BRIEF COMMUNICATION

African Ancestry vs. Creatine Kinase to Predict Hypertension Control: Time for a Change?

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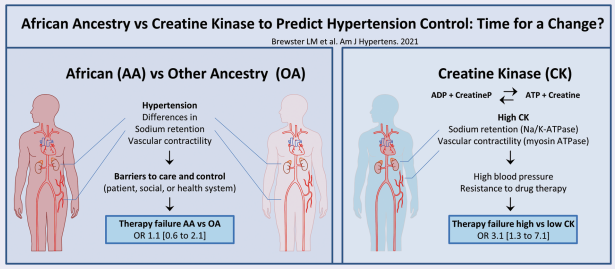
BACKGROUND
African ancestry patients are considered separately in hypertension guidelines because of more severe hypertension that is presumably harder to control. However, despite the perceived benefit in reducing health disparities, racial profiling in medicine is increasingly criticized for its potential of bias and stereotyping. Therefore, we studied whether creatine kinase (CK), an ATP-regenerating enzyme that enhances vascular contractility and sodium retention, could serve as a more proximate causal parameter of therapy failure than race/ancestry.

METHODS
In a random multiethnic population sample, we compared the performance of African ancestry vs. resting plasma CK as predictors of treated uncontrolled hypertension. Difference in area under the receiver operating curve (AUC) was the primary outcome.

RESULTS
We analyzed 1,405 persons of African, Asian, and European ancestry (40.2% men, mean age 45.5 years, SE 0.2). Hypertension prevalence was 39% in African vs. 29% in non-African ancestry participants vs. 41% and 27% by high and low CK tertiles. Control rates of treated patients were similar by ancestry (African ancestry patients 40%, non-African ancestry 41%; $P = 0.84$), but 27% vs. 53% in patients with high vs. low CK (22% vs. 67% in African and 32% vs. 52% in non-African participants). AUC was 0.51 [0.41–0.60] for African ancestry vs. 0.64 [0.55–0.73] for log CK ($P = 0.02$).

CONCLUSIONS
In contrast to African ancestry, CK might identify hypertensive patients at risk for therapy failure across different ancestry groups. Larger, prospective studies should establish whether resting plasma CK is clinically useful as an impartial method to help predict antihypertensive therapy failure.

GRAPHICAL ABSTRACT



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Hypertension guidelines advise a different initial therapeutic approach for persons of sub-Saharan African ancestry (African ancestry), because these patients are thought to have more severe, low renin hypertension that is difficult to control.[1–3] African heritage is the only ancestry group considered in association with treated uncontrolled hypertension, aside well-known factors such as education, socioeconomic circumstances, diabetes, obesity, and the presence of end-organ damage.[1–3] But population diversity in hypertension risk is not well reflected in the dichotomy of African or non-African ancestry,[4–9] and it is unclear how these guidelines should be applied to persons of self-defined "mixed" ancestry.[4,9] Furthermore, there is long-standing critique to the use of race, ethnicity, or ancestry in biomedicine as a "container" notion representing a combination of socioeconomic circumstances and biology, but without fully acknowledging the effect of structural racism.[4–6,10] Therefore, there is a need for specific (bio-) markers to predict hypertension treatment failure independent of race or ancestry.[4–9,10] We proposed that the enzyme creatine kinase (CK) is a marker for hypertension risk and response to treatment.[7,8,11] CK rapidly regenerates ATP near ATPases that generate blood pressure, catalyzing the reaction:

$$\text{Phosphocreatine} + \text{ADP} + \text{H}^+ \leftrightarrow \text{Creatine} + \text{ATP}$$

The enzyme is thought to increase vascular contractility and sodium retention.[7,8] High CK occurs with greater

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frequency in persons of African ancestry, but a substantial number of non-African ancestry persons also have rather high CK.[7,8,11] We and others have shown that in otherwise healthy people, resting plasma CK, a proxy for cytoplasmic CK, is strongly associated with blood pressure and failure of antihypertensive therapy.[7,8,11,12] However, it was not previously addressed whether CK rather than self-identified African ancestry could serve as a predictor of failure to achieve blood pressure control, which is the aim of the current analysis.

