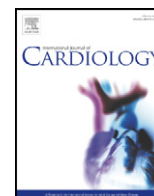


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International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Cardiovascular disease risk prediction in sub-Saharan African populations – Comparative analysis of risk algorithms in the RODAM study

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ARTICLE INFO

Article history:

Received 15 September 2017

Received in revised form 3 November 2017

Accepted 22 November 2017

Keywords:

Cardiovascular disease

Risk prediction

Risk assessment

Risk score

Primary prevention

Sub-Saharan Africa

Framingham

Pooled cohort equation

RODAM study

ABSTRACT

Background: Validated absolute risk equations are currently recommended as the basis of cardiovascular disease (CVD) risk stratification in prevention and control strategies. However, there is no consensus on appropriate equations for sub-Saharan African populations. We assessed agreement between different cardiovascular risk equations among Ghanaian migrant and home populations with no overt CVD.

Methods: The 10-year CVD risks were calculated for 3586 participants aged 40–70 years in the multi-centre RODAM study among Ghanaians residing in Ghana and Europe using the Framingham laboratory and non-laboratory and Pooled Cohort Equations (PCE) algorithms. Participants were classified as low, moderate or high risk, corresponding to <10%, 10–20% and >20% respectively. Agreement between the risk algorithms was assessed using kappa and correlation coefficients.

Results: 19.4%, 12.3% and 5.8% were ranked as high 10-year CVD risk by Framingham non-laboratory, Framingham laboratory and PCE, respectively. The median (25th–75th percentiles) estimated 10-year CVD risk was 9.5% (5.4–15.7), 7.3% (3.9–13.2) and 5.0% (2.3–9.7) for Framingham non-laboratory, Framingham laboratory and PCE, respectively. The concordance between PCE and Framingham non-laboratory was better in the home Ghanaian population (kappa = 0.42, $r = 0.738$) than the migrant population (kappa = 0.24, $r = 0.732$) whereas concordance between PCE and Framingham laboratory was better in migrant Ghanaians (kappa = 0.54, $r = 0.769$) than the home population (kappa = 0.51, $r = 0.758$).

Conclusion: CVD prediction with the same algorithm differs for the migrant and home populations and the interchangeability of Framingham laboratory and non-laboratory algorithms is limited. Validation against CVD outcomes is needed to inform appropriate selection of risk algorithms for use in African ancestry populations.

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1. Introduction

Cardiovascular diseases (CVDs) continue to pose a major public health challenge globally [1,2]. Current estimates show a dramatic shift in the global burden of disease from communicable, maternal, perinatal and nutritional causes to non-communicable diseases [2,3]. The annual mortality from CVDs is projected to increase from 17.5 million in 2012 to 22.2 million in 2030 consolidating their position as leading cause of death and disability worldwide [1]. CVDs are no longer considered the disease of affluent nations as >80% of deaths due to CVDs now occur in low- and middle-income countries (LMIC) [4,5].

The management of CVDs has been improving steadily over the last decade [2]. Deaths from CVDs have, for example, been dramatically reduced in many high-income countries [2]. However, certain ethnic minority groups and sub-Saharan African (SSA) populations have not experienced equivalent improvements in outcomes and continue to be disproportionately affected by CVDs [3,6]. Decreases in overall hospitalization rates for heart failure, for example, have been lower in African Americans compared to White Americans, although the overall rate has declined in recent years [7]. Mortality related to stroke also continues to be higher in African Americans than in White Americans [8]. In addition, the prevalence of CVD risk factors such as hypertension is also found to be higher among African descent populations residing in Europe, than their host populations [9,10].

Current guidelines have reiterated the need to simultaneously assess most risk factors as an effective way of stratifying risk for CVDs prevention and control [11]. This leads to estimation of total risk of CVDs to

identify high-risk groups for targeted treatments, a strategy that has been shown to be cost effective and result in significantly greater reductions in absolute risk [11,12]. Early identification, and appropriate treatment of patients with highest level of absolute CVD risk is of substantial health benefit [13]. This, however, requires reliable tools to identify individuals without overt CVD who are at high risk of a future CVD event, to enable effective implementation of preventive strategies.

