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Coronary Artery Calcium to Guide a Personalized Risk-Based Approach to Initiation and Intensification of Antihypertensive Therapy

Running Title: *McEvoy et al.; Incorporating CAC into risk-based BP treatment*

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Abstract

***Background*—**There is interest in using atherosclerotic cardiovascular disease (ASCVD) risk to personalize systolic blood pressure (SBP) treatment goals. Therefore, we studied whether Coronary Artery Calcium (CAC) can further guide the allocation of anti-hypertensive treatment intensity.

***Methods*—**We included 3,733 participants from the Multi-Ethnic Study of Atherosclerosis with SBP between 120-179mmHg. Within subgroups categorized by both SBP (120-139, 140-159, 160-179mmHg) and estimated 10-year ASCVD risk (using the ACC/AHA pooled-cohort equations), we compared multivariable-adjusted hazard ratios (HRs) for the composite outcome of incident ASCVD or heart failure, after further stratifying by CAC (0, 1-100, or >100). We estimated 10-year number-needed-to-treat (NNT_{10}) for an intensive SBP goal of 120mmHg by applying the treatment benefit recorded in meta-analyses to event rates within CAC strata.

***Results*—**Mean age was 65 years. There were 642 composite events over a median of 10.2 years. In persons with SBP <160mmHg, CAC stratified risk for events. For example, among those with ASCVD risk <15% and who had SBP of either 120-139 or 140-159mmHg, respectively, we found increasing HRs for events with CAC 1-100 (1.7 [95% CI, 1.0-2.6] or 2.0 [1.1-3.8]) and CAC >100 (3.0 [1.8-5.0] or 5.7 [2.9-11.0]), all relative to CAC=0. There appeared to be no statistical association between CAC and events when SBP was 160-179mmHg, irrespective of ASCVD risk level. Estimated NNT_{10} for a SBP goal of 120mmHg varied substantially according to CAC levels when predicted ASCVD risk <15% and SBP <160mmHg (e.g. NNT_{10} of 99 for CAC=0 and 24 for CAC>100, when SBP 120-139mmHg). However, few participants with ASCVD risk <5% had elevated CAC. Furthermore, NNT_{10} estimates were consistently low and varied less among CAC strata when SBP was 160-179mmHg or when ASCVD risk was ≥15% at any SBP level.

***Conclusions*—** Combined CAC-imaging and assessment of global ASCVD risk has potential to guide personalized SBP goals (e.g., choosing a traditional goal of 140 or a more intensive goal of 120 mmHg), particularly among adults with estimated ASCVD risk 5-15% and pre-hypertension or mild hypertension.

Key-words: Systolic BP; Antihypertensive therapy; CVD risk; Coronary Artery Calcium

Clinical Perspective

What is new?

- A given magnitude of BP lowering provides similar relative benefit at all levels of CVD risk, but greater absolute benefit (and therefore lower NNT) as risk increases; suggesting that high-risk individuals are more likely to benefit from intensive BP goals (e.g. systolic ≤120mmHg, as supported by SPRINT).
- To our knowledge, this is the first study to evaluate whether CAC may personalize the risk-based treatment of hypertension.
- Added to estimation of CVD risk and discussion of patient treatment preferences, CAC identifies individuals who may benefit from an intensive systolic BP goal of ≤120 mmHg versus a traditional goal of ≤140 mmHg.

What are the clinical implications?

- Information on CAC burden (particularly when CAC results have already been obtained for other reasons) may be considered when making personalized treatment decisions about blood pressure targets, particularly among persons with estimated cardiovascular disease risk between 5-15% and who have either pre-hypertension or mild hypertension.
- A precision medicine clinical trial evaluating risk-based blood pressure treatment goals, preferably incorporating CAC and not just risk-factor based estimations, is desirable.

Introduction

Elevated blood pressure (BP) is a major cause of heart disease, stroke, and heart failure, with over 972 million adults worldwide and approximately one in three U.S. adults diagnosed with hypertension.[1] While effective antihypertensive pharmacotherapies are widely available,[2] there has been recent controversy regarding the optimal systolic BP (SBP) threshold to initiate or intensify treatment. For example, relying on data from randomized trials (and excluding observational results), a 2014 report by the eighth panel appointed to the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-8) found no trial evidence to support initiating therapy until a SBP of 150 mmHg or higher in adults older than 60 who do not have diabetes or chronic kidney disease.[3] This recommendation was controversial[4] and differs from other guidelines and advisories, the majority of which recommend a lower threshold of 140 mmHg. Furthermore, after JNC-8 was released, the landmark Systolic Blood Pressure Intervention Trial (SPRINT)[5] reported significant improvements in outcomes, notably ASCVD and heart failure, among 9,361 high-risk non-diabetic hypertensive patients, older than 50, treated to a SBP target of 120 mm Hg or less versus the standard target of 140 mmHg or less. Thus, questions remain about whom to treat and with what treatment intensity, particularly among individuals with pre-hypertension or mild hypertension.

In this context, there has been heightened interest in the use of global ASCVD risk estimates - in conjunction with SBP – to guide initiation and titration treatment decisions for hypertension.[6-9] This strategy may allow providers to balance the tension between avoiding overtreatment among low risk persons who are unlikely to benefit and intensifying treatment to achieve lower SBP in higher-risk adults. Prior reports of risk-based allocation of BP therapy have

focused exclusively on risk estimates derived from traditional clinical risk factors such as those included in the ACC/AHA 2013 ASCVD risk score. [6, 8, 10, 11]

Coronary Artery Calcium (CAC), measured by non-contrast cardiac CT, is a powerful subclinical marker of absolute and relative ASCVD risk and has been demonstrated to add incremental prognostic information to risk estimates derived from traditional risk factors.[12-14] In addition, prior analyses have suggested that CAC testing has potential to personalize allocation of other preventive therapies (e.g., aspirin or statin) by identifying individuals who are unlikely to obtain net benefit (e.g., those with zero CAC generally have very low absolute ten-year risk and, hence, high estimated number-needed-to-treat [NNT]), as well as those who may be more likely to benefit due to high absolute risk (e.g., CAC>100).[15, 16]

Therefore, in this study we sought to determine whether CAC might inform the identification of primary prevention candidates who are more likely to benefit from initiation or titration of antihypertensive therapy to a more intensive SBP goal of 120 mmHg (compared to the current standard of 140 mmHg).

Methods

Study Participants

MESA is a multi-center, multi-ethnic, prospective observational cohort study.[17] Between July 2000 and August 2002, MESA recruited 6,814 men and women, aged 45 to 84 years, from four ethnic groups (Caucasian, African-American, Chinese-American, and Hispanic). Participants were enrolled from six geographically distinct U.S. communities. Exclusion criteria included clinical cardiovascular disease at baseline. All participants provided informed consent and the study was approved by the institutional review boards at all field centers.

The primary sample for this analysis excluded MESA participants with baseline systolic BP levels below 120 mmHg (n=2,939) and equal to or higher than 180 mmHg (n=136). We excluded persons with SBP <120 mmHg *a priori* because we determined that CAC screening among these adults for the purposes of BP management would be inappropriate due to the fact that treating adults with SBP <120 to even lower BPs (irrespective of CAC) is difficult to justify. We also excluded those with SBP ≥180 mmHg because, 1) this was an outlier SBP phenotype in the sample (just 1.9%), 2) SBP at this level is consistent with hypertensive urgency, is high risk, and requires rapid therapy- not CAC testing to target specific goals, and 3) we did not want to include individuals with possible secondary hypertension in the analysis. In addition, we excluded six persons with missing information on baseline systolic BP or BP medication use, leaving 3,733 participants in total. We also conducted secondary analyses using a subsample of MESA participants who fulfilled SPRINT criteria. [5] This subsample included only non-diabetics older than 50 with systolic BP ≥130 mmHg and who had any one of the following; Framingham CVD ten-year Risk ≥15% or left ventricular hypertrophy by EKG or ankle-brachial index <0.9 or estimated glomerular filtration rate between 20-59 mL/min/1.73 m^2. After exclusions, this subsample included 1,394 participants.

Cardiovascular Risk Factors

Race, family history of myocardial infarction, and smoking status were collected by self-report. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Diabetes was defined as a fasting blood glucose concentration of ≥126 mg/dL, self-report, or the use of insulin or oral hypoglycemic medications. Seated blood pressure was recorded after a minimum of 5 minutes rest as the mean of the last two of three seated measurements using a Dinamap Pro-100 automated oscillometric sphygmomanometer. [18] Participants were asked to

bring their medications to the clinic and antihypertensive and statin drug use was assessed with a medication inventory. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride measurements were performed in blood samples obtained after a twelve-hour fast. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation. The ten-year risk of hard ASCVD events for MESA participants was estimated using the ACC/AHA Pooled Cohort Equations (with Hispanics/Chinese calculated as White). [10]

Cardiac CT Protocol

The MESA scanning protocol has been published. [19] Cardiac CT was performed at baseline at three MESA sites using a cardiac-gated electron-beam CT scanner (Imatron C-150XL, GE-Imatron, San Francisco, CA) and at three sites using a four-slice multi-detector CT scanner. Both scanner-types produce near-identical results. [19] Intra-observer and inter-observer agreements were excellent ($\kappa = 0.93$ and $\kappa = 0.90$, respectively). While no action was required based on CAC results, participants were told they had no CAC or that the amount was less than average, average, or greater than average for their age and sex, and to discuss the results with their physicians.

Definition of Cardiovascular events

The primary endpoint of all-cause CVD or hospitalized heart failure was pre-specified to match the composite outcome used in SPRINT.[5] Secondary individual endpoints included all-cause CVD, heart failure, all-cause coronary heart disease (CHD), and stroke. At intervals of 9–12 months, an interviewer contacted each subject or a family member about outpatient diagnoses of CHD or CVD, interim hospitalizations, and deaths. Two physicians from the MESA mortality and morbidity review committee independently classified events; in the event of disagreement, the full committee adjudicated. With follow-up through 2012, MESA was successful in obtaining

information on 98% of reported hospitalized CVD and 95% of reported outpatient CVD encounters.

All-cause CHD events were defined as: myocardial infarction, death from CHD, probable angina resulting in revascularization, or resuscitated cardiac arrest. All-cause CVD events were defined as: all-cause CHD events plus cerebrovascular accident (CVA, transient ischemic attack, or ischemic or hemorrhagic stroke), CVA death, or other CVD death. MESA reviewers classified incident heart failure as definite, probable, or absent. Probable or definite hospitalized heart failure both required symptoms, such as shortness of breath or edema as a baseline criteria. Probable hospitalized heart failure further required heart failure diagnosed by a physician and patient receiving medical treatment for heart failure. To meet criteria for definite hospitalized heart failure, one or more additional factors, such as pulmonary edema by X-ray, poor left ventricular systolic function, or diastolic dysfunction, were also required. Participants who suffered both CVD and heart failure were censored from this analysis after the first event.

Statistical Analysis

In order to examine the potential implications of CAC testing for both intensification (e.g. titration) and initiation of BP therapy to a more intensive SBP goal, we included persons with and without baseline anti-hypertensive medication use (Table 1). We calculated proportions for categorical variables and either mean ± standard deviation or median ± interquartile range for continuous variables with normal and non-normal distributions, respectively. Groups were compared using 2-sample t-test, Mann-Whitney, or Chi-square testing, as appropriate.

In survival analyses, participants were categorized into the following systolic BP categories, <140 mmHg (i.e. either 120-139 mmHg for the MESA study sample or 130-139 mmHg for the SPRINT-eligible subsample), 140-159 mmHg, and 160-179 mmHg. Then, to evaluate whether CAC can

personalize risk assessment among subgroups of varying SBP and ASCVD risk estimates, these BP categories were further stratified on the basis of, first, ten-year ASCVD risk (<15% or ≥15%[5,6,20] which was the median level of risk in our primary sample) and, second, CAC group (0, 1-100, >100). We compared crude event (incidence) rates, as well as Cox multivariable-adjusted hazard ratios, within each of these CAC strata.

Models were adjusted for age, sex, race/ethnicity category, BMI, fasting-glucose, diabetes status (yes/no), creatinine, smoking category, LDL-C, HDL-C, triglycerides, statin use, and family history of myocardial infarction (yes/no). In models where the sample was stratified by ASCVD (<15% or ≥15%), we adjusted for core demographics and variables not included in the ASCVD equation (BMI, creatinine, triglycerides, statin use, and family history of myocardial infarction). We conducted sensitivity analyses with more parsimonious models adjusted just for, 1) demographics alone (age, sex, and race/ethnicity), and 2) using the 13 variables included in the primary model, we constructed a propensity score for the composite outcome within each of the CAC subgroups and adjusted the model for this score as a single variable.

We estimated a 10-year number needed to treat to prevent the primary outcome of all-cause CVD or HF (NNT_{10}) with treatment initiation or intensification to a systolic goal of 120 mmHg. This was calculated by applying the expected relative risk reduction derived either from meta-analysis (22% reduction in CHD, 41% reduction in stroke and 24% reduction in heart failure for each 10 mmHg lowering of systolic BP[21]) in the primary sample, or directly from SPRINT (25% relative reduction for a target of 120 mmHg versus a target of 140 mmHg[5]) in the secondary analysis of the SPRINT-eligible subsample. The NNT_{10} was calculated directly as the reciprocal of the absolute risk difference at the median follow-up of the cohort on the basis of Kaplan-Meier estimates and was subsequently adjusted to a NNT_{10} according to the Altman-Anderson method.[22]

In a sensitivity analysis, using the same statistical techniques, we modeled NNT_{10} for a systolic goal of 130 mmHg. We also conducted a sensitivity analysis of NNT_{10} for a goal of 120mmHg that included lower cut-points of 10-year estimated ASCVD risk (<5% or <10%). Finally, we estimated NNT_{10} for a goal of 120mmHg to prevent each of the individual endpoints included in the main composite (CHD, stroke, and heart failure) and we also conducted analyses in the diabetic-subgroup of our primary MESA sample.

Results

Baseline characteristics of the primary sample and of the SPRINT-eligible subsample, stratified by anti-hypertensive medication use, are shown in Table 1. Except for a lower proportion of males and being less likely to smoke, persons receiving BP therapy at baseline were older and had a higher burden of ASCVD risk factors than those who were not on BP therapy at baseline. Those receiving BP therapy also had higher SBP than those not on therapy. Diastolic BP levels, while clinically similar (75.6 vs. 76.2 mmHg), were statistically lower among those on BP therapy. The distribution of CAC also differed according to baseline BP treatment status (Figure 1).

Over a median (interquartile range) follow-up of 10.2 (9.7–10.7) years, 642 primary composite outcome events (all-cause CVD or heart failure) occurred in the sample overall. Figure 2 demonstrates that cumulative event-free survival was significantly lower, in both the primary sample and SPRINT-eligible subsample, among individuals with CAC 1-100 and >100, compared to those with zero CAC. Similar trends were demonstrated after stratification by baseline systolic BP category (eFigure 1). These trends were also qualitatively similar for the individual outcomes of CHD, stroke, and heart failure (eFigure 2).

Among persons in the primary sample who were not on baseline BP therapy, event rates were low for those with zero CAC and either SBP between 120-139 mmHg (5.6 per 1,000 person-years) or SBP between 140-159 mmHg (7.4 per 1,000 person-years). However, event rates appeared to be high, irrespective of CAC level, in persons with untreated SBP between 160-179 mmHg (ranging from approximately 20 to 40 per 1,000 person-years, Table 2). In general, event rates were also consistently higher among those on baseline BP therapy compared to untreated individuals, within each of the BP and CAC strata. Of note, however, persons not on BP therapy with SBP between 120-139 mmHg and CAC >100 had a similar event rate (24.3 per 1,000 person-years) as individuals on therapy with both poorly controlled hypertension (SBP 160-179 mmHg) and CAC=0 (20.2 per 1,000 person-years).

Adjusted Cox models confirmed that, relative to CAC=0, CAC 1-100 and CAC >100 carried incremental excess in hazard for events among persons with SBP in the 120-139 mmHg and 140-159 mmHg ranges, irrespective of baseline treatment status (Table 2). However, associations between CAC and hazard for events among those with SBP 160-179 mmHg were not statistically significant, either with or without baseline therapy. All of these trends were qualitatively similar in the SPRINT-eligible subsample.

