Baseline and Follow-up 6-Min Walk Distance and Brain Natriuretic Peptide Predict 2-Year Mortality in Pulmonary Arterial Hypertension

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Background: Six-minute walk distance (6MWD) and brain natriuretic peptide (BNP) levels at baseline and after initiation of treatment have been associated with survival in patients with pulmonary arterial hypertension. Our objective was to determine the individual and additive ability of pretreatment and posttreatment 6MWD and BNP to discriminate 2-year survival in patients with pulmonary arterial hypertension.

Methods: We included patients enrolled in two randomized clinical trials of ambrisentan who had 2-year follow-up (N = 370). 6MWD and BNP were assessed before and after 12 weeks of treatment. Receiver operating characteristic curve analyses were performed to identify optimal cut-offs that defined subgroups with a high 2-year mortality. Classification and regression tree analysis was used to determine the incremental prognostic value of combined assessments.

Results: 6MWD at baseline and after 12 weeks of therapy were similarly discriminatory of 2-year survival (c-statistics = 0.77 [95% CI 0.70-0.84] and 0.82 [95% CI 0.75-0.88], respectively), whereas change in 6MWD from baseline to week 12 was not discriminating. The same observation was true of BNP at baseline and after 12 weeks of therapy (c-statistics = 0.68 [95% CI 0.60-0.76] and 0.74 [95% CI 0.66-0.82], respectively). After consideration of baseline 6MWD, there was no prognostic information added by the week 12 6MWD or BNP at either time point.

Conclusions: 6MWD and BNP values at baseline or week 12 identified a population with an elevated risk of death at 2 years. A repeat assessment of 6MWD or BNP after 12 weeks of ambrisentan therapy did not provide additional prognostic information beyond that obtained from baseline values.

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Abbreviations: 6MWD = 6-min walk distance; 6MWD-B = 6-min walk distance at baseline; ARIES = Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study; BNP = brain natriuretic peptide; CART = classification and regression tree; CTD = connective tissue disease; IPAH = idiopathic pulmonary arterial hypertension; NPV = negative predictive value; PAH = pulmonary arterial hypertension; PAH-CTD = pulmonary arterial hypertension associated with connective tissue disease; PPV = positive predictive value; RCT = randomized clinical trial; REVEAL Registry = Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management; ROC = receiver operating characteristic

Pulmonary arterial hypertension (PAH) is a progressive pulmonary vasculopathy associated with reduced survival. Studies of new treatments have demonstrated variable impact on symptoms, functional capacity, quality of life, and mortality. Accurate risk stratification of the patient with PAH is important, as it could inform selection of appropriate treatment. Indeed, current guidelines advocate for the serial assessment of certain biomarkers as a means to deter-

mine the effectiveness of a given treatment strategy, and some have recommended that failure to meet certain goals should warrant escalation of treatment.¹

For editorial comment see page 285

Six-minute walk distance (6MWD) is an easily obtained, reproducible metric which has been used as the primary outcome for nearly every randomized

clinical trial (RCT) in PAH.² Higher baseline or post-treatment 6MWD is associated with better survival.³⁻⁵ Brain natriuretic peptide (BNP) is a neurohormone released by the myocardium in response to pressure and/or volume overload, and BNP has been a secondary outcome measure in many RCTs in PAH. Higher baseline and follow-up circulating BNP levels have been associated with an increased risk of mortality in PAH.⁶ The discriminative utility and the optimal cut-offs of these biomarkers necessary to distinguish high-risk from low-risk patients in the clinic are less clear.

We determined whether baseline and follow-up 6MWD and plasma BNP levels discriminated between patients who died or were alive at 2 years in RCTs of patients treated with ambrisentan. We also determined whether the changes with treatment in 6MWD and plasma BNP levels from baseline to 12 weeks discriminated outcomes. Some of the results of these analyses have been previously reported in the form of an abstract.⁷

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the University of Pennsylvania (approval No. 814307). Additional details of the methods and statistical analysis are provided in e-Appendix 1.

