UNIVERSIDADE FEDERAL DE MINAS GERAIS

Faculdade de Medicina

Programa de Pós-Graduação em Ciências da Saúde: Saúde do Adulto

ULTRASSOM INTRA-CORONARIANO NA AVALIAÇÃO LONGITUDINAL DA PROGRESSÃO VOLUMÉTRICA DA ATEROSCLEROSE CORONARIANA E SEU VALOR DIAGNÓSTICO EM RELAÇÃO À RESERVA DE FLUXO FRACIONADA:

Meta-análises

BRUNO RAMOS NASCIMENTO

Belo Horizonte

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Meta-análises

Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde: Saúde do Adulto da Faculdade de Medicina da Universidade Federal de Minas Gerais, como requisito parcial à obtenção do grau de Doutor.

Área de concentração: Ciências Aplicadas à Saúde do Adulto.

Orientador: Prof. Antônio Luiz Pinho Ribeiro.
Co-orientador: Prof. Marco Aurélio A. Costa

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EPÍGRAFE

"Senhor, não mereço isto.
Não creio em vós para vos amar.
Trouxestes-me a São Francisco
E me fazeis vosso escravo.
Não entrarei, senhor, no templo,
Seu frontispício me basta.
Vossas flores e querubins
São matéria de muito amar.
Dai-me, senhor, a só beleza
Destes ornatos.
E não a alma.
Pressente-se a dor de homem,
Paralela à das cinco chagas.
Mas entro e, senhor, me perco
Na rósea nave triunfal.
Por que tanto baixar o céu?
Por que esta nova cilada?
Senhor, os púlpitos mudos
Entretanto me sorriem.
Mais que vossa igreja, esta
Sabe a voz de me embalar.
Perdão, senhor, por não amar-vos."

Carlos Drummond de Andrade, "São Francisco de Assis"

RESUMO:

A tomada de decisões para pacientes com doença coronariana intermediária ainda é um dilema no laboratório de Hemodinâmica, dada a conhecida limitação da angiografia planar em determinar a morfologia da doença e seu significado funcional. A utilização de avaliação fisiológica invasiva através da Reserva de Fluxo Fracionada (FFR) provou ser uma importante ferramenta complementar a necessidade de intervenção em lesões coronarianas intermediárias. O ultrassom intra-coronariano (IVUS), um método capaz de prover imagens tomográficas de todas as camadas vasculares em alta definição, tem sido proposto como um método alternativo nesta tomada de decisões. Entretanto, considerando-se a natureza multifatorial da repercussão hemodinâmica de uma placa, vários estudos já foram realizados buscando avaliar qual área luminal mínima ao IVUS melhor se correlaciona com um FFR significativo (0,75 ou 0,80), mas não há uma análise combinada de acurácia destes estudos publicada.

Grande esforço tem sido feito para se entender os mecanismos envolvidos no padrão de progressão da aterosclerose coronária. Consideráveis evidências sugerem que o processo de formação da placa aterosclerótica se inicia na infância e progride lentamente através da idade adulta, quando as manifestações clínicas da doença ocorre, após um longo período silencioso. O IVUS tem sido amplamente utilizado para a avaliação longitudinal de progressão da placa coronariana, sendo que variáveis derivadas de suas medidas são propostas como desfechos avaliados na investigação da efetividade de medidas clínicas. No entanto, a avaliação quantitativa de progressão temporal da placa coronariana, buscando-se determinar um modelo preditivo desta evolução ainda não foi feito.

Este projeto é composto de duas meta-análises: 1- meta-análise de estudos que compararam a área luminal mínima medida ao IVUS com o FFR, buscando determinar o melhor ponto de corte que se correlacione com lesões funcionalmente significativas, para a realização de análise combinada da acurácia diagnóstica do IVUS versus o FFR. 2- meta-análise de estudos que avaliaram longitudinalmente a progressão percentual do volume de placa coronariana ao IVUS, com ou sem intervenções específicas na janela de tempo avaliada, objetivando testar se, neste período, existe associação linear entre o tempo de seguimento e o percentual de progressão da placa aterosclerótica.

A partir destas meta-análises, concluímos que a acurácia combinada da área luminal mínima ao IVUS para predizer um FFR significativo é limitada e ainda não bem estabelecida, dada a significativa heterogeneidade metodológica observada. Com base nestes dados, seu impacto na decisão clínica (efeito sobre a probabilidade pré-teste) é moderado a baixo, com performance discretamente superior para excluir doença significativa. A mudança do volume de placa coronariana, avaliada pelo IVUS, ainda é um método em padronização, e parece não haver associação entre a variação percentual ou absoluta da placa e o tempo, sugerindo não linearidade do processo, tanto para o agrupamento de todos os braços quanto para os braços controle em separado.

Descritores: Ultrassonografia de Intervenção, Reserva Fracionada de Fluxo Miocárdico, Doença da Artéria Coronariana, Precisão da Medição Dimensional, Metanálise

LISTA DE ABREVIATURAS E SIGLAS

IVUS	Ultrassom intravascular (*intravascular ultrasound*)
FFR	Reserva de fluxo fracionada (*Fractional flow reserve*)
MHz	Megahertz
ALM	Área luminal mínima
%PVC	Percentual de mudança no volume de placa (*Percent plaque volume change*)
ΔPV	Mudança absoluta no volume de placa *(Delta plaque volume)*
TCE	Tronco da coronária esquerda
IC	Intervalo de confiança
LR+	Razão de verossimilhança (*Likelyhood ratio*) positiva
LR-	Razão de verossimilhançaa (*Likelyhood ratio*) negativa
VPP	Valor preditivo positivo
VPN	Valor preditivo negativo
QUADAS	*Quality Assessment of Studies of Diagnostic Accuracy Approach*
sROC	Curva receptor / operador sumária (*Summary receiver operator curve*)
CFR	Reserva de fluxo coronario (*Coronary flow reserve*)
DA	Artéria descendente anterior
CX	Artéria circunflexa
CD	Artéria coronaria direita
AUC	Área sob a curva (*Area under sROC*)
FUp	Tempo de seguimento (*Follow up*)
LDL	Lipoproteína de baixa densidade
%LDLDif	Diferença percentual na lipoproteina de baixa densidade
RCT	Ensaio clinic randomizado controlado
SCA	Síndrome coronariana aguda

NURD	*Non-uniform rotational distortion*
ICP	Intervenção coronariana percutânea
AE	Angina estável
AI	Angina instável
IAM	Infarto agudo do miocárdio

SUMÁRIO[1]

[1] Este trabalho foi revisado de acordo com as novas regras ortográficas aprovadas pelo Acordo Ortográfico assinado entre os países que integram a Comunidade de Países de Língua Portuguesa (CPLP), em vigor no Brasil desde 2009.

[2] Este artigo foi publicado na *Catheterization and Cardiovascular Interventions*: Catheter Cardiovasc Interv. 2013 Jun 4. doi: 10.1002/ccd.25047. [Epub ahead of print].

1 INTRODUÇÃO

O ultrassom intra-coronariano (IVUS) e a reserva de fluxo fracionada (FFR) são importantes ferramentas diagnósticas auxiliares no laboratório de Hemodinâmica. O IVUS foi a primeira modalidade de imagem intra-vascular utilizada em associação à coronariografia (luminograma), suprindo suas limitações e obtendo imagens em alta resolução de toda a parede vascular, além de fornecer informações importantes sobre seus constituintes e permitir análises adicionais sobre a gravidade da lesão coronariana (situação em que seu valor prognóstico já foi demonstrado[3,4]) e sua progressão. O FFR é um método funcional invasivo, com capacidade de avaliar a repercussão hemodinâmica de uma estenose coronariana representando o percentual do fluxo miocárdico normal que poderá ser atingido a despeito desta estenose. O valor do método na tomada de decisão sobre quais lesões merecem intervenção já foi demonstrado de forma robusta na literatura[5,6].

Metodologicamente, o IVUS é realizado com um cateter transdutor (de estado sólido ou rotacional) provido de um sistema de troca rápida (*short-rail*) avançado no vaso através de um fio-guia 0,014. O catéter, através de frequências entre 20 e 40 MHz, usa ondas de som refletidas para avisualização da parede vascular em um formato tomográfico bidimensional, semelhante a um corte transversal histológico, com alta resolução (até 150 μm) e baixa penetração (4 a 8 mm). O recuo mecânico do catéter a uma velocidade constante (em geral 0,5 mm/s) permite a reconstrução de imagens tridimensionais[7]. Já o FFR pode ser medido durante a angiografia coronariana, com um fio-guia pressórico com capacidade de medir pressões simultaneamente com a pressão da aorta através do catéter-guia. Este gradiente é igual a 1,0 em um vaso normal. Deve-se buscar fluxo coronariano máximo durante a medida com o uso de adenosina intra-venosa. Um valor de FFR de 0,80

[3] Abizaid A, Mintz GS, Pichard AD, Kent KM, Satler LF, Walsh CL, et al. Clinical, intravascular ultrasound, and quantitative angiographic determinants of the coronary flow reserve before and after percutaneous transluminal coronary angioplasty. American Journal of Cardiology. 1998;82(4):423-8.
[4] Abizaid AS, Mintz GS, Mehran R, Abizaid A, Lansky AJ, Pichard AD, et al. Long-term follow-up after percutaneous transluminal coronary angioplasty was not performed based on intravascular ultrasound findings: importance of lumen dimensions. Circulation. 1999;100(3):256-61.
[5] Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. Journal of the American College of Cardiology. 2010;56(3):177-84.
[6] Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. Journal of the American College of Cardiology. 2007;49(21):2105-11.
[7] Honda Y, Fitzgerald PJ, Yock PG. Intravascular Imaging Techniques. In: Baim DS, editor. Grossman's Cardiac Catheterization, Angiography, & Intervention: Lippincott Williams & Wilkins; 2006. p. 371 - 94.

ou menor (0,75 em alguns artigos) identifica estenoses coronarianas potencialmente cusadoras de isquemia com razoável acurácia e boa correlação com testes provocativos[8,9,10].

