

Intravascular ultrasound measures of coronary atherosclerosis are associated with the Framingham risk score: an analysis from a global IVUS registry

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KEYWORDS

Intravascular ultrasound, coronary heart disease, vulnerable plaque

Abstract

Aims: In addition to an adjunctive imaging platform during coronary angiography, intravascular ultrasound (IVUS) with Virtual Histology™ (VH) is increasingly being used to quantify coronary atherosclerosis. The relationship between VH-IVUS measures of coronary atherosclerosis and traditional cardiovascular risk factors has not been completely described. The objective of this study was to determine if an association exists between VH-IVUS measures of coronary atherosclerosis and the Framingham risk score in a prospective, multinational registry.

Methods and results: Patients enrolled from 2004-2006 at 37 multinational centres in the prospective VH-IVUS Global Registry were analysed. All subjects underwent diagnostic coronary angiography followed by IVUS. A Framingham risk score (FRS) was calculated for each subject, then stratified into three exclusive estimates (<10%, 10-19%, or ≥20%) for future coronary heart disease (CHD) event risk over 10 years. Among 531 patients, plaque volume of the most diseased 10 mm segment increased with increasing FRS (P=0.006, adjusted for multiple comparisons). Patients with higher FRS estimates of CHD risk had a higher proportion of plaque classified as thin cap fibroatheroma compared with patients in the middle and lower risk score categories (21.4% vs 15.2% and 11.3%, respectively, P=0.008, adjusted for multiple comparisons).

Conclusions: Using data from a large, multinational VH-IVUS registry we describe an association between the Framingham risk score and VH-IVUS measures of atherosclerosis within the most diseased 10 mm segment, namely plaque volume and the proportion of thin cap fibroatheroma.

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Introduction

Coronary atherosclerotic complications are the leading causes of worldwide mortality, responsible for >7 million global deaths in 2002¹. In the United States, 12% of the population has diagnosed coronary heart disease (CHD), resulting in ~4 million annual inpatient hospital admissions². While models to predict future cardiovascular events use traditional risk factors to estimate the likelihood of complications of coronary atherosclerosis^{3,4}, less is known about the relationship between future risk of vascular events and intravascular ultrasound (IVUS) measures of coronary atherosclerosis.

IVUS is commonly used to optimise device sizing and is increasingly being used in clinical trials to quantify the severity of coronary atherosclerosis in clinical practice and randomised trials⁵⁻⁸. IVUS provides transmural imaging of the coronary artery wall with reproducible measures of coronary atherosclerosis⁹. Innovation in cardiovascular imaging over the past decade has resulted in the ability to characterise tissue of atherosclerotic lesions. Virtual Histology (VH)TM-assisted IVUS is a validated method¹⁰⁻¹⁴ that utilises the mathematical technique of autoregressive modelling to classify IVUS-radiofrequency data into one of four colour-coded plaque components: 1) fibrous, 2) fibrofatty, 3) dense calcium, and 4) necrotic core^{11,13,14}. This platform can be extended by defining a specific plaque phenotype using a VH-IVUS image based on a simplified, plaque classification scheme developed by Virmani et al¹⁵. Using this nomenclature, non-atherosclerotic intimal deposits are termed “intimal xanthoma” or “adaptive intimal thickening”. Progressive atherosclerotic plaque is classified as pathological intimal thickening, thin cap fibroatheroma (TCFA), fibroatheroma, and fibrocalcific.

The objective of this study was to determine whether VH-IVUS measures of plaque composition are associated with the Framingham risk score (FRS) in the prospective, multinational Global VH-IVUS registry.

Methods

Patient population

Subjects were enrolled during 2004-2006 in the VH-IVUS Global Registry, a prospective registry at 37 multinational centres. Patients underwent coronary angiography followed by IVUS at the discretion of the operator for one or more indications: 1) assessment of an indeterminate lesion, 2) investigation of a culprit lesion for optimal device sizing, 3) post-stent assessment, or 4) clarification of extent of disease. There were 531 patients with analysable VH-IVUS images of native coronary vessels, pullback length >10 mm, and complete clinical and laboratory values to estimate the FRS. Diabetes was determined by reported history or by the presence of active treatment (pharmacologic or diet). Acute coronary syndromes were classified as unstable angina, non-ST-elevation MI, or ST-elevation MI according to American College of Cardiology / American Heart Association guidelines¹⁶. Each enrolling centre's institutional review board approved this study.