ARIES (Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study)-1 and ARIES-2 were concurrent, phase 3, double-blind, placebo-controlled RCTs of ambrisentan for the treatment of PAH.⁸ Patients were randomized to placebo or ambrisentan at doses of 5 mg or 10 mg (ARIES-1) and 2.5 mg or 5 mg (ARIES-2) for 12 weeks. ARIES-E was the long-term extension study for subjects who completed ARIES-1 or ARIES-2, the details of which have been previously published.⁹ In ARIES-E, subjects receiving placebo in ARIES-1 or ARIES-2 were randomized in a blinded fashion to ambrisentan doses as described; those receiving ambrisentan during the first 12 weeks were continued on their

current dose. Subjects continued their ambrisentan at fixed doses for 24 weeks, after which their dose could be further adjusted as clinically indicated.

Detailed inclusion and exclusion criteria for ARIES-1 and ARIES-2 (and ARIES-E) have been published previously.⁸ Three hundred and eighty-three subjects received at least one dose of ambrisentan in ARIES-1, ARIES-2, or ARIES-E and comprised the study cohort. This included three subjects who completed ARIES-1 or ARIES-2 but did not enter ARIES-E. Subjects with missing 2-year vital status were excluded from the primary analyses, but were included in sensitivity analyses.

6MWD and BNP level were assessed at baseline (6MWD-B and BNP-B, respectively) and after 12 weeks of ambrisentan (6MWD-12w and BNP-12w, respectively). Survival data were collected prospectively for all subjects. After completion of ARIES-E, site investigators provided the vital status of each subject at the last known date or date of death. These data were used to determine vital status at 2 years after the first dose of ambrisentan.

RESULTS

There were 383 subjects in the study cohort (Fig 1). We excluded 13 who did not have 2-year survival status data from the primary analyses, leaving 370 subjects in the study sample for the 6MWD analysis. Thirty-seven additional subjects were excluded from the BNP analyses due to missing baseline BNP values, leaving 333 in the study sample. Baseline demographics of the study samples and those excluded are presented in Tables 1 and 2, for descriptive purposes only. Most patients had idiopathic PAH (IPAH), while approximately one-third had connective tissue disease (CTD). The mean $\pm$ SD 6MWD-B ($n = 370$) and 6MWD-12w ($n = 350$) were 348 ± 85 m and 388 ± 90 m, respectively. The study sample for the 6MWD analysis was similar to those excluded except that those excluded were more likely to have PAH associated with CTD (PAH-CTD) (Table 1). The median (interquartile range [IQR]) BNP-B ($n = 333$) and BNP-12w ($n = 317$) were 138 (47-350) pg/mL and 77 (28-188) pg/mL, respectively. The study sample for the BNP analysis was similar to those excluded except that excluded subjects tended to be somewhat younger (Table 2). Imputation for missing data was performed and is described in e-Appendix 1.

Of the 370 subjects, 348 (94%) were still receiving ambrisentan monotherapy at 12 weeks, one (0.3%) was receiving ambrisentan therapy plus other PAH therapy, and 22 (5.9%) had an unknown treatment regimen as these patients had discontinued the therapeutic part of the study. At 2 years, 214 (58%) remained on ambrisentan monotherapy, 45 (12%) added therapy to ambrisentan, and 111 (30%) were unknown as they had discontinued the therapeutic part of the study.

The cumulative incidence of death at 2 years was 15% ($n = 55$). Data on cause of death were available for 42 subjects (76%); right ventricular failure

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FIGURE 1. Study population. 6MWD = 6-min walk distance; ARIES = Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study; BNP = brain natriuretic peptide.

and pulmonary hypertension were the most common causes of death, though multiple causes/adverse events could be ascribed to a single subject. None of the subjects underwent lung transplantation. The c-statistic for 2-year survival was 0.77 (95% CI, 0.70-0.84) for 6MWD-B and 0.82 (95%CI, 0.75-0.88) for 6MWD-12w (Fig 2A) (P for comparison = .06). The

c-statistic for change-from-baseline 6MWD (Δ 6MWD) was only slightly better than chance (0.61; 95% CI, 0.52-0.69) (Fig 2B) and was significantly lower than that for both 6MWD-B (P = .01) and 6MWD-12w (P < .001).