Conhecido o valor prognóstico do FFR, a área luminal mínima (ALM) derivada do IVUS tem sido proposta como uma alternativa morfológica mais simples para determinar a gravidade de lesões intermediárias[11,12], mesmo havendo outros fatores determinantes de gravidade da placa conhecidos (ex: extensão da lesão, o diâmetro de referência do vaso, a morfologia e excentricidade da lesão, dentre outros). Alguns estudos com amostras modestas já foram realizados com o objetivo de determinar o melhor ponto de corte da ALM que se correlacione com FFR significativo, com significativa variabilidade entre os resultados encontrados. Não existe na literatura nenhuma meta-análise que tenha buscado agrupar o valor diagnóstico da ALM derivada do IVUS em relação ao FFR buscando estudar a acurácia global do método na determinação da doença coronariana funcionalmente significativa.

Outra aplicabilidade do IVUS na prática clínica e no campo da pesquisa é a avaliação longitudinal da progressão da aterosclerose coronariana. Consideráveis evidências sugerem que o processo de formação da placa aterosclerótica se inicia na infância e progride lentamente através da idade adulta, quando as manifestações clínicas da doença ocorrem, após um longo período silencioso[13,14]. Diversos testes complementares, têm sido utilizados para definir os marcadores de progressão da placa e os efeitos de terapias clínicas sobre eles[15,16], e o IVUS se destaca neste campo de pesquisa. Através de estudos que utilizaram algumas variáveis derivadas do IVUS (área de placa em cortes transversais, volume de placa, volume percentual de placa), demonstrou-se a eficácia de alguma terapias, como as estatinas e os beta-bloqueadores em alterar o processo de progressão da placa, enquanto outras, como anti-oxidantes e lipoproteína de alta densidade

[8] De Bruyne B, Pijls NH, Bartunek J, Kulecki K, Bech JW, De Winter H, et al. Fractional flow reserve in patients with prior myocardial infarction. Circulation. 2001;104(2):157-62.
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[12] Takagi A, Tsurumi Y, Ishii Y, Suzuki K, Kawana M, Kasanuki H. Clinical potential of intravascular ultrasound for physiological assessment of coronary stenosis: relationship between quantitative ultrasound tomography and pressure-derived fractional flow reserve. Circulation. 1999;100(3):250-5.
[13] Ross R. The pathogenesis of atherosclerosis--an update. New England Journal of Medicine. 1986;314(8):488-500.
[14] Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature. 1993;362(6423):801-9.
[15] Arsenault BJ, Kritikou EA, Tardif JC. Regression of Atherosclerosis. Curr Cardiol Rep. 2012;14:443 - 9.
[16] Mintz GS, Garcia-Garcia HM, Nicholls SJ, Weissman NJ, Bruining N, Crowe T, et al. Clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound regression/progression studies. EuroIntervention. 2011;6(9):1123-30.

reconstituída falharam neste aspecto[17,18,19,20,21]. Assim, passou-se a utilizar dados do IVUS como desfechos na avaliação de eficácia terapêutica sem, no entanto, se conhecer completamente a natureza evolutiva da aterosclerose coronariana.

Dados numéricos derivados de estudos que buscaram a avaliação da progressão da placa coronariana em diferentes momentos do tempo através de medidas seriadas com o IVUS podem fornecer dados importantes na geração de hipóteses sobre o comportamento temporal da aterosclerose em grupos de pacientes submetidos a propedêutica invasiva, na presença de fatores de risco cardiovascular.

[17] Bedi U, Singh M, Singh P, Molnar J, Khosla S, Arora R. Effects of statins on progression of coronary artery disease as measured by intravascular ultrasound. Journal of Clinical Hypertension. 2011;13(7):492-6.
[18] Rodriguez-Granillo GA, Agostoni P, Garcia-Garcia HM, Biondi-Zoccai GG, McFadden E, Amoroso G, et al. Meta-analysis of the studies assessing temporal changes in coronary plaque volume using intravascular ultrasound. American Journal of Cardiology. 2007;99(1):5-10.
[19] Tardif JC, Gregoire J, L'Allier PL, Ibrahim R, Anderson TJ, Reeves F, et al. Effects of the antioxidant succinobucol (AGI-1067) on human atherosclerosis in a randomized clinical trial. Atherosclerosis. 2008;197(1):480-6.
[20] Tardif JC, Gregoire J, L'Allier PL, Ibrahim R, Lesperance J, Heinonen TM, et al. Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: a randomized controlled trial. JAMA. 2007;297(15):1675-82.
[21] Sipahi I, Tuzcu EM, Wolski KE, Nicholls SJ, Schoenhagen P, Hu B, et al. Beta-blockers and progression of coronary atherosclerosis: pooled analysis of 4 intravascular ultrasonography trials. Annals of Internal Medicine. 2007;147(1):10-8.

2- ARTIGO 1: Diagnostic accuracy of intravascular ultrasound derived minimal lumen area compared to fractional flow reserve – meta-analysis

Pooled accuracy of IVUS luminal area versus FFR

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Abstract:

Introduction: Although intravascular ultrasound minimal luminal area (IVUS-MLA) is one of many anatomic determinants of lesion severity, it has been proposed as an alternative to fractional flow reserve (FFR) to assess severity of coronary artery disease.

Objective: Pool the diagnostic performance of IVUS-MLA and determine its overall accuracy to predict the functional significance of coronary disease using FFR (0.75 or 0.80) as the gold standard.

Methods: Studies comparing IVUS and FFR to establish the best MLA cut-off value that correlates with significant coronary stenosis were reviewed from a Medline search using the terms *"fractional flow reserve" and "ultrasound"*. DerSimonian Laird method was applied to obtain pooled accuracy.

Results: Eleven clinical trials, including 2 left main (LM) trials (total N= 1759 patients, 1953 lesions) were included. The weighted overall mean MLA cut-off was 2.61 mm^2 in non-LM trials and 5.35 mm^2 in LM trials. For non-LM lesions, the pooled sensitivity of MLA was 0.79 (CI 0.76 – 0.83) and specificity was 0.65 (CI 0.62 – 0.67). Positive likelihood ratio (LR) was 2.26 (CI 1.98 – 2.57) and LR- was 0.32 (CI 0.24 – 0.44). Area under the sROC curve for all trials was 0.848. Pooled LM trials had better accuracy: sensitivity = 0.90, specificity = 0.90, LR+ = 8.79, LR- = 0.120.

Conclusion: Given its limited pooled accuracy, IVUS MLA's impact on clinical decision in this scenario is low and may lead to misclassification in up to 20% of the lesions. Pooled analysis points towards lower MLA cut-offs than the ones used in current practice.

Key words: CAD – Coronary Artery Disease, FFR – Fractional Flow Reserve, IVUS – Intravascular ultrasound, PCI: Percutaneous Coronary Intervention.

Introduction:

Therapeutic decision making for patients with intermediate coronary artery disease remains a dilemma in the catheterization laboratory. The limitation of planar coronary angiography to determine disease morphology or its functional significance is well known. The use of invasive physiologic assessment by means of fractional flow reserve (FFR) has proven to be an important complementary tool to determine the safety of deferral of intervention in intermediate coronary lesions(1,2). Because of its higher spatial resolution and imaging of the vascular wall, intravascular ultrasound (IVUS) is superior to angiography in determining lesion severity(3,4). Although, it is understood that the determinants of hemodynamic lesion severity include not only lesion minimal luminal area (MLA) but also lesion length, reference vessel diameter, lesion morphology, eccentricity, entrance and exit angles, and area of myocardium subtended by the lesion, IVUS MLA has been proposed as a simple anatomic alternative to FFR to determine the severity of disease in intermediate coronary lesions(5-8). However, given the numerous other factors related to hemodynamic lesion severity, the accuracy of IVUS MLA as an indicator of lesion severity remains questionable.(7,9) Indeed, recent studies suggest that the proposed thresholds of MLA (4.0 mm^2 for non left main and 6.0 mm^2 for left main) best stratify lesions that should be deferred from PCI(5-7). Several investigations of modest sample size have been conducted to establish MLA cutoff values that determine the physiologic significance (FFR <0.75 or <0.80) and have led to significant variation in MLA thresholds. Furthermore, intermediate left main lesions may be more suitable for IVUS assessment given the more consistent area of myocardium subtended and reference diameter. We therefore conducted a meta-analysis of studies comparing IVUS MLA versus FFR for assessment of intermediate lesions. Our aim was to pool the diagnostic performance of the IVUS MLA and determine its overall accuracy for functional assessment of coronary stenosis using FFR as the gold standard.

Methods:

This work follows Cochrane handbook for diagnostic test studies meta-analysis and PRISMA statement for systematic reviews(10,11). Initially, a search in the main

Databases (Medline, Scielo, Cochrane) was performed, searching for papers with similar objectives and methodology. No similar study was found.

A systematic Medline search was performed with the MeSH terms *(("ultrasonography"[Subheading] OR "ultrasonography"[All Fields] OR "ultrasound"[All Fields] OR "ultrasonography"[MeSH Terms] OR "ultrasound"[All Fields] OR "ultrasonics"[MeSH Terms] OR "ultrasonics"[All Fields]) AND fractional[All Fields] AND flow[All Fields] AND reserve[All Fields]) AND (English[lang] OR Spanish[lang]*, looking for trials in English and Spanish, published until March, 2012, that performed IVUS and FFR in human coronary lesions in any topography (including left main -LM) lesions, and compared the MLA measured by IVUS with the significant FFR defined by the trial (0.80 or 0.75) to determine the best MLA cut-off value that correlates with functionally significant stenosis. Besides the systematic search, the reviewers were allowed to gather additional references by citation tracking of published reviews on this subject and the "Related Articles" section in the Pubmed website. Trials were included regardless of the best MLA cut-off found.

The paper selection criteria were: 1- randomized-controlled trials or observational studies, with prospective or retrospective data collection; 2- use of IVUS and FFR in the same sets of patients at a certain time frame, aiming to correlate MLA and the selected FFR cut-off; 3- trials with and without interventions guided by the complimentary tools; 4- demographic, angiographic, IVUS and FFR data systematically reported; 5- diagnostic performance tests provided (sensitivity, specificity) and the positive and negative predictive values (PPV and NPV) could be provided by the paper or calculated based on other given information; 6- best cut-off value for MLA should established based on these tests; 7- trials with or without follow-up data; 8- FFR cut-off of 0.75 or 0.80.

