8-Year Outcomes of a Program for Early Prevention of Cardiovascular Events
A Growth-Curve Analysis

Du Feng, PhD; M. Christina Esperat, PhD, RN, FAAN; Amy L. Doneen, RN, BSN, MSN, ARNP; Bradley Bale, MD; Huaxin Song, PhD; Alexia E. Green, PhD, RN, FAAN

Background: Early identification of cardiovascular diseases allows us to prevent the progression of these diseases. The Bale/Doneen Method, a prevention and treatment program for heart attacks and ischemic strokes, has been adopted nationally in primary care and specialty clinics. Objectives: The main purpose of this study was to evaluate the effect of the Bale/Doneen Method on lipoproteins and carotid intima-media thickness (IMT) for cardiovascular disease prevention and reduction. A secondary purpose was to illustrate the use of latent growth-curve analysis in studying trajectories of clinical outcomes and biomarkers in individual patients over time.

Method: This retrospective analysis is based on 576 patients at a nurse-managed ambulatory clinic who received the heart attack prevention and treatment program from 2000 to 2008. All patients were white; 61% were men; mean age was 55.5 years. Outcome measures include hemoglobin A1c, fasting blood sugar, plaque burden score (PBS), high-density lipoprotein, low-density lipoprotein (LDL), mean carotid artery IMT, and lipoprotein-associated phospholipase A2 test results. Latent growth-curve analysis was used in modeling changes in these outcome measures. Results: On average, mean IMT score decreased by 0.01 per year ($P < .001$), PBS decreased by 0.17 per year ($P < .001$), LDL decreased by 5.19 per year ($P < .001$), and lipoprotein-associated phospholipase A2 decreased by 3.6 per year ($P < .05$). Hemoglobin A1c increased by 0.04 per year ($P < .001$). Significant sex and age differences in the initial level and/or rate of change of mean IMT, PBS, fasting blood sugar, high-density lipoprotein, and LDL scores were found. Discussion: The current findings suggest that the Bale/Doneen Method is effective in generating a positive effect on the atherosclerotic disease process by achieving regression of disease in the carotid arteries.

KEY WORDS: cardiovascular disease, early prevention, treatment program

Cardiovascular diseases (CVDs) are the leading cause of mortality in developed countries. Atherosclerosis and, subsequently, atherosclerosis are cardiovascular (CV) processes that lead to most of these mortalities.1 Two leading factors that are thought to facilitate progression are oxidative stress and inflammation2; both are important in the pathogenesis of atherosclerotic changes.3-5 Prevention of progression of these processes is at the center of the management of CVD. A hallmark in prevention is identification of biomarkers (eg, hemoglobin A1c [HgbA1C], low-density lipoprotein [LDL], plaque burden score [PBS], and intima-media thickness [IMT]) early in disease6 so that comprehensive and intensive management may be instituted to ameliorate the progression of the process.

Metabolic syndrome is a prominent factor leading to the alarming increase in the incidence of chronic disease in the US population. This factor is among the most predominant precursors of the onset of CVD and therefore merits focus in the prevention efforts to control and prevent these chronic conditions. Another prominent factor, obesity, is thought to involve inflammatory
processes and oxidative stress. In a study of the association between inflammatory markers and insulin resistance (IR) carried out in an elderly population, possible determinants of the homeostasis model assessment index, including four inflammatory markers (leukocyte count, erythrocyte sedimentation rate, high-sensitivity C-reactive protein, and C3 complement the 5 elements of the metabolic syndrome, total cholesterol, physical activity, as well as 4 indicators of adiposity (body mass index, waist circumference, percentage body fat, and hepatic steatosis) were studied. Of the 4 inflammatory markers simultaneously assessed in the subjects, only serum complement C3 was significantly associated with IR. It is imperative that more investigations be conducted to support the use of biomarkers of oxidative stress and inflammatory processes in the refinement of the classification of disease progress and to personalize the treatment approaches to the individual.

Various definitions of metabolic syndrome exist in the literature. In the current study, we used the US National Cholesterol Education Program (NCEP) definition, which requires at least 3 of 5 of the following criteria: (1) central obesity, waist circumference equal to or greater than 102 cm or 40 in for men and equal to or greater than 88 cm or 35 in for women; (2) dyslipidemia, triglyceride (TG) level 1.7 mmol/L (150 mg/dL) or greater; (3) dyslipidemia, high-density lipoprotein-cholesterol (HDL-C) level less than 40 mg/dL for men and less than 50 mg/dL for women; (4) blood pressure (BP) 130/85 mm Hg or greater (or treated for hypertension); and (5) fasting plasma glucose level 6.1 mmol/L (110 mg/dL) or greater.