The optimal cutoffs for 6MWD-B (< 250 m) and 6MWD-12w (< 300 m) using receiver operating characteristic (ROC) curve analysis and their sensitivity, specificity, and positive and negative predictive values (PPVs and NPVs, respectively) for predicting mortality at 2 years are shown in Table 3. Fifty-eight (15.7%) and 72 (19.4%) subjects had 6MWD values

Table 1—Subject Characteristics for Primary 6MWD Analysis

Characteristics	Study Sample (n = 370)	Excluded (n = 13)
Age, y	51 ± 15	50 ± 9
Female, %	79	85
White, %	77	62
BMI, kg/m ²	27 ± 6 (n = 369)	29 ± 6
Idiopathic PAH, %	64	31
PAH-CTD, %	32	54
PAH-other, %	4	15
6MWD-B, m	348 ± 85	332 ± 90
BNP-B, pg/mL	138 (47-350) (n = 333)	50 (26-90) (n = 12)
WHO class, %		
I	3	0
II	42	54
III	47	38
IV	8	8
mPAP, mm Hg	49 ± 14	45 ± 16 (n = 12)
mRAP, mm Hg	8 ± 5 (n = 362)	8 ± 4 (n = 12)
Cardiac index, L/min/m ²	2.5 ± 0.8 (n = 357)	2.4 ± 0.7 (n = 11)
PVR, Wood units	11 ± 6 (n = 360)	10 ± 6 (n = 11)
Creatinine, μmol/L	89 ± 27 (n = 364)	86 ± 32

Values are mean ± SD except BNP, which is median (IQR). 6MWD-B = 6-min walk distance at baseline; BNP-B = brain natriuretic peptide at baseline; CTD = connective tissue disease; IQR = interquartile range; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; PAH = pulmonary arterial hypertension; PAH-CTD = pulmonary arterial hypertension associated with connective tissue disease; PVR = pulmonary vascular resistance; WHO = World Health Organization.

Table 2—Subject Characteristics for Primary BNP Analysis

Characteristics	Study Sample (n = 333)	Excluded (n = 50)
Age, y	52 ± 15	47 ± 13
Female, %	79	80
White, %	79	62
BMI, kg/m ²	27 ± 6 (n = 332)	29 ± 5
Idiopathic PAH, %	64	58
PAH-CTD, %	32	36
PAH-other, %	4	6
6MWD-B, m	348 ± 86	339 ± 84
BNP-B, pg/mL	138 (47-350)	50 (26-90) (n = 12)
WHO class, %		
I	3	4
II	43	42
III	47	44
IV	8	10
mPAP, mm Hg	49 ± 14	52 ± 15 (n = 49)
mRAP, mm Hg	8 ± 5 (n = 326)	9 ± 5 (n = 48)
Cardiac index, L/min/m ²	2.5 ± 0.8 (n = 320)	2.4 ± 0.7 (n = 48)
PVR, Wood units	11 ± 7 (n = 323)	11 ± 5 (n = 48)
Creatinine, μmol/L	88 ± 25 (n = 332)	94 ± 39 (n = 45)

Values are mean ± SD except BNP, which is median (IQR). See Table 1 for expansion of abbreviations.

FIGURE 2. ROC curves for predicting risk of death at 2 years. A, Baseline and week 12 6MWD. B, Change in 6MWD. CFB = change from baseline; ROC = receiver operating characteristic. See Figure 1 legend for expansion of other abbreviations.

below these respective cutoffs. We could not identify an adequate cutoff for Δ 6MWD or the percent change from baseline in 6MWD. Kaplan-Meier curves showed that subjects in the lower quartiles of 6MWD-B (Fig 3A) or 6MWD-12w (Fig 3B) had an increased risk of death over 2 years compared with those in the higher quartiles ($P < .001$ for both).