IVUS analysis

Qualitative analysis was performed according to the ACC expert consensus on IVUS¹⁷. Plaque volume was derived using the Trapezoidal^{18,19} rule within the defined segment as follows: (external elastic membrane volume - lumen volume).

Vessels were imaged with 20 MHz IVUS catheters (Eagle Eye[®] Gold, Volcano Corp., Rancho Cordova, CA, USA) during continuous motorised pullback at 0.5 mm/s (R-100[™] and TrakBack[®] II, Volcano Corp.) Software (pcVH V2.2, Volcano) was used to calculate geometric and composition data for each VH-IVUS frame. VH-IVUS is a validated^{10-14,20,21} method that uses the mathematical technique of autoregressive modelling to classify the IVUS radiofrequency data into one of four colour-coded plaque components for human coronary atherosclerosis: 1) fibrous (green), 2) fibrofatty (light-green), 3) dense calcium (white), and 4) necrotic core (red).

VH-IVUS borders were drawn by technicians at the Cleveland Clinic Department of Biomedical Engineering (Cleveland, OH, USA) or the Cardiovascular Research Foundation (New York, NY, USA) and verified at Cardialysis-Erasmus Research Lab (Rotterdam, The Netherlands). Analyses of the medial-adventitial and luminal borders were performed in each analysable cross-sectional frame for the entire pullback length.

Patients undergoing single-vessel IVUS during diagnostic catheterisation or before percutaneous coronary intervention were included in this analysis. The VH-IVUS region of interest was the most diseased 10 mm segment, identified by summarising plaque volume in contiguous cross sections over an axial distance of 10 mm. The segment with the greatest plaque volume constituted the most diseased 10 mm.

Phenotypic classification

VH-IVUS frames were assigned a phenotype using an automated pixel detection algorithm (Volcano Corp.) based on a modified histopathological classification scheme developed by Virmani et al¹⁵ (Figure 1) and expert consensus guidelines for analysing and interpreting VH-IVUS images²². Inter-observer variability in phenotypic classification is removed by the algorithm. Confluence for each compositional element was set at a minimal area for this study. A confluent area was defined as a circular area represented by continuous composition of the same tissue type for a minimum diameter of approximately 12 pixels or 0.08 mm² on a 400x400 VH-IVUS image. Intimal deposits are described by Virmani et al as either intimal thickening or intimal xanthoma. We referred to this collective entity as adaptive intimal thickening, which was classified as any plaque <600 µm on any VH-IVUS frame. Atherosclerotic plaque consisted of plaque ≥600 µm thick and was assigned to one of four other phenotypes as follows: 1) pathological intimal thickening: predominantly fibrous tissue with or without >15% fibrofatty tissue and without either confluent necrotic core or confluent dense calcium; 2) fibrocalcific: confluent dense calcium without confluent necrotic core; 3) fibroatheroma: confluent necrotic core not at the lumen or, if at the lumen surface, then not exceeding 14 pixels along the circumference of the lumen on three






Lesion Type	Brief Description	Sample Frame
ID-AIT	<600 μm thick on any IVUS frame. Histopathologically, this type of lesion is termed "intimal xanthoma."	
ID-PIT	>600 μm thick and predominantly fibrous tissue with or without >15% fibrofatty tissue and without either confluent necrotic core or confluent dense calcium	
ID-FC	>600 μm thick and confluent dense calcium without confluent necrotic core.	
ID-FA	>600 μm thick and confluent necrotic core not at the lumen or if at the lumen surface, ≤ 14 pixels along lumen circumference on 3 consecutive frames with or without confluent dense calcium.	
ID-TCFA	>600 μm thick, >50% plaque burden and confluent necrotic core extending >14 pixels along the circumference of the lumen on 3 consecutive frames with or without confluent dense calcium.	

Figure 1. Virtual Histology-IVUS defined classification system for plaque phenotypes. IVUS: intravascular ultrasound; AIT: adaptive intimal thickening, PIT: pathological intimal thickening; FA: fibroatheroma; TCFA: thin cap fibroatheroma; FC: fibrocalcific.

consecutive frames; 4) TCFA: plaque burden >50% and confluent necrotic core extending >14 pixels along the circumference of the lumen on three consecutive frames. These definitions are specific to a VH-IVUS image dimension of 400x400, transcribed by the pcVH software V 2.2.