METHODS

Study population

We analyzed a dataset of 1,405 participants of the "Surinamese in the Netherlands: Study on EThnicity and health" (SUNSET) study.[7,8] The institutional review committee approved the study. Participants gave written informed consent before inclusion. The methods of the SUNSET study have been published previously.[8] In brief, the registration office in Amsterdam, the Netherlands, provided a random population sample of 1,000 White European-Dutch and 2,000 Surinamese-Dutch noninstitutionalized persons (mainly of West-African and South-Asian ancestry) aged 34–60 years. Participants were requested to abstain from heavy exercise during 3 days before clinical examination. Walking, driving a car and normal daily activities were allowed, but leisure sports activities or heavy exercise were disadvised. Clinical examination included blood pressure assessed with an Omron M4 oscillometric device (Omron Healthcare Europe BV, Hoofddorp, the Netherlands) with the subject seated, using an appropriately adjusted cuff size on the nondominant arm supported at heart level. Blood pressure was calculated as the mean of the first 2 consecutive readings that had a maximum of 5 mm Hg difference, or the 2 readings with the smallest quantitative difference out of a maximum of 6 readings.[8] Laboratory studies included (resting) plasma CK activity estimated with automated analyzers (Roche/Hitachi Systems, Roche Diagnostics, Indianapolis, IN) according to procedures recommended by the International Federation of Clinical Chemistry. Hypertension was defined as systolic blood pressure ≥140 or diastolic ≥90 mm Hg, or receiving antihypertensive drug therapy, with control achieved at <140 and <90 mm Hg. End-organ damage was assessed with the Rose Questionnaire (history of intermittent claudication, myocardial infarction or angina pectoris, stroke, or transient ischemic attack).

Outcome measures and sample size

We assessed performance characteristics of CK vs. self-defined ancestry (African vs. non-African) in predicting treated uncontrolled hypertension in a real-world, population setting. Accuracy, established by comparison of the areas under the receiver operating characteristic curves (AUC or concordance (*C*) statistics) was the primary outcome.[13] The AUC indicates the ability of the test to correctly classify those with vs. without the condition of interest, with higher scores indicating better prediction.[13] With an estimated difference of 0.15 in the AUC,[7,8,11] we calculated to need around 125 participants to achieve a power of 0.8 at an alpha of 0.05.

Statistical analysis

We present baseline characteristics, blood pressure levels and treatment status by self-defined African or non-African ancestry, and by low and high CK in tertiles. CK values were log transformed to the base of 10, with outliers (using the Dixon/Reed rule) and the extreme 2.5% CK values excluded to account for undiagnosed tissue damage or unaccounted exercise, and to avoid overly influential observations due to a heavy right tail of the distribution of CK.[7,8] We reincluded these values in sensitivity analyses. We assessed sensitivity, specificity, likelihood ratios, positive and negative predictive values, and odds ratio of CK vs. African ancestry in predicting treatment failure. In addition, we assessed the correlation between therapy failure with ancestry (African vs. non-African) vs. log CK, and with covariables age, sex, glucose, BMI (body mass in kg/height in meters squared), the presence of end-organ damage, and education level (expressed at the percentage of persons with primary education only) before entering variables into in binary logistic regression analysis to assess the association with treated uncontrolled hypertension for African ancestry vs. log CK, and calculate AUC. We used the Youden index to find the optimal cut-point (maximizing the Youden function or difference between true positive rate and false positive rate over all possible cut-point values). Established covariables age, sex, glucose, and BMI,[7,8] were entered in the model using forced entry and backward selection. Other variables were included based on a *P* value <0.10 in univariate analysis. We reassessed outcomes using cutoff points of systolic <130 and diastolic <80 mm Hg after treatment.[3] Missing data were not imputed. We limit the use of *P* values and communicate statistical uncertainty surrounding estimates through 95% confidence intervals given between square brackets. Data in parentheses are standard errors of the mean (SE) unless indicated otherwise. Statistical analyses were performed with SPSS software package for Windows version 25.0 (SPSS, Chicago, IL) and MedCalc version 19.4 (MedCalc Software, Ostend, Belgium).

