flow diagram for cohort development.** ACCORD, Action to Control Cardiovascular Risk in Diabetes; aTRH, apparent treatment-resistant hypertension; BP, blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial.



**Supplemental Figure S2. Unadjusted hazard ratios and 95% confidence intervals stratified by apparent treatment-resistant hypertension definition and cumulative exposure category.** Cumulative exposure is modeled as a time-dependent categorical variable. aTRH, apparent treatment-resistant hypertension; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.



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