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Primary Cardiovascular Disease Prevention: Risk Factors Control vs. Imaging Subclinical Atherosclerosis

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Highlights

The burden of cardiovascular disease in developed countries has shown dramatic improvements over the last 50 years, largely due the identification and control of major risk factors including, smoking hypertension and high cholesterol. However, due to the significant increase in obesity and diabetes CVD incidence rates will not reduce as far over over the next years. Risk prediction in asymptomatic individuals remains a major challenge. Primary preventive treatment is currently based on the assessment of individual's global risk mainly through screening of conventional risk factors and their treatment with lifestyle intervention and pharmacotherapy, often based on multivariate risk equations, and yet a large proportion of CVD still occurs in individuals who are classified as carrying low- or intermediate-risk according to the risk scores. Atherosclerosis is the most common pathophysiologic process underlying CVD, often after a prolonged asymptomatic phase during which it may be possible to modify the course of the disease. Unlike conventional probabilistic risk scores, non-invasive imaging techniques such as carotid intima-media thickness (CIMT) along with plaque assessment (Figure 2), measured by B-mode ultrasound, and coronary calcium scoring (CAC) detected by CT scan have the advantage of direct visualization of the consequences of atherosclerosis on the arterial system. We consider the proposal that imaging of subclinical atherosclerosis is superior to risk equations as it directly identifies the disease and can effectively predict the risk of future CV events in low- and intermediate-risk individuals. In addition, imaging can improve the adherence to guidelines based treatment in patients and their physicians.

Keywords: atherosclerosis, primary prevention, risk factors

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Introduction

During the last four decades a substantial fall in cardiovascular disease (CVD) mortality has been observed worldwide[1] to a large extent attributable to the reduction of major risk factors[2]. However, due to the significant increase in obesity and diabetes CVD incidence rate will not reduce, thus making the prevalence of CVD increasing over the next years[3]. Risk prediction in asymptomatic individuals is a major challenge. Decision to commence treatment in primary prevention is currently based on the assessment of individual's global risk rather than focusing on single risk factors[4]. Current primary prevention strategies are based on the recognition of individuals at high risk of developing CVD, through screening of conventional risk factors and their treatment with lifestyle intervention and pharmacotherapy[5]. Several multivariate risk equations incorporating age, gender, lipid profile, smoking and blood pressure, have been developed for determining the 10-year coronary event risk and individuals requiring preventive treatments, even in the absence of clinical manifestations of disease[6-8]. Although these CV risk equations are useful in predicting the population risk, there is no clear evidence that their use in individuals translate into reduction of CVD[9,10]. A large proportion of CVD occurs in individuals who are classified as carrying low- or intermediate-risk according to the risk scores,[11-13] indicating that the predictive value of the risk equations based on conventional risk factors is relatively low. Furthermore, the distribution of serum cholesterol and blood pressure in patients who developed CVD largely overlaps with

those who did not[14]. Conversely, about one fifth of patients with coronary artery disease (CAD) do not carry any of the conventional risk factors[12]. The age of initiation and the rate of progression of atherosclerosis may markedly differ among individuals and cannot be predicted by risk factors based assessment models. Moreover, conventional risk screening tools do not give information about the pathophysiologic consequences of the risk exposure and do not take into account the length of exposure which can greatly increase the CVD risk[15,16].

Atherosclerosis is the most common pathophysiologic process underlying CVD[17]. Some components of the atherogenesis may explain the limited value of risk scores. The systemic inflammatory vascular process that results in atherosclerosis starts in early life and progresses with age[18]. Therefore, atherosclerosis has a prolonged asymptomatic phase during which it is possible to modify the course of the disease, and the rate of progression of the lesions which may vary among individuals. Endothelial dysfunction, activation of inflammatory cells, smooth muscle proliferation and coronary calcification may occur at early stages even in the absence of clinical manifestations[19,20]. Thus, subclinical atherosclerosis should be considered as an early indicator of atherosclerotic burden and a memory of lifetime risk factor exposure. Its timely recognition is an important clinical target that can prevent or slow the progression to overt CVD.