Framingham risk classification

FRS was calculated for each patient using β -coefficients to compute the linear function as previously described by Wilson and colleagues⁴. Briefly, the FRS is a validated, gender-specific model that uses age, diabetes mellitus, total or low density lipoprotein cholesterol, high density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, and smoking to predict 10-year risk of coronary events including fatal or nonfatal MI or sudden death. Scores were stratified by <10%, 10-19%, or $\geq 20\%$ 10-year risk for a CHD event.

Statistical analysis

Demographic data were analysed using student t-tests for continuous and χ^2 tests for categorical data. Individual CHD estimates were calculated using Framingham linear function equations, with subjects stratified by <10%, 10-19%, or $\geq 20\%$ risk for CHD events over 10-years. Comparisons between Framingham strata were performed using Kruskal-Wallis tests adjusting the P-values for multiple comparisons using a Bonferroni-Holm test. Plaque volume and the TCFA phenotype held significance after the multiple comparison adjustment. To further evaluate plaque volume and TCFA, individual multivariable generalised linear models were developed using a Gamma distribution and Log link function. Estimates and 95% confidence intervals from the models were graphically represented. Statistical significance was defined as $P \leq 0.05$. Analyses were conducted using SAS Version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline demographics of study patients are shown in Table 1. Left anterior descending was the target IVUS vessel in 261 (49.2%) patients, right coronary artery in 161 (30.3%), left circumflex in 92 (17.3%), and left main in 17 (3.2%). IVUS was performed during diagnostic angiography in 50.6% and prior to PCI in 49.4% of patients.

Greyscale IVUS measures of coronary atherosclerosis in the most diseased 10 mm segment increased with increasing FRS (Figure 2A). After adjustment for multiple comparisons, the difference in median [IQR] plaque volume was statistically significant between the <10%, 10-19%, and $\geq 20\%$ FRS groups (79.9 [65.3-105.4] mm^3 , 92.7 [73.7-117.4] mm^3 , and 98.8 [78.2-125.9] mm^3 , respectively, $P < 0.001$).

The percentage distribution of plaque phenotypes for the most diseased 10 mm segment is shown in Table 2. Compared with the <10% FRS category, TCFA was nearly two-fold greater in the $\geq 20\%$ category. The proportion of the remaining plaque phenotypes was similar between FRS categories.

Figure 2 demonstrates the relationship between plaque volume and TCFA by FRS expressed as categorical (A & C) and continuous (B & D) variables. In both cases, both plaque volume and TCFA increased with increasing FRS.

Table 1. Population characteristics.

	Framingham Risk Category			P-Value
	<10% n=182	10-19% n=187	$\geq 20\%$ n=162	
Age (yrs)	58.4 \pm 13.2	61.5 \pm 8.3	68.3 \pm 8.6	<0.001
Female	77 (42.3)	38 (20.3)	12 (7.4)	<0.001
Diabetes				
Insulin-treated	24 (13.2)	43 (23.0)	62 (38.3)	<0.001
	10 (41.7)	10 (23.3)	15 (24.2)	
Framingham risk score	6.4 \pm 2.3	14.5 \pm 2.6	32.1 \pm 10.6	<0.001
Presenting syndrome				0.43
No angina	47 (26.4)	33 (18.8)	30 (20.0)	
Stable angina	77 (43.3)	85 (48.3)	67 (44.7)	
Acute coronary syndrome	54 (30.3)	58 (33.0)	53 (35.3)	
History of myocardial infarction	53 (29.8)	62 (33.3)	43 (26.5)	0.39
Hypertension	103 (56.6)	122 (65.2)	124 (76.5)	<0.001
Dyslipidaemia	120 (66.3)	133 (71.9)	109 (67.7)	0.49
Smoking				
Current	43 (23.6)	42 (22.6)	40 (24.7)	0.90
Previous	37 (26.6)	52 (36.1)	67 (54.5)	<0.001
History of coronary artery bypass grafting	9 (4.9)	8 (4.3)	9 (5.6)	0.86
Congestive heart failure	9 (5.0)	19 (10.2)	10 (6.2)	0.14
Admission blood pressure (mm Hg)				
Systolic	127.5 \pm 22.9	140.2 \pm 24.3	147.7 \pm 24.4	<0.001
Diastolic	71.3 \pm 12.1	77.7 \pm 12.0	77.6 \pm 12.8	<0.001