**Early Identification and Prevention of Cardiovascular Disease**

Another hallmark in the prevention of CVD is the early identification of the presence and progress of atherogenesis and arteriosclerosis among high-risk individuals. An important step in the diagnosis and management of individuals with risk factors for CVD is the classification of people into risk categories. Currently, in office-based practice, use of algorithms of conventional risk factors is standard practice. In the adult population within the United States, it is estimated that fully two-thirds are classified as intermediate risk based on these components of this prevention/treatment program are now being integrated nationally into primary care clinics and specialty clinics around the country. Components of this prevention/treatment program are grounded in a disease treatment paradigm and include aggressive management of CV risk factors and clinical outcomes (eg, heart attack, stroke, and diabetes mellitus) through evaluation, medication, and lifestyle management. All of the medications used are Food and Drug Administration approved. All of the lifestyle advice is guided by nutrigenomics, prescribed by the healthcare provider, which incorporates information on individual genetics and specific needs for certain nutrients.

Lifestyle is emphasized as the number 1 way to reduce CV risk. Patients were educated on the importance of arterial inflammation as the reason arterial disease develops and as the trigger plaque for heart attacks and strokes. They were taught the numerous modifiable issues that can generate arterial disease and how to manage those issues to mitigate risk—numerous lifestyle modifications that can have a positive influence on arterial inflammation. These included instructions on physical activity, proper diet, adequate sleep, anxiety management, weight control, nicotine cessation, and oral health. Thus, patients were coached about the importance of mitigating inflammation via proper lifestyle. The importance of exercise to enhance insulin sensitivity and avoid migrating on to type 2 diabetes was discussed with most of the patients. Daily exercise was encouraged with a mixture of aerobic and resistive training. Dietary advice was come and that the approach to prevention of progress of the disease be appropriately individualized.

State of the science technology in the diagnosis of CVD has progressed to the point that test modalities for assessment of arterial function and structure in asymptomatic subjects are possible. Vascular ultrasonography and tonometry are some of the most promising among these modalities. Measurement of IMT with B-mode ultrasonography scans in the carotid arteries can now determine the presence of atherosclerotic process in the vascular structure. This diagnostic tool has the clear advantage of being a noninvasive procedure that could be conducted repeatedly or frequently. The establishment of quality control in the performance of the test and the standardization of the procedures for measurement may enable the integration of this diagnostic procedure into clinical practice, in addition to existing CV risk stratification algorithms.

**The Prevention Program: The Bale/Doneen Method**

The Bale/Doneen Method was developed by Dr Bradley Bale and Amy Doneen, ARNP, for the prevention and treatment of heart attacks and ischemic strokes in all primary and secondary prevention patients. This method is now being integrated nationally into primary care clinics and specialty clinics around the country. Components of this prevention/treatment program are grounded in a disease treatment paradigm and include aggressive management of CV risk factors and clinical outcomes (eg, heart attack, stroke, and diabetes mellitus) through evaluation, medication, and lifestyle management. All of the medications used are Food and Drug Administration approved. All of the lifestyle advice is guided by nutrigenomics, prescribed by the healthcare provider, which incorporates information on individual genetics and specific needs for certain nutrients.

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The main purpose of current study was to evaluate the effects of prevention/treatment program on lipoproteins on their most unique characteristics. The Bale/Doneen Method is a method of delivering evidence- and outcome-based medical care using a system anchored in the disease of atherosclerosis rather than the standard practice of delivering preventative care based solely on risk factors. All decisions for assessment and treatment are based on the presence of atherosclerosis and the subsequent impact on the atherosclerotic process in this model of primary and secondary CVD prevention/treatment. Table 1 shows the 6 basic elements to the method, which hinge on patient education.

It should be noted that the Bale/Doneen Method allows for a very personalized approach to maintain health and wellness. The healthcare providers are able to tailor their management for individual patients based on their most unique characteristics.