The titles returned by the systematic search were then peer reviewed by two researchers (A: M.D, MSc and B: M.D, MSc, Ph.D.), according to the previously established inclusion criteria. Exclusion by title, abstract and full text analyses was independently performed and discrepancies in each stage were solved by consensus after discussion. The quality of studies was assessed using the Quality Assessment of Studies of Diagnostic Accuracy Approach - QUADAS(12), which contains 14 items specifically developed to assess the quality of primary studies of diagnostic tests. Each of the 14 items is rated as "yes", "no", or "unclear", with "yes" always indicating a good response. QUADAS covers risk of bias, applicability and reporting quality. The 14 items are shown in the Appendix.

The selected articles were read in full to confirm eligibility and their data (demographic, angiographic, IVUS and FFR-derived data) was tabulated and reviewed for the statistical analysis. The second researcher independently double-checked the extraction of primary data from every study. The papers were divided in left main and non-left main (non-LM) trials. The analysis was performed with all the trials together and separately for LM and non-LM trials, and additionally for articles with FFR cut-offs of 0.80 versus 0.75.

Pooled accuracy data:

The meta-analysis of the pooled accuracy data was performed using the Meta-Disc software (Copyright: Hospital Ramon y Cajal and Universidad Complutense de Madrid), version 1.4(13). We aimed to merge sensitivity (S), specificity (E), positive and negative likelihood ratios (LR+ and LR-) and to build a summary receiver operator curve (sROC) of the merged data.

To calculate sensitivity and specificity values for the tests, we cross-tabulated each result against the reference standard (FFR cut-off). We extracted raw data from primary studies to fill in the values of a diagnostic 2 x 2 table: true positives, false positives, true negatives, and false negatives. When studies did not provide confidence intervals for sensitivity or specificity, we estimated them from the reported 2 x 2 table using Wilson score method(14). In order to test variation due to a threshold effect (i.e., differences between in cut-off values to define positive tests) between studies, we examined the correlation between sensitivity and specificity of all included studies using Spearman's coefficient. A negative correlation arises when a threshold effect is present(15). Study results were then pooled using a DerSimonian Laird method, applied to obtain pooled results of sensitivities, specificities, LR+ and LR-. The LR for a positive result is sensitivity divided by 1- specificity and tells how much the odds of the disease increase when a test is positive. A LR+ is useful to assess the impact on diagnosis of a positive test result for an individual. The LR for a negative result is 1- sensitivity divided by specificity and tells how much the odds of the disease decrease when a test is negative. The estimate is independent of the disease prevalence. The pooled LR is a useful tool for diagnostic performance, when it can be used in the Bayes rule: Post-test odds = pre-test odds x LR. In addition, sensitivities and specificities were summarized using a sROC curve(16), where the diagnostic accuracy is shown by plotting 1-specificity against sensitivity; the area under the curve (AUC) and the Q* index were used to summarize the curve. The AUC

ranges from 0.5 (no discrimination) to a theoretical maximum of 1(17). The Q-point (Q*, where sensitivity equals specificity) obtained from the sROC curve was used as a measure of global accuracy(17).

Heterogeneity of accuracy measures was explored with the I^2 estimate (inconsistency measure) from Cochran *Q* according to the formula: I^2 = 100% x (Cochran *Q* – degrees of freedom) / Cochran *Q*, that describes the percentage of variability of the effect that is due to heterogeneity rather than chance (18,19).

Additionally, meta-regression (Littenberg and Moses Linear model(17)) was performed between potential sources of heterogeneity: age, sex, hypertension (HTN), diabetes mellitus (DM), smoking habit and external elastic membrane (EEM) area and the diagnostic odds ratio (DOR, obtained from LR+ divided by LR-), weighted by inverse variances(20), to evaluate the association of these variables with the global diagnostic performance. The threshold effect was included in all models, as recommended when differences in accuracy measures may potentially occur due to different cut-offs or thresholds used(13,20).

Results:

The initial search returned 198 titles. Eleven papers were included after peer review: abstract and full-text exclusions (Figure 1). Among these, there were 2 LM and 9 non-LM trials. The study quality analysis as assessed by QUADAS tool showed that all the studies met more than 10 criteria (Table 1).

The angiographic, IVUS and FFR characteristics of the included trials are tabulated in Table 1. A total of 1759 patients and 1953 lesions were considered for analysis; the mean age was 61.9 years, 71.3% were male, 64% had hypertension, 29% had diabetes mellitus and 41% were smokers. The significant FFR was < 0.80 in 7 trials and 0.75 in 4 trials. Six trials used intravenous adenosine(21-26) to measure FFR at maximum hyperemia, 4 trials used intracoronary adenosine(27-30) and 1 trial used intracoronary papaverine(8). The sensitivity of MLA cutoffs to predict significant FFR ranged from 0.67 to 0.92 and specificity ranged from 0.54 to 0.92.

The overall mean MLA cut-off was 2.61 mm^2 in non-LM trials (range from 2.36 to 4.00 mm^2) and 5.35 mm^2 in LM trials (4.80 to 5.90 mm^2). Analyzing the accuracy data, we observed a wide variability for sensitivity and specificity among the trials. The LRs had a lower variability. In all situations, sensitivity and specificity were independent (r = -0.118

p = 0.729 for all trials, and r = 0.300 p = 0.433 for non-LM trials). For this reason, sensitivity and specificity were considered appropriate for meta-analyses, as they behaved independently when they were pooled from various primary studies to generate separate averages(31). There was substantial heterogeneity for FFR accuracy measures, considering the I^2 statistic values (figures 2 and 3).

When all the trials were pooled, the combined sensitivity of MLA to predict significant FFR was 0.80 (CI 0.77 – 0.83, I^2 = 58.1%), and specificity was 0.66 (CI 0.63 – 0.68, I^2 = 79.9%). The LR+ was 2.47 (CI 2.06 – 2.95, I^2 = 64.7%), and LR- was 0.29 (CI 0.22 – 0.40, I^2 = 60.5%). The area under summary ROC for all the trials was 0.848, Q* = 0.779 (Figure 2). The pooled DOR was 10.19 (CI 6.12 – 16.93, I^2 = 67.7%).

When only the non-LM trials were analyzed separately, the accuracy measures were similar: sensitivity = 0.79 (CI 0.76 – 0.83, I^2 = 61.1%), specificity = 0.65 (CI 0.62 – 0.67, I^2 = 66.7%), LR+ = 2.26 (CI 1.98 – 2.57, I^2 = 39.1%), LR-: 0.32 (CI 0.24 – 0.44, I^2 = 59.2%), area under summary ROC: 0.793, Q* = 0.737 (Figure 3). The 2 LM trials alone, however, had a better diagnostic performance: sensitivity = 0.90 (CI 0.73 – 0.97, I^2 = 0%), specificity = 0.90 (CI 0.80 – 0.96, I^2 = 65.1%), LR+ = 8.79 (2.47 – 31.24, I^2 = 62.4%), LR- = 0.120 (CI 0.047 – 0.305, I^2 = 0%).

The non-LM trials were then divided according to the FFR cut-off: 0.80 and 0.75. The diagnostic performances of the pooled trials with each cut-off were slightly different, with a tend toward better accuracy with 0.75. The comparison of accuracy data is tabulated in table 2.

In the meta-regression models, the only variable that associated with accuracy was mean age: coefficient (β) = -0.372 (CI: 0.49 - 0.97, rDOR: 0.69, p = 0.037). The other variables showed no association with DOR: sex – β = 0.059 (CI: 0.98 – 1.15, rDOR: 1.06, p = 0.128); HTN - β = 0.014 (CI: 0.92 - 1.12, rDOR: 1.01, p = 0.738); DM - β = 0.039 (CI: 0.89 – 1.21, rDOR: 1.04, p = 0.5534); smoking - β = 0.047 (CI: 1.00 - 1.10, rDOR: 1.05, p = 0.0605), EEM area - β = 0.089 (CI: 0.75 - 1.58, rDOR: 1.09, p = 0.5781).

Discussion:

The use of an anatomical metric (IVUS MLA) as a surrogate to physiological assessment of coronary severity has been a topic of intense debate over the past decade. The present report provides the first compilation of available clinical data on IVUS and FFR comparisons. By the pooled results presented, IVUS imaging of non-LM lesions has

limited accuracy to predict functionally significant stenosis when compared to FFR; however, for LM lesions IVUS MLA appears to have better accuracy to predict significant FFR.

MLA by IVUS showed, in general, a sensitivity of 0.80 (95% CI 0.77 - 0.83) and a specificity of 0.66 (95% CI 0.63 - 0.68), with similar accuracy when non-LM trials are analyzed separately. When only the 2 LM trials were analyzed, there is better sensitivity and specificity (± 0.90), but these data should be evaluated carefully given the small number (110) of patients observed. The data suggest that a cross-sectional measurement of MLA by IVUS has a limited accuracy with a little better discriminative capacity for non-significant disease, i.e. to rule out significant stenosis and defer coronary revascularization, rather than to define functionally significant lesions and indicate intervention. These findings have a similar trend when compared to the first trials of IVUS as a prognostic tool (4,6) where, given its relatively high negative predictive value, MLA had a higher potential to exclude than to predict the presence of ischemia. However, based on this pooled sensitivity, one should realize that IVUS may lead to misclassification in up to 20% of the lesions, even when used to rule out functional obstruction.

There was, however, considerable heterogeneity in sensitivity and specificity (Figures 2 and 3) in LM and non-LM trials, denoted by the I^2 index values found (considered high above 50%), meaning that a substantial percentage of the total variability in the accuracy measures is due to true heterogeneity, that is, to between-studies variability(18). Such variability may be partly explained by different MLA cut-offs found. However, we should also consider an implicit threshold effect caused by factors related to the methodology of the studies and the limitations of FFR itself to explain both the heterogeneity of tests and the variation of the best MLA cut-off value. Besides the explicit differences in cut-off definitions, this overall effect may be caused by other implicit differences between studies. Lesion location reflecting amount of myocardium at jeopardy, which varied widely between studies, and reference vessel diameter - with one trial considering only small vessels with a diameter <3.0 mm(30) – may have influenced the results, as well as lesion length, not adequately reported by most of the trials. Sequential lesions, diffuse or multivessel disease and patients with LM lesions are anatomical scenarios that may influence FFR results and its ability to infer the severity of a lesion (32,33). The prevalence of lesions in the proximal segment of the vessels (reported in some articles – table 1) may be a confounder and influence IVUS correlation with FFR, both because of the larger reference areas in proximal segments and myocardial mass beyond

the obstruction that may impact the FFR results. Moreover, the use of different routes of adenosine administration (and also the use of papaverin in one trial) to achieve maximum vasodilation for FFR is also a limitation, since some variability in the results have been reported(34), which is methodologically not desirable for the gold-standard test.