Unlike conventional probabilistic risk scores, non-invasive imaging techniques such as carotid intima-media thickness (CIMT) (Figure 1) along with plaque assessment (Figure 2), measured by B-mode ultrasound, and coronary calcium scoring (CAC) detected by CT scan (Figure 3), have the advantage of direct visualization of the consequences of atherosclerosis on the arterial wall, allowing measurement of the lifetime cumulative effects of all risk factors[21-23]. Being a systemic disease, the severity of atherosclerosis in one arterial territory is associated with the involvement of other arteries, although coronary and carotid are the two predominantly involved systems.

A positive association has been reported between the extent of cross-sectional measurements of CIMT and the risk of

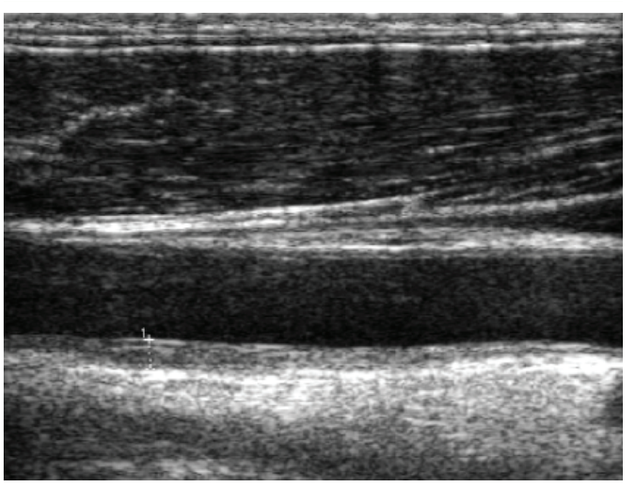

Figure 1. Ultrasound scan of carotid artery showing increased CIMT without plaque

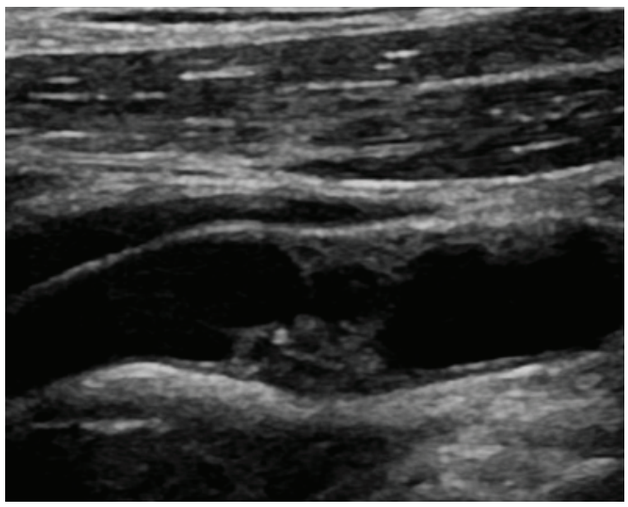

Figure 2. Large carotid plaque with irregular surface determining an unstable feature.

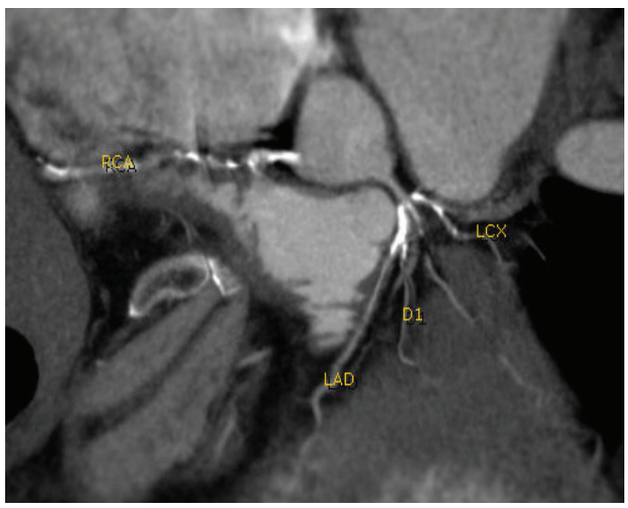

Figure 3. CT scan of the heart showing extensive coronary calcifications

subsequent CV events in general populations, independent of traditional risk factors[24,25]. However, the addition of CIMT to traditional CV risk prediction models is associated with only small or no improvement in the performance of the model[26-28]. However, CIMT when associated with information about additional carotid plaques formations can significantly improve the CV risk prediction[29]. Several studies indicate that reduction of atherosclerosis burden with risk factors control results in reduction in CV events[30,31]. Although statin treatment has been associated with slower progression of CIMT, there is no definitive evidence of a relationship between CIMT regression or progression and CV subsequent events[24,32-35]. Methodological and biological explanations may account for this discordance. The mean annual change in CIMT is very small, far less than 1 mm [36],thus measurements done several months after the first measurement by different sonographers, at different carotid sites, may produce large variability[37-38]. In addition, CIMT reflects both intimal thickening due to atherosclerosis and smooth muscle remodeling of the muscular