The c-statistic for 2-year survival was 0.68 (95% CI, 0.60-0.76) for BNP-B and 0.74 (95% CI, 0.66-0.82)

Table 3—Prediction of Mortality at 2 Years by 6MWD

Parameter	Baseline 6MWD < 250 m	Week 12 6MWD < 300 m
No. of subjects with positive test, No. (%)	58 (15.7)	72 (19.4)
Sensitivity, % (95% CI)	53 (48-58)	64 (59-69)
Specificity, % (95% CI)	91 (88-94)	88 (85-92)
Positive predictive value, % (95% CI)	50 (45-55)	49 (44-55)
Negative predictive value, % (95% CI)	92 (89-94)	93 (91-96)
Accuracy, % (95% CI)	85 (82-89)	85 (81-88)

Values below cutoff indicate a positive test. See Table 1 for expansion of abbreviations.

for BNP-12w (Fig 4A) (P for comparison = .08). The c-statistic for change-from-baseline BNP (Δ BNP) was no better than chance (0.47; 95% CI, 0.37-0.58) (Fig 4B) and was significantly lower than both BNP-B ($P = .01$) and BNP-12w ($P < .001$).

In a similar fashion, we selected cutoffs for BNP-B (≥ 350 pg/mL) and BNP-12w (≥ 330 pg/mL) (Table 4). Eighty-four (25.2%) and 45 (13.5%) subjects had BNP values above these cutoffs, respectively. Similar to Δ 6MWD, no adequate cutoff for Δ BNP was identified. Analyses were repeated using the percent change from baseline BNP and yielded similar results. Kaplan-Meier curves showed that subjects in the higher quartiles of BNP-B (Fig 5A) or BNP-12w (Fig 5B) had an increased risk of death over 2 years compared with those in the lower quartiles of BNP ($P < .001$ for both).

Classification and regression tree (CART) analysis incorporated both 6MWD and BNP measures in subjects with complete baseline values ($n = 333$). CART showed that after consideration of 6MWD-B, there was no significant additional information provided by 6MWD-12w or BNP at either time point.

Sensitivity analyses were performed after imputing subjects with missing follow-up as dead or alive. The results were similar to the primary analysis (data not shown). Additional sensitivity analyses were performed stratifying by study region (Latin America, North America/Australia, eastern Europe, western Europe/Israel) and did not reveal evidence of geographic bias (data not shown). We also performed a subset analysis in patients with IPAH and heritable PAH (e-Tables 1, 2), which yielded results similar to those from the main analysis, except that the c-statistic for BNP-12w was significantly higher than that for BNP-B (0.78, 95% CI, 0.68-0.88 vs 0.67, 95% CI 0.56-0.77; $P = .01$) (e-Figs 1, 2). However, similar to the overall study sample, CART analysis of the IPAH/heritable subgroup showed that after consideration of baseline 6MWD, no significant additional information was provided by other measures.

FIGURE 3. Kaplan-Meier analysis of 2-year survival using quartiles. A, Stratified by baseline 6MWD. B, Stratified by week 12 6MWD. *P* values for between-group comparisons derived from the log-rank test. See Figure 1 legend for expansion of abbreviations.

DISCUSSION

In this study, we assessed the ability of baseline and 12-week 6MWD and BNP levels to discriminate PAH patients with a high vs low risk of death at 2 years after treatment with ambrisentan. Both 6MWD at baseline and at 12 weeks after treatment displayed moderately strong predictive ability for discriminating patients at high and low risks of death at 2 years. Similar findings were observed for baseline and 12-week BNP levels, although these were somewhat weaker predictors. A baseline 6MWD < 250 m (or < 300 m after 12 weeks of treatment) was associated with about a 50% risk of death at 2 years vs 8% risk of death for subjects above these cutoffs. A baseline BNP of ≥ 350 pg/mL (or ≥ 330 pg/mL after 12 weeks of treatment) was associated with a 25% to 40% risk of death at 2 years vs a 10% risk of death for those below these cutoffs. To our knowledge, our report is the

first to compare the ability of noninvasive testing performed before and after short-term treatment to identify “high-risk” patients. Notably, although we observed a trend toward better predictive ability of follow-up testing as compared with baseline testing, there were no statistical or clinical differences in the discriminatory power provided by either follow-up assessment compared with the baseline assessment.