Besides the qualitative analysis, potential explanations for heterogeneity adequately provided by most of the trials (demographics, risk factors and vessel size) were statistically explored by meta-regression. Although age – the only factor associated with accuracy – may be related to vascular changes (e.g. diffuse disease, endothelial dysfunction and impaired response to vasodilation), the values are quite similar and reflect the usual demographics of coronary artery disease. The clinical relevance of this statistical association is unclear and dispenses sub-group analysis.

Due to the variability observed – related to implicit or explicit differences between trials - sensitivity and specificity may not reflect test accuracy adequately(18). This is partially addressed by the pooled likelihood ratios, a statistical measure of great utility to assess the diagnostic impact of a positive or negative test, given a known pre-test probability. The evaluation of the LR + and LR- can allow better inferences about the pooled accuracy of IVUS MLA to predict a significant FFR, reducing the impact of different MLA cutoff points among the trials. The estimate can also minimize the effect of the disease prevalence in the study population. Considering that demographics and risk factors – that may have some variability among studies (table1) – are intrinsically related to prevalence, LR analysis may be a tool to deal with heterogeneity in meta-analyses of diagnostic tests(35). Based on the pooled LR data (figures 2 and 3), one may be able to conclude that a positive or negative test (IVUS MLA) has moderate to low impact on post-test probability for clinical decision-making when the FFR is considered the gold standard.

The sROC curve is also an additional tool for this assessment, allowing inferences about the overall accuracy despite the wide variability of sensitivity and specificity found, once it incorporates the use of different thresholds (MLA cut-offs). The AUC and the Q* are the applicable summaries of discriminatory power for its interpretation. AUC is optimally large in homogeneous studies but declines as heterogeneity increases, given a fixed DOR. In the presence of significant heterogeneity, like in our data, it can be interpreted as the upper bound for accuracy estimates. It's recommended, in this case, to evaluate the Q*: a robust measure (the point of sROC symmetry, where sensitivity equals specificity), invariant to heterogeneity. As AUC declines with heterogeneity, the lower

limit passes through Q*; thus, it can be deduced as the lower bound of the estimate(16,18). The Q* values found in this analysis (between 0.7 and 0.8) denote a moderate pooled accuracy of IVUS MLA.

The above findings highlight the limitation of comparing single cross-sectional measurements with a method (FFR) that takes into account the entire coronary vasculature, even considering statistical methods that overcome some of the meta-analysis methodological limitations.

Regarding the individual methodology of the articles, the initial trials (8,27,28,30) used the FFR cutoff value of 0.75, similarly to the first studies that defined the prognostic value of the method to stratify lesions with indication for revascularization (2,36,37), while more recent investigations adopted a less validated but more clinically relevant cutoff of 0.80 (1,38). Considering this an additional explanation for heterogeneity, a subgroup analysis was carried out. Although there were differences between the results with these two cutoff points, it does not seem to significantly influence the sensitivity and specificity of the method. However, there is a slightly greater impact of FFR < 0.75 in the diagnostic decision (LRs and DORs) from the pooled data (Table 2).

Significantly lower MLA cut-off points were reported in recent studies compared to early investigations, even when compared to studies involving coronary flow reserve (CFR)(4-6). Conservative thresholds tend to increase sensitivity and the number of false positives, reducing the impact of a positive test on decision-making. Although the evaluation of the weighted average of the best-MLA threshold is not a suitable method to define functionally significant lesions in a pooled analysis (specially when the pooled accuracy is limited), this meta-analysis points towards MLAs significantly lower than the ones used for decision-making in current clinical practice.

There is a relative paucity of data to extrapolate the functional and prognostic information derived from FFR to the IVUS MLA metric, particularly for non-LM lesion assessment, with data available from only 2 trials. It appears that IVUS MLA may be slightly more applicable for deferring revascularization, but not useful for recommending revascularization(7,39). Although there is also a grey zone of 0.75-0.80 for FFR, superior outcomes following an FFR guided revascularization strategy based on an FFR cutoff of 0.80 has established that value as the clinically recommended threshold. Large scale prospective clinical trials similar to FAME – Fractional flow reserve versus Angiography for Multivessel Evaluation(38) with standardized measurements including lesion length,

reference vessel diameter may be warranted to further clarify the appropriate thresholds for safely guiding revascularization based on IVUS measurements.

Limitations:

The relative small number of trials comparing IVUS MLA to FFR, with limited samples, may have influenced the outcomes and are the main limitations for accuracy analysis. Although there are robust statistical tools to deal with heterogeneity, the implicit methodological differences and different thresholds found make it harder to transpose the findings to the clinical setting and to make a definitive conclusion about IVUS MLA accuracy. Patient-level meta-analysis of the current trials could add to the current analysis, and more detailed data reporting could help establish cut-offs and accuracy for specific vessels and angiographic scenarios.

Conclusion:

The present data highlights the need of careful interpretation of the IVUS MLA criteria, given its limited pooled accuracy data compared to FFR. Its impact on clinical decision in this scenario is low, and remains not well established. The wide variation of the IVUS-derived MLA that correlates with functionally significant stenosis among trials reflects the great spectrum of anatomical variations of the coronary artery disease, and makes it difficult to determine a single cut-off point to guide decision-making in the catheterization laboratory. This meta-analysis, however, points towards lower MLA cut-offs than the ones used in current clinical practice to define functionally significant stenoses.

Conflicts of interest disclosures: None.

Table 1: Angiographic, IVUS and FFR characteristics of the selected trials.

Paper	QUADAS Tool Score	Patients / Lesions	Age (mean)	Sex (%male)	HTN / DM / Smokers (N)	Topography (LM/LAD/LCX/RCA)	MLA at lesion site (Mean ± SD)	FFR Cut-off	Best MLA Cut-off	Sensitivity	Specificity
Takagi *et al*. 1999(1)	11	42 / 51	60.0	88.1	NP	0 / 25 / 6 / 20	3.89 ± 2.02	0.75	3.00	0.83	0.923
Briguori *et al*. 2001(2)	11	43 / 53	NP	86.0	31/5/14	0 / 33 / 6 / 14 (Proximal: 30.3%, Mid: 52.8%)	3.90 ± 2.50	0.75	4.00	0.92	0.54
Jasti *et al*. 2004(3)	13	55 / 55	62.0	76.4	50/20/39	55 / 0 / 0 / 0 (Ostium: 36.4%, Mid: 5.5%, Distal: 58.1%)	7.65 ± 3.00	0.75	5.90	0.93	0.95
Lee *et al*. 2010(4)	13	94 / 94	58.0	77.7	61/38/34	0 / 66 / 12 / 16 (Proximal: 58.5%, Mid: 41.5%	2.30 ± 1.00	0.75	2.00	0.879	0.789
Kang *et al*. 2011(5)	11	201 / 236	61.0	71.6	144/123/61	0 / 157 / 26 / 53	2.60 ± 1.00	0.80	2.40	0.90	0.60
Ben Dor *et al*. 2011(6)	11	84 / 92	63.9	58.3	NP	0 / 61 / NP / NP	NP	0.80	3.20	0.692	0.683
Koo *et al*. 2011(7)	12	252 / 267	62.1	88.1	150/81/49	0 / 198 / 20 / 49 (LAD proximal: 20.6%, Mid: 57.9%)	3.00 ± 1.10	0.80	2.75	0.69	0.65
Kang *et al*. 2011(8)	11	55 / 55	60.0	74.5	27/16/31	55 / 0 / 0 / 0 (Ostium: 49%, Mid: 18%, Distal: 33%)	4.90 ± 2.40	0.80	4.80	0.89	0.83
Ben Dor *et al*. 2012(9)	12	185 / 205	64.5	66.5	152/47/39	0 / 115 / 31 / 47	3.50 ± 1.3	0.80	3.09	0.69	0.71
Gonzalo *et al*. 2012(10)	12	56 / 61	62	83.9	40/19/25	0 / 30 / 15 / 16	2.61 ± 0.89	0.80	2.36	0.67	0.65

Kang *et al*. 2012(11)	12	692 / 784	62	72.0	409/224/ 339	0 / 528 / 68 / 188 (Proximal: 37%, Mid: 51%)	2.70 ± 1.10	0.80	2.40	0.84	0.63

Abbreviations: LM: left main; QUADAS: Quality Assessment of Studies of Diagnostic Accuracy Approach; HTN: hypertension; DM: *diabetes mellitus*; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; FFR: fractional flow reserve; MLA: minimal luminal area; NP: not provided.

Table 2: Comparison of diagnostic performance of IVUS-derived MLA between non-LM trials with FFR cut-offs of 0.80 and 0.75.

Trials (non-LM):	**Sensitivity**	**Specificity**	**LR+**	**LR-**	**AUC – Summary ROC / Q***
FFR < 0.80 (N = 1470)	0.78 (CI 0.74 – 0.82)	0.64 (CI 0.61 – 0.67)	2.19 (CI 2.01 – 2.39)	0.37 (CI 0.27 – 0.51)	0.772 / 0.712
FFR < 0.75 (N = 179)	0.87 (CI 0.77 – 0.83)	0.73 (CI 0.64 – 0.81)	3.84 (3.47 – 10.01)	0.17 (CI 0.09 – 0.30)	0.907 / 0.839

Abbreviations: LM: left main; LR+: positive likelihood ratio; LR-: negative likelihood ratio; AUC: area under curve; ROC: receiver operator curv**e.** FFR < 0.80: 6 non-LM trials; FFR < 0.75: 3 non-LM trials. Diagnostic odds ratio: < 0.75 = 13.53, (CI: 13.53 – 107.30); < 0.80 = 6.72 (CI: 4.42 – 10.23).

Figures:

Figure 1: Flowchart of article exclusions by peer review.