Data are n (%), or mean + SD

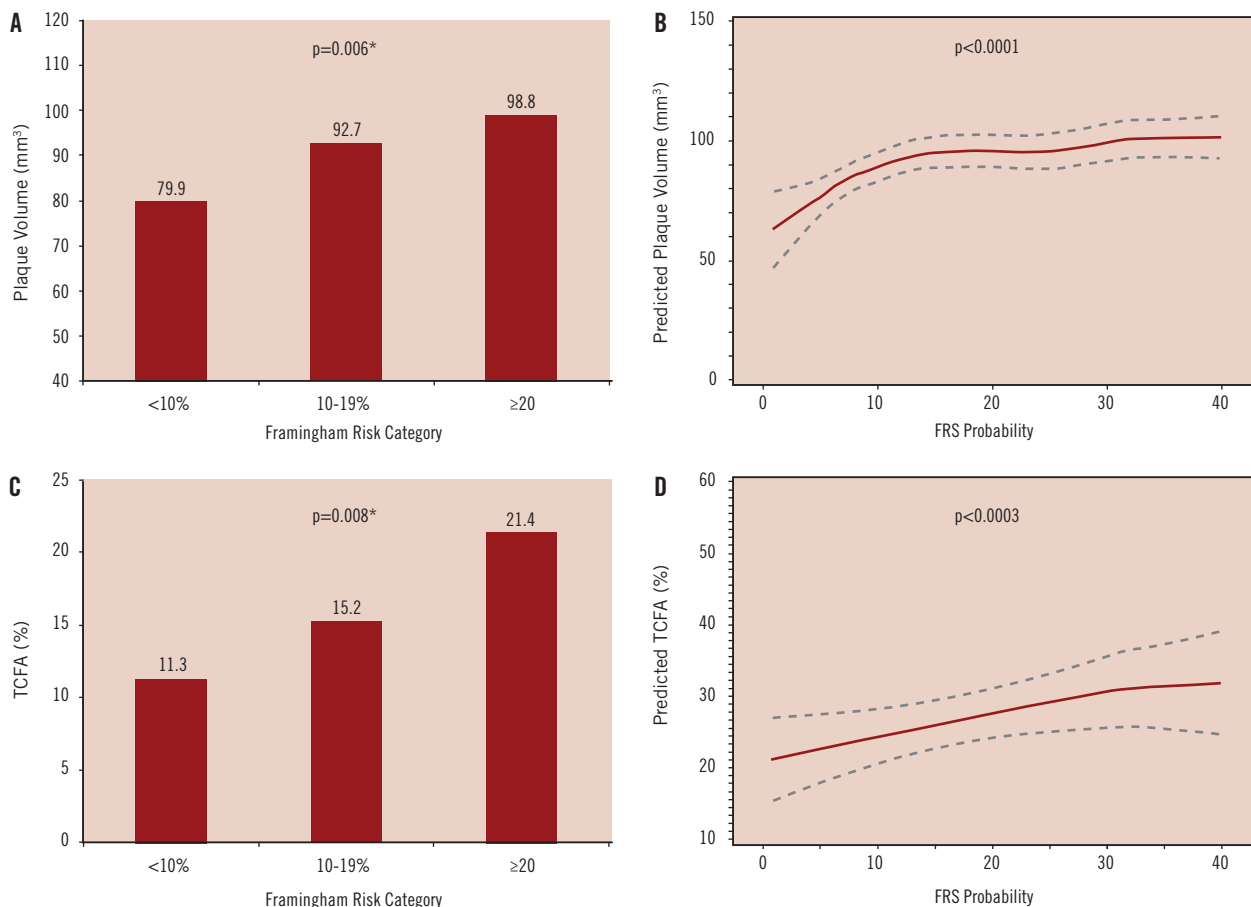


Figure 2. Associations between plaque volume, thin cap fibroatheroma plaque and Framingham risk category. Data in A & C are expressed as categorical variables; B & D display estimated regression line (solid) and 95% confidence interval (dashed). *P-value adjusted for multiple comparisons.