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wall, hence the rate of annual CIMT change over time is non-linear and may be different among individuals[35]. Overall, the available results indicate that CIMT has a limited incremental value compared with conventional risk prediction scores and its use in clinical practice to improve CV risk assessment is not recommended by current guidelines[5,39]. New imaging modalities, such as intima-media grey-scale median (IM-GSM) and fully automated on-screen carotid intima-media thickness measurement have been recently introduced[40,41]. IM-GSM can differentiate between adaptive intimal thickening due to remodeling from pathological intimal thickening as a result of early atherosclerosis. Fully automated on-screen CIMT measurement minimizes the operator bias and can greatly improve the accuracy and reproducibility of measurements.

Carotid plaques are more effective than CIMT in predicting future CV events and are strictly associated with conventional risk factors and with other measures of atherosclerotic disease, such as aortic stiffness[42-44]. The assessment of carotid disease has been traditionally based on the degree of stenosis in order to evaluate the clinical risk. However, the development of symptoms does not follow a linear relationship with the degree of stenosis[45]. A compensatory outward remodeling may accommodate a large plaque with negligible hemodynamic effects[46]. Therefore, a clinically meaningful estimate of the burden of carotid disease relies on the direct assessment of the plaque morphology which is a measure of the effects of atherosclerosis. B-mode ultrasound is widely used in the assessment of plaque area for predicting future events[47]. The recently introduced three-dimensional ultrasound technology allows accurate quantification of the plaque volume[48]. The wide range of volume that can be detected enables more accurate assessment of regression or progression of the disease in single individuals[49]. Characteristics of plaque morphology, including surface irregularity, echolucency, degree of luminal stenosis and calcification, are strictly related with CV risk factors and have been shown to accurately predict the development of both coronary and cerebrovascular events[43,50]. Plaque composition, ranging from echolucent high-risk plaques to echodense stable ones, evaluated with standardized methods based on grey-scale pixel analysis,[51] can identify individuals at high risk of CV events[52,53]. Lipid-lowering therapy has been shown to modify the plaque composition and its ultrasound echogenicity even after few months of treatment[54].

The progression of intimal atherosclerosis results in coronary artery calcification (CAC). In symptomatic patients, CAC has been shown to compromise myocardial perfusion even in the absence of significant luminal stenosis[55]. CAC quantification, assessed by CT scan, improves risk prediction beyond traditional risk factors[56-58]. When CAC score is added to the risk model, patients at intermediate risk according to conventional score, are accurately reclassified into low or high risk categories. In a large study of individuals at intermediate risk, the net reclassification index (NRI), which indicates the proportion of individuals correctly reclassified to higher or lower risk categories by incorporating a new test into the risk assessment model, showed that one in five and one in three were reclassified to low and high risk categories, respectively[59]. In appropriately selected asymptomatic individuals the addition of CAC to conventional risk factors may greatly improve the clinical risk prediction[60-62]. However, the relationship between CAC, risk factors and coronary stenosis is complex. About one fifth of asymptomatic individuals with CAC Agatston score zero have significant coronary stenosis at coronary angiography[63]. Conversely, about one third without high levels of conventional risk factors have extensive CAC[64]. Only age and male gender are strictly related to CAC. Although quantification of CAC scoring is limited by costs and radiation exposure, scanning of CAC has been proposed to monitor CVD progression and the effects of treatment[65]. The degree of baseline CAC score is the most important determinant for progression, which is more rapid when the baseline CAC score is high[66]. Traditional risk factors seem less important for CAC progression. CAC progression is not affected by lipid-lowering treatment with statins, even if LDL cholesterol is reduced[67]. Overall, these observations support the hypothesis that arterial calcification and atherosclerosis are different pathologic process which frequently coexist[68,69].