**Purpose of the Current Study**

The main purpose of current study was to evaluate the effect of the prevention/treatment program on lipoproteins, carotid IMT (cIMT), and lipoprotein-associated phospholipase A2 (Lp-PLA2) for CVD reduction in patients recruited from a nurse-managed ambulatory clinic in Northwestern United States that specializes in heart attack prevention and intervention. Components of this early prevention program include aggressive management of CV risk factors and clinical outcomes (eg, heart attack, stroke, and diabetes mellitus) through evaluation, medication, and lifestyle management. All of the medications used are Food and Drug Administration approved. All of the lifestyle advice is common and could be prescribed by any healthcare provider.

A secondary purpose was to illustrate the use of latent growth-curve analysis (GCA), as well as its advantages, in studying trajectories of clinical outcomes and biomarkers in individual patients over time. This multilevel statistical method can appropriately evaluate intraindividual change by modeling individual trajectories of outcomes, capture interindividual variability in change over time, and examine factors that explain the interindividual differences in growth trajectories. Although not used often in nursing research, multilevel growth-curve modeling techniques have become commonly used approaches to the study of change over time in epidemiology and social behavioral fields. The advantages of GCA over the traditional repeated-measures analysis of variance in analyzing longitudinal data have been well documented.

This article is, to the authors’ knowledge, 1 of the few to examine the use of GCA in studying changes in CV patients over a clinical trajectory. As more and more nursing researchers use longitudinal designs to study the clinical outcomes of CVD treatment and prevention, the availability of longitudinal data will create a shift toward the use of newer statistical models, such as the GCA, to the study of change over time. This statistical method can be of particular interest to nursing from a clinical point of view, as well as a way to test theoretical models.

<table>
<thead>
<tr>
<th>Components of the Bale/Doneen Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Components</strong></td>
<td></td>
</tr>
<tr>
<td>1. Education</td>
<td>Each patient is educated about the disease state of atherosclerosis and understands how myocardial infarctions and ischemic strokes occur.</td>
</tr>
<tr>
<td>2. Disease</td>
<td>Each patient is evaluated for the presence of atherosclerosis, using noninvasive office-based techniques, to find asymptomatic vascular disease, and is monitored annually with an intima-media thickness (IMT) test to follow the individual trajectory of atherosclerotic disease. In addition, all patients are monitored annually with a carotid IMT test to follow the atherosclerotic disease over time in the individual patient.</td>
</tr>
<tr>
<td>3. Inflammation</td>
<td>Biomarkers are used to routinely determine the inflammatory state of the vascular system. Endothelial markers include hs-C-reactive protein, microalbumin/creatinine urine ratio, and fibrinogen. Lipoprotein-associated phospholipase A2 (Lp-PLA2) is evaluated for intima activity. Patients were instructed to have these assessed at least biannually.</td>
</tr>
<tr>
<td>4. Root causes</td>
<td>The root cause or causes of the atherosclerotic process are determined and managed for each patient. Root causes of atherosclerosis can include insulin resistance, lipo(a), familial hyperlipidemia, potentially myeloperoxidase, and vitamin D deficiency. Appropriate follow-up testing for effective management of a root cause was done on average quarterly to semiannually.</td>
</tr>
<tr>
<td>5. Optimal goals</td>
<td>Goals of therapy are set based on peer-reviewed, reliable research and guidelines, with optimal targets in an attempt to minimize risk and often going beyond the values set for the standard of care. Attainment of goals was evaluated, on average, every 3–6 months.</td>
</tr>
<tr>
<td>6. Genetics</td>
<td>Genetic information is obtained on patients to aid in the assessment of their cardiovascular risk and to help guide therapy. These tests were never repeated. Their clinical utility never expires, unlike other biomarkers. This makes them arguably the least expensive tests performed.</td>
</tr>
</tbody>
</table>
Methods

Study Design, Sample, and Setting
This retrospective analysis is based on a deidentified data set containing medical, laboratory, and demographic information on 576 patients who were followed over 8 years in the Heart Attack Prevention Clinic in Northwestern United States, with at least 2 carotid imaging scans between January 2000 and June 2008. Clinic patients were referred to the clinic by their primary care physicians or self-referred because of CV risk factors such as hyperlipidemia, hypertension, diabetes, smoking, and family history or known CVD.