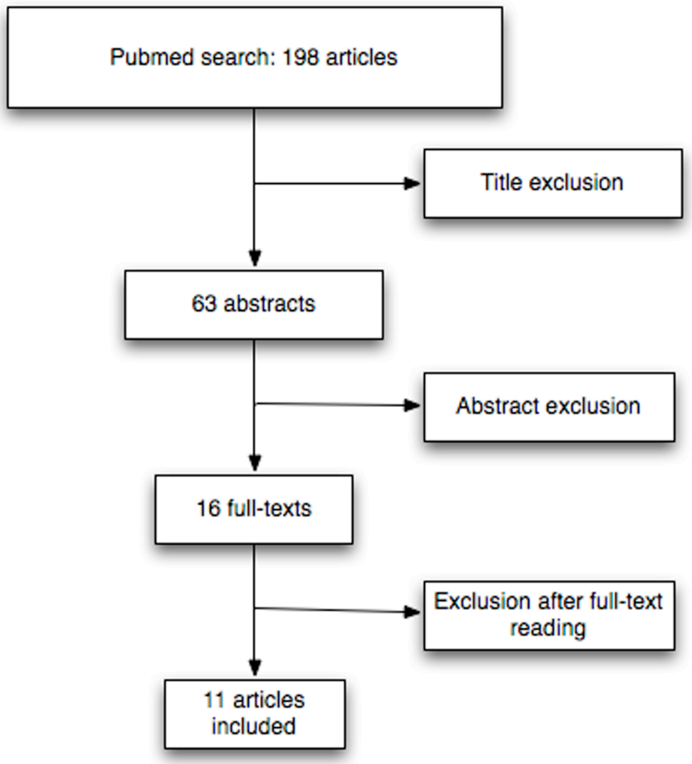


Figure 2: Diagnostic performance (combined sensitivity, specificity and Summary Receiver Operator Curve) of the LM and non-LM trials pooled together. sROC: Summary receiver operator curve: area under curve (AUC), and Q* statistic with their standard errors (SE). The upper and lower lines indicate 95% confidence intervals (CIs).

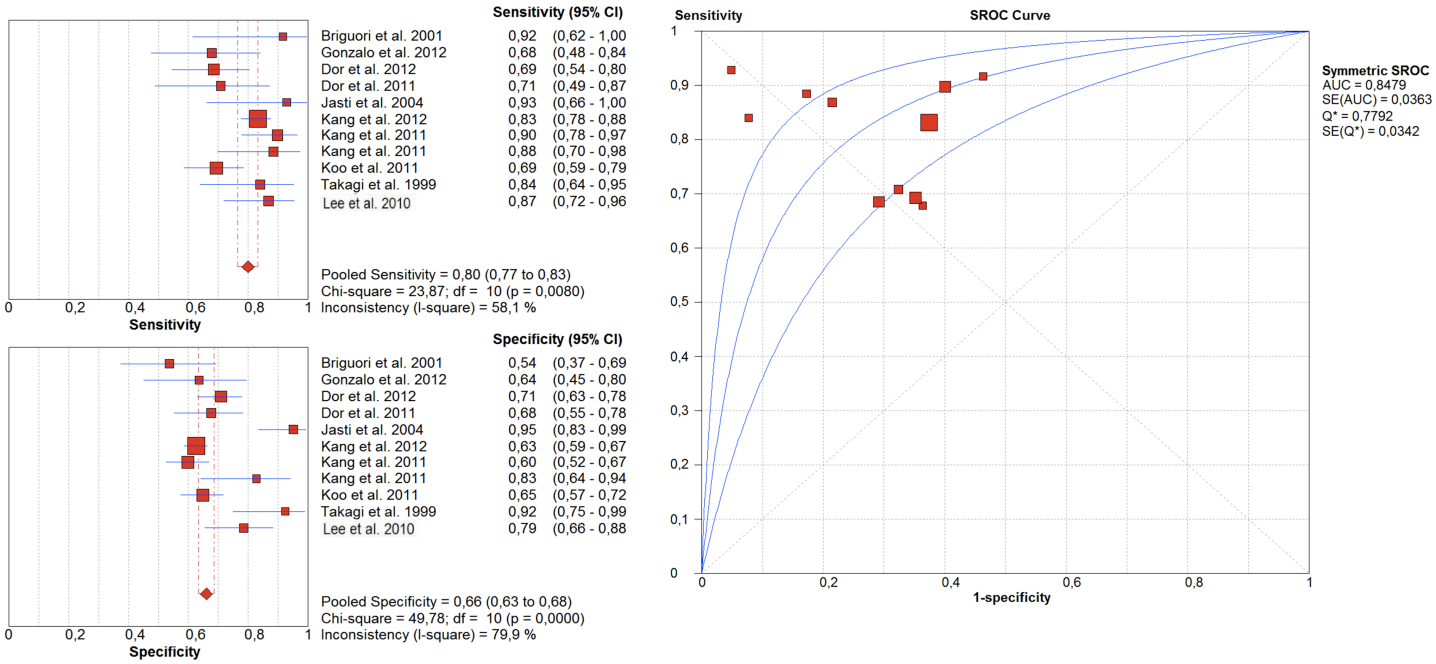
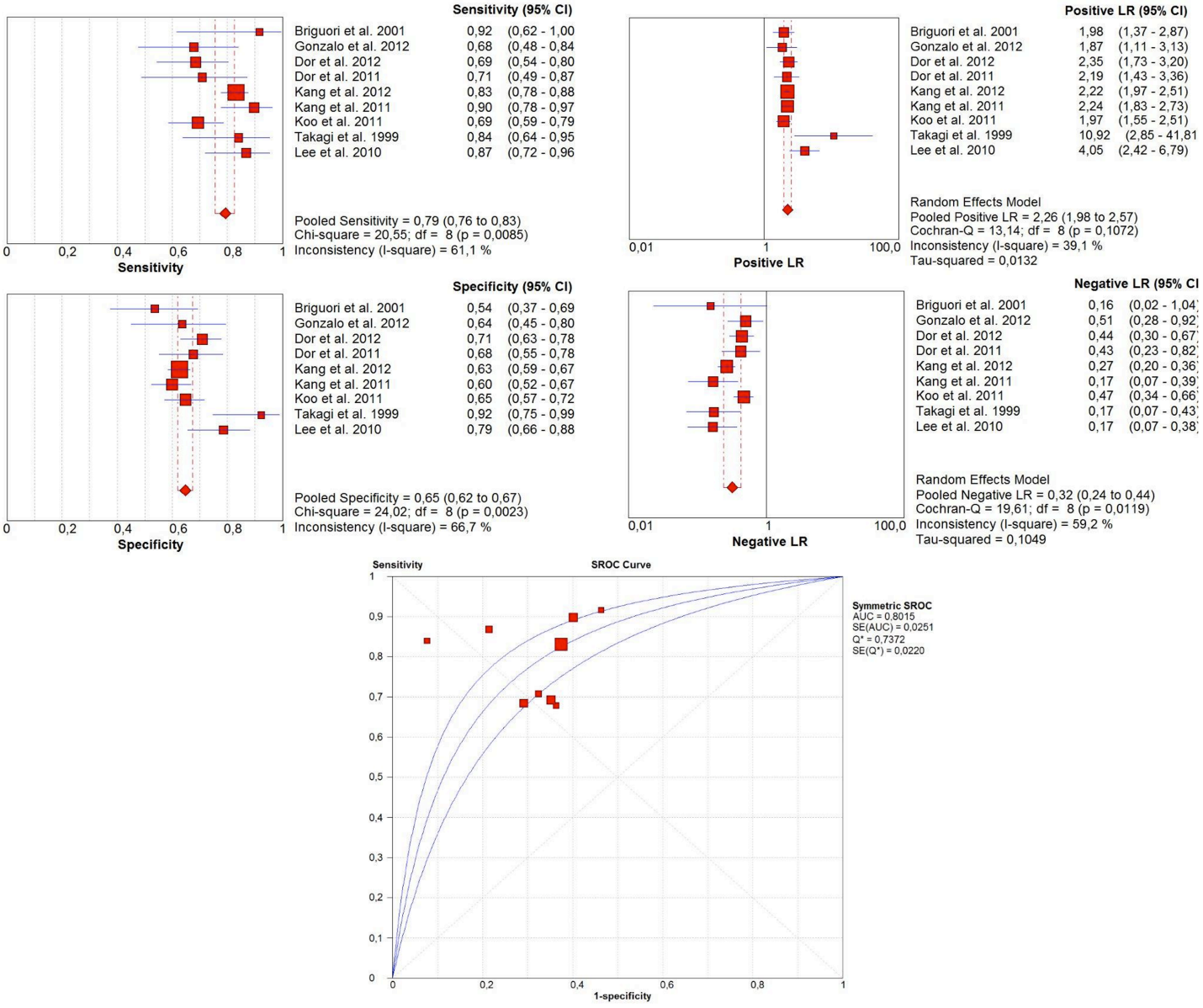


Figure 3: Diagnostic performance (combined sensitivity, specificity, LR+, LR- and Summary Receiver Operator Curve) of the non-LM trials. sROC: Summary receiver operator curve: area under curve (AUC), and Q* statistic with their standard errors (SE). The upper and lower lines indicate 95% confidence intervals (CIs). LR+: positive likelihood ratio; LR-: negative likelihood ratio.



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Appendix 1:

1- QUADAS tool criteria.

Item	YES	NO	UNCLEAR
1- Was the spectrum of patients representative of the patients who will receive the test in practice?	( )	( )	( )
2- Were selection criteria clearly described?	( )	( )	( )
3- Is the reference standard likely to correctly classify the target condition?	( )	( )	( )
4- Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	( )	( )	( )
5- Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	( )	( )	( )
6- Did patients receive the same reference standard regardless of the index test result	( )	( )	( )
7- Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	( )	( )	( )
8- Was the execution of the index test described in sufficient detail to permit replication of the test?	( )	( )	( )
9- Was the execution of the reference standard described in sufficient detail to permit its replication?	( )	( )	( )
10- Were the index test results interpreted without knowledge of the results of the reference standard?	( )	( )	( )
11- Were the reference standard results interpreted without knowledge of the results of the index test?	( )	( )	( )
12- Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	( )	( )	( )
13- Were uninterpretable/ intermediate test results reported?	( )	( )	( )
14- Were withdrawals from the study explained?	( )	( )	( )

3- ARTIGO 2: Progression Of Native Coronary Artery Disease Measured By Intravascular Ultrasound: Systematic Review And Meta-Analysis

Plaque progression measured by IVUS: meta-analysis

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Abstract:

Introduction: Efforts have been made to understand the mechanisms of atherosclerosis progression. Systematic analysis of intravascular ultrasound (IVUS) as a tool to evaluate coronary plaque development pattern in the presence or absence of specific therapies is not available.