Table 2. Percentage of IVUS-defined plaque phenotypes in the most diseased 10 mm segment.

	Framingham Risk Category			P-Value*
	<10% n=182	10-19% n=187	≥20% n=162	
Adaptive intimal thickening (%)	0.0 (0.0-3.2)	0.0 (0.0-14.2)	0.0 (0.0-0.0)	0.006
Pathologic intimal thickening (%)	10.5 (0.0-32.7)	5.3 (0.0-27.5)	6.4 (0.0-25.0)	0.64
Fibroatheroma (%)	20.4 (5.4-37.5)	24.0 (9.5-45.8)	24.1 (9.3-47.8)	0.63
Thin cap fibroatheroma (%)	11.3 (0.0-38.1)	15.2 (0.0-41.7)	21.4 (4.5-53.3)	0.008
Fibrocalfific (%)	0.0 (0.0-4.7)	0.0 (0.0-5.6)	0.0 (0.0-4.9)	0.66

Data are median (IQR); * P-value adjusted for multiple comparisons

Discussion

Whether a relationship exists between the quantity of coronary plaque and risk of atherosclerotic complications is not known²³. There are limited studies linking IVUS measures to future cardiovascular risk²⁴ and no studies to date describing the association between plaque phenotype and future cardiovascular risk. However, there are many IVUS studies evaluating the efficacy

of various pharmacologic agents on delaying plaque progression or initiating the process of plaque regression^{5-8,25-29}. There are two novel findings from our work: 1) patients at greater risk for a future cardiovascular event as measured by the FRS have greater plaque volume in the most diseased 10 mm segment; 2) the proportion of TCFA is greater in the most diseased 10 mm segment in patients with higher Framingham risk scores.

The primary outcome variable for this analysis was the Framingham risk score, which was not designed to estimate future cardiovascular risk in a VH-IVUS population but rather to estimate future cardiovascular risk in a primary prevention cohort. However, we believe its use is acceptable for the following reasons: 1) there is no clinical model currently available to estimate future risk of secondary events; 2) it is commonly believed that traditional cardiovascular risk factors associated with the index event will also be associated with risk for secondary events³⁰⁻³⁴; 3) the FRS was developed and validated in a population of patients without clinically overt heart disease. In fact, 60% of the current study population did not have a history of complications of coronary atherosclerosis at the time of angiography and IVUS, thus these patients may have been eligible in the original FRS validation cohort.

Use of VH-IVUS to define plaque phenotypes may enhance the ability to estimate future cardiovascular risk. Phenotyping allows

one to describe a VH-IVUS frame on the basis of plaque composition, confluence of the compositional elements, and the relationship of confluent compositional elements to the lumen and vessel wall. Phenotyping may provide needed clarity in estimating future risk of cardiovascular events. Nevertheless, our findings, specifically with respect to TCFA, should be considered preliminary. Although histopathologically-defined TCFA is associated with sudden cardiac death¹⁵ and thus is a logical candidate imaging biomarker to estimate the risk for future death and MI, there are multiple caveats to our use of TCFA. First, VH-IVUS and histopathologically-defined TCFA are not equivalent. Although VH-IVUS is a validated platform to quantify plaque composition, its resolution differs from histopathology. For example, cap thickness of histopathologically-derived TCFA is <65 µm which is beyond the resolution of current IVUS platforms. Second, histopathologic sections of an artery visualise an axial distance of 4 µm, compared with 300 µm on VH-IVUS. Third, consensus definitions for IVUS-defined phenotypes have only recently emerged²², although our phenotype classification scheme was based on a histopathologic system developed using sudden cardiac death subjects ranging from early intimal deposition (adaptive intimal thickening) through progressive atherosclerotic plaque phenotypes (pathological intimal thickening, TCFA, fibroatheroma, and fibrocalcific)¹⁵. We believe the ongoing PROSPECT trial (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) (<http://clinicaltrials.gov#NCT00180466>) will establish whether a link exists between TCFA, plaque burden and symptomatic plaque rupture. PROSPECT has fully enrolled 700 patients with acute coronary syndromes undergoing multivessel IVUS and will specifically explore the morphologic and compositional features of rupture-prone plaque. Patients will be followed for up to five years for recurrent events. Since our analysis consisted of only one vessel per patient, inherent sampling bias cannot be discounted, nor can we comment on plaque burden or composition in other, non-analysed, vessels. Due to the cross-sectional design of this study, we cannot establish a relationship between TCFA, plaque rupture, and complications of coronary atherosclerosis. Evaluation in a study with longitudinal follow-up using both volumetric and compositional measures of coronary plaque is necessary to determine whether increased risk of adverse events can be localised to a segment of a coronary artery. In the most diseased 10 mm segment of a single coronary artery, VH-IVUS demonstrated greater quantity of plaque and a greater proportion of plaque classified as TCFA in patients with greater Framingham risk scores. These data suggest that patients with CHD have unique plaque characteristics which may be potentially useful in studying the future location and risk of plaque rupture, evaluating novel plaque-modulating therapies, and expanding the biological understanding of human coronary atherosclerosis.