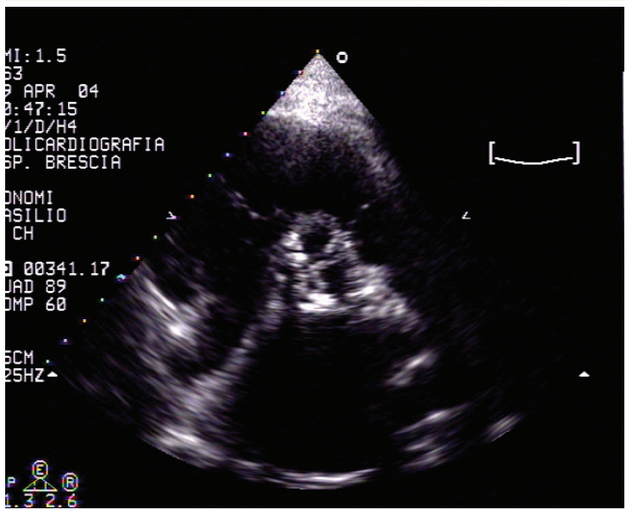

Figure 4. 2D parasternal short axis view. Calcific aortic wall without stenosis. The aortic cusps are thickened for sclerosis and calcium deposition, although systolic opening is preserved.

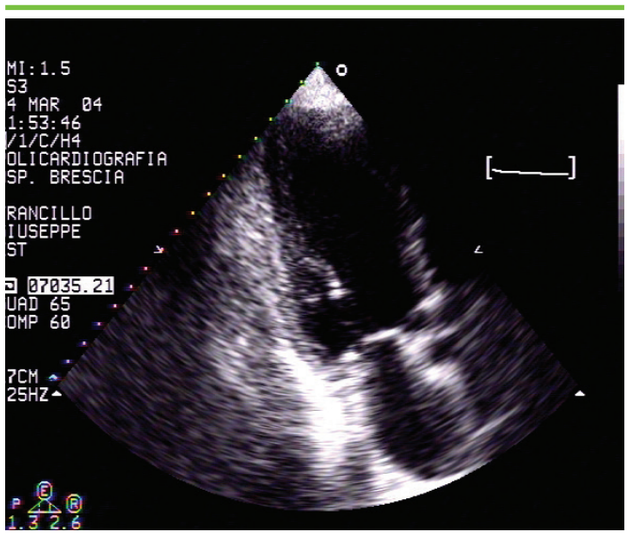

Figure 5. 2D apical three-chamber view showing calcific aortic valve, mitral annulus and papillary muscle.

Significant CAC is associated with calcification in aortic and mitral valve (Figures 4 and 5)[70,71]. This may suggest the presence of a common atherosclerotic pathway, although there are structural and histological differences. Aortic valve and mitral annulus calcifications have been recently assessed by echocardiography as a tool to reclassify low- and intermediate risk patients to a higher risk class[28,72]. A semi-quantitative echocardiographic calcium score including aortic valve and root, the mitral valve and annulus, and the sub-mitral apparatus, showed a moderate correlation with coronary calcium[73]. Although echocardiography is not an ideal method for detection of valvar calcification because of its low specificity in distinguishing between calcification and dense collagen, this non-invasive technique might be used in routine clinical practice as a low cost and radiation free calcium score based reclassification of cardiac risk.

A further, but usually underestimated, advantage of imaging subclinical atherosclerosis compared to conventional risk-assessment tools, is the possibility to visualize the vascular effects of asymptomatic atherosclerosis. Despite the development of several global CV risk algorithm based on clinical risk factors, there is a large gap between the prevention guidelines and their adherence and control of CV risk factors[10]. There are some possible explanations: risk estimation tools are not routinely used in clinical practice and the judgements of physicians tend to be subjective[74]; whether the risk is correctly communicated to the patients and whether they clearly understand the information is unknown[75]; as a consequence, adherence to treatment is inadequate[76].

Visualization of subclinical atherosclerosis may stimulate physicians to provide appropriate pharmacological prescriptions and enhance patient's motivation to adhere to medications treatment and adopt lifestyle changes. VIPVIZA, a large study using pictorial information about patients carotid ultrasound results has shown a significant improvement in the risk scoring and total and LDL-cholesterol at 1-year follow-up[77]. Although compared to control group the overall difference was small, it is well known that even small reduction in the risk factors have long-term benefit at population level[78]. However, smaller studies using CAC score or carotid plaques ultrasound showed conflicting results[79,80].