Table 3 demonstrates findings after individuals within each SBP category, both untreated and treated combined, were stratified by estimated ten-year ASCVD risk (above or below the sample median of 15%). Those with CAC=0 had low event rates in both the 120-139 mmHg (4.6 per 1,000 person-years) and 140-159 mmHg BP categories (6.9 per 1,000 person-years), as long as ASCVD risk was <15%. Event rates were comparably higher (>7.5 per 1,000 person-years) in all persons with SBP between 160-179 mmHg. Furthermore, persons with baseline ASCVD risk

≥15% at all levels of baseline SBP also had higher event rates, again irrespective of CAC level (ranging from approximately 13 to 46 per 1,000 person-years).

Adjusted Cox models demonstrated increased hazard for events with CAC 1-100 and CAC >100 (versus CAC=0) among those who had SBP levels in the range of 120-139 mmHg and 140-159 mmHg, but, no statistical association of CAC with CVD among those with SBP 160-179 mmHg (Table 3**)**. Excess relative hazard with increasing CAC strata was most pronounced in those with estimated ASCVD risk <15%. Parsimonious demographic-adjusted and propensity score-adjusted models produced similar results (eTables 1-4). As in Table 2, all of these trends were qualitatively similar in the SPRINT-eligible subsample. None of the hazard ratios presented in Table 3 demonstrated any interaction by race/ethnicity.

The absolute differences in event rates according to baseline CAC translated into substantial variation in estimated NNT_{10} to prevent all-cause CVD or heart failure with BP lowering to a SBP goal of 120 mmHg. For example, a low NNT_{10} (between 4 and 8), was estimated for persons with CAC >100 in both the SBP 140-159 and 160-179 mmHg categories, irrespective of baseline estimated ASCVD risk (Table 4). In contrast, participants with CAC=0 had higher estimated NNT_{10} at all levels of baseline SBP and ASCVD risk. Persons with SBP <140 mmHg, ASCVD risk <15% and zero CAC had the highest NNT_{10} estimates (NNT_{10}= 99). Likely due to the higher baseline SBP and ASCVD risk in those who were SPRINT eligible, with higher consequent event rates, all NNT_{10} levels were relatively low in this sub-sample. The NNT_{10} results were qualitatively similar when the sample overall was stratified by baseline treatment status (as such, NNT_{10} for a goal SBP of 120 mmHg was similar for both initiation of BP therapy and intensification of prior therapy, eTable 5). Because CAC stratifies absolute risk for CHD, stroke,

and heart failure, the NNT_{10} trends seen for the composite outcome are mirrored in each of the individual outcomes (eTable 6).

Figure 3 summarizes the range of NNT_{10} estimates after stratification by baseline CAC, with findings most widely dispersed among those with ASCVD risk <15% and who had either pre-hypertension or mild hypertension. In addition, sensitivity analyses evaluating lower ASCVD risk cut-points suggested that, among participants with SBP 120-139 mmHg, 32% of persons with ASCVD risk <7.5% had CAC>0 (with NNT_{10} estimates for a 120 mmHg SBP goal of 76 for CAC1-100 and 47 for CAC>100), whereas CAC>0 was less frequent and NNT_{10} estimates were higher among those with ASCVD risk <5% (e.g., NNT_{10} estimates for a 120 mmHg SBP goal of 180 for the 20% with CAC 1-100 and 37 for the 3% with CAC>100) (eTable 7).

The exploratory analysis of diabetics in our sample suggested that NNT_{10} estimates were low, irrespective of CAC, among those with 10-year ASCVD risk ≥15%. Too few diabetics in our sample had ASCVD risk <15% to judge whether CAC has any role in guiding risk-based BP therapy in this setting (eTable 8). Finally, eTable 9 demonstrates our NNT_{10} estimates from the sensitivity analysis evaluating a SBP goal of 130mmHg. As expected, NNT_{10} estimates were higher (i.e., less benefit) when targeting 130 mmHg compared to 120 mmHg systolic, particularly among those at highest risk due to elevated baseline CAC.

Discussion

Our results add to an emerging body of literature suggesting that ASCVD risk may be useful in defining more personalized BP goals and could guide a precision medicine approach for both initiation and intensification of anti-hypertensive treatment. First, CAC was a powerful determinant of absolute risk for the composite of all-cause CVD or heart failure. Second, persons

with zero CAC in both the prehypertension (120-139 mm Hg) and mild hypertension (140-159 mmHg) SBP categories had low ten-year event rates (e.g., <7.5 per 1,000 person-years). This was particularly true for those not already on BP therapy at baseline in whom the decision to initiate treatment may be under consideration, but also applied to persons on baseline therapy in whom intensification of treatment may be considered. All participants with SBP >160 mmHg had high event rates, irrespective of CAC levels.

Third, CAC may be most suitable for guiding therapeutic decisions (specifically, either initiation or intensification to a more intensive systolic goal of 120 mmHg) when both SBP is between 120-159 mmHg and ten-year ASCVD has been estimated as <15%. In these individuals, CAC=0 yielded a higher estimated NNT for persons with SBP 140-159 (NNT_{10}= 36), and, above all, for those with SBP between 120 and 139 mmHg (NNT_{10}= 99), suggesting lower likelihood for benefit. The latter group consists of those in whom the decision to treat to a more intensive goal of 120 mmHg (compared to the traditional goal of 140 mmHg) may be most challenging in the context of results from SPRINT. Given that 97% of MESA participants with estimated ASCVD risk <5% have CAC <100 and NNT_{10} estimates ranging from 180-273, our sensitivity analyses suggest that CAC may be most practical for this purpose when SBP is between 120 and 159 mmHg and estimated ASCVD risk is between 5 and 15%.

The above inferences are most appropriately applied to general community intermediate to low risk populations similar to MESA. Our secondary analysis results suggest that the relatively few adults fulfilling strict SPRINT eligibility criteria (just 7.6% of the overall U.S. population[23]) are, by definition, high risk for CVD or heart failure and the further use of CAC imaging in these individuals may be less helpful in deciding SBP goals.

The traditional paradigm of allocating BP therapy solely on BP values makes intuitive and physiological sense. However, data have consistently demonstrated that, while the relative risk reduction in events per unit of SBP lowering is the same, the absolute risk reduction, NNT, and, hence, clinical efficacy of BP treatment increases as baseline absolute ASCVD risk increases. [8] In fact, the idea of using baseline ASCVD risk to guide BP therapy is not new. [24, 25] Moreover, the concept of using risk to allocate ASCVD prevention therapies has taken center stage after the release of 2013 ACC/AHA guidelines for the treatment of cholesterol in adults, which recommend statins be considered based on an ASCVD risk of ≥7.5% and not solely on LDL-C values. [26] Indeed, recent data from the Heart Outcomes Prevention Evaluation (HOPE)-3 trial support the concept of risk-based allocation of BP therapy. In this study, 12,705 intermediate risk adults with baseline SBP of 138 mmHg were randomized to placebo or to a combination of 12.5mg hydrochlorothiazide and 16mg candesartan. Despite a relative SBP reduction of 6 mmHg (which was notably less than the 14.8 mmHg achieved in SPRINT), the intermediate risk adults enrolled in HOPE- 3 did not derive benefit. [27] Thus, SPRINT supports intensive BP control (SBP goal of 120 mmHg) in high risk patients, whereas HOPE-3 suggested that intermediate risk patients may be suitable for less stringent SBP goals. However, our findings introduce the potential value of CAC testing in this intermediate risk group in order to reclassify individual risk and inform more personalized intensive SBP goals in those with advanced subclinical atherosclerosis.

Presumably BP values will always be important in allocating antihypertensive therapy and our data support this. Specifically, participants in our analysis with SBP >160 mmHg, had high event rates and low NNT, irrespective of baseline ASCVD risk or CAC. With the exception of those with ASCVD risk <15% and CAC=0, this was also true for persons with BP 140-159 mmHg. Nonetheless, adding ASCVD risk into BP treatment decisions could potentially allow

consideration of therapy for large number of persons with SBP levels that, prior to SPRINT, were otherwise not typically considered to benefit from treatment initiation or intensification (e.g. those with SBP 120-139 mmHg). [6] For example, Karmali et al. found that most excess ASCVD events occur in persons with BP levels considered at goal by JNC-8 and that the vast majority of those who suffer these events have elevated ASCVD risk. [11]

Estimating risk based on traditional risk factors alone can be misleading[28] and CAC has been repeatedly shown to improve the accuracy of risk assessment. [29, 30] Furthermore, we have previously shown that CAC may inform NNT estimation for other ASCVD prevention therapies. [15, 16] In addition, CAC and intensive BP control such as that used in SPRINT both have supportive evidence for cost-effectiveness. [31, 32] As such, our data could extend the utility of CAC to guiding risk-based determination of more personalized systolic BP goals in persons with mild hypertension and pre-hypertension. This may be relevant for deciding whether to refer for CAC-imaging but is particularly meaningful for those who have already had CAC testing for other reasons.

Importantly, our analyses incorporate clinically relevant information on both baseline BP and estimated ASCVD risk into the calculation of CAC-based NNT estimates. This is crucial as we believe that CAC should not be used in isolation in this context. Specifically, as long as ASCVD risk is <15% and SBP is between 120-159 mmHg, our results suggest the potential for CAC=0 to allow more liberal BP treatment goals, like 140 mmHg for example, particularly if based on individual patient preferences. [33] Indeed, CAC may be most helpful in cases where physicians are considering intensifying treatment to a SPRINT-based SBP goal of <120 mm Hg among persons with SBP between 120-139 mmHg (i.e. levels below the current traditional goal of 140 mmHg). In this setting, when ASCVD risk is <15%, a CAC=0 yields a NNT_{10} of approximately 100, information which could guide the clinical-patient treatment discussion. Of

note, given the low burden of CAC and events among those with ASCVD estimates <5%, CAC-imaging to guide personalized SBP goals may be best suited to persons with estimated ASCVD risk 5-15%.

While we found that CAC-based NNT_{10} estimates were generally higher for a target of 130 mmHg (vs. 120 mmHg), the overall message was the same: NNT_{10} estimates for the prevention ASCVD or heart failure suggest that lower systolic targets (e.g. either 120 or 130 mmHg) may be superior to the traditional target of 140 mmHg when; 1) systolic BP is >160 mmHg, 2) estimated CVD risk using traditional risk factors is >15%, and, most importantly, 3) when CAC>100 among those individuals currently in the therapeutic 'grey zone' (i.e., those with SBP in the prehypertension and mild hypertension range and who are intermediate risk by CVD risk scores).

Our analysis has some limitations. While we believe that our findings may have important clinical implications and can guide future investigation, they are hypothesis-generating due to the observational nature of the data and the limited numbers of events among certain subgroups. The latter consideration is most relevant among those with SBP 160-179 mmHg and for our SPRINT-eligible subsample. Our NNT estimates are based on a number of assumptions (in particular that the relative risk reduction for BP therapy is similar among CAC strata), nonetheless, we feel they are informative. While some have argued that SPRINT SBP values cannot easily be translated into routine care[34], we note that the MESA BP measurement protocol was nearly identical to SPRINT and that MESA also used automated oscillometric BP measurement devices. Because MESA was not designed to capture accurate time-to-event data on side effects of anti-hypertensive medication (e.g. electrolyte imbalance or injurious falls), we do not have absolute event rates for these outcomes among CAC strata and are unable to generate number-needed-to-

harm estimates. For simplicity, we did not incorporate information on diastolic BP because the optimal goal for this parameter (80-89 mmHg) is more widely agreed upon, because diastolic BP does not typically add to ASCVD risk estimation over and above SBP, and because so few MESA participants had isolated diastolic hypertension (n=40, 0.6%).

Conclusions

Assessment of CAC may inform more personalized BP goals (e.g., choosing between a traditional SBP goal of 140 mmHg or a more intensive goal of 120 mmHg), particularly among persons with baseline ten-year ASCVD risk estimates between 5-15% and who have systolic BP levels between 120-159 mmHg. Specifically, among these individuals, CAC >100 appears to identify those who would likely benefit from an intensive systolic BP goal of 120 mmHg, whereas CAC=0 identifies individuals who may be suitable for more traditional SBP goals; thereby avoiding unnecessary intensification of medication and instead focusing on healthy lifestyle measures. A trial of risk-based allocation of BP treatment goals, preferably incorporating CAC, is needed.

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Disclosure

Dr. Budoff serves on a speakers' bureau for GE Healthcare. The remaining authors have no competing interests to declare.

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Table 1. Baseline characteristics of the MESA sample (N=3,733) and the SPRINT-eligible subsample (N= 1,394), according to baseline blood pressure (BP) therapy

	MESA Study Sample		P-value*	Sprint-Eligible Subsample		P-value*
	No BP Therapy (N= 1964)	BP Therapy (N= 1769)		No BP Therapy (N= 613)	BP Therapy (N= 781)	
Age, years	63.4 (±9.9)	66.1 (±9.3)	<0.001	69.0 (±7.9)	69.4 (±7.8)	0.51
Male	1004 (51)	796 (45)	<0.001	412 (67)	401 (51)	<0.001
Race			<0.001			<0.001
White	757 (38)	548 (31)		253 (41)	280 (36)	
Black	505 (26)	700 (40)		148 (24)	278 (36)	
Hispanic	464 (24)	349 (20)		139 (23)	146 (19)	
Chinese	238 (12)	172 (10)		73 (12)	77 (10)	
Body Mass Index, kg/m^2	28.3 (±5.3)	29.8 (±5.6)	<0.001	27.7 (±4.6)	28.8 (±5.32)	<0.001
Systolic BP, mmHg	137.2 (±13.4)	141.2 (±14.1)	<0.001	147.2 (±12.3)	148.4 (±12.2)	0.035
Diastolic BP, mmHg	76.2 (+8.8)	75.6 (+9.5)	0.02	78.5 (+9.0)	77.6 (+9.6)	0.17
Fasting Glucose, mg/dL	97.0 (±30.7)	103.8 (±33.0)	<0.001	92.1 (±10.5)	93.7 (±11.4)	0.01
Diabetes	174 (9)	385 (22)	<0.001	-	-	
Smoking Status			<0.001			<0.001
Current Smoker	269 (14)	167 (9)		88 (14)	80 (10)	
Never Smoker	942 (48)	932 (53)		249 (40)	391 (50)	
Former Smoker	747 (38)	661 (38)		273 (45)	306 (40)	
LDL-C, mg/dL	120.8 (+30.9)	113.4 (+31.1)	<0.001	125.1 (+30.8)	116.7 (+30.9)	<0.001
HDL-C, mg/dL	51.2 (±14.9)	50.4 (±14.1)	0.18	48.8 (±14.2)	50.7 (±14.3)	<0.005
Triglycerides, mg/dL	116 (79-164)	113 (81-166)	0.92	122 (87-166)	113 (83-165)	0.12
Creatinine, mg/dL	0.94 (±0.21)	1.0 (±0.29)	<0.001	1.01 (±0.22)	1.04 (±0.28)	0.07
Family History of MI	771 (42)	801 (49)	<0.001	238 (43)	359 (50)	0.001
10 year ASCVD Risk, %	14 (±11)	22 (±0.15)	<0.001	21 (±22)	24 (±12)	<0.001
ASCVD Risk Score Categories			<0.001			<0.001
<7.5%	683 (35)	276 (16)		23 (4)	29 (4)	
7.5-15%	552 (28)	402 (23)		192 (32)	160 (21)	
>15%	716 (37)	1072 (61)		393 (65)	584 (75)	

Values are for number (%), median (IQR) or mean (±SD)

*P values are for differences between groups using 1-way ANOVA, Kruskal–Wallis testing, or $\chi 2$, as appropriate.

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; MESA, multi-ethnic study of atherosclerosis; and MI, myocardial infarction.