The clinical setting for this study specializes in making a comprehensive assessment of patients’ CVD risk to determine their current arterial health status and, subsequently, to design a customized regimen of medication, diet, and exercise. The clinic protocols may include medications such as statins, angiotensin-converting enzyme inhibitors, niacin, fibrates, and β-blockers, all of which have been shown to slow the progression of IMT.20–23

Procedure
The institutional review board of the academic institution with which the authors are associated approved the study, and all patients provided written informed consent before their medical records were entered into an electronic registry. Participation in this registry was completely voluntary, and only arbitrary numbers were used to identify participants to ensure confidentiality. No monetary incentive was given for taking part in the registry. Data entered into the deidentified data set included a detailed medical history questionnaire filled out by participants with a focus on coronary artery disease (CAD); IMT scan results such as mean IMT and PBS; other laboratory test results such as HgbA1C, fasting blood sugar (FBS), HDL, LDL, and Lp-PLA2; as well as medication history. In most cases, participants underwent ultrasound examinations of the carotid artery at 1-year intervals and took other laboratory tests on regular schedules. All patients received the same individualized Bale/Doneen Method protocol.

Measurement
At enrollment, each patient completed a medical history, medication history, physical examination, a panel of blood tests, and anthropometric measurements. Current or past smokers were defined as those patients who were using cigarette, pipe, cigar, or chew tobacco or had been these in the past. The blood tests consisted standard laboratory results, including HgbA1C, FBS, HDL, and LDL. In addition, carotid artery IMT scans and Lp-PLA2 tests were performed among our study participants.

Carotid Intima-Media Thickness Assessment
Carotid artery IMT is assessed by B-mode ultrasound. Mean common IMT was defined as the mean of six 10-mm measurements taken from the left and right anterior, posterior, and lateral common carotid views. One of the primary outcome measures was the presence or absence of carotid artery plaque as demonstrated by IMT. Plaque was defined as an IMT of greater than 1.2 mm in the common, bifurcation, and internal carotid artery. A PBS was defined as the sum of all plaques identified in a single patient.

Research has validated the use of IMT as a reliable and noninvasive measure of disease-related arterial wall changes.24,25 Intima-media thickness has been used as a surrogate marker of CVD and risk of a CV event, as well as means of identifying atherosclerosis and following its progress.26,27 Although a small increase in IMT may be an adaptive response to changes in BP and blood flow, there is consensus that IMT levels greater than 0.9 mm are indicative of atherosclerotic vascular disease and end-organ damage.28 Atherosclerosis of the large- and medium-sized arteries is associated with plaque formation, inflammation, endothelial dysfunction, thrombosis, and acute or chronic luminal obstruction resulting in abnormal blood flow to target organs.29

Lipoprotein-Associated Phospholipase A2
Lipoprotein-associated phospholipase A2 is a fatty enzyme that is produced by inflammatory cells (macrophages, T-lymphocytes, and mast cells) and hydrolyzes oxidized phospholipids in LDL. This rupture-prone substance builds up in the artery wall from various risk factors including elevated LDL cholesterol and can be used to determine risk levels for both heart events and stroke. The Lp-PLA2 test detects the presence of the more dangerous soft, rupture-prone plaque hiding in the lining of arteries. Existing studies have indicated that Lp-PLA2 appears to be an independent marker of CV risk30–32 and that Lp-PLA2 is strongly correlated with several CV risk factors, especially lipid fractions, and with the degree of carotid artery atherosclerosis.33

Our previous studies also suggested use of Lp-PLA2 results for finding individuals whose outcome by standard cardiac screening may be low risk but may actually be at a higher risk after evaluation of the Lp-PLA2 result. Thus, the Lp-PLA2 was monitored over the study period as a genotypic marker for CV risk.

Insulin Resistance
Evidence is accumulating that there is an insulin-related CAD risk. For example, research has shown that IR is responsible for most of CVDs34–37 and that IR is positively correlated with elevated TG, low HDL, BP, plasminogen activator inhibitor 1, and brachial-ankle pulse wave velocity in a clinical sample.38 This condition can be identified before a patient experiencing
an heart attack or stroke or becoming diabetic. In the current study, IR risk was defined as TG/HDL-C ratio of 3.5 or greater, fasting glucose level of 100 mg/dL or greater, 2-hour glucose tolerance of 140 mg/dL or greater, or metabolic syndrome, whereas metabolic syndrome was defined by NCEP criteria.34

Framingham Risk Score
The 10-year CVD risk was determined using the Framingham Risk Score (FRS) as calculated in National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III). Risk factors included in determining FRS were age, gender, total cholesterol, HDL-C, smoking, systolic BP, and the use of antihypertensive agents. All participants were categorized, based on NCEP-ATP III, into 3 groups: FRS less than 10%, FRS 10% to 20%, and FRS greater than 20% (ie, CAD or CAD-risk equivalent).