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References

1. The ten leading causes of death by broad income group 2002. Geneva: World Health Organization, 2007.
2. 2005 National hospital discharge survey. Hyattsville, MD: National Center for Health Statistics, 2007.
3. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937-52.
4. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837-47.
5. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, Davignon J, Erbel R, Fruchart JC, Tardif JC, Schoenhagen P, Crowe T,

- Cain V, Wolski K, Goormastic M, Tuzcu EM. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *Jama*. 2006;295:1556-65.
6. Nissen SE, Tardif JC, Nicholls SJ, Revkin JH, Shear CL, Duggan WT, Ruzyllo W, Bachinsky WB, Lasala GP, Tuzcu EM. Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med*. 2007;356:1304-16.
 7. Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, Berman L, Shi H, Buebendorf E, Topol EJ. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *Jama*. 2004;292:2217-25.
 8. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, Crowe T, Howard G, Cooper CJ, Brodie B, Grines CL, DeMaria AN. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *Jama*. 2004;291:1071-80.
 9. Nishimura RA, Edwards WD, Warnes CA, Reeder GS, Holmes DR, Jr., Tajik AJ, Yock PG. Intravascular ultrasound imaging: *in vitro* validation and pathologic correlation. *J Am Coll Cardiol*. 1990;16:145-54.
 10. Fujii K, Carlier SG, Mintz GS, Wijns W, Colombo A, Bose D, Erbel R, de Ribamar Costa J, Jr., Kimura M, Sano K, Costa RA, Lui J, Stone GW, Moses JW, Leon MB. Association of plaque characterization by intravascular ultrasound virtual histology and arterial remodeling. *Am J Cardiol*. 2005;96:1476-83.
 11. Nair A, Calvetti D, Vince DG. Regularized autoregressive analysis of intravascular ultrasound backscatter: improvement in spatial accuracy of tissue maps. *IEEE Trans Ultrason Ferroelectr Freq Control*. 2004;51:420-31.
 12. Nair A, Kuban BD, Obuchowski N, Vince DG. Assessing spectral algorithms to predict atherosclerotic plaque composition with normalized and raw intravascular ultrasound data. *Ultrasound Med Biol*. 2001;27:1319-31.
 13. Nair A, Margolis MP, Kuban BD, Vince DG. Automated Coronary Plaque Characterisation With Intravascular Ultrasound Backscatter: *Ex Vivo* Validation. *EuroIntervention* 2007;3:113-120.
 14. Nasu K, Tsuchikane E, Katoh O, Vince DG, Virmani R, Surmely J-F, Murata A, Takeda Y, Ito T, Ehara M, Matsubara T, Terashima M, Suzuki T. Accuracy of *In Vivo* Coronary Plaque Morphology Assessment: A Validation Study of *In Vivo* Virtual Histology Compared With *In Vitro* Histopathology. *J Am Coll Cardiol*. 2006;2405-2412.
 15. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*. 2000;20:1262-75.
 16. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Jr., Chavey WE, 2nd, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol*. 2007;50:e1-e157.
 17. Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, Pinto FJ, Rosenfield K, Siegel RJ, Tuzcu EM, Yock PG. American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2001;37:1478-92.
 18. Abramowitz M, Stegun I. Handbook of Mathematical Functions with Formulas, Graphs, and Mathematical Tables, 9th printing. New York: Dover, 1972:885.
 19. Whittaker E, Robinson G. The Trapezoidal and Parabolic Rules. The Calculus of Observations: A Treatise on Numerical Mathematics, 4th ed. New York: Dover, 1967:156-158.
 20. Moore MP, Spencer T, Salter DM, Kearney PP, Shaw TR, Starkey IR, Fitzgerald PJ, Erbel R, Lange A, McDicken NW, Sutherland GR, Fox KA. Characterisation of coronary atherosclerotic morphology by spectral analysis of radiofrequency signal: *in vitro* intravascular ultrasound study with histological and radiological validation. *Heart*. 1998;79:459-67.
 21. Nair A, Kuban BD, Tuzcu EM, Schoenhagen P, Nissen SE, Vince DG. Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. *Circulation*. 2002;106:2200-6.
 22. Garcia-Garcia HM, Mintz GS, Lerman A, Vince DG, Margolis MP, van ES GA, Morel MA, Nair A, Virmani R, Burke AP, Stone GW, Serruys P. Tissue Characterisation Using Intravascular Radiofrequency Data Analysis: Recommendations for Acquisition, Analysis, Interpretation and Reporting. *EuroIntervention* 2009;5:177-189.
 23. Brown BG, Zhao XQ. Is intravascular ultrasound the gold standard surrogate for clinically relevant atherosclerosis progression? *J Am Coll Cardiol*. 2007;49:933-8.
 24. von Birgelen C, Hartmann M, Mintz GS, van Houwelingen KG, Deppermann N, Schmermund A, Bose D, Eggebrecht H, Neumann T, Gossel M, Wieneke H, Erbel R. Relationship between cardiovascular risk as predicted by established risk scores versus plaque progression as measured by serial intravascular ultrasound in left main coronary arteries. *Circulation*. 2004;110:1579-85.
 25. Matsuzaki M, Hiramori K, Imaizumi T, Kitabatake A, Hishida H, Nomura M, Fujii T, Sakuma I, Fukami K, Honda T, Ogawa H, Yamagishi M. Intravascular ultrasound evaluation of coronary plaque regression by low density lipoprotein-apheresis in familial hypercholesterolemia: the Low Density Lipoprotein-Apheresis Coronary Morphology and Reserve Trial (LACMART). *J Am Coll Cardiol*. 2002;40:220-7.
 26. Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata T, Sato H, Daida H. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH Study. *Circulation*. 2004;110:1061-8.
 27. Scharlt M, Bocksch W, Koschyk DH, Voelker W, Karsch KR, Kreuzer J, Hausmann D, Beckmann S, Gross M. Use of intravascular ultrasound to compare effects of different strategies of lipid-lowering therapy on plaque volume and composition in patients with coronary artery disease. *Circulation*. 2001;104:387-92.
 28. Takagi T, Yoshida K, Akasaka T, Hozumi T, Morioka S, Yoshikawa J. Intravascular ultrasound analysis of reduction in progression of coronary narrowing by treatment with pravastatin. *Am J Cardiol*. 1997;79:1673-6.