Objective: To investigate the pattern of coronary plaque volume progression by serial IVUS from published prospective trials.

Methods: Medline search was performed with 6 MeSH terms to identify trials that evaluated volumetric plaque progression by IVUS. Study arms (treatment or placebo) were pooled for meta-regression, considering the % plaque volume change (%PVC) and absolute change (ΔPV) as responses, and follow up (FU) time, risk factors and therapies as independent variables.

Results: The search returned 1451 titles; 42 papers remained after exclusions: 10,169 patients (86 arms, 24 control); mean FU: 16.3 months. Univariate meta-regression (all arms), showed no linear association between %PVC and FU time (β = -0.384/month, p = 0.563), and significant association between statins and % change in LDL (ΔLDL%) and %PVC (β = -3.848, p = 0.008 and β = 2.235, p = 0.002). For placebo arms, only baseline LDL associated with %PVC. In the multivariate model, FU time also showed no association with %PVC (β = 0.351, p = 0.696). The variables associated with %PVC were statins and ΔLDL%. There was no association between FU time and ΔPV.

Conclusion: There seems to be no linear association between %PVC or ΔPV and FU time (similar findings for control arms), suggesting that, regardless of specific therapies, atherosclerotic evolution is not linear.

Key-words: intravascular ultrasound, coronary plaque, progression, meta-analysis.

Condensed abstract:

This meta-analysis aimed to investigate the coronary plaque progression pattern by pooling data from published trials. Univariate analysis showed no linear association between % plaque volume change (%PVC) and follow-up (FU) time, and significant association between statins and % change in LDL (ΔLDL%), with similar findings in the multivariate models. Considering placebo arms, there was also no association between %PVC and FU time. There was also no association between FU time and ΔPV. This data suggests that atherosclerotic evolution is not linear and raises questions about the validity of prior studies that assumed a linear progressive nature of atherosclerosis.

Introduction:

Atherosclerotic cardiovascular disease is the leading cause of morbidity and mortality worldwide(1-3). The process of atherosclerosis begins in childhood and progresses, in most cases silently, into adulthood when the disease becomes clinically manifested in the forms of claudication, angina, critical limb ischemia, stroke, or acute coronary syndromes(4,5). Much effort has been made to understand the mechanisms and to develop therapies to prevent progression of atherosclerosis in humans.

Initial studies have proposed a continuous progression of atheroma since childhood, while others refuted such predictable temporal evolution of this complex disease(4,6-9). Different methodologies have been used to define surrogate markers of plaque progression and the effects of established medical therapies on atherosclerosis(8,10). Initial studies utilized coronary angiography to evaluate changes in stenosis severity over time, as planar X-ray angiography provides no information on arterial wall thickness or plaque burden. Contemporary studies have utilized intravascular ultrasound (IVUS) due to its ability to provide tomographic imaging of the entire thickness of the coronary artery wall(11,12). IVUS derived metrics such as vessel, plaque and lumen areas, volumes and percent volumes became the new standard to monitor atherosclerosis progression and to evaluate anti-atherosclerosis properties of different drugs(10,13).

Some therapies, such as statins and beta-blockers, have demonstrated significant effect in reducing plaque progression based on pooled data analysis, while antioxidants and reconstituted high-density lipoprotein have failed to do so(8,14-18). There is a wealth of data from several large clinical trials using sophisticated serial imaging endpoints that would allow a better understanding of the degree and linearity of coronary disease progression in human adults overtime. Somewhat surprising, there has been no systematic analysis of pooled data from these studies focused on atherosclerosis itself. Therefore, our aim was to investigate the pattern of coronary plaque volume progression overtime by pooling data from large prospective clinical trials utilizing serial IVUS imaging.

Methods

Selection of articles

Initially, a search in the databases (Medline, Scielo, Cochrane) was performed for papers with similar objectives and methodology. No similar study was found. A Medline

systematic search was performed with 6 different MeSH terms: 1- *Atherosclerotic Plaque Regression AND ("Coronary Vessels"[Mesh] AND "Ultrasonography Invasive"[Mesh])*, 2- *Atherosclerotic Plaque Regression AND "Ultrasonography, Interventional"[Mesh]*, 3- *"Plaque Regression" (Limits Activated: Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, Controlled Clinical Trial, Journal Article, MEDLINE, Systematic Reviews, All Adult: 19+ years)*, 4- *"Plaque Regression" AND "Coronary"*, 5- *plaque AND progression AND IVUS AND (Humans[Mesh] AND Clinical Trial[ptyp] AND adult[MeSH])*, 6- *Plaque AND progression AND ultrasound AND (Humans[Mesh] AND Clinical Trial[ptyp] AND adult[MeSH])*, looking for articles published until September 1st, 2012, that evaluated volumetric plaque progression measured by IVUS in native human coronary arteries at least 2 points in time. Citation tracking of published articles and from the Medline "Related Articles" section was allowed. Studies were included regardless of the medical or interventional treatments performed, with or without comparison between treatment arms. Inclusion criteria: 1- objectives: articles that performed IVUS volumetric analysis, at least two points in time in coronary arteries of human adults, aiming to evaluate plaque progression; 2- minimum sample size: 50 patients; 3- type: randomized-controlled trials or observational studies, prospective or retrospective data collection; 4- any pharmacological or interventional treatment performed; 5- reasonable IVUS volumetric data analysis provided, with complete description of IVUS methodology; 6- demographic and clinical data described in full; 7- defined inclusion criteria, sample selection explained; 8- longitudinal analysis made in any time interval.

Selection was made independently by two coauthors (BRN and DC). Selected titles were then reviewed and exclusion by title, abstract and full text was performed. The selected articles were read in full to confirm eligibility and doubts or disagreements were solved by consensus. Data were extracted by one coauthor directly from the full-length articles to structured tables containing the descriptive variables and test results of interest for statistical analysis. Data entry was double-checked by the other coauthor. Inclusion of additional data supplied by authors and contributors was permitted.

Endpoints

Percent plaque volume change (%PVC) over time was the primary endpoint evaluated. When not provided by the trial, it was calculated from the baseline and final

plaque volumes, with the formula: *[(plaque volume 2 – plaque volume 1) / plaque volume 1] x 100*.

Absolute change of plaque mean volume (mm^3 – ΔPV) from baseline to follow-up (FU) was the secondary endpoint. It was obtained from the original studies or calculated (differences in arithmetic means). When the standard error of the absolute differences was not available, it was estimated by using the reported confidence intervals, standard deviations and p-values(19).

Statistical analysis

Heterogeneity between studies was estimated by the I^2 statistic. Egger's test was performed to analyze the impact of several factors on the size of the effect measure(20). The analytic modeling was based on naïve indirect comparisons(21).

Univariate and multivariate random-effects meta-regression models(22) (mixed linear models with indirect comparisons) were adjusted using SAS/STAT® Software, version 9.2 (*Copyright SAS Institute Inc., Gary, NC, USA*) and SPSS® for Macintosh Software, version 20.0 (*Copyright IBM Corporation, Armonk, NY, USA*), considering the %PVC and ΔPV as the response variables, and FU time (defined as mean age at enrollment + mean follow-up interval), hypertension (HTN), diabetes *mellitus* (DM), current smoking, statin (whether any statin was tested in the arm), LDL percent change (ΔLDL%), baseline low density lipoprotein (LDL_1) and baseline plaque volume as independent variables (co-factors). The study arms were weighted by sample size (pondering the variance-covariance matrix of the errors) for %PVC and by inverse variance for ΔPV. Separate models were adjusted for all study arms (control and treatment) and for control arms (in which no specific drug was tested).

When necessary, adequate mathematical transformations (e.g. Box-Cox) were performed for analysis of variance, with the comparison of means by the Fisher test and adjustment for co-variables. A p value < 0.05 was considered to be statistically significant.

Results

The Medline searches returned 1451 titles. The article selection flowchart is depicted in figure 1. Forty-seven papers were included in the database after peer review. Among these, 5 papers were excluded from the final analysis because of incomplete 3D

plaque volume data, remaining 42 articles, 86 study arms, published from 2003 to 2012. Thirty-two (76.2%) were randomized-controlled trials (RCTs).

Qualitative analysis

The overall sample size was 10169 patients. Pooling the demographic data from the included trials, the weighted average mean age was 59.3 years, 65% of the patients had hypertension, 32% diabetes *mellitus* and 28% were smokers. Among the 86 study arms, there are 24 control arms and 62 active treatment arms. Statins were tested in 24 (57%) trials, followed by increasing high-density lipoprotein therapies (6 trials) and anti-hypertensive drugs (6 trials). The weighted average mean follow up time was 16.3 (range 0.6 to 36) months. Thirteen trials (31%) enrolled acute coronary syndromes (ACS) patients. The detailed characteristics of the included articles are described in Table 1. Most investigations used the CVIS IVUS equipment (*Boston Scientific Corporation, Natick, MA*), with similar acquisition methodology, and performed IVUS in long proximal segments (Table 1).

In 34 study arms (39.5%) there was statistically significant plaque volume regression, while plaque volume did not change in 36 arms (41.8%); in only 7 (8.1%) there was significant plaque progression between serial IVUS assessment. The within-group statistical difference was not reported for 9 arms. The median %PVC was -2.65 (-4.67 - -0.60), and the median ΔPV was -3.40 (-6.30 – 0.40) mm^3. Numerically, plaque volume increased in 19 arms. There was evidence of heterogeneity for ΔPV (I^2 = 97.9% for pooled arms and 98.9% for control arms). Egger's test was negative (B0 = 0.820, CI: -2.861 to 4.501, 1-tailed p = 0.329), suggesting the absence of small arms effects.