Lower cardiac output and stroke volume, greater right ventricular end-diastolic volume, and lower right ventricular ejection fraction at baseline are strong determinants of survival in PAH irrespective of the level of pulmonary vascular resistance.¹⁰⁻¹² Since exercise capacity reflects the ability of the cardiopulmonary system to augment oxygen delivery, it is not surprising that 6MWD in our study was associated with mortality, as it was in other studies.³⁻⁵

Using multivariable analysis, both the Registry to Evaluate Early and Long-Term PAH Disease Management

FIGURE 4. ROC curves for predicting risk of death at 2 years. A, Baseline and week 12 BNP. B, Change in BNP. See Figure 1 and 2 legends for expansion of abbreviations.

(REVEAL Registry) and French observational PAH registries have shown 6MWD to be an independent predictor of survival.^{13,14} These studies published hazard ratios for death based on certain cutoffs or per-meter increments of 6MWD. However, these estimates may be difficult to apply clinically, since subjects were assessed at various time points in their disease course in the REVEAL Registry, and the absolute risks of death were not provided. The prediction models derived from these registries do not account for changes in response

Table 4—Prediction of Mortality at 2 Years by BNP

Parameter	Baseline BNP ≥ 350 pg/mL	Week 12 BNP ≥ 330 pg/mL
No. of subjects with positive test, No. (%)	84 (25.2)	45 (13.5)
Sensitivity, % (95% CI)	45 (39-50)	38 (33-44)
Specificity, % (95% CI)	78 (74-82)	91 (87-94)
Positive predictive value, % (95% CI)	25 (20-30)	40 (35-45)
Negative predictive value, % (95% CI)	90 (86-93)	90 (87-93)
Accuracy, % (95% CI)	73 (69-78)	83 (79-87)

Values above cutoff indicate a positive test. See Table 1 for expansion of abbreviations.

to treatment. Moreover, the inclusion of prevalent patients and missing data in the REVEAL Registry could affect the results. More recently, the REVEAL Registry investigators published a validation study of their risk prediction rule in “incident” patients (likely similar to those untreated patients entering the ARIES studies).¹⁵ This study showed a prediction rule c-statistic for 1-year mortality (0.72) that was similar to the c-statistic of 6MWD and 2-year mortality in the current study. It is, therefore, possible that information from a standardized 6-min walk test could perform as well as more complex methods of calculating risk.

BNP is produced by myocardial tissue in response to stretch and has previously been associated with mortality in PAH. Nagaya et al⁶ showed that a decline in BNP levels with treatment was associated with a lower risk of death. They found that a level < 180 pg/mL after 3 months of follow-up conferred a significantly improved prognosis through 4 years of follow-up.⁶ More recently, the N-terminal prohormone of BNP also has been identified as an independent predictor of death.¹⁶ As with 6MWD, analyses from the REVEAL Registry identified BNP as an independent predictor of mortality with a level > 180 or < 50 pg/mL being associated with an increased or reduced risk of death, respectively.¹⁷

While the 12-week assessments of 6MWD and BNP did discriminate long-term outcomes in our study, they were not significantly better than baseline values in the cohort. In the IPAH/heritable subgroup, BNP-12w was a statistically significantly better predictor than BNP-B. However, in both the overall cohort and the IPAH/heritable subgroup, the lack of incremental, clinically important prognostic information after a therapeutic intervention suggests that these metrics should not serve as sole triggers to prompt changes in clinical management intended to improve survival. Change-from-baseline values (Δ 6MWD and Δ BNP) provided no useful prognostic information.

These conclusions differ from the results of a recent study suggesting that an increase in 6MWD after

FIGURE 5. Kaplan-Meier analysis of 2-year survival using quartiles. A, Stratified by baseline BNP level. B, Stratified by week 12 BNP level. *P* values for between-group comparisons derived from the log-rank test. See Figure 1 legend for expansion of abbreviations.

12 weeks of subcutaneous treprostinil was associated with improved survival in a multivariate model.¹⁸ Limitations of this study were the exclusion of $> 50\%$ of the study sample due to missing 6MWD at 12 weeks and possible selection bias, censoring of patients at the time of discontinuation of treprostinil therapy, and lack of data on the discriminative properties of the 6MWD. Some of the data for this study was collected more than a decade ago, potentially limiting generalizability to contemporary patients.