Reporting guidelines

This report is in accord with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline and the Standards for Reporting Diagnostic accuracy studies (STARD) statement.

RESULTS

Demographic, clinical, and test characteristics are depicted in Table 1. Data on serum CK, blood pressure, and ancestry were available in 1,444 subjects. CK activity ranged between 14 and 5,783 IU/l (median 111 IU/l), *z*-score for skewness: 228.5. After the exclusion of 3 outliers and CK > p.97.5 (n = 36), the *z*-score for skewness was 22.3. Log

Table 1. Creatine kinase vs. African ancestry to predict treated uncontrolled blood pressure

	By ancestry[g]		By CK[k]	
Clinical parameter	**Non-AA[h] (*n* = 785)**	**AA (*n* = 552)**	**Low CK (*n* = 468)**	**High CK (*n* = 468)**
Male, %	48	30	24	56
Age, y[a]	47 (0.2)	44 (0.3)	46 (0.3)	45 (0.3)
BMI, kg/m^2[a]	26 (0.2)	28 (0.2)	26 (0.2)	28.0 (0.2)
SBP, mm Hg[a]	125 (0.7)	128 (0.9)	123 (0.9)	130 (0.9)
DBP, mm Hg[a]	81 (0.4)	84 (0.5)	79 (0.5)	85 (0.5)
Glucose, mmol/l[a]	5.9 (0.1)	5.7 (0.1)	5.7 (0.1)	5.8 (0.1)
CK, IU/l	94 (66–136)	144 (97–213)	66 (53–75)	198 (166–259)
Primary educ. only, %	28	20	21	27
End-organ damage, %	9	20	13	14
Hypertension 140/90, %	29	39	27	41
Treated, %[b]	33	34	34	31
Tr. uncontr.,%[c]	59	60	47	73
Diagnostic performance[d]	AA (vs. non-AA)		High CK (vs. low CK)	
Sensitivity, %[e]	50.0 [39.2–60.9]		68.3 [55.3–79.4]	
Specificity, %[e]	51.7 [38.4–64.8]		59.0 [42.1–74.4]	
+LR	1.03 [0.74–1.45]		1.66 [1.10–2.51]	
−LR	0.97 [0.70–1.34]		0.54 [0.34–0.84]	
PPV, %	61.1 [52.9–68.7]		71.7 [62.6–79.2]	
NPV, %	40.5 [33.0–48.4]		55.0 [43.9–65.7]	
C-Statistic univariable[f]	AA (vs. non-AA)		Log CK	
AA vs. CK	0.51 [0.41–0.60]		0.64 [0.55–0.73]	
C-Statistic multivariable	AA (vs. non-AA)		Log CK	
AA vs. CK (+BMI, age)	0.63 [0.53–0.73][i]		0.68 [0.59–0.77]	
AA vs. CK (+BMI, age, sex, glucose)	0.65 [0.56–0.74][j]		0.69 [0.60–0.77]	

Abbreviations: BMI, body mass index; CK, resting plasma creatine kinase; DBP, diastolic blood pressure; Educ., education; +/−LR, positive and negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; SBP, systolic blood pressure; Tr. uncontr., treated uncontrolled hypertension.

[a]Data are mean (SE); CK, median (interquartile range); data in square brackets are 95% confidence intervals. Point estimates are rounded to whole numbers except for glucose, SE, and estimates with confidence intervals.

[b]Subjects with hypertension, %.

[c]Of treated subjects, %.