Coronary Artery Disease
Patients also reported their diagnosis of CAD, angina pectoris, previous MI, heart failure, cardiac surgery, arrhythmia, or hypertension. Coronary artery disease was defined as any history of acute coronary syndrome, percutaneous coronary intervention, coronary bypass grafting, or presence of coronary artery calcification. Coronary artery disease equivalency was defined as history of cerebral vascular accident, presence of peripheral arterial disease, diabetes, or FRS of 20% or higher.

Data Analysis
Strategy
Descriptive statistics were obtained for all background variables using SPSS 20.0.39 Bivariate correlations (Pearson r) between continuous measures at baseline (eg, mean IMT and Lp-PLA2) were calculated. Chi-square tests were performed to evaluate the association between key categorical variables (eg, presence/absence of IR risk and atherosclerosis).

Furthermore, because observations (clinical outcomes or tests) over time are “nested” within a patient in the current study, a statistical technique known as GCA was used in modeling changes in the outcome measures among patients at the nurse-managed ambulatory clinic who received the heart attack prevention program. Specifically, the method used in the current study, the latent curve GCA, was conducted through hierarchical linear modeling.17,19,40,37

The modeling of change was accomplished by a series of 2-level analyses using linear functions. The level 1 analysis captures within-subject variability (ie, individual change over time), whereas level 2 analyses capture between-subject variability. At level 1, each subject’s measure on the outcome variable is regressed onto the time variable (in this case, years since baseline), resulting in a regression equation (in this case, a linear equation) that represents each individual patient’s growth curve. The coefficients that make up the regression equation are the individual growth parameters: the intercept, which indicates the patient’s initial level of the outcome measure, and the linear slope, which indicates the patient’s rate of change of the outcome measure. At level 2, each growth parameter obtained from level 1 is modeled by a regression equation that captures the population main effect plus the variability resulting from each individual. The level 2 equations for the current study consist of 2 linear regression equations, linking the patient’s trajectories of change to patient-related characteristics (eg, age at enrollment, gender), which are considered as correlates of change.

Similarly, level 1 and level 2 equations were used for all clinical outcome variables, to test whether male and female and older versus younger patients responded differently to the intervention. Missing data were handled using the full information maximum likelihood estimation method, based on its advantages over the traditional missing data techniques.41,42

Results
Sample Descriptive Statistics
All patients in this sample were white, and 61% (n = 344) were men. Mean (SD) age at the time of enrollment was 55.5 (10.2) years. Most (89%) had hyperlipidemia, 58% had hypertension, 56% had metabolic syndromes (ie, those who had at least 3 of the following risk factors: TG >150 mg/dL; FBS >100 mg/dL; BP >130/85 mm Hg; waist circumference >35 or >40 in for women or men, respectively; and HDL <50 or <40 mg/dL for women or men, respectively), 5% were diabetic, and 37% were past or present smokers. Regarding adjusted FRS at baseline, 66% were at moderate risk (ie, 10% > FRS), 24% were at moderately high risk (ie, 20% > FRS > 10%), and 10% were at high risk (ie, FRS > 20%). Twenty-five percent of study participants showed indications of CAD or CAD equivalent. Although an initial IMT value at or above 0.9 mm is indicative of atherosclerotic vascular disease according to European Society of Hypertension-European Society of Cardiology guidelines,43 we used a more conservative cutoff point of 1.2 mm as indication of the presence of carotid plaque (ie, carotid atherosclerosis was defined as an isolated intimal thickening of ≥1.2 mm). Carotid plaque was identified in 64% of patients with moderate FRS risk, 87% of patients at moderately high FRS risk, and 89% of patients at high FRS risk. It should be noted that 18% of our study population were asymptomatic primary prevention patients. Further details about the demographic and medical characteristics of the sample can be found in Table 2.
Fixed estimates predicting the 2 random effects, intercept ($\pi_{0i}$) and linear slope ($\pi_{1i}$), for each of the outcome measures are presented in Table 3. The intercepts show the initial status of each measure at baseline, and the slopes indicate the rate of change. Overall, combining male and female patients of all ages, mean IMT score decreased by 0.01 per year ($P < .001$) on average, PBS decreased by 0.17 per year ($P < .001$), LDL decreased by 5.19 per year ($P < .001$), and Lp-PLA$_2$ decreased by 3.6 per year ($P < .05$). The linear slope of FBS was not statistically significant, indicating that the FBS level was stable over time. On the other hand, HgbA1C increased by 0.04 per year ($P < .001$) on average. Variances of both the intercept and the linear slope of all the study variables are significant, indicating heterogeneity (ie, interindividual differences) in the initial level and change rate of these clinical outcomes (see Table 3). Figures 1A through H show the group growth curve of the clinical outcomes of interest.