Table 2. Crude Event Rates* and Adjusted† Hazard Ratios (95% Cls) for Incident ASCVD or Heart Failure in the MESA study sample and the SPRINT-eligible subsample, according to baseline systolic BP (with or without therapy) and stratified by CAC

		MESA Study Sample				Sprint-Eligible Subsample			
		N (%)	n (%)	Crude event rates (95% CI) *	Adjusted HR (95% CI) †	N (%)	n (%)	Crude event rates (95% CI) *	Adjusted HR (95% CI) †
SBP <140‡									
No BP therapy	CAC=0	635 (50)	40 (6)	5.6 (4.1, 7.6)	1.0	61 (29)	5 (8)	7.3 (3.0, 17.6)	1.0
	CAC 1-100	363 (29)	47 (13)	12.1 (9.1, 16.1)	**1.6 (1.01, 2.6)**	69 (33)	8 (12)	11.3 (5.6, 22.5)	1.4 (0.4, 4.6)
	CAC>100	263 (21)	61 (23)	24.3 (18.9, 31.3)	**3.0 (1.8, 5.0)**	14 (18)	14 (18)	19.0 (11.3, 32.1)	1.4 (0.4, 4.9)
BP Therapy	CAC=0	369 (41)	28 (8)	7.0 (4.8, 10.1)	1.0	47 (22)	3 (6)	6.0 (1.9, 18.7)	1.0
	CAC 1-100	258 (29)	35 (14)	12.8 (9.2, 17.8)	1.3 (0.7, 2.2)	79 (37)	13 (16)	15.6 (9.1, 28.9)	3.1 (0.8, 11.6)
	CAC>100	274 (30)	86 (31)	35.5 (28.7, 43.8)	**2.6 (1.6, 4.3)**	90 (42)	21 (23)	26.0 (17.0, 40.0)	**4.8 (1.3, 17.5)**
SBP 140-159									
No BP therapy	CAC=0	225 (41)	19 (8)	7.4 (4.7, 11.7)	1.0	94 (32)	11 (12)	10.2 (5.6, 18.4)	1.0
	CAC 1-100	162 (29)	27 (17)	16.5 (11.3, 24.1)	**1.9 (1.01, 3.7)**	89 (30)	15 (17)	17.2 (10.4, 28.6)	1.9 (0.8, 4.6)
	CAC>100	162 (29)	54 (33)	36.9 (29.0, 49.5)	**5.2 (2.7, 10.2)**	112 (38)	37 (33)	36.5 (26.4, 50.4)	**3.8 (1.7, 8.7)**
BP Therapy	CAC=0	243 (36)	31 (13)	11.9 (8.4, 17.0)	1.0	125 (30)	13 (10)	9.6 (5.6, 16.5)	1.0
	CAC 1-100	183 (27)	40 (22)	21.8 (16.0, 29.7)	**1.7 (1.01, 2.8)**	126 (30)	28 (22)	21.3 (15.4, 32.3)	**2.1 (1.01, 4.4)**
	CAC>100	240 (36)	80 (33)	38.8 (29.0, 49.5)	**2.3 (1.4, 3.7)**	164 (40)	55 (33)	39.2 (30.1, 51.1)	**2.9 (1.5, 5.9)**
SBP 160-179									
No BP therapy	CAC=0	57 (37)	9 (16)	16.7 (8.7, 32.1)	1.0	38 (35)	6 (16)	15.5 (6.9, 34.4)	1.0
	CAC 1-100	47 (30)	15 (32)	34.4 (20.7, 57.1)	1.1 (0.2, 5.5)	34 (31)	11 (32)	38.3 (20.3, 66.2)	2.3 (0.8, 6.9)
	CAC>100	50 (32)	16 (32)	37.1 (22.7, 60.6)	1.9 (0.1, 26.0)	37 (34)	12 (32)	36.4 (20.7, 64.1)	1.1 (0.3, 3.9)
BP Therapy	CAC=0	70 (35)	14 (20)	20.2 (12.0, 34.1)	1.0	55 (37)	9 (16)	15.8 (8.2, 30.4)	1.0
	CAC 1-100	57 (30)	14 (26)	26.6 (15.7, 44.9)	1.0 (0.5, 2.0)	43 (29)	10 (23)	25.1 (13.5, 46.5)	2.3 (0.7, 6.9)
	CAC>100	70 (35)	26 (37)	44.6 (30.4, 65.5)	1.2 (0.6, 2.3)	52 (35)	17 (33)	36.3 (23.8, 61.6)	2.9 (0.9, 9.3)

*Event rates are per 1,000 person years. †Adjusted for age, sex, race, BMI, fasting glucose, diabetes status, creatinine, smoking category, LDL-C, HDL-C, triglycerides,statin use and family history of MI. Significant Hazard Ratios are in bold (p<0.05). N (%) and n (%) represent numbers of persons and events in each category.

‡ <140 SBP is 120-139 for the MESA study sample and 130-139 for the SPRINT-eligible subsample

SBP indicates systolic blood pressure in mmHg; CAC, coronary artery calcium; all other abbreviations as per Table 1

Table 3. Crude Event Rates* and Adjusted† Hazard Ratios (95% Cls) for Incident ASCVD or Heart Failure in the MESA study sample and the SPRINT-eligible subsample, according to baseline systolic BP, stratified by ASCVD risk and sub-stratified by CAC

		MESA Study Sample				Sprint-Eligible Subsample			
		N (%)	**n (%)**	**Crude event rates (95% CI) ***	**Adjusted HR (95% CI) †**	**N (%)**	**n (%)**	**Crude event rates (95% CI) ***	**Adjusted HR (95% CI) †**
SBP <140‡									
ASCVD risk <15%	CAC=0	796 (59)	42 (5)	4.6 (3.4, 6.2)	1.0	54 (36)	4 (7)	6.8 (2.5 , 18.1)	1.0
	CAC 1-100	387 (29)	41 (11)	9.5 (7.0, 12.9)	**1.7 (1.01, 2.6)**	58 (39)	7 (12)	11.1 (5.3, 23.3)	2.3 (0.6, 8.9)
	CAC>100	164 (12)	33 (20)	19.7 (14.0, 27.7)	**3.0 (1.8, 5.0)**	38 (25)	10 (26)	26.7 (14.4, 49.6)	2.9 (0.8, 10.3)
ASCVD risk ≥15%	CAC=0	198 (25)	25 (13)	12.7 (8.6, 18.8)	1.0	53 (20)	4 (8)	6.9 (2.6, 18.5)	1.0
	CAC 1-100	230 (29)	41 (18)	18.2 (13.4, 24.7)	1.3 (0.7, 2.2)	88 (33)	14 (16)	15.7 (9.3, 26.6)	2.1 (0.7, 6.8)
	CAC>100	371 (46)	33 (20)	35.0 (29.1, 42.1)	**2.6 (1.6, 4.3)**	130 (48)	25 (19)	21.7 (14.6, 32.1)	2.4 (0.8, 7.6)
SBP 140-159									
ASCVD risk <15%	CAC=0	264 (56)	21 (8)	6.9 (4.5, 10.6)	1.0	93 (47)	9 (10)	8.3 (4.3, 15.9)	1.0
	CAC 1-100	131 (28)	18 (14)	12.8 (8.1, 20.3)	**2.0 (1.1, 3.8)**	59 (30)	10 (17)	16.8 (9.0, 31.2)	2.3 (0.9, 6.0)
	CAC>100	80 (19)	32 (40)	43.4 (30.7, 61.4)	**5.7 (2.9,11.0)**	47 (24)	20 (43)	45.9 (29.6, 71.1)	**4.6 (1.8, 11.6)**
ASCVD risk ≥15%	CAC=0	198 (27)	28 (14)	13.6 (9.4, 19.7)	1.0	124 (25)	15 (12)	11.3 (6.8, 18.8)	1.0
	CAC 1-100	213 (29)	49 (23)	23.7 (17.9, 31.4)	**1.7 (1.1, 2.8)**	156 (31)	33 (21)	21.5 (15.3, 30.3)	**1.9 (1.01, 3.6)**
	CAC>100	316 (43)	101 (32)	37.6 (30.9, 45.6)	**2.3 (1.5, 3.8)**	225 (45)	71 (32)	36.6 (29.0, 46.2)	**2.6 (1.4, 5.00)**
SBP 160-179									
ASCVD risk <15%	CAC=0	48 (53)	4 (8)	7.9 (3.0, 21.2)	1.0	27 (49)	2 (7)	6.4 (1.6, 25.7)	1.0
	CAC 1-100	29 (32)	7 (24)	21.8 (10.4, 45.7)	1.0 (0.2, 5.8)	18 (33)	4 (22)	20.1 (7.5, 53.5)	38.5 (0.3, 526.7)
	CAC>100	14 (15)	3 (21)	19.8 (6.4, 61.3)	4.0 (0.4,40.2)	10 (18)	3 (30)	29.2 (9.4, 90.5)	3.9 (0.1, 839.4)
ASCVD risk ≥15%	CAC=0	77 (29)	19 (25)	26.7 (17.0, 41.9)	1.0	64 (32)	13 (20)	20.7 (12.0, 35.6)	1.0
	CAC 1-100	78 (30)	22 (28)	34.3 (22.6, 52.1)	1.0 (0.5, 2.0)	59 (29)	17 (30)	34.0 (21.1, 54.7)	1.5 (0.7, 3.5)
	CAC>100	106 (41)	39 (37)	45.9 (33.6, 62.9)	1.1 (0.6, 2.1)	78 (39)	26 (33)	39.5 (26.9, 58.0)	1.3 (0.6, 2.9)

*Event rates are per 1,000 person years. †Adjusted for age, sex, race, BMI, creatinine, triglycerides, statin use and family history of MI.
Significant Hazard Ratios are in bold (p<0.05). N (%) and n (%) represent numbers of persons and events in each category.
‡ <140 SBP is 120-139 for the MESA study sample and 130-139 for the SPRINT-eligible subsample
SBP indicates systolic blood pressure in mmHg; CAC, coronary artery calcium; all other abbreviations as per Table 1

Table 4. Estimated 10-year NNT for the prevention of ASCVD or heart failure with blood pressure (BP) therapy to a target systolic BP of 120 mmHg, stratified by ASCVD risk and sub-stratified by CAC

		MESA Study Sample			Sprint-Eligible Subsample		
		Mean (SD) SBP	**10 year cumulative incidence (95% CI)**	**NNT ***	**Mean (SD) SBP**	**10 year cumulative incidence (95% CI)**	**NNT †**
SBP <140‡							
ASCVD risk <15%	CAC=0	129 (6)	0.04 (0.03, 0.06)	99	135 (2)	0.08 (0.03, 0.19)	39
	CAC 1-100	129 (6)	0.09 (0.06, 0.12)	52	135 (3)	0.09 (0.04, 0.21)	32
	CAC>100	129 (6)	0.19 (0.13, 0.26)	24	134 (3)	0.2 (0.12, 0.39)	14
ASCVD risk ≥15%	CAC=0	130 (6)	0.12 (0.08, 0.17)	29	135 (3)	0.08 (0.03, 0.20)	35
	CAC 1-100	131 (6)	0.18 (0.13, 0.24)	21	136 (3)	0.15 (0.09, 0.25)	19
	CAC>100	130 (6)	0.27 (0.25, 0.35)	15	135 (3)	0.21 (0.15, 0.30)	13
SBP 140-159							
ASCVD risk <15%	CAC=0	147 (5)	0.05 (0.03, 0.09)	36	147 (6)	0.06 (0.02, 0.13)	31
	CAC 1-100	147 (6)	0.12 (0.08, 0.20)	15	148 (6)	0.19 (0.11, 0.33)	9
	CAC>100	147 (6)	0.38 (0.28, 0.50)	5	147 (6)	0.39 (0.27, 0.55)	5
ASCVD risk ≥15%	CAC=0	150 (6)	0.10 (0.07, 0.16)	15	150 (6)	0.09 (0.05, 0.16)	20
	CAC 1-100	148 (5)	0.19 (0.15, 0.26)	9	148 (5)	0.18 (0.13, 0.25)	10
	CAC>100	148 (6)	0.32 (0.27, 0.38)	5	148 (6)	0.31 (0.25, 0.38)	6
SBP 160-179							
ASCVD risk <15%	CAC=0	167 (5)	0.07 (0.02, 0.20)	20	166 (5)	0.04 (0.01, 0.26)	33
	CAC 1-100	168 (6)	0.18 (0.08, 0.37)	18	168 (7)	0.22 (0.09, 0.49)	6
	CAC>100	166 (4)	0.14 (0.04, 0.46)	8	166 (4)	0.20 (0.05, 0.59)	7
ASCVD risk ≥15%	CAC=0	168 (6)	0.24 (0.15, 0.35)	5	168 (6)	0.18 (0.11, 0.31)	7
	CAC 1-100	168 (6)	0.28 (0.19, 0.41)	4	168 (6)	0.29 (0.19, 0.44)	5
	CAC>100	168 (6)	0.34 (0.25, 0.44)	4	169 (7)	0.32 (0.22, 0.44)	4

*NNT for the MESA study sample is calculated as follows; for each SBP category, we took the mean SBP in this category and subtracted 120 to get the target BP reduction. (e.g. if mean is 130 mmHg in the SBP <140 mmHg category then, **to achieve 120 mmHg**, the target reduction would be 10 mmHg). For each 10 mmHg reduction we estimate a 22% reduction in CHD, 41% reduction in stroke and 24% reduction in HF.

†NNT for the SPRINT subsample assumes a 25% relative reduction in the main outcome

‡ <140 SBP is 120-139 mmHg for primary sample and 130-139 mmHg for SPRINT subsample

SBP indicates systolic blood pressure in mmHg; CAC, coronary artery calcium; NNT, number needed to treat, all other abbreviations as per Table 1

Figure Legends

Figure 1. CAC distribution by anti-hypertension treatment status in the primary MESA sample overall (3,733 U.S. adults aged 45 to 84 years with Systolic BP 120-180 mmHg) and the SPRINT-eligible subsample (N=1,394).