Imaging of subclinical atherosclerosis is superior to risk equations as it directly identifies the disease and can effectively predict the risk of future CV events in low- and intermediate-risk individuals. In addition, imaging can improve the adherence to guidelines based treatment in patients and their physicians.

Declarations of Interest

The authors declare no conflicts of interest.

Acknowledgements

The authors state that they abide by the "Requirements for Ethical Publishing in Biomedical Journals" [81].

References

1. Roth GA, Abate D, Abate KH, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 2018;392:1736-88.
2. Tunstall-Pedoe H, Kuulasmaa K, Mähönen M, Tolonen H, Ruokokoski E. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA Project populations. The Lancet 1999;353:1547-57.
3. Fuster V, Mearns BM. The CVD paradox: mortality vs prevalence. Nature Reviews Cardiology 2009;6:669.
4. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology 2014;63:2889-934.
5. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice European Heart Journal 2016;37:2315-81.
6. Wilson PW, D'Agostino RB, Levy D, Belanger A, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837-47.
7. Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. European Heart Journal 2003;24:987-1003.
8. Donfrancesco C, Palmieri L, Cooney M-T, et al. Italian cardiovascular mortality charts of the CUORE project: are they comparable with the SCORE charts? European Journal of Cardiovascular Prevention & Rehabilitation 2010;17:403-9.
9. Collins DRJ, Tompson AC, Onakpoya IJ, Roberts N, Ward AM, Heneghan CJ. Global cardiovascular risk assessment in the primary prevention of cardiovascular disease in adults: systematic review of systematic reviews. BMJ Open 2017;7:e013650 DOI: 10.1136/bmjopen-2016-.
10. Kotseva K, De Bacquer D, De Backer G, et al. Lifestyle and risk factor management in people at high risk of cardiovascular disease. A report from the European Society of Cardiology European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) IV cross-sectional survey in 14 European regions. European Journal of Preventive Cardiology 2016;23:2007-18.
11. Cooney M-T, Dudina A, Whincup P, et al. Re-evaluating the Rose approach: comparative benefits of the population and high-risk preventive strategies. European Journal of Cardiovascular Prevention & Rehabilitation 2009;16:541-9.
12. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of Conventional Risk Factors in Patients With Coronary Heart Disease. JAMA 2003;290:898-904.
13. Rodgers A, Ezzati M, Vander Hoorn S, et al. Distribution of Major Health Risks: Findings from the Global Burden of Disease Study. PLOS Medicine 2004;1:e27.
14. Law MR, Wald NJ, Morris JK. The Performance of Blood Pressure and other Cardiovascular Risk Factors as Screening Tests for Ischaemic Heart Disease and Stroke. Journal of Medical Screening 2004;11:3-7.
15. Sniderman AD, Furberg CD. Age as a modifiable risk factor for cardiovascular disease. The Lancet 2008;371:1547-9.
16. Fuster V, Lois F, Franco M. Early identification of atherosclerotic disease by noninvasive imaging. Nature Reviews Cardiology 2010;7:327-33.
17. Ross R. Atherosclerosis — An Inflammatory Disease. New England Journal of Medicine 1999;340:115-26.
18. Strong JP, Malcom GT, McMahan C, et al. Prevalence and extent of atherosclerosis in adolescents and young adults: Implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. JAMA 1999;281:727-35.
19. Libby P, Theroux P. Pathophysiology of Coronary Artery Disease. Circulation 2005;111:3481-8.
20. Vancheri S, Milino V, Henein M, Tamburino C. Angina in Patients with Non-obstructive Coronary Angiograms: Six-years Follow-up. International Cardiovascular Forum Journal 2017;11:55-9 DOI:10.17987/icfj.v11i0.441.
21. Erbel R, Budoff M. Improvement of cardiovascular risk prediction using coronary imaging: subclinical atherosclerosis: the memory of lifetime risk factor exposure. European Heart Journal 2012;33:1201-13.
22. Ibrahimi P, Jashari F, Nicoll R, Bajraktari G, Wester P, Henein MY. Coronary and carotid atherosclerosis: How useful is the imaging? Atherosclerosis 2013;231:323-33.
23. Shah PK. Screening Asymptomatic Subjects for Subclinical Atherosclerosis: Can We, Does It Matter, and Should We? Journal of the American College of Cardiology 2010;56:98-105.
24. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB. Carotid-Wall Intima–Media Thickness and Cardiovascular Events. New England Journal of Medicine 2011;365:213-21.
25. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007;115.
26. Den Ruijter HM, Peters SE, Anderson TJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: A meta-analysis. JAMA 2012;308:796-803.