Based on the interindividual differences found at level 2 analysis, a conditional linear model was used to test sex and age at baseline as level 2 covariates. Table 4 presents the unstandardized coefficients, showing the effects of sex and age at baseline on the initial levels ($\beta_{01}$ and $\tau_{01i}$, respectively) as well as on the rate of change ($\beta_{02}$ and $\tau_{02i}$, respectively). For mean IMT, the coefficients revealed that men had significantly higher mean IMT scores at baseline compared with women ($B = 0.04$, $P < .001$) and older patients had significantly higher mean IMT scores at baseline compared with younger patients ($B = 0.01$, $P < .001$). However, older patients showed a faster decrease in mean IMT scores, as evidenced by the negative effect of age on linear slope ($B = -0.0004$, $P < .01$). Similarly, the second column of Table 4 shows that men had significantly higher PBS scores at baseline compared with women ($B = 0.80$, $P < .05$) and that older patients had significantly higher PBS scores at baseline compared with younger patients ($B = 0.18$, $P < .001$). However, there are no significant sex or age effects on

### Table 2: Baseline Patient Demographic Characteristics (N = 576)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%) or Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55.5 ± 10.2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.5 ± 5.0</td>
</tr>
<tr>
<td>Male</td>
<td>344 (61)</td>
</tr>
<tr>
<td>White</td>
<td>576 (100)</td>
</tr>
<tr>
<td>Current or past smoker</td>
<td>209 (36)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25 (5)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>512 (89)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>325 (58)</td>
</tr>
<tr>
<td>CAD/CAD equivalent</td>
<td>143 (25)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>321 (56)</td>
</tr>
<tr>
<td>Insulin resistant</td>
<td>417 (73)</td>
</tr>
<tr>
<td>Adjusted Framingham Risk Score</td>
<td></td>
</tr>
<tr>
<td>&lt;10%</td>
<td>370 (66)</td>
</tr>
<tr>
<td>10%–20%</td>
<td>141 (24)</td>
</tr>
<tr>
<td>&gt;20%</td>
<td>58 (10)</td>
</tr>
<tr>
<td>Carotid plaque—PBS score ≥1.2 mm</td>
<td>(85)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CAD, coronary artery disease; PBS, plaque burden score.

### Table 3: Unstandardized Coefficients of the Unconditional Linear Growth-Curve Models of Mean Intima-Media Thickness, Plaque Burden Score, Hemoglobin A1c, Fasting Blood Sugar, Fasting Insulin Level (Insulin), High-Density Lipoprotein, Low-Density Lipoprotein, and Lipoprotein-Associated Phospholipase A2