A) Primary Sample Untreated

B) Primary Sample on BP treatment

C) Sprint subsample Untreated

D) Sprint subsample on BP treatment

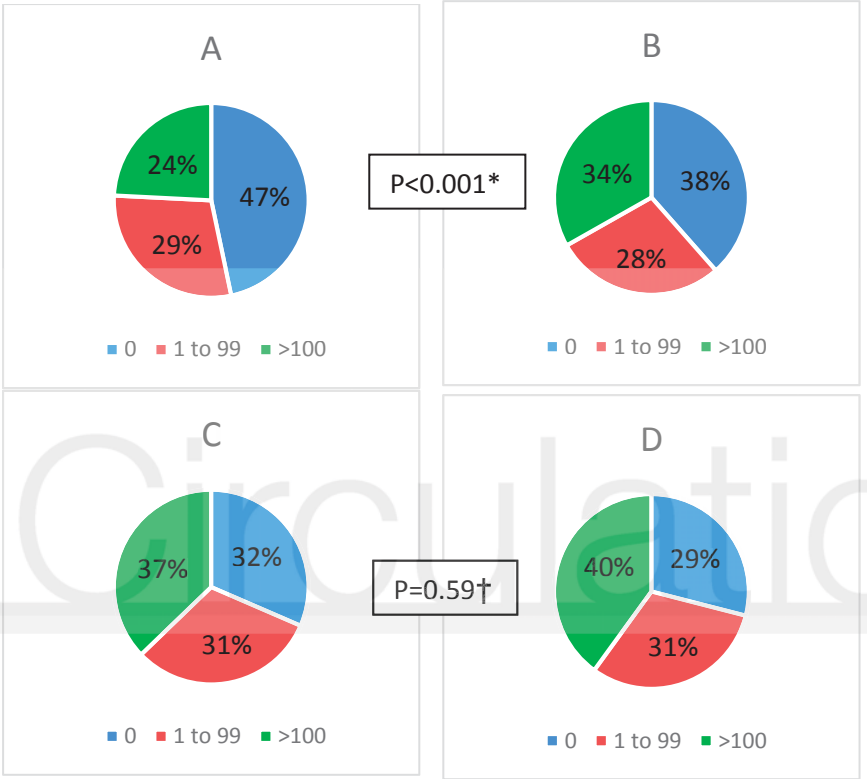
* p value comparing CAC level among treated to untreated in the primary sample

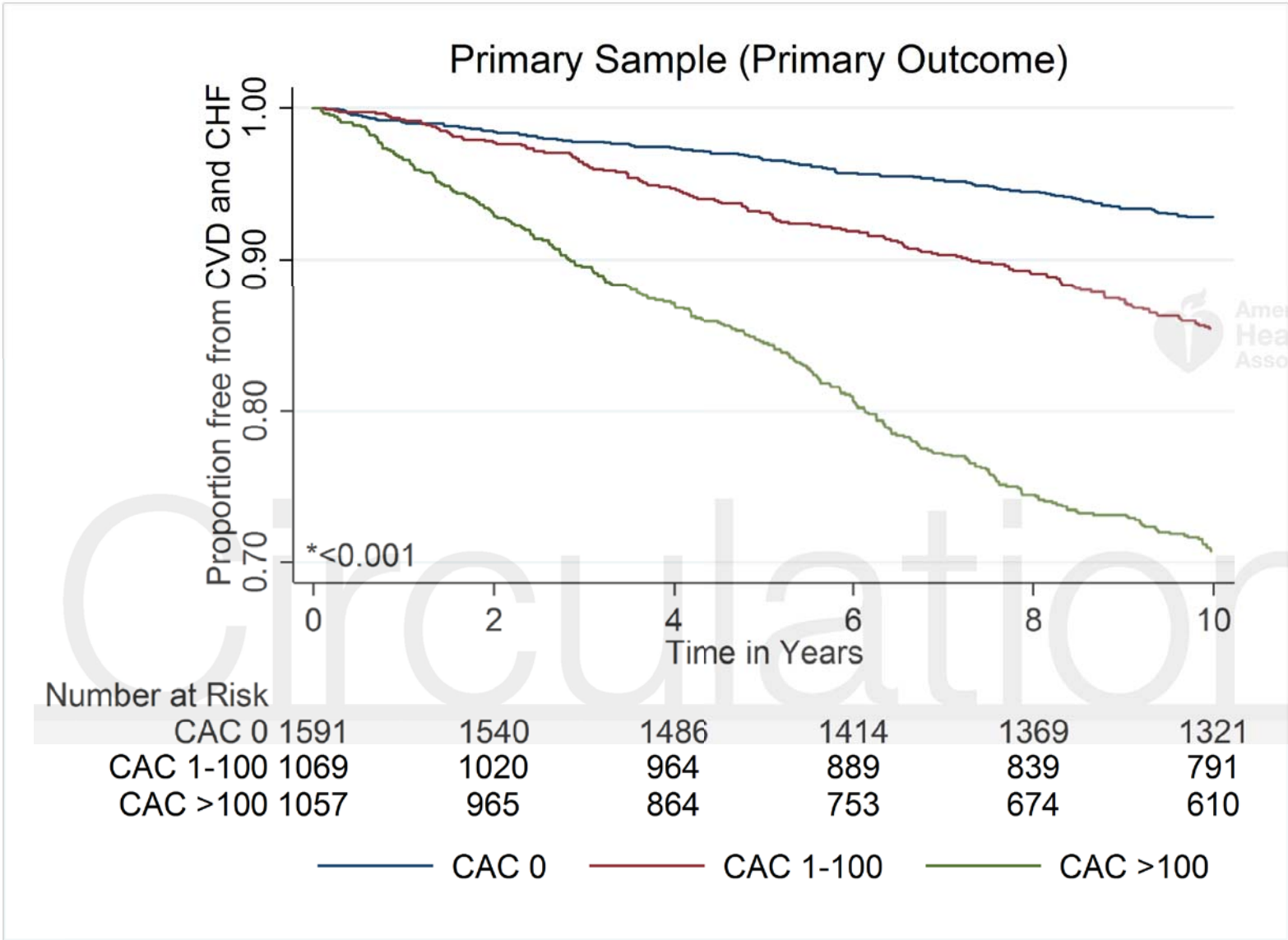
† p value comparing CAC level among treated to untreated in SPRINT sub-sample

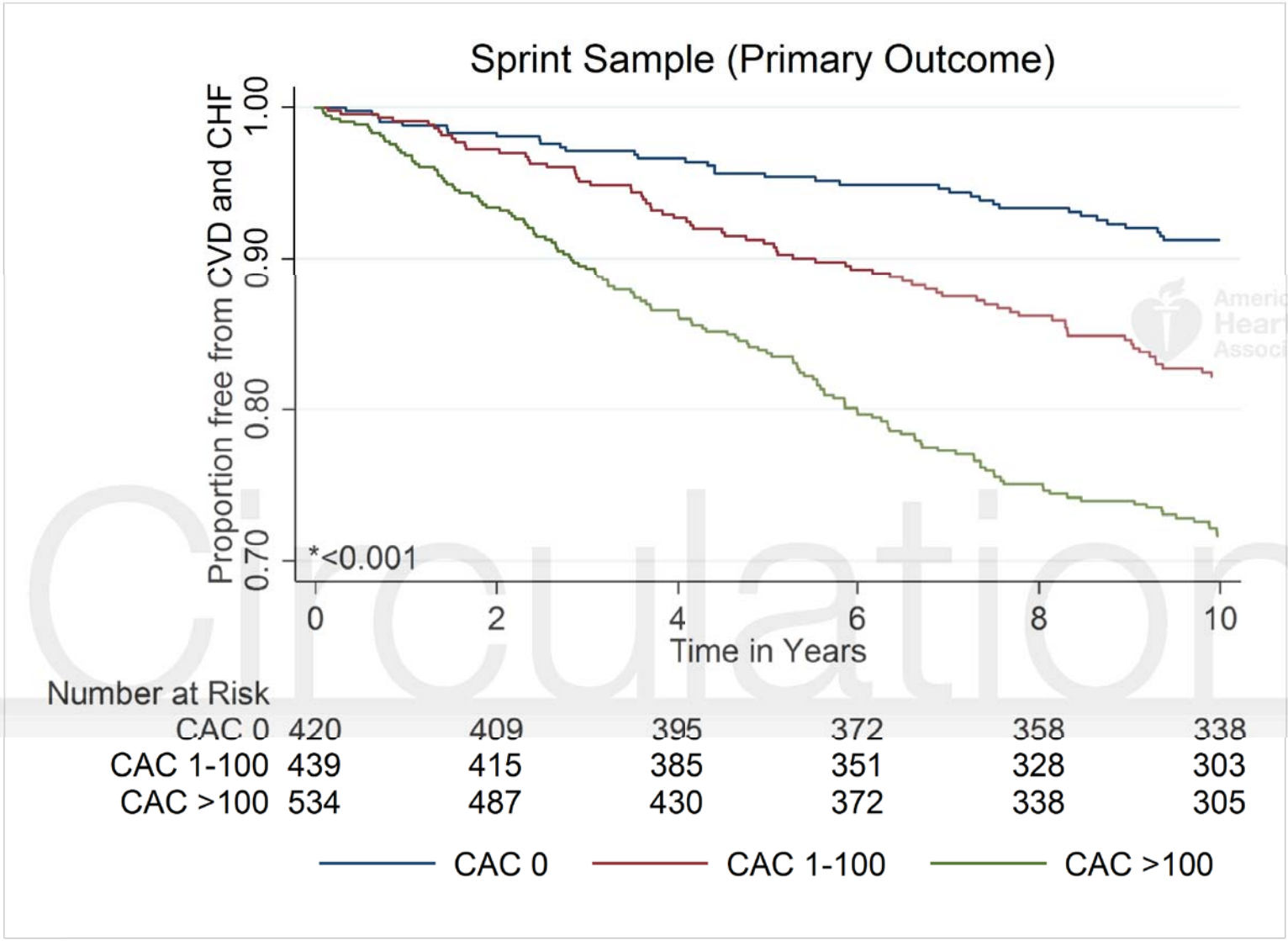
Figure 2. Kaplan-Meier curves for survival free from the primary outcome of all-cause CVD or heart failure in the primary MESA study sample and the SPRINT-eligible subsample, according to categories of CAC.

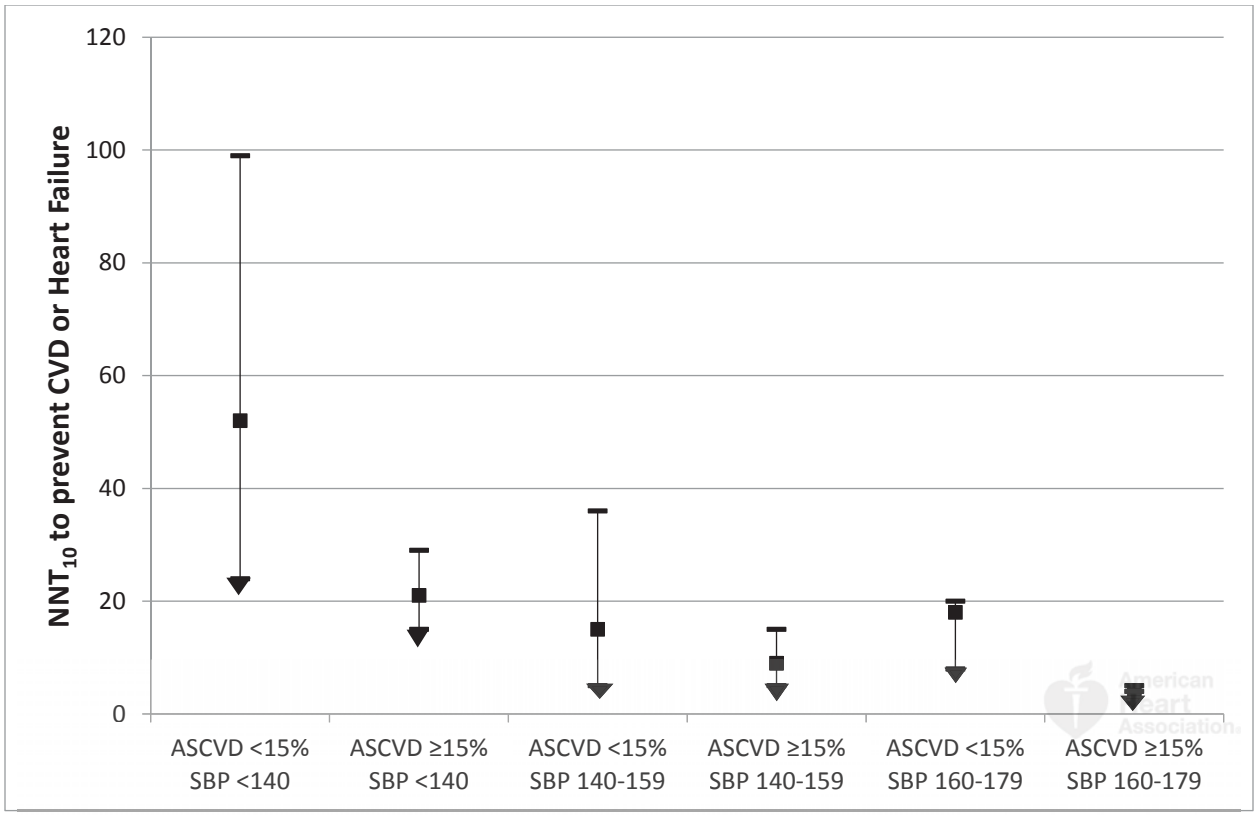
* P value by Log-Rank testing

Figure 3. CAC Stratifies a Range of Estimated Number Needed to Treat to a target systolic BP of 120 mmHg; among Categories of Baseline Systolic BP and ASCVD risk (primary MESA study sample, N=3,733).The NNT estimates within each category of ASCVD risk (calculated using traditional risk factors according to the 2013 ACC/AHA pooled cohort equations[14]) and Systolic BP consist of mean NNT_{10} for persons with CAC=0 (upper limit), mean NNT_{10} for persons with CAC 1-100 (solid square), and mean NNT_{10} for persons with CAC >100 (lower limit)









Coronary Artery Calcium to Guide a Personalized Risk-Based Approach to Initiation and Intensification of Antihypertensive Therapy

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Coronary Artery Calcium to guide a personalized risk-based approach to initiation and intensification of antihypertensive therapy: findings from a population-based cohort study

eTABLE 1- Crude Event Rates* and Demographic-adjusted† Hazard Ratios for Incident ASCVD or Heart Failure in the MESA study sample and the SPRINT-eligible subsample, according to baseline systolic BP (with or without BP therapy) and stratified by CAC

		MESA Study Sample (N=3,733)				Sprint-Eligible Subsample (N= 1,394)			
		N (%)	n (%)	Crude event rates (95% CI) *	Adjusted HR (95% CI) †	N (%)	n (%)	Crude event rates (95% CI) *	Adjusted HR (95% CI) †
SBP <140‡									
No BP therapy	CAC=0	635 (50)	40 (6)	5.6 (4.1, 7.6)	1.0	61 (29)	5 (8)	7.3 (3.0, 17.6)	1.0
	CAC 1-100	363 (29)	47 (13)	12.1 (9.1, 16.1)	**1.8 (1.1, 2.7)**	69 (33)	8 (12)	11.3 (5.6, 22.5)	1.5 (0.5, 4.7)
	CAC>100	263 (21)	61 (23)	24.3 (18.9, 31.3)	**3.1 (1.9, 4.9)**	14 (18)	14 (18)	19.0 (11.3, 32.1)	2.2 (0.7, 6.6)
BP Therapy	CAC=0	369 (41)	28 (8)	7.0 (4.8, 10.1)	1.0	47 (22)	3 (6)	6.0 (1.9, 18.7)	1.0
	CAC 1-100	258 (29)	35 (14)	12.8 (9.2, 17.8)	1.6 (0.96, 2.7)	79 (37)	13 (16)	15.6 (9.1, 28.9)	3.2 (0.9, 11.4)
	CAC>100	274 (30)	86 (31)	35.5 (28.7, 43.8)	**3.5 (2.2, 5.7)**	90 (42)	21 (23)	26.0 (17.0, 40.0)	**4.5 (1.3, 15.9)**
SBP 140-159									
No BP therapy	CAC=0	225 (41)	19 (8)	7.4 (4.7, 11.7)	1.0	94 (32)	11 (12)	10.2 (5.6, 18.4)	1.0
	CAC 1-100	162 (29)	27 (17)	16.5 (11.3, 24.1)	**2.2 (1.2, 4.0)**	89 (30)	15 (17)	17.2 (10.4, 28.6)	1.7 (0.8, 3.7)
	CAC>100	162 (29)	54 (33)	36.9 (29.0, 49.5)	**4.7 (2.6, 8.4)**	112 (38)	37 (33)	36.5 (26.4, 50.4)	**3.3 (1.6, 6.9)**
BP Therapy	CAC=0	243 (36)	31 (13)	11.9 (8.4, 17.0)	1.0	125 (30)	13 (10)	9.6 (5.6, 16.5)	1.0
	CAC 1-100	183 (27)	40 (22)	21.8 (16.0, 29.7)	1.6 (0.9, 2.5)	126 (30)	28 (22)	21.3 (15.4, 32.3)	**2.0 (1.02, 3.9)**
	CAC>100	240 (36)	80 (33)	38.8 (29.0, 49.5)	**2.4 (1.5, 3.9)**	164 (40)	55 (33)	39.2 (30.1, 51.1)	**3.0 (1.6, 5.8)**
SBP 160-179									
No BP therapy	CAC=0	57 (37)	9 (16)	16.7 (8.7, 32.1)	1.0	38 (35)	6 (16)	15.5 (6.9, 34.4)	1.0
	CAC 1-100	47 (30)	15 (32)	34.4 (20.7, 57.1)	1.8 (0.8, 4.1)	34 (31)	11 (32)	38.3 (20.3, 66.2)	2.3 (0.8, 6.1)
	CAC>100	50 (32)	16 (32)	37.1 (22.7, 60.6)	1.3 (0.6, 3.2)	37 (34)	12 (32)	36.4 (20.7, 64.1)	1.4 (0.5, 3.9)
BP Therapy	CAC=0	70 (35)	14 (20)	20.2 (12.0, 34.1)	1.0	55 (37)	9 (16)	15.8 (8.2, 30.4)	1.0
	CAC 1-100	57 (30)	14 (26)	26.6 (15.7, 44.9)	1.3 (0.6, 2.9)	43 (29)	10 (23)	25.1 (13.5, 46.5)	1.7 (0.66, 4.3)
	CAC>100	70 (35)	26 (37)	44.6 (30.4, 65.5)	**2.2 (1.1, 4.7)**	52 (35)	17 (33)	36.3 (23.8, 61.6)	2.3 (0.96, 5.6)

*Event rates are per 1,000 person years. †Adjusted for age, sex, and race. Significant Hazard Ratios are in bold ($p<0.05$). N (%) and n (%) represent numbers of persons and events in each category, respectively.