29. von Birgelen C, Hartmann M, Mintz GS, Baumgart D, Schmermund A, Erbel R. Relation between progression and regression of atherosclerotic left main coronary artery disease and serum cholesterol levels as assessed with serial long-term (> or =12 months) follow-up intravascular ultrasound. *Circulation*. 2003;108:2757-62.
30. Wood D, De Backer G, Faergeman O, Graham I, Mancia G, Pyorala K. Prevention of coronary heart disease in clinical practice: recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention. *Atherosclerosis*. 1998;140:199-270.
31. Smith SC, Jr., Blair SN, Criqui MH, Fletcher GF, Fuster V, Gersh BJ, Gotto AM, Gould KL, Greenland P, Grundy SM, et al. Preventing heart attack and death in patients with coronary disease. *Circulation*. 1995;92:2-4.
32. Grover SA, Paquet S, Levinton C, Coupal L, Zowall H. Estimating the benefits of modifying risk factors of cardiovascular disease: a comparison of primary vs secondary prevention. *Arch Intern Med*. 1998;158:655-62.
33. Genest J, Pedersen TR. Prevention of cardiovascular ischemic events: high-risk and secondary prevention. *Circulation*. 2003;107:2059-65.
34. Wong ND, Cupples LA, Ostfeld AM, Levy D, Kannel WB. Risk factors for long-term coronary prognosis after initial myocardial infarction: the Framingham Study. *Am J Epidemiol*. 1989;130:469-80.