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DOI: 10.17987/icfj.v19i0.633

27. van den Oord SCH, Sijbrands EJG, ten Kate GL, et al. Carotid intima-media thickness for cardiovascular risk assessment: Systematic review and meta-analysis. Atherosclerosis 2013;228:1-11.
28. Gaibazzi N, Rigo F, Facchetti R, et al. Differential incremental value of ultrasound carotid intima-media thickness, carotid plaque, and cardiac calcium to predict angiographic coronary artery disease across Framingham risk score strata in the APRES multicentre study. European Heart Journal-Cardiovascular Imaging 2016;17:991-1000.
29. Nambi V, Chambless L, Folsom AR, et al. Carotid Intima-Media Thickness and Presence or Absence of Plaque Improves Prediction of Coronary Heart Disease Risk: The ARIC (Atherosclerosis Risk In Communities) Study. Journal of the American College of Cardiology 2010;55:1600-7.
30. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. The Lancet 2002;360:7-22.
31. The ALLHAT Officers Coordinators, for the ALLHAT Collaborative Research Group. Major Outcomes in Moderately Hypercholesterolemic, Hypertensive Patients Randomized to Pravastatin vs Usual CareThe Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002;288:2998-3007.
32. Lorenz MW, Polak JF, Kavousi M, et al. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. The Lancet 2012;379:2053-62.
33. Costanzo P, Perrone-Filardi P, Vassallo E, et al. Does Carotid Intima-Media Thickness Regression Predict Reduction of Cardiovascular Events?: A Meta-Analysis of 41 Randomized Trials. Journal of the American College of Cardiology 2010;56:2006-20.
34. Goldberger ZD, Valle JA, Dandekar VK, Chan PS, Ko DT, Nallamothu BK. Are changes in carotid intima-media thickness related to risk of nonfatal myocardial infarction? A critical review and meta-regression analysis. American Heart Journal 2010;160:701-14.
35. Lorenz MW, Gao L, Ziegelbauer K, et al. Predictive value for cardiovascular events of common carotid intima media thickness and its rate of change in individuals at high cardiovascular risk - Results from the PROG-IMT collaboration. PloS one 2018;13:e0191172.
36. Groot Ed, Hovingh GK, Wiegman A, et al. Measurement of Arterial Wall Thickness as a Surrogate Marker for Atherosclerosis. Circulation 2004;109:III-33-III-8.
37. Delaney JAC, Scherzer R, Polak J, et al. Effect of inter-reader variability on outcomes in studies using carotid intima media thickness quantified by carotid ultrasonography. European Journal of Epidemiology 2010;25:385-92.
38. Polak JF, Funk LC, O'Leary DH. Inter-Reader Differences in Common Carotid Artery Intima-Media Thickness Implications for Cardiovascular Risk Assessment and Vascular Age Determination. Journal of Ultrasound in Medicine 2011;30:915-20.
39. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology 2014;63:2935-59.
40. Jashari F, Ibrahimi P, Johansson E, Gronlund C, Wester P, Henein MY. Carotid IM-GSM is better than IMT for identifying patients with multiple arterial disease. Scandinavian Cardiovascular Journal 2018;52:93-9.
41. Vanoli D, Lindqvist P, Wiklund U, Henein M, Näslund U. Fully automated on-screen carotid intima-media thickness measurement: A screening tool for subclinical atherosclerosis. Journal of Clinical Ultrasound 2013;41:333-9.
42. Inaba Y, Chen JA, Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: A meta-analysis. Atherosclerosis 2012;220:128-33.
43. Pletsch-Borba L, Selwaness M, van der Lugt A, Hofman A, Franco OH, Vernooij MW. Change in Carotid Plaque Components: A 4-Year Follow-Up Study With Serial MR Imaging. JACC: Cardiovascular Imaging 2018;11:184-92.
44. Zureik Ma, Temmar Ma, Adamopoulos Ca, et al. Carotid plaques, but not common carotid intima-media thickness, are independently associated with aortic stiffness. Journal of Hypertension 2002;20:85-93.
45. Inzitari D, Eliasziw M, Gates P, et al. The Causes and Risk of Stroke in Patients with Asymptomatic Internal-Carotid-Artery Stenosis. New England Journal of Medicine 2000;342:1693-701.
46. Korshunov VA, Schwartz SM, Berk BC. Vascular Remodeling. Arteriosclerosis, Thrombosis, and Vascular Biology 2007;27:1722-8.
47. Spence DJ, Eliasziw GM, Dicicco GM, Hackam GD, Galil GR, Lohmann GT. Carotid Plaque Area: A Tool for Targeting and Evaluating Vascular Preventive Therapy. Stroke: Journal of the American Heart Association 2002;33:2916-22.
48. Sillesen H, Muntendam P, Adourian A, et al. Carotid Plaque Burden as a Measure of Subclinical Atherosclerosis: Comparison With Other Tests for Subclinical Arterial Disease in the High Risk Plaque BioImage Study. JACC Cardiovascular Imaging 2012;5:681-9.
49. Ainsworth CD, Blake CC, Tamayo A, Beletsky V, Fenster A, Spence JD. 3D Ultrasound Measurement of Change in Carotid Plaque Volume. Stroke 2005;36:1904-9.