‡ <140 SBP is 120-139 for the MESA study sample and 130-139 for the SPRINT-eligible subsample

SBP indicates systolic blood pressure in mmHg; CAC, coronary artery calcium; all other abbreviations as per Table 1

eTABLE 2- Crude Event Rates* and Demographic-adjusted† Hazard Ratios for Incident ASCVD or Heart Failure in the MESA study sample and the SPRINT-eligible subsample, according to baseline systolic BP, stratified by ASCVD risk and sub-stratified by CAC

		MESA Study Sample (N=3,733)				Sprint-Eligible Subsample (N= 1,394)			
		N (%)	n (%)	Crude event rates (95% CI) *	Adjusted HR (95% CI) †	N (%)	n (%)	Crude event rates (95% CI) *	Adjusted HR (95% CI) †
SBP <140‡									
ASCVD risk <15%	CAC=0	796 (59)	42 (5)	4.6 (3.4, 6.2)	1.0	54 (36)	4 (7)	6.8 (2.5 , 18.1)	1.0
	CAC 1-100	387 (29)	41 (11)	9.5 (7.0, 12.9)	**1.7 (1.1, 2.7)**	58 (39)	7 (12)	11.1 (5.3, 23.3)	2.0 (0.59, 6.9)
	CAC>100	164 (12)	33 (20)	19.7 (14.0, 27.7)	**3.2 (1.9, 5.2)**	38 (25)	10 (26)	26.7 (14.4, 49.6)	**4.0 (1.2, 14.1)**
ASCVD risk ≥15%	CAC=0	198 (25)	25 (13)	12.7 (8.6, 18.8)	1.0	53 (20)	4 (8)	6.9 (2.6, 18.5)	1.0
	CAC 1-100	230 (29)	41 (18)	18.2 (13.4, 24.7)	1.5 (0.9, 2.4)	88 (33)	14 (16)	15.7 (9.3, 26.6)	2.4 (0.77, 7.3)
	CAC>100	371 (46)	33 (20)	35.0 (29.1, 42.1)	**2.9 (1.9, 4.6)**	130 (48)	25 (19)	21.7 (14.6, 32.1)	2.9 (0.98, 8.7)
SBP 140-159									
ASCVD risk <15%	CAC=0	264 (56)	21 (8)	6.9 (4.5, 10.6)	1.0	93 (47)	9 (10)	8.3 (4.3, 15.9)	1.0
	CAC 1-100	131 (28)	18 (14)	12.8 (8.1, 20.3)	1.8 (0.9, 3.4)	59 (30)	10 (17)	16.8 (9.0, 31.2)	2.0 (0.79, 5.0)
	CAC>100	80 (19)	32 (40)	43.4 (30.7, 61.4)	**5.5 (3.0, 10.1)**	47 (24)	20 (43)	45.9 (29.6, 71.1)	**5.0 (2.1, 11.5)**
ASCVD risk ≥15%	CAC=0	198 (27)	28 (14)	13.6 (9.4, 19.7)	1.0	124 (25)	15 (12)	11.3 (6.8, 18.8)	1.0
	CAC 1-100	213 (29)	49 (23)	23.7 (17.9, 31.4)	**1.7 (1.1, 2.7)**	156 (31)	33 (21)	21.5 (15.3, 30.3)	1.8 (0.95, 3.3)
	CAC>100	316 (43)	101 (32)	37.6 (30.9, 45.6)	**2.5 (1.6, 4.0)**	225 (45)	71 (32)	36.6 (29.0, 46.2)	**2.7 (1.5, 4.8)**
SBP 160-179									
ASCVD risk <15%	CAC=0	48 (53)	4 (8)	7.9 (3.0, 21.2)	1.0	27 (49)	2 (7)	6.4 (1.6, 25.7)	1.0
	CAC 1-100	29 (32)	7 (24)	21.8 (10.4, 45.7)	2.3 (0.65, 8.2)	18 (33)	4 (22)	20.1 (7.5, 53.5)	3.3 (0.61, 18.3)
	CAC>100	14 (15)	3 (21)	19.8 (6.4, 61.3)	3.2 (0.65, 15.4)	10 (18)	3 (30)	29.2 (9.4, 90.5)	6.6 (0.93, 46.6)
ASCVD risk ≥15%	CAC=0	77 (29)	19 (25)	26.7 (17.0, 41.9)	1.0	64 (32)	13 (20)	20.7 (12.0, 35.6)	1.0
	CAC 1-100	78 (30)	22 (28)	34.3 (22.6, 52.1)	1.3 (0.66, 2.4)	59 (29)	17 (30)	34.0 (21.1, 54.7)	1.8 (0.83, 3.8)
	CAC>100	106 (41)	39 (37)	45.9 (33.6, 62.9)	1.6 (0.86, 2.4)	78 (39)	26 (33)	39.5 (26.9, 58.0)	1.7 (0.81, 3.4)

*Event rates are per 1,000 person years. †Adjusted for age, sex, and race. Significant Hazard Ratios are in bold ($p<0.05$). N (%) and n (%) represent numbers of persons and events in each category, respectively.

‡ <140 SBP is 120-139 for the MESA study sample and 130-139 for the SPRINT-eligible subsample

SBP indicates systolic blood pressure in mmHg; CAC, coronary artery calcium; all other abbreviations as per Table 1

eTABLE 3- Crude Event Rates* and Propensity score-adjusted† Hazard Ratios for Incident ASCVD or Heart Failure in the MESA study sample, according to baseline systolic BP (with or without therapy) and stratified by CAC

		MESA Study Sample			
		N (%)	**n (%)**	**Crude event rates (95% CI) ***	**Adjusted HR (95% CI) †**
SBP <140‡					
No BP therapy	CAC=0	635 (50)	40 (6)	5.6 (4.1, 7.6)	1.0
	CAC 1-100	363 (29)	47 (13)	12.1 (9.1, 16.1)	1.5 (0.9, 2.4)
	CAC>100	263 (21)	61 (23)	24.3 (18.9, 31.3)	**2.3 (1.4, 3.7)**
BP Therapy	CAC=0	369 (41)	28 (8)	7.0 (4.8, 10.1)	1.0
	CAC 1-100	258 (29)	35 (14)	12.8 (9.2, 17.8)	1.4 (0.8, 2.5)
	CAC>100	274 (30)	86 (31)	35.5 (28.7, 43.8)	**3.6 (2.2, 6.2)**
SBP 140-159					
No BP therapy	CAC=0	225 (41)	19 (8)	7.4 (4.7, 11.7)	1.0
	CAC 1-100	162 (29)	27 (17)	16.5 (11.3, 24.1)	**2.1 (1.1, 4.0)**
	CAC>100	162 (29)	54 (33)	36.9 (29.0, 49.5)	**4.8 (2.5, 8.8)**
BP Therapy	CAC=0	243 (36)	31 (13)	11.9 (8.4, 17.0)	1.0
	CAC 1-100	183 (27)	40 (22)	21.8 (16.0, 29.7)	1.5 (0.9, 2.6)
	CAC>100	240 (36)	80 (33)	38.8 (29.0, 49.5)	**2.2 (1.3, 3.7)**
SBP 160-179					
No BP therapy	CAC=0	57 (37)	9 (16)	16.7 (8.7, 32.1)	1.0
	CAC 1-100	47 (30)	15 (32)	34.4 (20.7, 57.1)	1.2 (0.5, 2.9)
	CAC>100	50 (32)	16 (32)	37.1 (22.7, 60.6)	1.0 (0.4, 2.5)
BP Therapy	CAC=0	70 (35)	14 (20)	20.2 (12.0, 34.1)	1.0
	CAC 1-100	57 (30)	14 (26)	26.6 (15.7, 44.9)	1.0 (0.4, 2.4)
	CAC>100	70 (35)	26 (37)	44.6 (30.4, 65.5)	1.6 (0.7, 3.7)

*Event rates are per 1,000 person years. †Adjusted for a propensity score for the outcome of Incident CVD or heart failure, derived within each CAC group using the 13 variables included in the main model.
‡ <140 SBP is 120-139 for the MESA study sample and 130-139 for the SPRINT-eligible subsample
SBP indicates systolic blood pressure in mmHg; CAC, coronary artery calcium; all other abbreviations as per Table 1. Significant Hazard Ratios are in bold ($p<0.05$). N (%) and n (%) represent numbers of persons and events in each category, respectively.

eTABLE 4- Crude Event Rates* and Propensity score-adjusted† Hazard Ratios for Incident ASCVD or Heart Failure in the MESA study sample, according to baseline systolic BP, stratified by ASCVD risk and sub-stratified by CAC

		MESA Study Sample			
		N (%)	**n (%)**	**Crude event rates (95% CI) ***	**Adjusted HR (95% CI) †**
SBP <140‡					
ASCVD risk <15%	CAC=0	796 (59)	42 (5)	4.6 (3.4, 6.2)	1.0
	CAC 1-100	387 (29)	41 (11)	9.5 (7.0, 12.9)	**1.6 (1.01, 2.6)**
	CAC>100	164 (12)	33 (20)	19.7 (14.0, 27.7)	**3.0 (1.8, 5.0)**
ASCVD risk ≥15%	CAC=0	198 (25)	25 (13)	12.7 (8.6, 18.8)	1.0
	CAC 1-100	230 (29)	41 (18)	18.2 (13.4, 24.7)	1.2 (0.7, 2.1)
	CAC>100	371 (46)	33 (20)	35.0 (29.1, 42.1)	**2.5 (1.6, 4.1)**
SBP 140-159					
ASCVD risk <15%	CAC=0	264 (56)	21 (8)	6.9 (4.5, 10.6)	1.0
	CAC 1-100	131 (28)	18 (14)	12.8 (8.1, 20.3)	1.8 (0.9, 3.5)
	CAC>100	80 (19)	32 (40)	43.4 (30.7, 61.4)	**4.9 (2.5, 9.3)**
ASCVD risk ≥15%	CAC=0	198 (27)	28 (14)	13.6 (9.4, 19.7)	1.0
	CAC 1-100	213 (29)	49 (23)	23.7 (17.9, 31.4)	1.6 (0.99, 2.7)
	CAC>100	316 (43)	101 (32)	37.6 (30.9, 45.6)	**2.4 (1.5, 3.9)**
SBP 160-179					
ASCVD risk <15%	CAC=0	48 (53)	4 (8)	7.9 (3.0, 21.2)	1.0
	CAC 1-100	29 (32)	7 (24)	21.8 (10.4, 45.7)	2.4 (0.7, 8.3)
	CAC>100	14 (15)	3 (21)	19.8 (6.4, 61.3)	1.4 (0.2, 8.4)
ASCVD risk ≥15%	CAC=0	77 (29)	19 (25)	26.7 (17.0, 41.9)	1.0
	CAC 1-100	78 (30)	22 (28)	34.3 (22.6, 52.1)	1.0 (0.5, 2.0)
	CAC>100	106 (41)	39 (37)	45.9 (33.6, 62.9)	1.3 (0.7, 2.4)

*Event rates are per 1,000 person years. †Adjusted for a propensity score for the outcome of Incident CVD or heart failure, derived within each CAC group using the 13 variables included in the main model.
‡ <140 SBP is 120-139 for the MESA study sample and 130-139 for the SPRINT-eligible subsample
SBP indicates systolic blood pressure in mmHg; CAC, coronary artery calcium; all other abbreviations as per Table 1. Significant Hazard Ratios are in bold ($p<0.05$). N (%) and n (%) represent numbers of persons and events in each category, respectively.

E-Table 5. Estimated 10-year NNT* for the prevention of ASCVD or heart failure with blood pressure (BP) therapy to a target systolic BP of 120 mmHg, stratified by treatment status, ASCVD risk and by CAC

		MESA Study Sample (Not on HTN Therapy at baseline, N= 1964)			**MESA Study Sample (On HTN Therapy at baseline, N=1769)**		
		Mean (SD) SBP	10 year cumulative incidence (95% CI)	NNT *	Mean (SD) SBP	10 year cumulative incidence (95% CI)	NNT †
SBP <140‡							
ASCVD risk <15%	CAC=0	129 (6)	0.04 (0.03, 0.07)	87	129 (6)	0.04 (0.02, 0.08)	90
	CAC 1-100	128 (6)	0.08 (0.05, 0.13)	56	130 (6)	0.09 (0.05, 0.16)	40
	CAC>100	129 (6)	0.19 (0.12, 0.29)	24	129 (6)	0.18 (0.11, 0.30)	24
ASCVD risk ≥15%	CAC=0	130 (6)	0.10 (0.05, 0.20)	32	131 (6)	0.13 (0.08, 0.20)	25
	CAC 1-100	131 (6)	0.18 (0.11, 0.27)	18	131 (6)	0.17 (0.11, 0.25)	20
	CAC>100	130 (6)	0.24 (0.18, 0.32)	15	131 (6)	0.34 (0.27, 0.41)	10
SBP 140-159							
ASCVD risk <15%	CAC=0	147 (6)	0.06 (0.03, 0.11)	26	147 (5)	0.05 (0.02, 0.11)	32
	CAC 1-100	147 (6)	0.10 (0.05, 0.19)	19	147 (6)	0.17 (0.09, 0.31)	10
	CAC>100	147 (6)	0.38 (0.26, 0.53)	4	147 (6)	0.39 (0.24, 0.58)	5
ASCVD risk ≥15%	CAC=0	150 (6)	0.06 (0.02, 0.15)	24	150 (6)	0.13 (0.08, 0.21)	12
	CAC 1-100	148 (5)	0.20 (0.13, 0.31)	9	148 (5)	0.19 (0.13, 0.27)	8
	CAC>100	148 (6)	0.31 (0.23, 0.42)	6	149 (6)	0.33 (0.26, 0.40)	5
SBP 160-179							
ASCVD risk <15%	CAC=0	168 (6)	0.04 (0.01, 0.27)	27	165 (5)	0.10 (0.03, 0.36)	12
	CAC 1-100	168 (6)	0.11 (0.03, 0.37)	10	168 (7)	0.30 (0.11, 0.67)	4
	CAC>100	166 (4)	0.10 (0.02, 0.53)	14	166 (3)	0.25 (0.16, 0.94)	6
ASCVD risk ≥15%	CAC=0	168 (7)	0.28 (0.14, 0.50)	4	169 (6)	0.22 (0.12, 0.37)	5
	CAC 1-100	168 (6)	0.39 (0.22, 0.62)	3	169 (6)	0.23 (0.13, 0.39)	5
	CAC>100	167 (6)	0.34 (0.21, 0.52)	4	169 (6)	0.34 (0.24, 0.48)	4

*See Table 4 of main paper for footnote

E-Table 6. Estimated 10-year NNT* for the prevention of each individual endpoint included in the composite (i.e., each of stroke, CHD or heart failure) with blood pressure (BP) therapy to a target systolic BP of 120 mmHg, stratified by ASCVD risk and by CAC

		Stroke		CHD		Heart Failure	
		10 year cumulative incidence (95% CI)	NNT *	10 year cumulative incidence (95% CI)	NNT †	10 year cumulative incidence (95% CI)	NNT ‡
SBP 120-139							
ASCVD risk <15%	CAC=0	0.02 (0.01, 0.03)	137	0.02 (0.01, 0.03)	260	0.01 (0.006, 0.02)	476
	CAC 1-100	0.01 (0.004, 0.03)	265	0.06 (0.04, 0.09)	83	0.02 (0.01, 0.04)	228
	CAC>100	0.03 (0.01, 0.08)	88	0.14 (0.09, 0.20)	36	0.03 (0.01, 0.08)	153
ASCVD risk ≥15%	CAC=0	0.04 (0.02, 0.09)	59	0.04 (0.02, 0.08)	109	0.06 (0.03, 0.10)	67
	CAC 1-100	0.04 (0.02, 0.07)	57	0.11 (0.07, 0.16)	38	0.05 (0.03, 0.09)	77
	CAC>100	0.06 (0.04, 0.09)	40	0.19 (0.15, 0.24)	23	0.10 (0.07, 0.14)	41
SBP 140-159							
ASCVD risk <15%	CAC=0	0.02 (0.01, 0.05)	66	0.02 (0.01, 0.05)	102	0.01 (0.002, 0.03)	190
	CAC 1-100	0.04 (0.02, 0.10)	33	0.08 (0.04, 0.14)	25	0.02 (0.004, 0.07)	95
	CAC>100	0.08 (0.04, 0.17)	17	0.29 (0.21, 0.41)	7	0.12 (0.07, 0.22)	16
ASCVD risk ≥15%	CAC=0	0.03 (0.02, 0.07)	42	0.02 (0.01, 0.05)	96	0.07 (0.04, 0.12)	26
	CAC 1-100	0.07 (0.04, 0.12)	19	0.10 (0.06, 0.15)	20	0.07 (0.04, 0.12)	27
	CAC>100	0.06 (0.04, 0.10)	21	0.21 (0.17, 0.26)	9	0.12 (0.09, 0.17)	15
SBP 160-179							
ASCVD risk <15%	CAC=0	0.07 (0.02, 0.20)	16	0.03 (0.004, 0.17)	49	0.03 (0.004, 0.17)	46
	CAC 1-100	0.11 (0.04, 0.30)	10	0.04 (0.01, 0.22)	36	0.04 (0.01, 0.22)	34
	CAC>100	-	-	0.07 (0.01, 0.41)	21	0.07 (0.01, 0.41)	20
ASCVD risk ≥15%	CAC=0	0.10 (0.05, 0.19)	11	0.07 (0.03, 0.17)	20	0.13 (0.07, 0.23)	10
	CAC 1-100	0.09 (0.04, 0.20)	12	0.20 (0.12, 0.33)	7	0.06(0.02, 0.16)	23
	CAC>100	0.10 (0.05, 0.18)	11	0.24 (0.17, 0.34)	6	0.10 (0.06, 0.19)	14

NNT for the MESA study sample is calculated as follows; for each 10 mmHg reduction we estimate a 41% reduction in stroke*****, 22% reduction in CHD†, and 24% reduction in HF‡.