Many CVD risk algorithms have been developed for different populations. The first Framingham risk score (FRS) was developed around 1967 by Cornfield and Truett [14], and since then, FRS has been redeveloped several times, simplified through point score, recalibrated for use in other populations, while new algorithms have also been developed for populations in other settings. Current Framingham risk algorithms include age, gender, smoking status, blood pressure levels and blood cholesterol levels [15]. For resource limited settings, where blood lipid determinations for screening purposes are less feasible and far too costly, [16] the Framingham model has been modified by replacing cholesterol with body mass index (BMI) [15]. The extent of its applicability, has however not been extensively elucidated, particularly in sub-Saharan Africa.

The choice of a CVD risk-estimation system should be based on its robustness and ability to address clinically relevant risk factors, leading to a measurable health gain [11]. There is conflicting evidence as to the appropriateness of available risk scores to adequately capture the ethnic and socioeconomic disparities relating to CVDs. The Framingham equation, which has been used widely for assessing CVD risk for instance, has been recently criticized for inaccurate estimation of risk among ethnic minority groups [17–21]. A study on the performance of Framingham cardiovascular risk scores by ethnic groups in New Zealand for instance found that the original risk prediction score underestimates risk for the combined high-risk ethnic populations [22]. The QRISK2, developed and validated among individuals from different ethnic groups in England and Wales, although shown to perform better than Framingham, [23,24] also performed poorly in identifying high risk African Caribbeans [24]. The Pooled Cohort Equations (PCE), developed and validated among Caucasian and African American men and women with no clinical atherosclerotic CVD [25], has been shown to comparatively and appropriately estimate CVD risk in ethnic minority populations [26,27].

Despite the development and extensive use of risk prediction equations to estimate CVD risk in different populations of other geographical settings, little can be said of SSA. There have been no population-based studies conducted in most countries of SSA for the development of CVD risk algorithms for these populations. There is little evidence on the comparability of existing risk algorithms in identifying high-risk individuals among sub-Saharan African populations [28]. Further, although the Framingham non-laboratory algorithm was developed for limited

Table 1
Risk factor profile stratified by RODAM site.

Variables	Total N = 3586	Ghana N = 1564	Europe N = 2022	p-Value
Men, N (%)	1396 (40.0)	513 (33.4)	883 (43.6)	<0.001
Age, years	51.6 ± 0.1	52.4 ± 0.2	51.0 ± 0.2	<0.001
Mean systolic BP, mm Hg	134.2 ± 0.3	129.8 ± 0.5	137.6 ± 0.4	<0.001
Antihypertensives, N (%)	928 (25.9)	208 (13.3)	720 (35.6)	<0.001
Total cholesterol, mmol/L	5.13 ± 0.02	5.10 ± 0.03	5.15 ± 0.02	0.063
LDL cholesterol, mmol/L	3.30 ± 0.02	3.31 ± 0.03	3.30 ± 0.02	0.872
HDL cholesterol, mmol/L	1.34 ± 0.01	1.24 ± 0.01	1.42 ± 0.01	<0.001
Diabetes, N (%) ^a	443 (12.4)	160 (10.2)	283 (14.0)	<0.001
Smoking, N (%)				
– Current	104 (2.9)	23 (1.5)	81 (4.0)	<0.001
– Past	307 (8.6)	128 (8.2)	179 (8.9)	
BMI, kg/m ²	27.5 ± 0.1	25.3 ± 0.1	29.2 ± 0.1	<0.001

Data are presented as means ± standard error of the mean (SEM) unless stated otherwise; BP = Blood pressure; HDL = High density lipoprotein; LDL = Low density lipoprotein; BMI = Body mass index.

^a Based on self-report, use of hypoglycemic medication or fasting plasma glucose > = 7 mmol/L (WHO criteria).