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>IMT</th>
<th>PBS score</th>
<th>HgbA1C</th>
<th>FBS</th>
<th>Insulin</th>
<th>HDL</th>
<th>LDL</th>
<th>Lp-PLA2</th>
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</thead>
<tbody>
<tr>
<td>Fixed effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept, $\pi_{0i}$</td>
<td>0.79$^b$</td>
<td>5.30$^b$</td>
<td>5.37$^b$</td>
<td>96.61$^b$</td>
<td>8.84$^b$</td>
<td>46.48$^b$</td>
<td>131.14$^b$</td>
<td>189.73$^b$</td>
</tr>
<tr>
<td>Linear slope, $\pi_{1i}$</td>
<td>-0.01$^b$</td>
<td>-0.17$^b$</td>
<td>0.04$^b$</td>
<td>0.26</td>
<td>0.06</td>
<td>1.40$^b$</td>
<td>-5.19$^b$</td>
<td>-3.60$^c$</td>
</tr>
<tr>
<td>Random effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept variance</td>
<td>0.03</td>
<td>21.65</td>
<td>1.85</td>
<td>638.70</td>
<td>10.95</td>
<td>303.27</td>
<td>1280.69</td>
<td>11605.78</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>1362.48$^b$</td>
<td>922.77$^b$</td>
<td>969.60$^b$</td>
<td>682.36$^b$</td>
<td>313.43$^c$</td>
<td>1238.21$^b$</td>
<td>1009.07$^b$</td>
<td>360.24$^d$</td>
</tr>
<tr>
<td>df</td>
<td>438</td>
<td>338</td>
<td>417</td>
<td>392</td>
<td>273</td>
<td>457</td>
<td>457</td>
<td>295</td>
</tr>
<tr>
<td>Linear slope variance</td>
<td>0.0004</td>
<td>0.29</td>
<td>0.01</td>
<td>15.87</td>
<td>0.58</td>
<td>3.73</td>
<td>15.62</td>
<td>219.25</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>1008.97$^b$</td>
<td>666.003$^b$</td>
<td>658.91$^b$</td>
<td>599.43$^b$</td>
<td>372.02$^b$</td>
<td>807.56$^b$</td>
<td>762.34$^b$</td>
<td>359.12$^d$</td>
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<tr>
<td>df</td>
<td>438</td>
<td>338</td>
<td>417</td>
<td>392</td>
<td>273</td>
<td>457</td>
<td>457</td>
<td>295</td>
</tr>
<tr>
<td>Level 1 error variance</td>
<td>0.002</td>
<td>1.42</td>
<td>0.08</td>
<td>96.61</td>
<td>24.77</td>
<td>69.48</td>
<td>522.73</td>
<td>1116.74</td>
</tr>
<tr>
<td>Reliability of OLS regression coefficient estimate</td>
<td>0.59</td>
<td>0.53</td>
<td>0.61</td>
<td>0.30</td>
<td>0.06</td>
<td>0.43</td>
<td>0.34</td>
<td>0.25</td>
</tr>
<tr>
<td>Initial status</td>
<td>0.48</td>
<td>0.40</td>
<td>0.41</td>
<td>0.32</td>
<td>0.11</td>
<td>0.31</td>
<td>0.22</td>
<td>0.25</td>
</tr>
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Abbreviations: FBS, fasting blood sugar; HDL, high-density lipoprotein; HgbA1C, hemoglobin A1c; IMT, intima-media thickness; LDL, low-density lipoprotein; OLS, ordinary least-squares; Lp-PLA$_2$, lipoprotein-associated phospholipase A2; PBS, plaque burden score.

$^a$The level 1 equation is $Y_{it} = \pi_{0i} + \pi_{1i} \times Time_{i} + e_{it}$, where $Y_{it}$ represents the repeatedly measured outcome variable for individual $i$ at time $t$; time is measured in weeks.

$^bP < .001$.

$^cP < .05$.

$^dP < .01$.

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the rate of change in PBS. Other significant effects found at level 2 are as follows: Men had significantly higher FBS scores, higher HDL scores, and lower LDL scores at baseline compared with women ($B = 5.47$, $P < .05$) and older patients had significantly higher HDL scores at baseline compared with younger patients ($B = 0.29$, $P < .05$).

### Discussion

The current findings seem to suggest that the Bale/Donneen Method is effective in generating a positive effect on the atherosclerotic disease process, namely, achieving regression of disease in the carotid arteries. This was demonstrated by a significant decrease in mean common carotid artery IMT (CCA-IMT) and PBS. It seems logical to speculate that this may result in a decrease in CV events. The medical management resulted in a positive effect on at least 3 important CV risk factors: LDL, HDL, and Lp-PLA2. Several previous studies also demonstrated regression along with a positive effect on both LDL and HDL.44-46 Extended-release niacin was used in a large percentage of the patients treated with the Bale/Donneen Method, which probably accounts for the positive effect on both LDL and HDL. The slight increase in HgbA1c may be explained by the use of niacin and statins. Despite this increase, there was a positive effect on atherosclerosis. This fits some of the recently published data that question the benefit of aggressive HgbA1c targets to reduce CV events.47,48 It is interesting that the FBS did not increase significantly. Niacin is known to have a synergistic effect with statins on reducing the levels of Lp-PLA2.49 A recent study generated a strong signal that Lp-PLA2 may be causal of atherosclerosis. If that is the case, it seems logical to speculate that the positive therapeutic effect on Lp-PLA2 may have also contributed to regression of disease. There were numerous other variables measured, but not analyzed, in these data that may have also contributed to the regression results, such as BP. Perhaps, 1 of the most salient issues regardless of knowing for sure all of the reasons for the results is that these data indicate that there is a method available to manage CV risk that is clinically applicable and that can generate regression of atherosclerosis.