E-Table 7. Estimated 10-year NNT for the prevention of ASCVD or heart failure with blood pressure (BP) therapy to a target systolic BP of 120 mmHg, stratified by 3 levels of ASCVD risk and sub-stratified by CAC

A- ASCVD risk levels of **<7.5%,** 7.5-14.9%, and ≥15%

		MESA Study Sample			
		N (%)	**Mean (SD) SBP**	**10 year cumulative incidence (95% CI)**	**NNT ***
SBP <140‡					
ASCVD risk <7.5%	CAC=0	516, 69 %	128.3 +/- 5.7	0.019 (0.010, 0.04)	183
	CAC 1-100	185, 25 %	128.8 +/- 5.9	0.05 (0.03, 0.095)	76
	CAC>100	43, 6 %	127.8 +/- 5.9	0.121 (0.05, 0.268)	47
ASCVD risk 7.5-14.9%	CAC=0	280, 46 %	129.3 +/- 5.7	0.090 (0.06, 0.131)	39
	CAC 1-100	202, 33 %	129.1 +/- 6.0	0.118 (0.079, 0.174)	35
	CAC>100	121, 20 %	129.4 +/- 5.6	0.209 (0.145, 0.296)	19
ASCVD risk ≥15%	CAC=0	198, 25 %	130.5 +/- 5.8	0.116 (0.077, 0.173)	29
	CAC 1-100	230, 29 %	131.0 +/- 5.8	0.177 (0.132, 0.237)	21
	CAC>100	372, 46 %	130.27 +/- 5.8	0.265 (0.249, 0.348)	15
SBP 140-159					
ASCVD risk <7.5%	CAC=0	122, 66 %	146.8 +/- 5.2	0.034 (0.013, 0.088)	44
	CAC 1-100	52, 27 %	146.0 +/- 5.0	0.063 (0.021, 0.183)	32
	CAC>100	21, 11 %	147.5 +/- 5.7	0.393 (0.219, 0.635)	5
ASCVD risk 7.5-14.9%	CAC=0	142, 51 %	147.6 +/- 5.7	0.068 (0.036, 0.127)	23
	CAC 1-100	79, 28 %	147.9 +/- 5.8	0.167 (0.099, 0.276)	10
	CAC>100	59, 21 %	146.5 +/- 5.6	0.378 (0.268, 0.515)	5
ASCVD risk ≥15%	CAC=0	198, 27 %	149.6 +/- 6.0	0.102 (0.066, 0.156)	15
	CAC 1-100	213, 29 %	147.9 +/- 5.3	0.195 (0.145, 0.258)	9
	CAC>100	316, 43 %	148.3 +/- 5.6	0.320 (0.269, 0.378)	5
SBP 160-179					
ASCVD risk <7.5%	CAC=0	11, 55 %	169.1 +/- 6.3	0	-
	CAC 1-100	8, 40 %	164.5 +/- 4.8	0	-
	CAC>100	1, 5 %	160.5	0	-
ASCVD risk 7.5-14.9%	CAC=0	37, 52 %	165.8 +/- 5.0	0.086 (0.028, 0.243)	13
	CAC 1-100	21, 30 %	168.7 +/- 6.5	0.238 (0.107, 0.481)	5
	CAC>100	13, 18 %	166.5 +/- 3.7	0.077 (0.011, 0.43)	18
ASCVD risk ≥15%	CAC=0	77, 29 %	168.2 +/- 6.0	0.236 (0.154, 0.353)	5
	CAC 1-100	78, 30 %	168.2 +/- 5.8	0.284 (0.190, 0.411)	5
	CAC>100	106, 41 %	168.2 +/- 5.8	0.339 (0.254, 0.444)	4

B- ASCVD risk levels of **<5%,** 5-14.9%, and ≥15%

		MESA Study Sample			
		N (%)	**Mean (SD) SBP**	**10 year cumulative incidence (95% CI)**	**NNT ***
SBP <140‡					
ASCVD risk <5%	CAC=0	373, 77 %	128.01 +/- 5.8	0.014 (0.006, 0.034)	273
	CAC 1-100	95, 20 %	128.5 +/- 5.9	0.022 (0.006, 0.086)	180
	CAC>100	15, 3 %	127.7 +/- 5.7	0.154 (0.040, 0.398)	37
ASCVD risk 5-14.9%	CAC=0	423, 49 %	129.2 +/- 5.6	0.090 (0.061, 0.131)	39
	CAC 1-100	292, 34 %	129.1 +/- 6.0	0.118 (0.079, 0.174)	34
	CAC>100	149, 17 %	129.1 +/- 5.7	0.209 (0.145, 0.296)	20
ASCVD risk ≥15%	CAC=0	198, 25 %	130.5 +/- 5.8	0.069 (0.048, 0.093)	29
	CAC 1-100	230, 29 %	131.0 +/- 5.8	0.106 (0.075, 0.149)	21
	CAC>100	372, 46 %	130.27 +/- 5.8	0.189 (0.134, 0.264)	15
SBP 140-159					
ASCVD risk <5%	CAC=0	70, 67 %	146.2 +/- 5.0	0.044 (0.014, 0.130)	33
	CAC 1-100	26, 25 %	145.1 +/- 5.3	0.080 (0.021, 0.284)	26
	CAC>100	8, 8%	146.8 +/- 6.3	0.417 (0.156, 0.820)	5
ASCVD risk 5-14.9%	CAC=0	194, 52 %	147.6 +/- 5.6	0.056 (0.030, 0.101)	28
	CAC 1-100	105, 28 %	147.6 +/- 5.5	0.136 (0.081, 0.223)	12
	CAC>100	72, 19 %	146.8 +/- 5.5	0.379 (0.278, 0.502)	5
ASCVD risk ≥15%	CAC=0	198, 27 %	149.6 +/- 6.0	0.102 (0.066, 0.156)	15
	CAC 1-100	213, 29 %	147.9 +/- 5.3	0.195 (0.145, 0.258)	9
	CAC>100	316, 43 %	148.3 +/- 5.6	0.320 (0.269, 0.378)	5
SBP 160-179					
ASCVD risk <5%	CAC=0	5, 56 %	169.4 +/- 6.0	0	-
	CAC 1-100	4, 44 %	163.8 +/- 6.0	0	-
	CAC>100	0, 0%	0	0	-
ASCVD risk 5-14.9%	CAC=0	43, 52 %	166.2 +/- 5.3	0.075 (0.025, 0.214)	15
	CAC 1-100	25, 30 %	168.2 +/- 6.2	0.200 (0.080, 0.416)	6
	CAC>100	14, 17 %	166.1 +/- 3.9	0.143 (0.038, 0.461)	10
ASCVD risk ≥15%	CAC=0	77, 29 %	168.2 +/- 6.0	0.236 (0.154, 0.353)	5
	CAC 1-100	78, 30 %	168.2 +/- 5.8	0.284 (0.190, 0.411)	5
	CAC>100	106, 41 %	168.2 +/- 5.8	0.339 (0.254, 0.444)	4

*See Table 4 of main paper for footnote

eTABLE 8- Crude Event Rates* and Demographic Adjusted† Hazard Ratios and estimated 10-year NNTs for Incident ASCVD or Heart Failure in the MESA study sub-sample with Diabetes, according to baseline systolic BP, stratified by ASCVD risk and sub-stratified by CAC

MAIN COMPOSITE OUTCOME (CVD or CHF)		MESA Sub-sample with DIABETES (N= 559)					
		N (%)	n (%)	Crude event rates (95% CI) *	10 year cumulative incidence (95% CI)	NNT †	Adjusted HR (95% CI) ‡
SBP 120-139							
ASCVD risk <15%	**CAC=0**	48, 63.2%	5, 10.4%	10.4(4.3, 25.1)	0.10 (0.04, 0.23)	35	1.0
	CAC 1-100	25, 32.9%	2, 8.0%	7.6 (1.9, 30.3)	0.04 (0.01, 0.27)	118	0.25 (0.01,12.5)
	CAC>100	3, 3.95%	0, 0.0%	-	-	-	-
ASCVD risk ≥15%	**CAC=0**	63, 30.4%	12, 19.1%	21.2 (12.1, 37.4)	0.16 (0.09, 0.29)	21	1.0
	CAC 1-100	58, 28.9%	15, 25.9%	28.9 (17.4, 47.9)	0.26 (0.16, 0.40)	15	0.88 (0.37, 2.1)
	CAC>100	86, 41.6%	36, 41.9%	47.7 (34.4, 66.2)	0.35 (0.25, 0.46)	10	**2.2 (1.1, 4.6)**
SBP 140-159							
ASCVD risk <15%	**CAC=0**	12, 50.0%	3, 25.0%	23.7 (7.6, 73.4)	0.18 (0.05, 0.54)	9	-
	CAC 1-100	8, 33.3%	3, 37.5%	42.7 (13.8, 132.5)	0.29 (0.08, 0.74)	5	-
	CAC>100	4, 16.7%	3, 75.0%	110.8 (35.7, 343.5)	0.75 (0.34, 0.99)	2	-
ASCVD risk ≥15%	**CAC=0**	60, 32.4%	13, 21.7%	22.3 (12.9, 38.3)	0.16 (0.09, 0.29)	10	1.0
	CAC 1-100	44, 23.8%	13, 29.6%	32.1 (18.6, 55.2)	0.23 (0.12, 0.39)	7	1.6 (0.65, 4.05)
	CAC>100	81, 43.8%	26, 32.1%	37.8 (25.7, 55.5)	0.33 (0.24, 0.45)	5	2.0 (0.85, 4.7)
SBP 160-179							
ASCVD risk <15%	**CAC=0**	2, 40.0%	0, 0.0%	0	0	-	-
	CAC 1-100	3, 60.0%	1, 33.33%	33.9 (4.8, 241.0)	0.33 (0.06, 0.95)	6	-
	CAC>100	-	-	-	0	-	-
ASCVD risk ≥15%	**CAC=0**	11, 19.3%	5, 45.5%	65.1 (27.1, 156.5)	0.47 (0.23, 0.79)	3	1.0
	CAC 1-100	19, 33.3%	5, 26.3%	33.8 (14.1, 81.1)	0.27 (0.11, 0.58)	5	0.29 (0.06, 1.4)
	CAC>100	27, 47.4%	13, 48.2%	68.5 (39.8, 118.0)	0.41 (0.25, 0.63)	3	1.01 (0.25, 4.1)

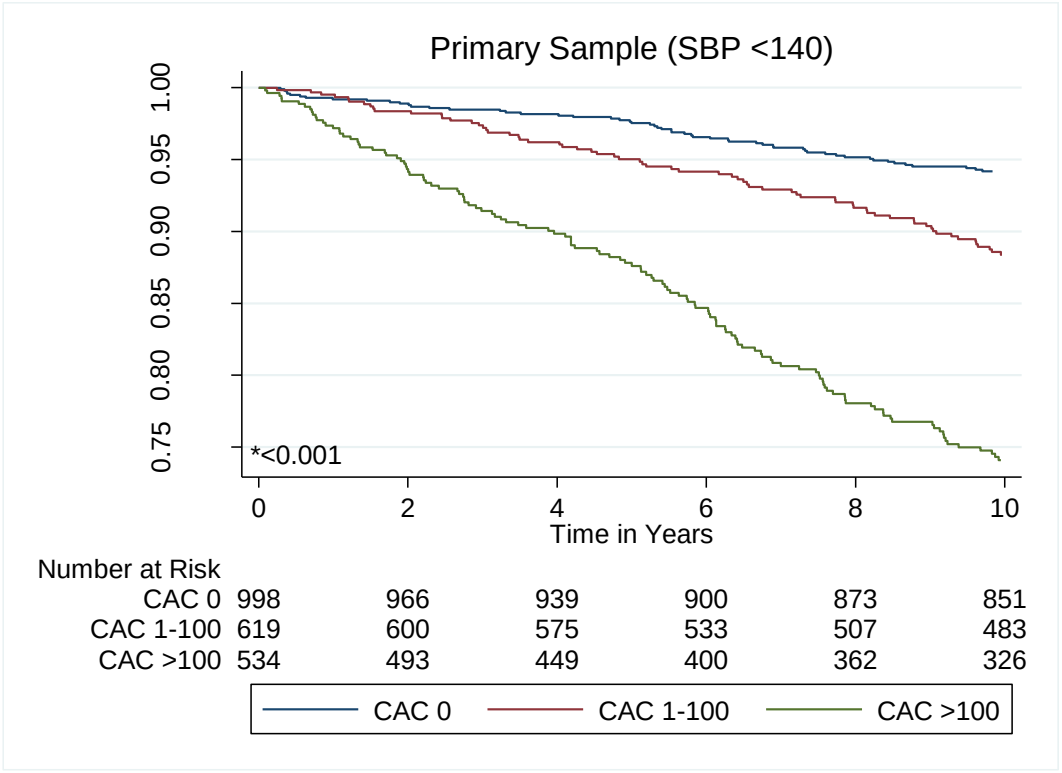
*See Tables 3 and 4 of main paper for footnote. Adjusted for age, sex, and race/ethnicity