50. Prati P, Tosetto A, Casaroli M, et al. Carotid Plaque Morphology Improves Stroke Risk Prediction: Usefulness of a New Ultrasonographic Score. Cerebrovascular Diseases 2011;31:300-4.
51. Östling G, Persson M, Hedblad B, Gonçalves I. Comparison of grey scale median (GSM) measurement in ultrasound images of human carotid plaques using two different softwares. Clinical Physiology and Functional Imaging 2013;33:431-5.
52. Jashari F, Ibrahimi P, Bajraktari G, Grönlund C, Wester P, Henein MY. Carotid plaque echogenicity predicts cerebrovascular symptoms: a systematic review and meta-analysis. European Journal of Neurology 2016;23:1241-7.
53. Hellings WE, Peeters W, Moll FL, et al. Composition of Carotid Atherosclerotic Plaque Is Associated With Cardiovascular Outcome. Circulation 2010;121:1941-50.
54. Kadoglou NPE, Sailer N, Moumtzouoglou A, Kapelouzou A, Gerasimidis T, Liapis CD. Aggressive lipid-lowering is more effective than moderate lipid-lowering treatment in carotid plaque stabilization. Journal of Vascular Surgery 2010;51:114-21.
55. Henein MY, Bengrid T, Nicoll R, Zhao Y, Johansson B, Schmermund A. Coronary calcification compromises myocardial perfusion irrespective of luminal stenosis. International Journal of Cardiology Heart & Vasculature 2017;14:41-5.
56. Blaha MJ, Mortensen MB, Kianoush S, Tota-Maharaj R, Cainzos-Achirica M. Coronary Artery Calcium Scoring: Is It Time for a Change in Methodology? JACC: Cardiovascular Imaging 2017;10:923-37.
57. Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE. Coronary Calcium Score and Cardiovascular Risk. Journal of the American College of Cardiology 2018;72:434-47.
58. Rozanski A, Gransar H, Shaw LJ, et al. Impact of Coronary Artery Calcium Scanning on Coronary Risk Factors and Downstream Testing: The EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) Prospective Randomized Trial. Journal of the American College of Cardiology 2011;57:1622-32.
59. Erbel R, Möhlenkamp S, Moebus S, et al. Coronary Risk Stratification, Discrimination, and Reclassification Improvement Based on Quantification of Subclinical Coronary Atherosclerosis: The Heinz Nixdorf Recall Study. Journal of the American College of Cardiology 2010;56:1397-406.
60. McClelland RL, Jorgensen NW, Budoff M, et al. 10-Year Coronary Heart Disease Risk Prediction Using Coronary Artery Calcium and Traditional Risk Factors: Derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) With Validation in the HNR (Heinz Nixdorf Recall) Study and the DHS (Dallas Heart Study). Journal of the American College of Cardiology 2015;66:1643-53.
61. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2010;122:2748-64.
62. Hecht H, Blaha MJ, Berman DS, et al. Clinical indications for coronary artery calcium scoring in asymptomatic patients: Expert consensus statement from the Society of Cardiovascular Computed Tomography. Journal of Cardiovascular Computed Tomography 2017;11:157-68.
63. Rosen BD, Fernandes V, McClelland RL, et al. Relationship Between Baseline Coronary Calcium Score and Demonstration of Coronary Artery Stenoses During Follow-Up: MESA (Multi-Ethnic Study of Atherosclerosis). JACC: Cardiovascular Imaging 2009;2:1175-83.
64. Oei H-HS, Vliegenthart R, Hofman A, Oudkerk M, Witteman JCM. Risk factors for coronary calcification in older subjects: The Rotterdam Coronary Calcification Study. European Heart Journal 2004;25:48-55.
65. Budoff MJ, Young R, Lopez VA, et al. Progression of Coronary Calcium and Incident Coronary Heart Disease Events: MESA (Multi-Ethnic Study of Atherosclerosis). Journal of the American College of Cardiology 2013;61:1231-9.
66. Min JK, Lin FY, Gidseg DS, et al. Determinants of Coronary Calcium Conversion Among Patients With a Normal Coronary Calcium Scan: What Is the "Warranty Period" for Remaining Normal? Journal of the American College of Cardiology 2010;55:1110-7.
67. Henein MY, Owen A. Statins moderate coronary stenoses but not coronary calcification: Results from meta-analyses. International Journal of Cardiology 2011;153:31-5.
68. Nicoll R, Henein MY. Arterial calcification: Friend or foe? International Journal of Cardiology 2013;167:322-7.
69. Nicoll R, Henein M. Arterial calcification: A new perspective? International Journal of Cardiology 2017;228:11-22.
70. Koulaouzidis G, Nicoll R, MacArthur T, Jenkins PJ, Henein MY. Coronary artery calcification correlates with the presence and severity of valve calcification. International Journal of Cardiology 2013;168:5263-6.
71. Utsunomiya H, Yamamoto H, Kunita E, et al. Combined presence of aortic valve calcification and mitral annular calcification as a marker of the extent and vulnerable characteristics of coronary artery plaque assessed by