[d]For treated uncontrolled hypertension in treated hypertensives.

[e]Test evaluation in paired samples; $P = 0.01$ for CK vs. AA.

[f]In univariable analysis, log CK, BMI, and age were the only statistically significant predictors of therapy failure but not sex, African ancestry, fasting plasma glucose, education level, or end-organ damage, please see main text.

[g]Self-defined.

[h]Non-AA, European, $n = 501$, South Asian, $n = 284$, excluding 68 of self-defined defined mixed or undisclosed ancestry; all these participants were included in the CK comparisons.

[i]The model is not significant with AA alone, thus BMI and age drive the results. Model with BMI and age, without AA 0.64 [0.55–0.73].

[j]Model without AA, 0.64 [0.56–0.73].

[k]Low vs. high CK tertiles.

transformation reduced the skewness to a *z*-score of 1.5. We included 1,405 participants (552 of African ancestry; 40.2% men) with a mean age of 45.5 (0.2) years. Hypertension rates in non-African vs. African ancestry participants were, respectively, 29% vs. 39%, compared with 27% vs. 41% in participants of all ancestries with low vs. high CK tertiles (Table 1). Control rates were similar by ancestry (40% in African ancestry vs. 41% in non-African ancestry participants; $P = 0.84$). Mean CK in patients with treated controlled and treated uncontrolled hypertension was, respectively, 124 (11) and 160 (9) IU/l. Control rates of patients with low vs. high CK were, respectively, 53% vs. 27% (67% vs. 22% for African ancestry and 52% vs. 32% in non-African participants), with better performance characteristics for

CK, depicted in Table 1 (odds ratio for noncontrol, African ancestry 1.1 [0.6–2.1], vs. CK 3.1 [1.3–7.1]). CK, age, and BMI (but not African ancestry or other variables) correlated significantly with therapy failure, Spearman's rho, respectively, 0.23, 0.17, and 0.19. The univariable *C*-statistic for <140/<90 was 0.51 [0.41–0.60] for African ancestry and 0.64 [0.55–0.73] for log CK ($P = 0.02$), cutoff point for CK 138 IU/l (Table 1).

In addition, BMI (*C*-statistic 0.62 [0.53–0.72]) and age (0.58 [0.50 (4)–0.64]) were statistically significant predictors of therapy failure, but not (male) sex (0.57 [0.48–0.66]), fasting plasma glucose (0.49 [0.39–0.59]), education level, or end-organ damage ($P > 0.10$). The *C*-statistic of the model including log CK, age, and BMI was 0.68 [0.60–0.77] (0.70 [0.58–0.83] for African and 0.68 [0.55–0.81] for non-African ancestry patients).

Reincluding patients with 2.5% highest CK levels ($n = 36$) did not alter the size or magnitude of the main outcomes (data not shown). Furthermore, although antihypertensive treatment in this study was aimed at <140/<90, when defining nonhypertensive as systolic blood pressure <130 and diastolic blood pressure <80, 817 participants were hypertensive (58%), with 19% treated and 2% of hypertensives (13% of treated patients) controlled. Control at <130/<80 mm Hg was 18% for non-African vs. 7% for African ancestry patients. CK in treated controlled vs. treated uncontrolled patients was 106 IU/l (18) vs. 152 (8) IU/l, with control at <130/<80 mm Hg for low vs. high CK, respectively, 21% vs. 5%. The univariable *C*-statistic for <130/<80 was 0.64 [0.52–0.77] for African ancestry and 0.66 [0.53–0.80] for log CK.

DISCUSSION

In this pilot study, we explored the performance of CK vs. African ancestry to predict antihypertensive treatment failure in a real-world setting. Performance characteristics including sensitivity, specificity, positive and negative likelihood ratios, AUC, and positive and negative predictive values were better for CK. In contrast to African ancestry, CK predicted failure to achieve blood pressure control at <140 mm Hg systolic and <90 diastolic. Importantly, the association with treatment failure was in African as well as non-African participants, across different treatment goals. The potential ancillary benefit of CK is better acceptability and wider clinical applicability to different ancestry groups.