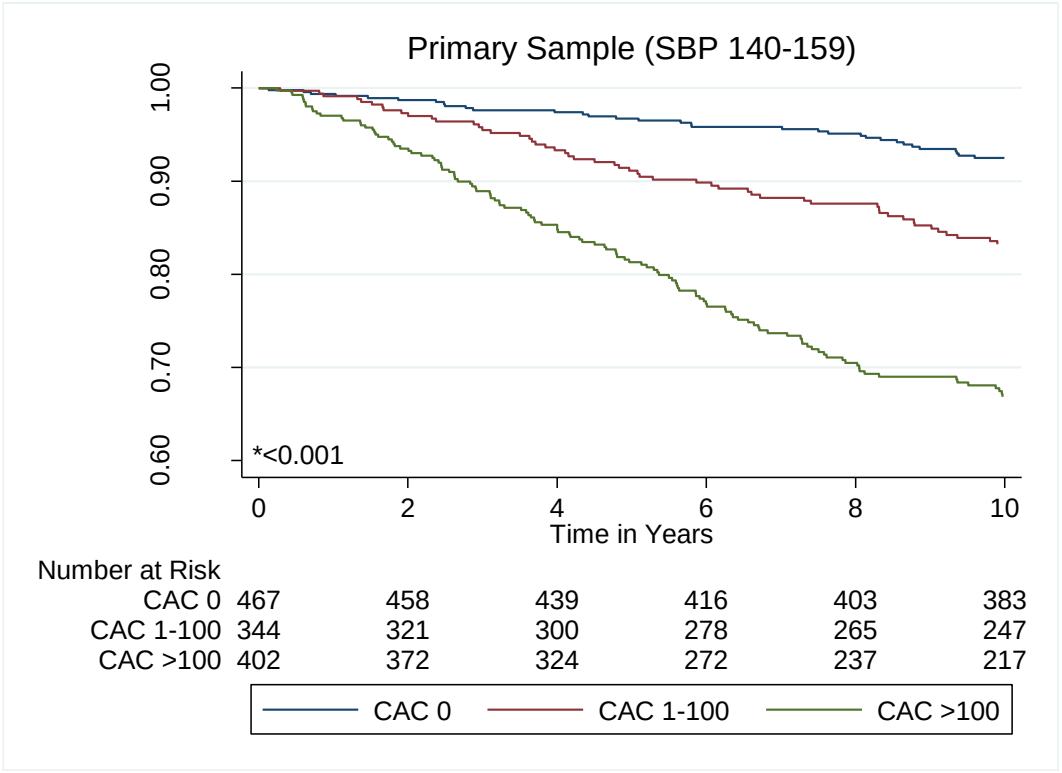
E-Table 9. Estimated 10-year NNT for the prevention of ASCVD or heart failure with blood pressure (BP) therapy to a systolic BP target of 130mmg versus a systolic target of 120 mmHg, stratified by ASCVD risk and sub-stratified by CAC

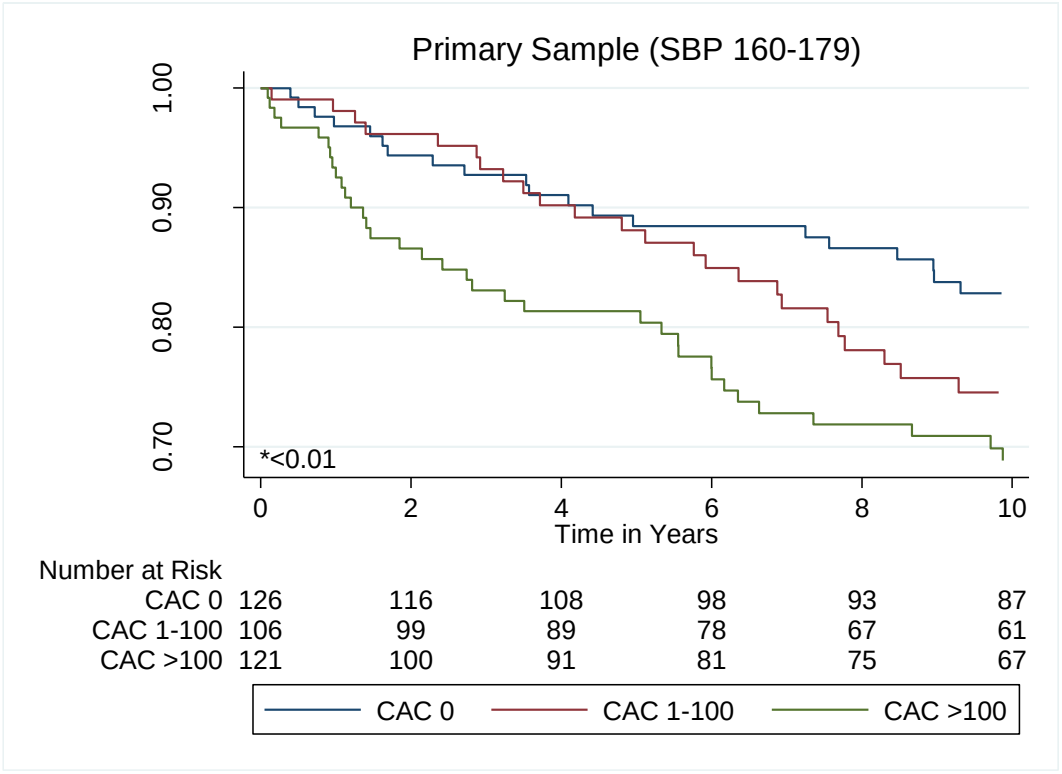
		MESA Study Sample			
		Mean (SD) SBP	10 year cumulative incidence (95% CI)	130 mmHg target NNT *	120 mmHg target NNT *
SBP <140†					
ASCVD risk <15%	CAC=0	134.7 (2.6)	0.05 (0.03, 0.08)	129	99
	CAC 1-100	134.7 (2.7)	0.11 (0.07, 0.17)	65	52
	CAC>100	134.8 (2.7)	0.20 (0.12, 0.32)	36	24
ASCVD risk ≥15%	CAC=0	135.4 (2.6)	0.12 (0.07, 0.20)	45	29
	CAC 1-100	135.4 (2.7)	0.17 (0.11, 0.25)	37	21
	CAC>100	135.2 (2.7)	0.20 (0.15, 0.27)	34	15
SBP 140-159					
ASCVD risk <15%	CAC=0	147.2 (5.5)	0.05 (0.03, 0.09)	50	36
	CAC 1-100	147.1 (5.6)	0.13 (0.08, 0.20)	21	15
	CAC>100	146.8 (5.6)	0.38 (0.29, 0.50)	7	5
ASCVD risk ≥15%	CAC=0	149.6 (6.0)	0.10 (0.07, 0.16)	19	15
	CAC 1-100	147.9 (5.3)	0.20 (0.15, 0.26)	12	9
	CAC>100	148.3 (5.6)	0.32 (0.27, 0.38)	7	5
SBP 160-179					
ASCVD risk <15%	CAC=0	166.6 (5.4)	0.07 (0.02, 0.20)	23	20
	CAC 1-100	167.6 (6.3)	0.18 (0.08, 0.37)	22	18
	CAC>100	166.1 (3.9)	0.14 (0.04, 0.46)	9	8
ASCVD risk ≥15%	CAC=0	168.2 (6.0)	0.24 (0.15, 0.35)	6	5
	CAC 1-100	168.2 (5.8)	0.29 (0.19, 0.42)	5	4
	CAC>100	168.2 (5.9)	0.34 (0.25, 0.44)	4	4

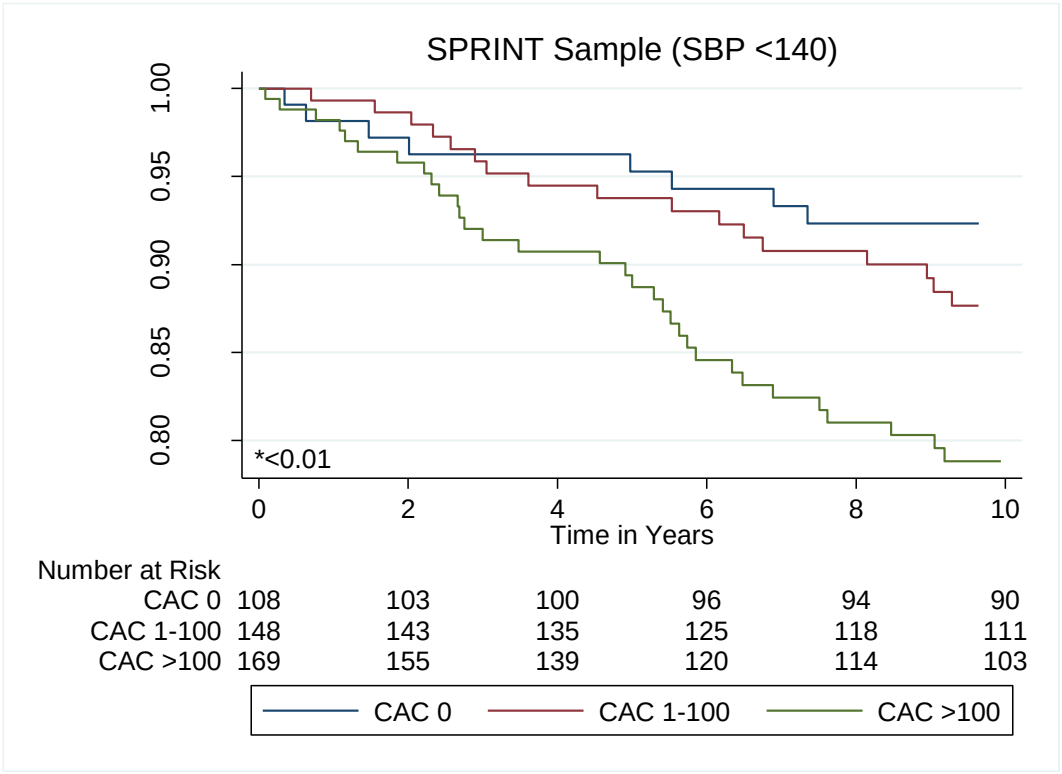
*See Table 4 of main paper for footnote. †Includes persons with SBP 131-139 for the target of 130 mmHg analysis, and those with SBP 121-139 for the target of 120 mmHg analysis.

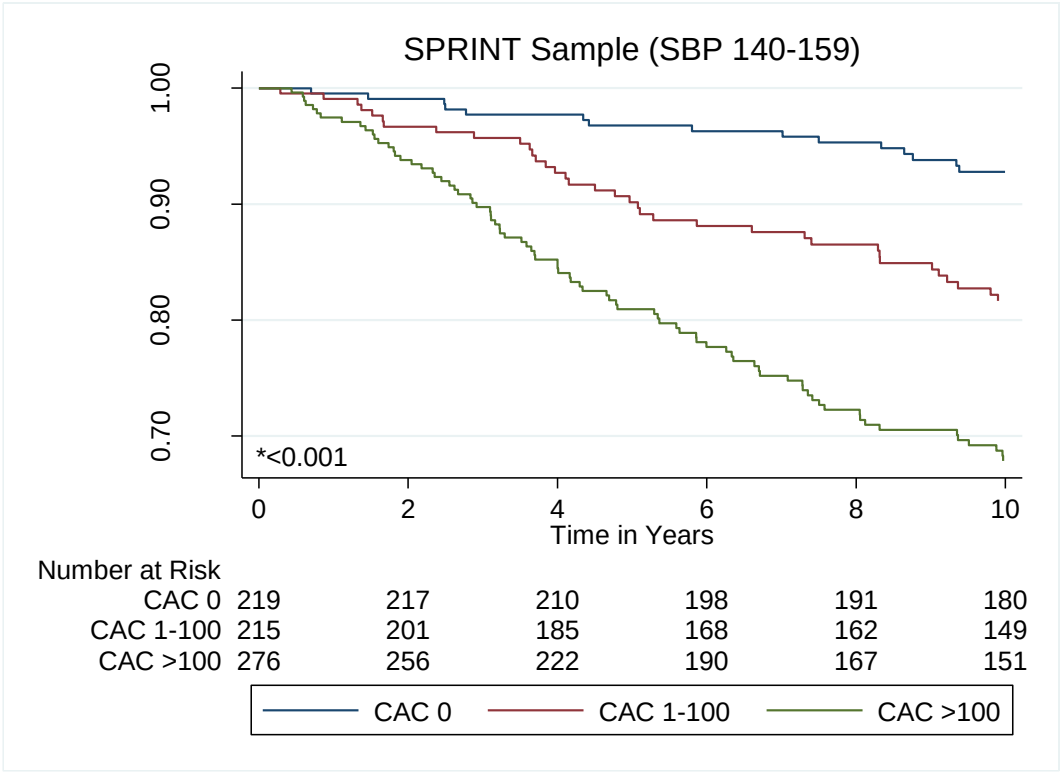
E-FIGURE 1- Kaplan-Meier curves for survival free from the primary outcome of all-cause CVD or heart failure in the primary study sample and the SPRINT-eligible subsample, according to categories of CAC, stratified by baseline systolic BP.

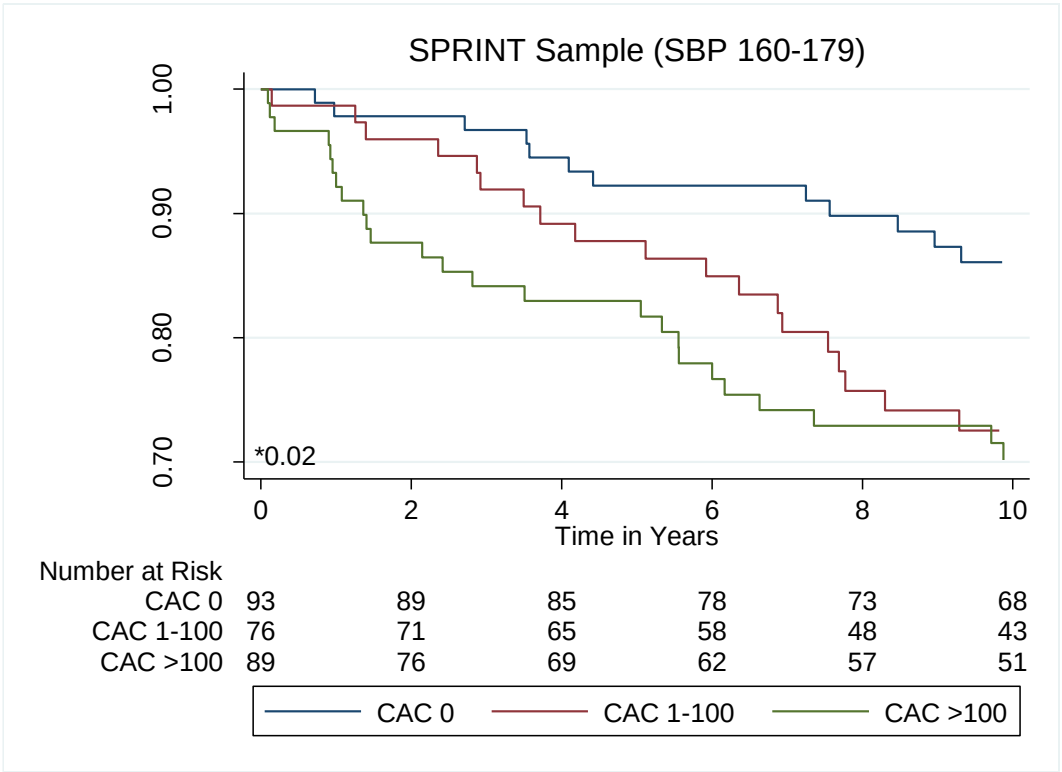





Primary Sample (SBP 160-179)
1.00
0.90
0.80
0.70
*<0.01
0
2
4
6
8
10
Time in Years
Number at Risk
CAC 0 126 116 108 98 93 87
CAC 1-100 106 99 89 78 67 61
CAC >100 121 100 91 81 75 67
CAC 0
CAC 1-100
CAC >100

