An Age- and Sex-Specific Peripheral Blood Gene Expression Score Correlates With Future Cardiovascular Events: Insights From The PROMISE Trial

Deepak V. Voora, MD; Adrian Colles, PhD; Kang Li, PhD; Udo Hoffmann, MD, MPH; James A. Wingrove, PhD; Brian Rhode, PhD; Lin Huang, PhD; Susan E. Daniels, PhD; Mark Monane, MD; Steven Rosenberg, PhD; Daniel B. Mark, MD, MPH; Irfan H. Shah, MD; William E. Kraus, MD; Geoffrey S. Ginsburg, MD, PhD; Pamela S. Douglas, MD, MPH; 1Duke Center for Applied Genomics & Precision Medicine, Duke University School of Medicine, Durham, NC; 2Department of Medicine, Duke University School of Medicine, Durham, NC; 3Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC; 4Massachusetts General Hospital, Harvard Medical School, Boston, MA; CardioDx, Inc., Redwood City, CA.

OBJECTIVES

1. Confirm the association between the ASGES and oCAD in nondiabetic patients in a lower risk population
2. Assess whether the ASGES is predictive of CAD-related events in nondiabetic patients
3. Compare risk of events in patients with a low ASGES vs. negative/low-risk noninvasive test result

METHODS

1. The ASGES was determined using an algorithm that incorporates age, sex, and the peripheral blood expression of 25 genes measured by real-time PCR in an automated fashion in the CardioDx CLIA laboratory.
2. Of the 3742 patients who participated in the PROMISE biomarker, 893 with diabetes, 439 who filed sample quality analysis, and 141 who had inflammatory medications were excluded.
3. The ASGES is reported as a score from 0 to 49.
4. An ASGES >15 is associated with higher likelihood of oCAD

RESULTS

1. 2370 patients (95% of PROMISE nondiabetic patients) met inclusion/exclusion criteria
2. In CTA arm, oCAD associated with ASGES >15
   - 115 of 1327 (8.7%) had oCAD
   - Odds ratio = 2.4 (95% CI, 1.3–4.5), P <0.001
   - Higher extent of CAD associated with continuous ASGES (Figure 1)
3. ASGES >15 associated with higher risk of primary clinical endpoint (Table 2)
   - An ASGES >15 associated with primary endpoint independent of Framingham risk score
   - Patients with an ASGES <15 had an event rate that was similar to those with negative/low-risk noninvasive test results.
4. Event rates in patients with ASGES >15 (n = 1058, 3.2%) were similar to those with negative/low-risk noninvasive test results (n = 1913, 2.6%)
5. The ASGES provided independent and incremental information beyond noninvasive test results for the primary endpoint (Table 2)

CONCLUSIONS

A peripheral blood-based biomarker, the ASGES, may be useful in identifying patients with higher likelihood of obstructive CAD and risk of primary composite endpoint events. Future studies will be needed to determine whether this approach can be used to modify risk factors or even to prevent disease progression and major cardiac events.

DISCLOSURES

This PROMISE substudy was supported in part by the National Heart, Lung, and Blood Institute (NHLBI) grants R01 HL125020, R01 HL116098, R01 HL132019, R01 HL125031, and R01 HL130064. Dr. Kraus has received consulting fees from CardioDx. Dr. Mark reported receiving research support from CardioDx. Authors L. Huang, S. Daniels, and M. Monane are employees of and hold stock in CardioDx. Other authors report no conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

SUMMARY AND CONCLUSIONS

1. An ASGES was measured at baseline in the PROMISE study associated with obstructive CAD in nondiabetic patients.
2. A higher ASGES was associated with a higher rate of revascularization procedures independent of Framingham risk score.
3. Patients with a low ASGES had an event rate that was similar to those with negative/low-risk noninvasive test results.

CONTACT INFORMATION

Deepak V. Voora, MD, 110 West 17th Street, Suite 1401, New York, NY 10011; dvoora@cardiodx.com