Univariate meta-regression (%PVC)

In the univariate analysis model, performed with all study arms pooled, there was no relation between %PVC and FU time (β = -0.38, p = 0.56), suggesting no linear association between plaque change and time interval. There was significant association between statin and ΔLDL% with %PVC (β = -3.85, p = 0.008 and β = 2.24, p = 0.002, respectively). LDL_1 and baseline plaque volume were not associated with %PVC (β = -0.042, p = 0.12 and β = 0.83, p = 0.15, respectively), and nor were HTN, DM and smoking. No other specific therapy was associated with %PVC.

When only the control arms were pooled, the only variable that showed an association with %PVC was LDL_1 ($\beta = 0.11$, $p = 0.008$ - table 2).

Multivariate meta-regression (%PVC)

The model adjusted for all study arms pooled showed no significant linear association between FU time and %PVC ($\beta = 0.35$, $p = 0.696$) in the presence of co-variables (confounders) that could possibly influence this association. The only variables that associated with %PVC were statin test and ΔLDL% ($\beta = -5.10$, $p = 0.022$ and $\beta = 2.05$, $p = 0.035$); however, when one of these two variables was excluded from the model, the other assumes a stronger association with %PVC (table 3). When LDL_1 and baseline plaque volume were added to the model, none had significant association with %PVC ($\beta = 1.17$, $p = 0.31$ and $\beta = 0.83$ and $p = 0.41$, respectively). In the presence of these variables, the association between FU time and %PVC remained not statistically significant ($\beta = 0.75$, $p = 0.41$).

In the model adjusted for the control arms there was also no linear association between FU time and %PVC ($\beta = 1.96$, $p = 0.37$), and none of the independent variables had significant association with %PVC. Among control arms, the association between ΔLDL% and %PVC did not reach statistical significance (Table 3).

Multivariate meta-regression (ΔPV)

In the meta-regression model adjusted for the co-variables, there was no significant linear association between FU time and ΔPV for the pooled arms ($\beta = -0.12$, $p = 0.67$). When ΔLDL% and statin test were included in the model, there was association only between the first and ΔPV ($\beta = 0.12$, $p = 0.039$, table 4). When ΔLDL% was excluded from the model, the association between statin test and FU time became significant ($\beta = -3.51$, $p = 0.008$). The distribution of ΔPV across FU times, stratified by statin test is depicted in Figure 2.

Discussion

The results of this pooled analysis suggest that progression of atherosclerosis in human adults does not have a linear behavior, raising questions about previous models that assume a predictable temporal evolution. There was no association between %PVC or

ΔPV and FU time in univariate or multivariate analyses. The multivariate models included variables which could, in theory, interact with plaque progression, and yet the results consistently supported the nonlinearity of the atherosclerotic process. The complexity of monitoring atherosclerosis overtime or the impact of therapies in its progression is illustrated by the observations of similar degrees of plaque regression or no change in plaque volumes in control groups of studies with completely different follow-up time points (6, 12, 18, 24 and 36 months(23-27)).

Initial hypotheses on the mechanisms involved in atherogenesis were postulated in the mid nineteenth century, and already suggested the vascular response to endothelial injury as the fundamental initiator of atherosclerosis. The classical risk factors associated with this injury, as well as vascular aspects – eg: shear stress – and their relationship with the progression of the disease have also been described(2-6,9,28). While there is no debate regarding its progressive nature, our understanding on the linearity or speed of disease progression remains limited. Furthermore, coronary atherosclerosis can present itself in different forms spanning from benign mild exertion stable angina to fatal acute myocardial infarction in no particular chronological order. These uncertainties pose considerable challenges to develop effective therapies to counteract the clinical consequences of atherosclerosis. The demographics of the present study sample, which included symptomatic patients with stable and unstable coronary artery disease, may allow inferences about an important period in the development of coronary artery disease, in which most risk factors are already present, and behavioral and pharmacological measures are being applied. At this stage, early vascular processes such as adaptive and pathological neointimal thickening, and even more advanced stages of atherosclerosis are already installed(4-6,28), and interventions have already been applied to alter the plaque "natural" progression, being it linear or not.

Methodologically, there is robust evidence about the reproducibility of IVUS to assess progression of atherosclerotic plaque, with acceptable intra and inter observer variability(29). Because the segment rather than individual sites are matched at baseline and follow up, assessment of small percentage changes in atheroma volume is possible with considerable statistical power(30). However, several IVUS surrogate endpoints, derived from crossectional and 3D analysis, have been used in plaque progression trials, with considerable methodological differences(11,30-32). It's also known that several factors such as non-uniform rotational distortion (NURD), motion artifacts, obliquity, calcification, the choice of segment to perform serial volumetric analysis (e.g: most

diseased segments versus moderate obstruction sites), pullback speed and branches affect plaque area measurements and decrease reproducibility(11). Recently, in order to understand the differences, similarities, limitations and pitfalls of the IVUS techniques used for this purpose, there has been an international effort to standardize this evaluation, and a Clinical Expert Consensus was published in 2011(10).

The considerable heterogeneity may indicate that a substantial percentage of the total variability in the effect measure is due to between-studies variability (true heterogeneity). Technically, there are some aspects to be considered for the interpretation of these findings. At first, about a quarter of the trials included patients with ACS, and volumetric plaque changes may be overestimated in these cases, once a thrombus can be inadequately included in plaque area in the initial evaluation(11,33). Moreover, %PVC – our primary endpoint - is highly dependent of lesion length, that may have an average 10% variation between anatomical landmarks in consecutive pullbacks(10,11). Minimal differences in pullback speed is a possible explanation for that(34). Only a small number of papers reported absolute change of percent atheroma volume (PAV), which has been recommended as the primary endpoint for plaque progression due to the smaller variability(10). The publication time frame of the papers (2001 – 2012) must also be cited: although image acquisition was similar for baseline and FU for most of the trials(10), technical improvements probably led to more accurate measurements over time.

The choice of most of the trials to perform IVUS in long proximal segments of non-target vessels is in accordance with current recommendations(10). Some of them, however, evaluated culprit vessels and peri-stent segments, that could possibly be subjected to the influence of intervention on vessel's geometry and to the dynamic changes of event-related segments.

The choice to perform pooled analysis of all arms grouped was due to the fact that, even in control arms, patients are subjected to the standard treatments in clinical practice, not receiving only the drug or intervention to be tested; e.g.: in trials in which statins were not tested, a proportion of patients among all groups were using the drug, and the same occurred with other classes. Thus, there is no way to clearly define the true control arms. We believe, therefore, that the combined analysis of all arms was suitable for the purpose of this meta-analysis and may reflect contemporary therapeutic practices. Further analysis was performed for placebo arms, as defined by the trial's protocol, and similarly there was no linear association between time and % PVC (tables 2 and 3). This analytic choice, however, may lead to statistical limitations. Merging arms of different trials (and

hererogeneous populations) potentially causes the loss of the intra-study randomization, and the multivariate meta-regression model is more accurate and better stablished for patient-level meta-analysis(22). These limitations - potential statistical pitfalls in pooled data interpretation – may be partially outweighted by additional tools, such as control-group sub-analysis. Furthermore, the power of indirect comparisons has been demonstrated in published meta-analyses(35).

Among the variables included in the models, we highlight the association between statin test / ΔLDL% and %PVC or ΔPV: these were predictors of volumetric plaque change in a given time frame, consistent with published meta-analyses(14,15) – that showed not only slower plaque progression mediated by statins, but also plaque regression as measured by IVUS(36,37). When both variables were included in the models, overfitting phenomenon was shown by the stronger association between statin test and %PVC or ΔPV in the models excluding ΔLDL%. Broadly it can analyzed as a tautology, as the effect of statins on plaque may be mediated by LDL change, that is much more precisely measured than statin therapy (that may differ in dosages, bioavailability, etc). Similarly, LDL change is probably mostly mediated by statins themselves. On the other hand, risk factors known to be involved in the pathogenesis of atherosclerosis(1,4,38) (hypertension, diabetes *mellitus*, smoking) did not have association with %PVC. Heterogeneity and the slight differences in the distribution of these factors among the arms may lead to underestimation of their effects by the models.

Besides the technical issues previously discussed, the relatively short FU time and the baseline optimal drug regimen applied to most of the patients may help explain the lack of plaque progression in most of the trials. Consistent use of standardized methodology and more robust clinical correlations are needed to turn intravascular imaging volumetric variables into applicable markers of atherosclerosis evolution, although these studies will always be flawed by the inherent non-linear and unpredictable time-frame for changes to occur in human coronary plaques. Whether changes in plaque composition leading to rupture, which might be more relevant to cardiovascular events than plaque burden itself, also occurs in a non-linear chronology has yet to be explored by the use of more advanced imaging technologies and methods. Finally, based on the demographics and clinical presentation, this meta-analysis involves mostly a sample of patients with established atherosclerosis, and the results do not provide insights about the triggers and the timing that subclinical atherosclerosis becomes clinically manifest, nor about the progression of subclinical disease.

Heterogeneity (potentially related to methodological issues, inclusion criteria, population characteristics, clinical and angiographic features) and statistical limitations make it difficult to extrapolate the results to a robust predictive mathematical model. Further assessment of plaque progression in association with composition, with larger and more homogeneous populations subjected to comparable therapeutic schemes perhaps merging new available IVUS features with new imaging modalities and molecular labeling agents may lead to complimentary insights about the evolutive nature of coronary atherosclerosis.

6. Conclusion:

The pooled volumetric IVUS data derived from the main published trials investigating plaque progression consistently shows that the use of statins and the percent change in LDL have significant correlation with plaque progression over time. However, the data revealed no linear association between %PVC or ΔPV and follow-up time, suggesting that the atherosclerotic evolution is not linear in this moderate to high-risk adult population in a weighted average time frame of 16 months. The present data raises question about the validity of prior studies using invasive imaging-based serial assessments that assumed a linear progressive nature of atherosclerosis, and provides important insights about its behavior in an usual demographic scenario. However, the period between childhood and the fourth decade of life remains as the "lost years" in our undersatdning of atherosclerosis development, with no consistent published data derived from IVUS or other methods(30). The remaining clinical challenges are the identification of the disease process and prevention of its initiation in the early subclinical stages.

Conflicts of interest to disclose: The authors declare no conflicts of interest in the preparation and presentation of this meta-analysis.

Table 1: Overall characteristics of the included articles.