This data set should be analyzed further in an attempt to ferret out all significant variables that may be associated with the positive results. It seems that the GCA is a valuable technique to accomplish this. These results should generate hypotheses for future randomized placebo controlled trials.

There are numerous weaknesses with the data. There was no placebo group. The patients were all white and motivated to enter a prevention clinic. Most of the patients were men. Perhaps, 1 of the greatest strengths is the fact that these data were generated in an ambulatory clinical setting and represent the first data published using long-term serial cIMT to monitor atherosclerosis in a nonacademic setting. This article, to the authors’ knowledge, is the first report to examine the utility of multilevel GCA in studying trajectories of clinical outcomes related to CVD.

### Limitations and Suggestions for Future Research

The current study is based on a single group of patients who were enrolled at 1 clinic in Northwestern United States. Future studies should include a comparison group and use the randomized control treatment design to evaluate the effectiveness of the prevention method. In fact, large, prospective, randomized controlled studies are needed to evaluate the impact of novel approaches to preventing and averting CVD. The significance of specific risk factors, including those not amenable to pharmacological treatment—diet, exercise, many sleep, and psychological issues—should be sorted out in larger studies. Another limitation lies in the lack of diversity of...
What’s New and Important

- The Bale/Doneen Method rests on a platform of assessing and monitoring arterial disease. It is anchored in inflammation being causal of atherosclerosis. The method comprehensively evaluates known sources for arterial inflammation and promotes optimal management of all identified contributors to the arterial “fire.” The methods of assessing and treating patients used by the Bale/Doneen Methods are available to any practitioner.
- Previous studies have indicated that patients who receive prevention and treatment of CVD through the Bale/Doneen Method show stabilization of the atherosclerotic disease process, a significant conversion of plaque morphology to 100% echogenic lesions by the fifth year of follow-up, and that echogenic carotid plaque is significantly less inflamed than nonechogenic plaque. Consistent with past studies, this article shows that the Bale/Doneen Method is effective in generating a positive effect on the atherosclerotic disease process by achieving regression of disease in the carotid arteries.
- The use of growth-curve modeling in examining changes in markers such as IMT and other biomarkers associated with CVD can improve the accuracy of CVD risk prediction and help identify effective treatments.

Summary

The Bale/Doneen Method for the prevention of heart attacks and strokes is a clinically based approach focused on the actual disease of atherosclerosis. The current standard of care supports managing the disease from a risk factor approach, which has proven to support recidivistic events and a lack of ability to determine asymptomatic vascular disease before the patient experiencing a clinically significant ischemic event. We have proven that our global disease treatment paradigm can be accomplished in the ambulatory setting and can demonstrate a direct impact on the atherosclerotic process. This GCA of cIMT test results demonstrates the effectiveness of a model focused on patient education, disease identification and monitoring, routine assessment of vascular inflammation, identifying and treating the root causes of atherosclerosis, setting optimal goals for management of risk factors, and using genetics to individualize care to the unique individual needs of the patient. These data support that a disease treatment paradigm, when applied in an ambulatory setting, causes a direct impact on the disease of atherosclerosis. None of the patients in this study had a CV event during the 8 years of follow-up despite the fact that many had atherosclerotic lesions and many were secondary prevention patients.

The purpose of this study was to evaluate CVD prevention/treatment methods based on data collected from a real clinical practice, a nurse-managed clinic, by examining changes in IMT and phenotypic and genotypic markers associated with CVD. Using these markers can improve the accuracy of CVD risk prediction and also help in selecting potentially effective treatment. Because the methods of assessing and treating patients used by the Bale/Doneen Methods are available to any practitioner, it is believed that analysis of this data will benefit the understanding of better CV prevention programs.

The multilevel growth-curve modeling technique appears to be well suited to complex modeling of multiple signs or symptoms and related outcomes. The method may enhance the ability of researchers to analyze results of the complex data that emerge when symptom clusters are being studied. The data include the process of change in clinical signs and symptoms and the relationship of such processes to other individual and clinical characteristics of patients, as well as to underlying mechanistic models.

REFERENCES