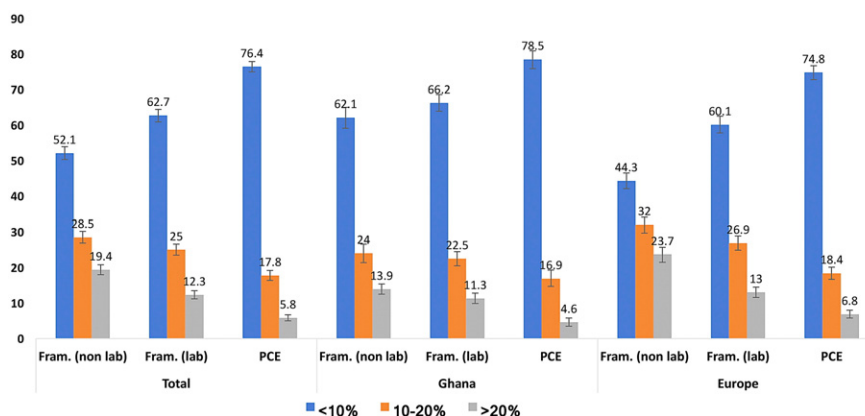


Fig. 1. Predicted 10-year CVD risk stratified by RODAM site. Lab; Laboratory, Fram; Framingham, PCE; Pooled Cohort Equation; p-value for distribution of CVD risk = Ghana $p < 0.001$; Europe $p < 0.001$.

resource settings, its exchangeability with the Framingham laboratory algorithm has also not been elucidated in SSA populations. This study aims to 1) compare the risk stratification of Framingham laboratory, Framingham non-laboratory and PCE among Ghanaians, and 2) compare CVD risk stratification between Ghanaian populations in Europe and Ghana.

2. Methodology

2.1. Study design and population

Details of the multi-centre Research on Obesity and Diabetes among African Migrants (RODAM) study including the recruitment and sample size estimations are published elsewhere [29]. In summary, in the RODAM study, 6385 Ghanaians from a homogenous population, aged 25 to 70 years, residing in Ghana or had migrated to different European countries were recruited, of whom 5898 were physically examined. This offers an advantage for direct comparisons of CVD risk stratification between the migrant and home populations. As a central feature of this study, at all study sites, a well standardized approach was used for data collection. All RODAM study participants aged 40 to 70 years (meeting the age range for both Framingham, 30–74 years and PCE, 40–74 years) and without history of clinical CVD ($n = 3586$) were included in the current analysis. Missing biomedical data [systolic BP, 12 (0.3%); BMI, 10 (0.3%); Cholesterol, 139 (3.6%); HDL Cholesterol, 142 (3.6%) and LDL Cholesterol, 139 (3.7%)] were excluded. For sensitivity analysis, these missing values were imputed using multiple imputation in SPSS® version 22. Comparatively, the outcomes for the imputed and incomplete dataset were the same.

2.2. Measurements

Information on demographics was obtained by structured questionnaire. Physical examinations were performed with validated devices according to standardized operational procedures across all study sites. Weight was measured twice in light clothing and without shoes with SECA 877 scales to the nearest 0.1 kg. Height was also measured twice without shoes with a portable stadiometer (SEC217) to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Overweight and obesity were defined as BMI ≥ 25 to <30 kg/m^2 and ≥ 30 kg/m^2 respectively.

Fasting venous blood samples were collected by trained research assistants in all sites, manually processed and immediately aliquoted according to standard operational procedures, and then temporarily stored at the local research location at -20 °C. The samples were then transported to the respective local laboratories for registration and storage at -80 °C and were subsequently transported to Berlin, Germany, for biochemical analysis to avoid intra-laboratory variability. Total cholesterol, high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol were determined using the ABX Pentra 400 chemistry analyzer (HORIBA ABX, Montpellier, France). Type-2 diabetes was defined according to the World Health Organization (WHO) diagnostic criteria (fasting glucose ≥ 7.0 mmol/L, or reported current use of medication prescribed to treat diabetes, or self-reported diabetes) [30]. Blood pressure was measured three times using validated semi-automated device (The Microlife WatchBP home) with appropriate cuffs in a sitting position after at least 5 min rest. The mean of the last two measurements was used in the analysis. Use of antihypertensives was assessed based on a 'Yes' or 'No' response to the question 'Do you use any antihypertensive medication, including combinations?'. Smoking status was based on either a 'Yes', 'No, but I used to smoke' or 'No, I've never smoked' response to the question 'Do you smoke at all?'.
 2.3. CVD risk

The 10-year risks of CVDs were estimated using the Framingham laboratory and non-laboratory algorithms (15) and the Pooled Cohort Equations (PCE) algorithm for African Americans [31]. The Framingham laboratory algorithm involves two sex-specific equations that use age, sex, total cholesterol, HDL-cholesterol, systolic blood pressure (SBP, BP) medication, diabetes, smoking while the same modelling principles were applied to produce simpler sex-specific models which replace total and LDL cholesterol with BMI [15]. The PCE algorithm on the other hand, is relatively new and has an explicit aim of being applicable to different ethnic groups. The model combines age, sex, total cholesterol, HDL-cholesterol, systolic blood pressure, use of antihypertensive medication, diagnosed with diabetes and smoking and have separate equations for African-American men and women. Predicted CVD risk was categorized into 'low' ($<10\%$), 'moderate' (10–20%) and 'high' ($>20\%$) [32].