64-multidetector computed tomography. Atherosclerosis 2010;213:166-72.

72. Gaibazzi N, Baldari C, Faggiano P, et al. Cardiac calcium score on 2D echo: correlations with cardiac and coronary calcium at multi-detector computed tomography. Cardiovascular Ultrasound 2014;12:43.
73. Pressman GS, Crudu V, Parameswaran-Chandrika A, Romero-Corral A, Purushottam B, Figueredo VM. Can total cardiac calcium predict the coronary calcium score? International Journal of Cardiology 2011;146:202-6.
74. Vancheri F, Strender LE, Montgomery H, Skaner Y, Backlund LG. General practitioners' coronary risk assessment and lipid-lowering treatment decisions in primary prevention: comparison between two European areas with different cardiovascular risk levels. Primary Health Care Research & Development 2008;9:248-56.
75. van Steenkiste B, van Der Weijden T, Timmermans D, Vaes J, Stoffers J, Grol R. Patients' ideas, fears and expectations of their coronary risk: barriers for primary prevention. Patient Education and Counseling 2004;55:301.
76. Chowdhury R, Khan H, Heydon E, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. European Heart Journal 2013;34:2940-8.
77. Näslund U, Ng N, Lundgren A, et al. Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA): a pragmatic, open-label, randomised controlled trial. The Lancet 2019;393:133-42.
78. Rose G. Sick individuals and sick populations. International Journal of Epidemiology 2001;30:427-32.
79. Johnson EJ, Gulanick EM, Penckofer ES, Kouba EJ. Does Knowledge of Coronary Artery Calcium Affect Cardiovascular Risk Perception, Likelihood of Taking Action, and Health-Promoting Behavior Change? The Journal of Cardiovascular Nursing 2015;30:15-25.
80. Rodondi N, Collet T-H, Nanchen D, et al. Impact of Carotid Plaque Screening on Smoking Cessation and Other Cardiovascular Risk Factors: A Randomized Controlled Trial. Archives of Internal Medicine 2012;172:344-52.
81. Shewan LG, Coats AJS, Henein MY. Authors' Responsibilities and Ethical Publishing. International Cardiovascular Forum Journal 2018;13:3-4, DOI: 10.17987/icfj.v13i0.525