We chose to optimize specificity (and PPV, the probability of death given a biomarker below/above the cutoff) while still trying to maintain sensitivity (and NPV) since identification of “high-risk” patients could warrant changes in initial management. Additional therapies, more intensive monitoring, or consideration of lung transplant evaluation for such patients may be useful; however, clinical trials of such approaches to treatment are necessary before firm recommendations

are made. Alternatively, trying to “rule out” a high-risk profile by prioritizing sensitivity (and NPV) would be unlikely to alter initial management strategies. Other studies have analyzed 6MWD and BNP either as continuous variables or stratified by median or other cut points with survival analysis to determine incremental risk. Such results do not reflect the predictive values of a “positive” or “negative” test when used in the clinic. For example, a hazard ratio of 2 is more difficult to apply to an individual patient compared with an absolute mortality risk of 40% at 2 years (in the “high-risk” subgroup from our baseline 6MWD analysis). The narrow confidence intervals around our c-statistics and derived cutoffs indicate precise estimates and adequate power.

Some guidelines advocate for a goal-oriented strategy for the management of patients with PAH based on reassessment of 6MWD and other goals after initiation of therapy (class 1 recommendation, level C evidence).¹⁹

Our data show that there is limited additional prognostic information gained by reassessment of 6MWD or BNP at 3 months after ambrisentan therapy initiation. Furthermore, the lack of prognostic information associated with changes in these end points on therapy calls into question their adequacy as surrogate end points in PAH clinical trials. We performed a pooled analysis of 10 RCTs of PAH therapies which suggested that placebo-corrected change in 6MWD explained only 22% of the variance in clinical events at 12 weeks, with a threshold effect of 41.8 m translating to a significant reduction in clinical outcomes.²⁰ These data suggest that 6MWD changes in response to interventions may not reliably lead to differences in important clinical outcomes. This also underscores the importance of assessing the distribution of responses, as has been done in more recent studies.^{21,22} We believe these data can inform future RCTs designed specifically to test the efficacy of a goal-oriented approach.

This study has several limitations. As the initial ARIES studies had 6MWD criteria for entry, the truncation of the distribution of 6MWD may have impaired our ability to discriminate outcomes. Also, the time of reassessment of 6MWD and BNP (12 weeks) may have been too brief to allow clinically important changes in 6MWD or BNP. In addition, a substantial portion of the study population (12%-42%) underwent modification of their treatment regimen during the 2-year follow-up period. This may have affected the ability of short-term changes in 6MWD and BNP after 12 weeks of ambrisentan monotherapy to discriminate long-term outcomes. This analysis was performed in a clinical trial population mostly comprised of IPAH and CTD-associated PAH and treated with ambrisentan at baseline, so that these results may not be generalizable to patients with other forms of PAH and other types of treatment. Finally, it is unclear whether 6MWD or BNP predict longer-term vital status or are indicative of quality of life or other disease manifestations.

In summary, we have found that baseline noninvasive measurements of PAH severity predict 2-year survival in PAH, but that week 12 follow-up assessments after initial treatment with ambrisentan do not provide additional prognostic information. While patients should be closely monitored after the initiation of any PAH therapy and improvement in 6MWD may be a relevant endpoint with respect to patients' quality of life, our data warrant further studies of how to best follow and manage patients with PAH.

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Author contributions: Drs Fritz and Kawut guarantee the integrity of the study.

Dr Fritz: contributed to study conception and design, data analysis and interpretation, as well as article drafting and revision, and gave final approval.

Ms Blair: contributed to data analysis and interpretation as well as article revision and gave final approval.

Dr Oudiz: contributed to data analysis and interpretation as well as article revision and gave final approval.

Dr Dufton: contributed to data analysis and interpretation as well as article revision and gave final approval.

Dr Olschewski: contributed to data analysis and interpretation as well as article revision and gave final approval.

Mr Despain: contributed to data analysis and interpretation as well as article revision and gave final approval.

Dr Gillies: contributed to data analysis and interpretation as well as article revision and gave final approval.

Dr Kawut: contributed to study conception and design, data analysis and interpretation, as well as article drafting and revision, and gave final approval.

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Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the "Supplemental Materials" area of the online article.

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