2.4. Data analysis

Data were analyzed using SPSS® version 22 [33]. Variables were summarized as count and proportions, mean and standard error of the mean (SEM) or median and 25th–75th percentiles. The inter-rater agreement between the various algorithms was assessed using the Kappa statistic, based on the classification of Landis and Kock [34]: poor-to-fair agreement ($kappa < 0.40$), moderate agreement ($kappa$ of 0.41–0.60), substantial agreement ($kappa$ of 0.61–0.80) and excellent agreement ($kappa$ of 0.81–1.0). The correlation between the predicted CVD risks was also assessed using the Spearman correlation; whereas the differences in the correlation coefficients across the various settings were tested using the Steiger's Z test [35]. All statistical tests were conducted at a significance level of $p < 0.05$.

Table 2
Cross-classification of participants by different risk equations.

	Framingham laboratory																								
	Framingham non-laboratory						Framingham laboratory																		
	All sites		Ghana		Europe		All sites		Ghana		Europe														
PCE	Low	1861	821	57	2739	966	252	9	1227	895	569	48	1512	2231	504	4	2739	1024	201	2	1227	303	2	1512	
	Med	4	193	441	638	4	115	146	265	0	78	295	373	18	376	244	638	9	144	112	265	9	232	132	373
	High	2	8	199	209	2	8	62	72	0	0	137	137	2	15	192	209	7	7	63	72	0	8	129	137
	Total	1867	896	697	3586	972	375	217	1564	895	647	480	2022	2251	895	440	3586	1035	352	177	1564	1216	543	263	2022
Kappa, 95% CI		0.31 (0.28, 0.34)				0.42 (0.37, 0.47)				0.24 (0.20, 0.28)				0.53 (0.50, 0.57)				0.51 (0.47, 0.56)				0.54 (0.50, 0.58)			
p-Value		<0.001				<0.001				<0.001				<0.001				<0.001				<0.001			
Agreement %		62.8				73.1				54.9				78.0				79.7				77.5			
Spearman correlation		0.723**				0.738**				0.732**				0.765**				0.758**				0.769**			
Steiger's Z (p-Value) ^a		1830	418	3	2251	943	92	0	1035	887	326	3	1216	0.39 (0.699)				-0.783 (p = 0.434)							
Framingham Laboratory	Low	37	572	286	895	29	256	67	352	8	316	219	543												
	Med	0	32	408	440	0	27	150	177	0	5	258	263												
	High	1867	1022	697	3586	972	375	217	1564	895	647	480	2022												
	Total	0.63 (0.60, 0.65)				0.74 (0.70, 0.77)				0.55 (0.52, 0.58)															
Kappa		<0.001				<0.001				<0.001															
p-Value		78.4				86.2				72.3															
% Agreement		0.830**				0.866**				0.866**															
Spearman correlation		4.75 (p < 0.0001)				4.75 (p < 0.0001)				4.75 (p < 0.0001)															
Steiger's Z (p-Value) ^a																									

^a Compares the difference in correlation (of risk algorithms) between Ghana and Europe.
 ** Significant at $p < 0.001$. Med: Medium, PCE: Pooled Cohort Equation.

3. Results

3.1. Background characteristics and CVD risk profile

Table 1 shows the background characteristics and risk factor profile of the study population. The mean age was 52 years and majority of the study subjects at both Ghana and European sites were women; 33.4% and 43.6% were men in Ghana and Europe respectively. The differences in distribution of CVD risk at both European and Ghana sites were statistically significant ($p < 0.001$). The mean (SE) SBP was higher among the European migrant population, 137.6 (0.4) mm Hg than those residing in Ghana, 129.8 (0.5) mm Hg ($p < 0.001$). About 35.6% of the Ghanaian population in Europe reported to have antihypertensive medication as compared to only 13.3% of their counterparts in Ghana ($p < 0.001$). The percentages of diabetics and current smokers were also higher among the migrant populations than non-migrants ($p < 0.001$).

