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Introduction - The utilization of internet cardiovascular risk calculators (i.e., pooled cohort equations) has been useful since their introduction over a decade ago. However, more recent clinical investigations have demonstrated their loss of accurate predictive ten-year risk in several large populations including obesity (1), young men (2), asymptomatic women (3), and different ethnic groups (4). The efforts to improve mathematical calculations by the American Heart Association, the Framingham Study, the Reynolds equations and others, have been met with confusion for patients and healthcare professionals because of their differing input variables and output recommendations (5). Their inherent limitations leading to inaccurate predictions include risk assessment at only one point in time and their inability to accurately input more or less (i.e., intermittent) exposure to major risk factors over the lifetime of the individual.

Risk Parameters - New investigations into cardiovascular pathophysiology have demonstrated that all major risks can be expressed by at least one of the following blood tests: 1) lipid profile, 2) Apolipoprotein B (Apo B), 3) Apolipoprotein (a) (Lp[a]), and 4) high sensitivity C-reactive protein (hsCRP). Because atherosclerosis is a chronic disease developing over the lifetime of the individual starting in infancy, an abnormality in any of these variables requires follow-up evaluation independent of that already necessitated by traditional clinical risk factors.

The prevalence of cardiovascular disease is increasing. Prevention of heart attacks and strokes requires identification of all individuals with an increased risk profile, and subsequent preventive therapy when indicated. The knowledge of the atherosclerotic plaque burden can support the clinical justification for introducing

improved lifestyle and pharmacological therapy. This approach avoids introducing unnecessary therapeutic interventions or frequent evaluations if no vessel atherosclerotic plaque is present.

Traditional risk calculator equations can be superseded by assessment of proven clinical risk factors and measurement of their mediators. In place of the traditional risk equations, the physician should identify a patient's family history of atherosclerosis, the past or current presence of hypertension, smoking, and diabetes, and order the four baseline blood tests listed above to assess cardiovascular risk. If any of these parameters are abnormal, then a coronary artery calcium scan (CAC scan) should be obtained if the patient's age is appropriate for subclinical atherosclerosis. Coronary artery calcium scanning has permitted the reclassification of individuals evaluated by a risk equation score (e.g., Framingham risk score) throughout the risk categories ranging from 12% to 15% in the low-risk category, 52% to 66% in the intermediate-risk category, and 34% to 36% in the high-risk category (6). In a recent change in policy, the American Heart Association now supports calcium scanning in most individuals with proven risk factors (7). Furthermore, coronary artery calcium heart scanning has become widely available at relatively minimal cost. Preventive treatment is not only inexpensive and safe but is effective in the clinical population (8).

Informative blood testing (table) - A lipid profile provides the following useful risk information – a total cholesterol, an HDL cholesterol, a triglyceride level, and a calculated LDL cholesterol. An HDL cholesterol concentration assesses the reverse cholesterol transport capability of the individual; a triglyceride level assesses the risk of elevated triglycerides (cardiovascular and pancreatitis), and an LDL cholesterol

assesses the potential atherosclerotic hazard of this lipoprotein remnant to atherosclerotic plaque formation. In addition, a non-HDL cholesterol level can be calculated from these lipids to provide an estimate of the total quantity of cholesterol contained in atherogenic particles.

Measuring Lp(a) provides an assessment of a very important independent risk factor (9). Lp(a) is genetically determined and minimally changes over the lifetime of the individual. It tends to be elevated in certain ethnic groups such as African Americans. Not only does it contain an atherogenic LDL particle but it also contains amino acid kringles (amino acid folds held together by disulfide bonds) that share homology with kringles on plasminogen. Their interaction results in an inhibition of thrombolysis and an increased risk of a coronary thrombosis. Lp(a) is highly susceptible to oxidation, making it available to macrophages that initiate atherosclerotic plaque formation. At autopsy, Lp(a) has been identified in atherosclerotic plaques. It has the undesirable properties of being proatherosclerotic, proinflammatory, and prothrombotic.

Apolipoprotein B (Apo B) is a constituent of all atherogenic particles. Since there is only one Apo B per particle, its quantification provides a precise assessment of the number of total atherogenic particles. This is important since many studies have shown that small, dense LDL cholesterol particles are more atherogenic than large LDL particles, even with the same total cholesterol particle content (10). Non HDL cholesterol does not provide this important information, since it only measures total particle cholesterol content. Recent data suggest that apo B must be reduced to reduce cardiovascular disease (11).

HsCRP is a surrogate marker for the severity of systemic inflammation (12). Inflammation is a critical component of the atherosclerotic process. It damages the arterial endothelium and thereby permits additional LDL cholesterol particles to enter the subendothelial space. It also stimulates the endothelial secretion of specific cytokines (e.g., VCAM-1) that increase the adherence of monocytes to the arterial wall. These monocytes then pass through the endothelium by diapedisis, internalize the oxidized LDL-cholesterol particle, and form fatty streaks, the precursor to atherosclerotic plaques.

Recent studies now demonstrate the value of atherosclerotic plaque burden as quantified by the coronary artery calcium scan's ten-year cardiovascular event prediction (13). The quantity of calcium is an excellent predictor of total atherosclerotic plaque. Alternatively, a zero calcium score provides assurance of protection from an atherosclerotic event for at least five years. A coronary calcium scan is noninvasive, requires approximately 10 minutes, and costs approximately $100. Guidelines for the appropriate use of CAC scanning have been published (14).