Global diversity in ancestry and increasing objections against racialization of health care create a need for other methods than the African/White-European dichotomy currently used to study the pathophysiology of hypertension and potential responses to antihypertensive drugs.[1–6,8,9,14–16] It has been advanced that race does not exist and therefore has no place in medicine, and that negative health outcomes related to African ancestry are largely racism related.[4–6,9,14] Human beings share 99.9% of their genetic makeup, and most of the remaining variation is between individuals rather than subpopulations.[6] Therefore, the so-called "one-drop rule," where a person with any African ancestor is classified as African, is unlikely of biological value.[4,6,14,17]

In the past 20 years, we and others have extensively studied the association between CK and blood pressure.[7,8,11,12] Ample evidence indicates that this ATP-regenerating enzyme, which is high in tissue and serum of hypertensives, increases vascular contractility and sodium retention. In line with this, CK has been linked to hypertension and treatment failure in different populations worldwide.[7,8,11,12] It should be noted that CK isoenzyme distribution is normal with hypertension. The relatively high resting plasma CK observed in otherwise healthy hypertensives does not reflect major organ damage, but nonresting plasma CK may underestimate the true association between intracellular CK and clinical parameters.[7,8,12] We previously showed that CK predicts therapy failure independent of ancestry.[7] However, CK had not been directly compared with African ancestry to assess the performance in predicting the response to treatment. Although relatively high CK occurs with greater frequency in persons of African ancestry,[7,8,11,12] high enzyme activity is also found in other population subgroups, and in line with the results of this study, African as well as White European and Asian patients with high CK are reported to have low hypertension control rates.[7,11,12]

There are some limitations to the presented results. The data suggested that CK better selected patients with therapy failure than African ancestry, BMI, or age. One could argue that the observed data reflect more intensive therapy in African ancestry patients, and that CK is not a better, but an "extra" predictor of therapy failure aside ancestry. On the other hand, the observed association of treatment failure in African and other ancestry populations with the "hidden" biomarker CK, unknown to the doctors during treatment, is less prone to bias than noticeable characteristics associated with ancestry.[10,12] The strong association of high CK with poor hypertension control in patients of different ancestries, strengthens the notion that CK could serve as a biological marker for hypertension control beyond race or ancestry. This was not a randomized trial, patients were treated according to their physicians' preferences, to the goal of <140 mm Hg systolic and <90 mm Hg diastolic blood pressure.[8] We are not informed about the details of the antihypertensive therapy or on whether specific drugs affect the association of CK with therapy failure. Our explorative pilot analysis is further limited by the cross-sectional design, the relatively small sample size, and the *post hoc* analysis, which should be considered hypothesis generating. Prospective studies with sufficient size to provide data by drug types and treatment intensity are needed to more precisely address the predictive performance of CK and its clinical utility.

It remains challenging to predict failure of antihypertensive therapy, since many heterogeneous patient and doctor-related causes may be involved. The presented data suggest that the ATP-generating enzyme CK might serve as a predictor of treated uncontrolled hypertension beyond "race." With the need for biomarkers in hypertension research and clinical medicine that represent biology rather than an entanglement of social and genetic factors,[14,15] CK is a well-studied, pathophysiologically relevant candidate.[7,8,10,11] Socioeconomic, health system, and other barriers to achieve hypertension control could be addressed separately and more explicitly.[14,15] Larger, prospective intervention studies will be needed to confirm the presented findings, and to assess whether antihypertensive drug class matters for hypertension control in patients with relatively high CK.[11]

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DISCLOSURE

L.M.B. is an inventor on patent WO/2012/138226, an "open" nonrestrictive patent request filed and published as "prior art" to protect the freedom of researchers to operate and share their innovative ideas on CK and CK inhibition without license or payment.

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