3.2. Estimated CVD risk and agreement across algorithms

As shown in Fig. 1, 19.4%, 12.3% and 5.8% of the Ghanaian population studied were predicted as having high 10-year CVD risk by Framingham non-laboratory, Framingham laboratory and PCE, respectively. Among the migrant population, 23.7% were predicted as high 10-year CVD risk as compared to 13.0% by Framingham laboratory and 6.8% by PCE. A similar trend was observed among the home populations, Fig. 1.

The median (25th–75th percentiles) 10-year absolute CVD risk was 9.5% (5.4–15.7), 7.3% (3.9–13.2) and 5.0% (2.3–9.7) for Framingham non-laboratory, Framingham laboratory and PCE respectively. As shown in Table 2, the kappa statistic (95%CI) for PCE compared with Framingham non-laboratory was 0.31 (95%CI 0.28–0.34) for the entire study population whereas it was 0.63 (0.60–0.65) when Framingham laboratory and non-laboratory were compared. The concordance between PCE and Framingham non-laboratory was better in the home Ghanaian population (kappa; 0.42; 95%CI 0.37–0.47, $r = 0.738$) than the migrant population (kappa; 0.24; 95%CI 0.20–0.28, $r = 0.732$) whereas concordance between PCE and Framingham laboratory was the inverse (Ghana kappa; 0.51; 95%CI 0.47–0.56, $r = 0.758$; Europe kappa; 0.54; 95%CI 0.50–0.58, $r = 0.769$).

The differences in correlation between PCE and the Framingham algorithms were statistically significant in the European ($Z = 2.99$; $p = 0.003$) but not the home Ghanaian populations (Ghana; $Z = 1.39$; $p = 0.163$), Table 3. The correlation in predictions for Framingham laboratory versus PCE and Framingham laboratory versus non-laboratory were statistically different for both the migrant and home populations. The correlation between Framingham laboratory and Framingham non-laboratory was significantly different between the migrant and home populations ($Z = 4.75$; $p < 0.0001$).

4. Discussion

This study assessed the agreement between the Framingham laboratory, Framingham non-laboratory and PCE algorithms in stratifying 10-year CVD risk of Ghanaian populations in Ghana and Europe. The main finding is that the degree of agreement between the risk estimates from different algorithms differs between home and migrant

populations. This study shows discrepancies in the risk assessment and identification of high-risk individuals between three popular scoring systems. The level of agreement between the various CVD risk scores was moderate between Framingham laboratory and non-laboratory and low between PCE and the Framingham algorithms, with discrepancies in prediction being higher among the Ghanaian migrant population than among the Ghanaian home populations. Migrant populations acquire certain health characteristics including smoking and high lipid diets, which influence their risk of CVDs over time [36]. This also indicates that migrant populations could develop some important risk factors and biomarkers relevant for their CVD risk prediction, but are not captured by the current risk equations.

Another important finding of this study was that, although the Framingham non-laboratory was designed to replace the laboratory equation in resource limited settings, interchangeability is limited. Compared to the laboratory equation, the non-laboratory equation ranked almost 1.5 times more people at higher absolute 10-year CVD risk among the Ghanaian population in Ghana, with just the replacement of cholesterol with BMI in the algorithm. This corroborates findings by Gray et al. [37] where the Framingham non-laboratory algorithm predicted more high absolute risk than the laboratory algorithm. This brings to question; the reliability of the BMI algorithm in predicting CVD risk even in resource limited settings, where these are proposed to be used. Currently, no CVD risk algorithm has been validated in any SSA population, nor for most low and middle-income countries. Incoherent estimations of an individual's risk have huge implications for clinical practice and the delivery of equitable care in risk based treatment.