Summary - In contrast to placing a patient in a specific risk category by risk equations, (e.g., low, intermediate, high, very high), just two categories are necessary: 1) very low risk and 2) significant potential risk. This categorization is easily determined from the assessment of the above evaluation. If all above measurements are within a normal range with no hypertension, smoking, diabetes, nor family history of atherosclerosis, then cardiovascular risk is minimal. However, if any of the tests are abnormal, then a coronary artery calcium scan should be obtained after considering the age of the individual and the severity of the risk factor. Treatment should be individualized for

each patient. Identifying individuals at risk, documenting early coronary atherosclerosis, and treating them aggressively will reduce the number one cause of death in the U.S., i.e., atherosclerotic cardiovascular disease (8).

References

1) Khera R, Pandey A, Ayers CR, Carnethon MR, Greenland P, Ndumele CE, et al. Performance of the pooled cohort equations to estimate atherosclerotic cardiovascular disease risk by body mass index. *JAMA Netw Open* 2020;3(10):e2023242.

2) Cook NR and Ridker PM. Calibration of the Pooled Cohort Equations for Atherosclerotic Cardiovascular Disease. *Ann Int Med* 2016;165(11):786-94.

3) Michos ED, Nasir K, Braunstein JB, Rumberger JA, Budoff MJ, Post WS, et al. Framingham risk equation underestimates subclinical atherosclerosis risk in asymptomatic women. *Atherosclerosis* 2006;184:201– 6.

4) Jung KJ, Jang Y, Oh DJ, Oh BH, Lee SH, Park SW, et al. The ACC/AHA 2013 pooled cohort equations compared to a Korean Risk Prediction Model for atherosclerotic cardiovascular disease. *Atherosclerosis* 2015;242(1):367-375. DOI: 10.1016/j.atherosclerosis.2015.07.033

5) deGoma EM, Dunbar RL, Jacoby D, French B. Differences in absolute risk of cardiovascular events using risk-refinement tests: A systematic analysis of four cardiovascular risk equations. *Atherosclerosis* 2013;227(1):172-177.

6) Hecht HS, Narula J. Coronary artery calcium scanning in asymptomatic patients with diabetes mellitus: a paradigm shift. *J Diabetes* 2012 Dec;4(4):342-350.

7) American Heart Association. Policy Guidance: Expanding Coverage of Cardiac Computed Tomography for Calcium Screening. *AHA*, 2019 Feb. https://www.heart.org/-/media/Files/About-Us/Policy-Research/Policy-Positions/Clinical-Care/Coronary-Artery-Calcium-Screening-2019.pdf

8) Giannini J, Padilla J, Eaton RP, Gonzales K, Schade DS. Prevention of coronary heart disease: A translational clinical challenge. *WJCD* 2022;12:11-23.

9) Wilson DP, Jacobson TA, Jone PH, Koschinsky ML, McNeal CJ, Nordestgaard BG and Orringer CE. Use of lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association. *J Clin Lipidology* 2019;13:374-392.

10) Sniderman AD, Lamarche B, Contois JH, and de Graaf J. Discordance analysis and the Gordian Knot of LDL and non-HDL cholesterol versus apoB. *Curr Opin Lipidol* 2014, 25:461–467.

11) Virani S. The Fibrates Story – a tepid end to a prominent drug, *N Engl J Med* 2022 387, 1991-1992, DOI: 10.1056/NEJMe2213208

12) Ridker PM. High-Sensitivity C-Reactive Protein: Potential Adjunct for Global Risk Assessment in the Primary Prevention of Cardiovascular Disease. *Circulation* 2001;103: 1813-1818. https://doi.org/10.1161/01.cir.103.13.1813

13) Erbel R, Mohlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, et al. Coronary Risk Stratification, Discrimination, and Reclassification Improvement Based on Quantification of Subclinical Coronary Atherosclerosis: The Heinz Nixdorf Recall Study. *J Am Coll Cardiol* 2010;56(17):1397-1406.

14) Schade DS, Obenshain S, Hickey M, Febbo J, Wann S, Eaton RP. Guidelines for the prevention of symptomatic cardiovascular disease, based upon the presence of coronary artery calcified plaque - Provided by the Society for the Prevention of Symptomatic Heart Disease. *WJCD* 2022;12(6):320-41.

Table – Important Risk Parameters to be Assessed to Categorize CVD Risk

Test	Normal Value	Key Points	What is assessed	Approximate Quest Cost	Limitations
Lp (a) Ref # 9	<30 mg/dl	Genetically determined. Not decreased by statins	A specific atherosclerotic particle that inhibits plasminogen	$50	Normal range is lab assay specific

Apo B Ref # 10	<90 mg/dl	Provides an accurate number of atherosclerotic particles	Identifies # of small LDL particles for improved risk assessment	$35	None
hsCRP Ref # 12	<1.0 mg/L	Assesses the degree of systemic inflammation (specify “high sensitivity”)	Measures low values of CRP Major risk for coronary artery atherosclerosis	$79	Also Increased during acute illness
LDL chol Ref # 8,10	< 70 mg/dl Lower is desirable	Accounts for 80% of total cholesterol in plasma	Usually calculated but if TG ↑ direct assay available	$156 for entire lipid panel	Does not include all atherogenic particles
CAC scan Ref # 6, 7,13,14	Zero (No calcified plaques)	Excellent noninvasive predictor of future CVD risk	Highly correlated with atherosclerotic plaque burden	$50 - $200 Widely available	Identifies only calcified plaques