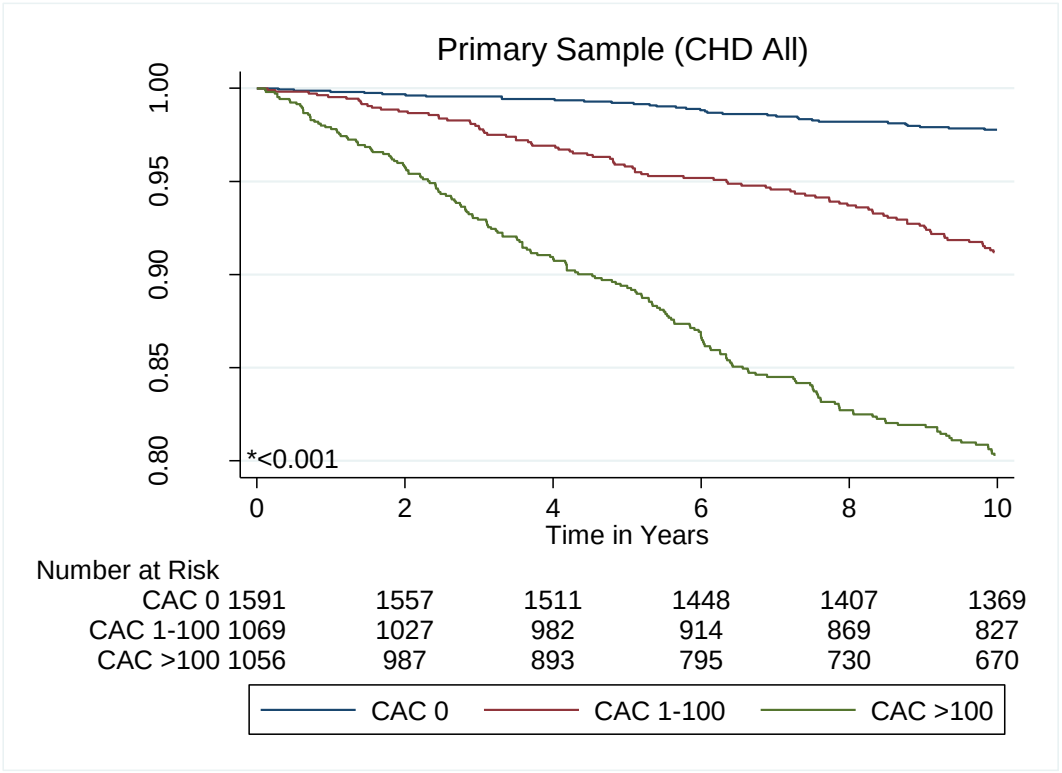

SPRINT Sample (SBP <140)
1.00
0.95
0.90
0.85
0.80
*<0.01
0
2
4
6
8
10
Time in Years
Number at Risk
CAC 0 108 103 100 96 94 90
CAC 1-100 148 143 135 125 118 111
CAC >100 169 155 139 120 114 103
CAC 0
CAC 1-100
CAC >100

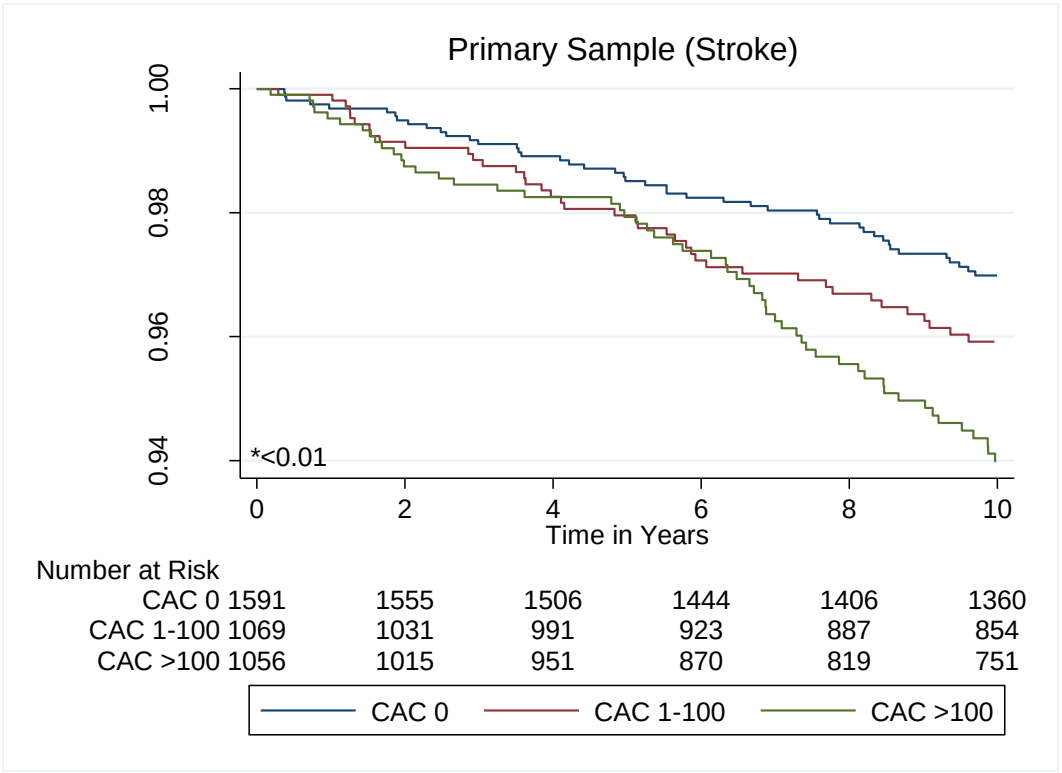


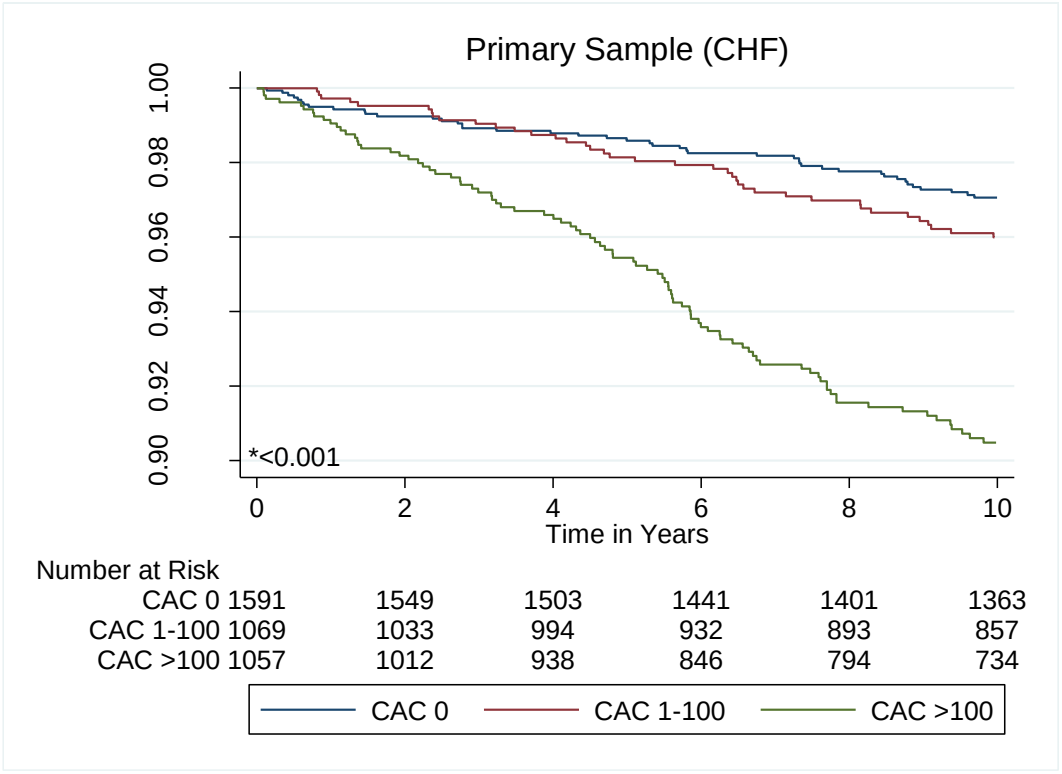


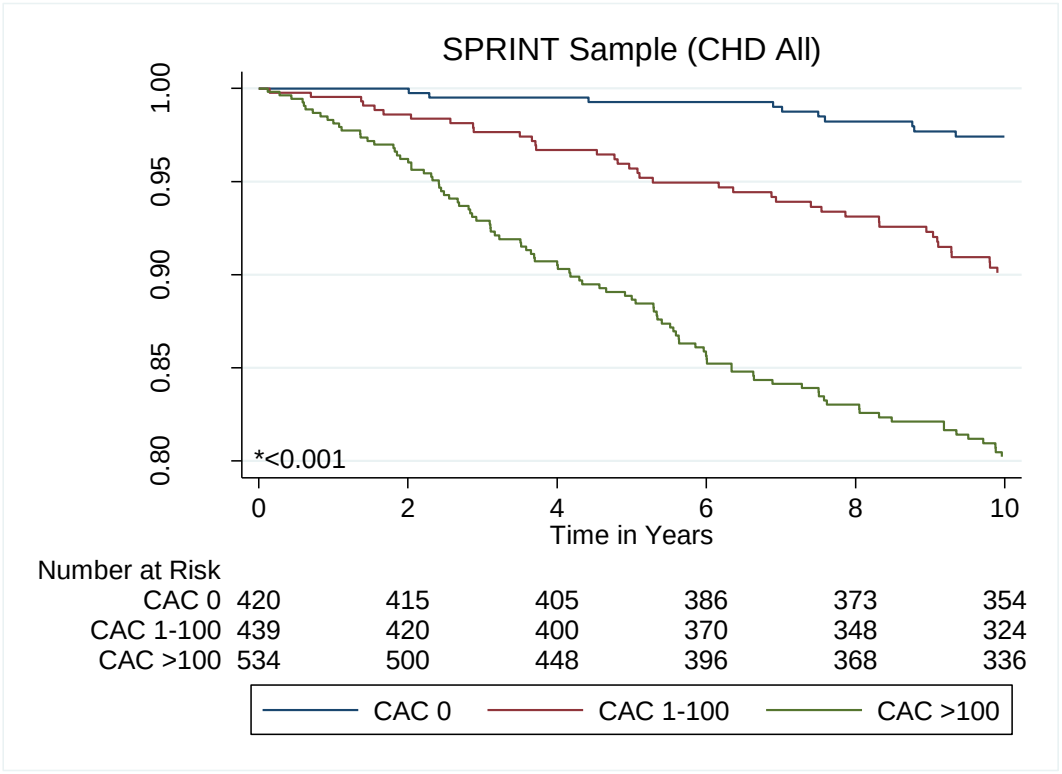
* P value by Log-Rank testing

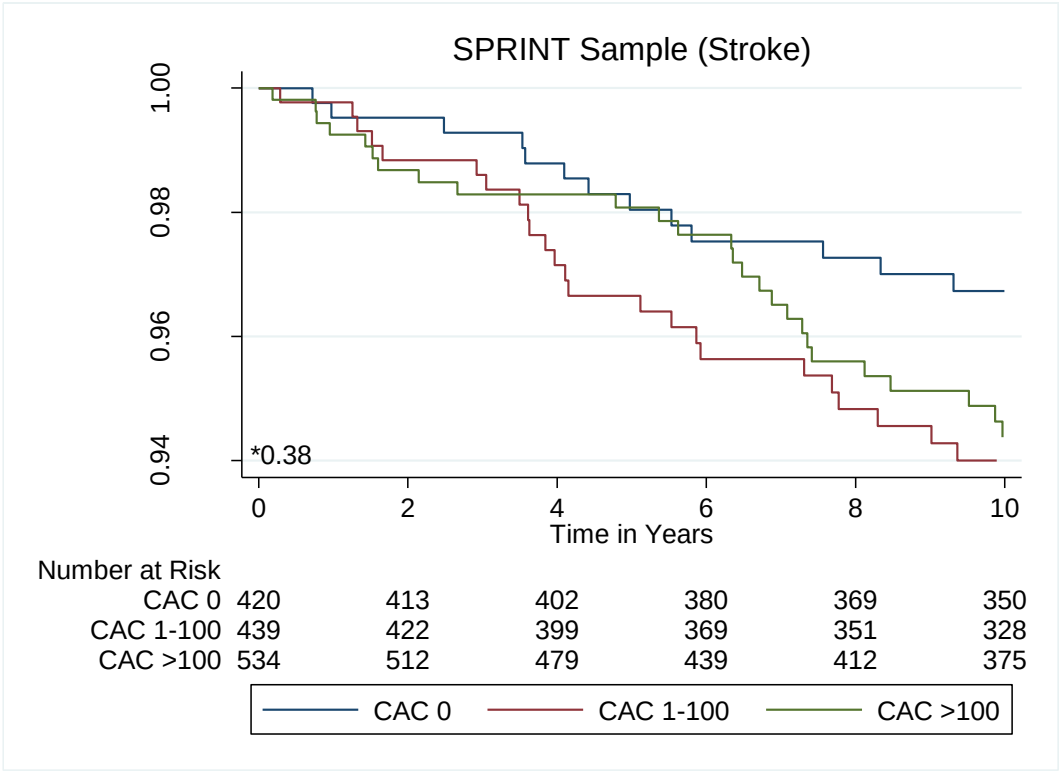
E-FIGURE 2. Kaplan-Meier curves for survival free from the individual outcomes of all-cause CHD, Stroke or heart failure in the primary sample and the SPRINT-eligible subsample, according to categories of CAC.

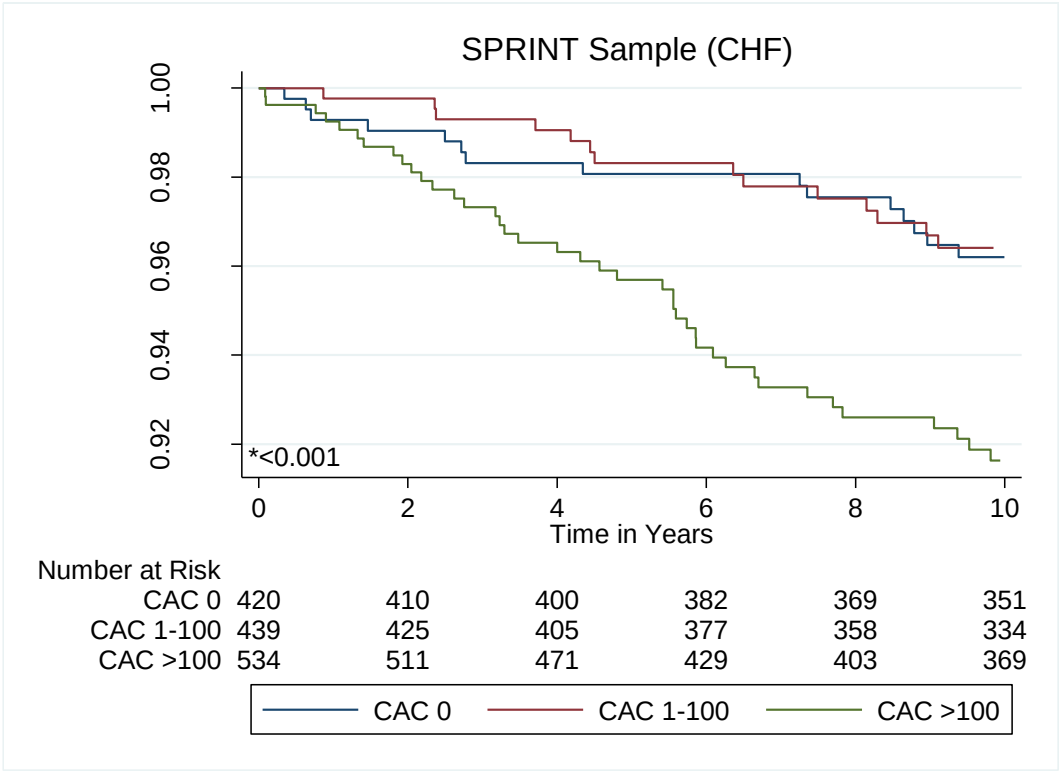





Primary Sample (CHF)
1.00
0.98
0.96
0.94
0.92
0.90
*<0.001
0
2
4
6
8
10
Time in Years
Number at Risk
CAC 0 1591 1549 1503 1441 1401 1363
CAC 1-100 1069 1033 994 932 893 857
CAC >100 1057 1012 938 846 794 734
CAC 0
CAC 1-100
CAC >100


SPRINT Sample (CHD All)
1.00
0.95
0.90
0.85
0.80
*<0.001
0
2
4
6
8
10
Time in Years
Number at Risk
CAC 0 420 415 405 386 373 354
CAC 1-100 439 420 400 370 348 324
CAC >100 534 500 448 396 368 336
CAC 0
CAC 1-100
CAC >100





* P value by Log-Rank testing