Finding of this study corroborates previous evidence, that, predicted CVD risk depends on the algorithm used. The Framingham non-laboratory and laboratory algorithms classified 2.5, and 4 times, respectively, more often Ghanaian participants to be high-risk individuals compared to PCE algorithm classification. This was more evident in the Ghanaian home population, where 9.4% and 12.3% were ranked at high risk by Framingham non-laboratory or laboratory equations as compared to only 3.1% by the PCE. This implies that when the same threshold is applied to the same population, prescriptions of statin and antihypertensive medication, as well as behavioral and dietary advice, will be more often recommended when the Framingham algorithms are applied. Mancini and Ryomoto [38], who compared risk algorithms to determine eligibility for statin therapy, also concluded from their findings that the choice of risk algorithm leads to systematic differences in risk categorization that can influence eligibility for lipid-lowering therapy. While this study did not observe actual events, previous validation studies that predicted absolute risk found the Framingham equation to typically overestimate CVD risk compared to other risk algorithms tested [17–21,39]. The study by Fulcher et al. found PCE, Framingham and QRISK2 to overestimate risk, however, PCE was seen to outperform Framingham scores when applied to primary prevention control arm patients in the Cholesterol Treatment Trialists' database [40]. The consideration of ethnicity in the development of PCE algorithms was to enhance its usability and accuracy in predicting CVD risk among ethnic minority populations and previous validation in these populations has shown an improvement in CVD risk prediction compared to existing algorithms (26,27).

Table 3
Differences in correlations between risk algorithms, measure in Ghana or Europe.

	Framingham non-laboratory versus PCE				Framingham laboratory versus Framingham non-laboratory			
	Ghana		Europe		Ghana		Europe	
	z-Score	p-Value	z-Score	p-Value	z-Score	p-Value	z-Score	p-Value
Framingham laboratory versus PCE	1.394	0.163	2.993	0.003	24.892	<0.0001	9.265	<0.0001
Framingham non-laboratory versus PCE					–	–	7.172	<0.0001

The lack of concordance in CVD predictions by different risk algorithms has been the subject of long debate. Previous comparative studies of different CVD risk algorithms in the general population also revealed the lack of concordance in the detection of high-risk cases and in the recommendations for treatment [41,42]. Studies that looked into risk prediction in specific populations also found differences in predictions and lack of concordance in predictions by different algorithms, including an underestimation by the PCE [43], underestimation [44,45] and overestimation by the Framingham [46]. Although only a prospective study will truly inform which of the three equations offers optimal sensitivity and specificity for the prediction in this population, defining the groups and which methods offers most discrepancies may help improve the clinical assessment of cardiovascular risk.

5. Conclusion

This study shows prediction of CVD risk to be reliant on the risk algorithm adopted. The Framingham laboratory and non-laboratory algorithms ranked more individuals to have high risk of 10-year CVD event than the PCE, with concordance and correlations differing between migrant and home populations of same ancestry. Although calculation of predicted risk of CVD may prove useful in the management of CVDs, it is important to validate the different laboratory and non-laboratory based risk algorithms used to evaluate CVD risk in ethnic minority groups and resource limited settings. This work demonstrates the urgent need for prospective studies among sub-Saharan African populations to enable the development or validation of population specific CVD risk algorithms for use among these populations.

Acknowledgement

The authors are very grateful to the research assistants, interviewers and other staff of the five research locations who have taken part in gathering the data and, most of all, the Ghanaian volunteers participating in the RODAM study. We gratefully acknowledge the advisory board members for their valuable support in shaping the RODAM study methods, Jan van Straalen from the Academic Medical Centre with standardization of the lab procedures and the Academic Medical Centre Biobank for their support in biobank management and high-quality storage of collected samples. We also grateful to Karien Stronks from the Academic Medical Centre, University of Amsterdam for her contribution to interpretation of study findings.

Sources of funding

The RODAM study was supported by the European Commission under the Framework Programme (Grant Number: 278901). DB is supported by the Global Health Scholarship Programme, University Medical Center Utrecht, The Netherlands. CG is supported by NutriAct – Competence Cluster Nutrition Research Berlin–Potsdam funded by the German Federal Ministry of Education and Research (FKZ: 01EA1408A-G).

Disclosures

None.

Author contributions

DB, KK-G, CA contributed to the conception or design of the work. DB, CA, KK-G, EB, KM, APK, DEG contributed to the analysis, or interpretation of data for the work. DB and KK-G drafted the manuscript. CA, EB, KM, Ad-A, PA-B, EO-D, SB, ID, MBS, JS, FM, JA, LS and KK-G contributed to the acquisition of data. All authors critically revised and commented on the manuscript and gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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