Reference:	Type:	Clinical presentations:	N:	Mean Age:	Male (N):	Follow up time (months):	IVUS site selection criteria:	Initial / final plaque volume (mean, mm^3)	Intervention:	Conclusion (statistical volume change):
1- Nissen *et al*. 2004(12)	RCT	Undergoing Cath (stable)	249	56.6	182	18	<50% stenosis throughout 30mm (non-PCI vessel)	194.5 / 199.6	Pravastatin	Progression (p=0.001)
			253	55.8	180			184.4 / 183.9	Atorvastatin	No change
2- Schartl *et al*. 2001(13)	RCT	Undergoing PCI (stable)	65	60.7	55	12	Distal to PCI lesion or at least 3 cm distal to the ostium in non-PCI vessels	121.3 / 122.5	A:Atorvastatin	Similar % change (A x B)
			66	59.8	56			104.7 / 114.3	B: No	
3- Okazaki *et al*. 2004(14)	RCT	Undergoing PCI for ACS	35	61.3	30	6	≥10mm distal to PCI site	69.6 / 61.4	Atorvastatin	Regression (p<0.001)
			35	62.5	30			59.5 / 63.7	No	Progression (p=0.0276)
4- Jensen *et al*. 2004(15)	Non-RCT	Post-Cath (<50% lesion)	40	57.7	N/A	3	≤50% plaque (non-PCI vessel)	45.8 / 45.6	No	No change
			40	57.7	N/A	12		45.6 / 41.9	Simvastatin	Regression (p<0.001)
5- Tani *et al*. 2005(16)	RCT	Post-PCI (stable)	23	62.0	13	6	≥10mm distal to PCI site	44 / 44	No	No change
			52	63.0	26			47 / 40	Pravastatin	Regression (P<0.001)
6- Nissen *et al*. 2006(17)	Non-RCT	Undergoing Cath (stable)	349	58.5	245	24	≤50% stenosis throughout 40mm (non-PCI vessel)	212.8 / 195.5	Rosuvastatin	Regression (p<0.001)
7- Nissen et al. 2006(18)	RCT	Post-Cath (lesion 20 – 50%)	268	59.6	192	18	≤50% stenosis throughout 30mm (non-PCI vessel)	196.5 / 190.9	No	Regression (p=0.001)
			266	58.8	175			198.1 / 196.8	Pactimibe	No change
8- Takashima *et al*. 2007(19)	Non-RCT	Planned or primary PCI (LAD or LCX)	41	65.1	35	6	LMCA, <30% stenosis	38.4 / 34.4	Pitavastatin	Regresson (p<0.001)
			41	65.1	35			35.7 / 38.8	No	Progression (p<0.01)
9- Takayama *et al*. 2009(20)	Non-RCT	Undergoing elective Catho or planned PCI	126	62.6	96	18	> 5mm proximal or distal to the PCI site	72.1 / 66.8	Rosuvastatin	Regression (p<0.001)
10- Hiro *et al*. 2009(21)	RCT	UA, MI (undergoing PCI)	125	62.5	103	9.3	Culprit vessel segment (ACS)	49.8 / 41.6	Pitavastatin	Regression (p<0.001)
			127	62.4	103	9.6		63.9 / 53.3	Atorvastatin	Regression (P<0.001)
11- Tardif *et al*. 2004(22)	RCT	SA, Post-UA, Post- MI, Post-PCI	154	58.0	124	18	≥40 mm beyond the ostium (30mm segment of interest)	202.4 / 199.9	No	No change
			157	58.6	125			191.9 / 197.1	Avasimibe 50mg	No change
			164	58.0	129			200 / 201.2	Avasimibe 250mg	No change
			164	58.7	137			202.3 / 204.3	Avasimibe 750mg	No change
12- Nissen *et al*. 2003(23)	RCT	Post-UA, Post-MI	12	60.7	6	1.25	≤50% stenosis throughout 30mm (non-PCI vessel)	172.6 / 169.8	No	No change
			23	56.8	16			292.5 / 280.4	ApoA-1 15mg/Kg	Regression (p=0.02)
			22	55.9	13			230.6 / 218	ApoA-1 45mg/Kg	Regression (p=0.007)
13- Tardif *et al*. 2007(24)	RCT	Post-UA, Post-MI	47	57.4	23	1.5	≤50% stenosis throughout 30mm (non-PCI vessel)	158.3 / 154.6	No	No change
			89	57.5	74			151 / 147.1	ApoA-1 40 – 80mg/Kg	Regression (p<0.001)
14- Tardif *et al*. 2008(25)	RCT	SA, Pre-PCI	49	61.0	40	12	≤50% stenosis throughout 40mm proximal segment (30mm of interest, non-PCI vessel)	177.6 / 177	0	No change
			183	61.0	146			164.8 / 161.4	AGI-1067 (Succinilbucol) 280mg	Regression (P=0.001)

15- Nissen *et al*. 2007(26)	RCT	SA,undergoing Cath	446	57.0	314	24	<50% stenosis throughout at least 40mm	198.7 / 192.4	A: No	More regression in B vs A (p=0.02)
			464	56.9	327			196.1 / 186.7	B: Torcetrapib	
16- Rodriguez-Granillo *et al*. 2007(27)	RCT	SA	96	57.5	77	36	≥ 30mm segment distal to an anatomic landmark	192 / 190	Perindopril	No change
			98	56.1	80			190 / 186	No	No change
17- Nissen *et al*. 2008(28)	RCT	Undergoing Cath (stable), >50% lesion	273	59.7	180	18	<50% stenosis throughout at least 40mm	219.8 / 217.7	Glimepiride	No change
			270	60.0	186			207.5 / 200.8	Pioglitazone	Regression (p<0.001)
18- Nissen *et al*. 2008(29)	RCT	Undergoing Cath (stable)	417	57.5	271	18	≤50% stenosis throughout 30mm (non-PCI vessel)	197.5 / 198.5	No	No change
			422	57.9	274			191.7 / 189.7	Rimonabant	Regression (p=0.03)
19- Luscher *et al*. 2009(30)	RCT	Undergoing Cath	114	59.1	92	18	<40% stenosis, LAD or LCX	157 / 157	Nifedipine	No change
			112	57.4	93			140 / 140	No	No change
20- Gerstein *et al*. 2010(31)	RCT	Undergoing Cath or PCI (stable)	229	60.2	151	18	≥20% stenosis (non-PCI vessel)	232.8 / 233.2	Glipizide	No change
			233	61.8	163			226.1 / 221.6	Rosiglitazone	Regression (p=0.049)
21- Yokoyama *et al*. 2005(32)	RCT	SA, undergoing PCI	20	62.1	18	6	<50% stenosis echolucent plaque, >10mm from PCI site	69.9 / 66	Atorvastatin	Regression (p=0.024)
			22	64.4	20			55.8 / 53.8	No	No change
22- Kawasaki *et al*. 2005(33)	RCT	SA	17	66.0	12	6	Mild to moderate stenosis, > 20mm from PCI site	159.2 / 155.4	Atorvastatin	No change
			18	67.0	13			166.2 / 164.6	Pravastatin	No change
			17	66.0	14			159 / 159	No	No change
23- Serruys *et al*. 2008(34)	RCT	SA,Post-UA, Post-MI	151	53.7	123	12	<50% stenosis throughout a 40mm nonintervented segment	313 / 308.1	No	No change
			172	59.4	140			327 / 322	Darapladib	Regression (p=0.033)
24- Nasu *et al*. 2009(35)	Non-RCT	SA	40	63.0	32	12	Target vessel (PCI), 30mm from ostium	440.2 / 403.8	Fluvastatin	Regression (p<0.001)
			40	62.0	31			432.9 / 443.7	No	No change
25- Hong *et al*. 2009(36)	RCT	Non-culprit, non-target de novo lesions (stable)	50	58.0	40	12	<50% stenosis, 10mm segment centered on minimal luminal área	88.3 / 86.3	Simvastatin	Regression (p<0.05)
			50	59.0	37			91.5 / 87.8	Rosuvastatin	Regression (p<0.01)
26- Toi *et al*. 2009(37)	RCT	Post PCI for ACS	80	62.3	64	0.6	<50% stenosis, diameter >3mm, 5-15mm segment, 5mm from PCI site	76.0 / 73.7	Pitavastatin	Regression (0.029)
			80	61.7	57			78.0 / 78.0	Atorvastatin	No change
27- Waseda *et al*. 2006(38)	Non-RCT	Post-PCI, de novo lesion in left-main artery	41	61.1	36	7.3	LMCA plaque, no plaque or PCI in LAD and PCX ostium	NP / NP	No	No change
			23	62.1	19			NP / NP	Losartan	Regression (p<0.01)
28- Hirohata *et al*. 2010(39)	RCT	SA, undergoing PCI	121	68.4	68	14	<50% stenosis throughout a 40mm, nonculprit vessel	208.8 / 215.9	No	Progression (p<0.01)
			126	67.8	76			230.2 / 227.6	Olmesartan	No change
29- Kojima *et al*. 2011(40)	RCT	Undergoing PCI (stable)	61	67.2	53	12	<25% stenosis in PCI vessel, nonculprit lesion >5mm from PCI site	60.2 / 57.4	Azelnidipine	Regression
			54	62.2	41			58.2 / 54	Amlodipine	Regression
30- Tani *et al*. 2010(41)	Non-RCT	Undergoing PCI (stable)	84	63.0	71	6	>25% stenosis in PCI vessel, noncuprit lesion	38.5 / 33.5	Pravastatin	Regression (p<0.001)
31- Hong *et al*. 2011(42)	RCT	Undergoing Cath, 30-70% lesion	65	59.0	49	11	30-70% stenosis, diseased segment (normal-to-normal)	166 / 166	Rosuvastatin	No change
			63	58	46			190 / 190	Atorvastatin	No change
32- Tani *et al*.	Non-	Undergoing Cath (stable)	56	63	48	6	≥10mm from PCI site	52.3 / 33.8	Pravastatin	Regression (p<0.001)

2009(43)	RCT									
33- Jensen *et al*. 2009(44)	RCT	Post-PCI (stent borders)	40	62.7	36	8	≥10mm distal to stent	154 / 152	No (Cypher stent)	No change
			34	62.2	26			153 / 166	No (Taxus stent)	Progression (p=0.01)
34- Yamada *et al*. 2007(45)	RCT	Undergoing Cath (stable)	26	66.7	22	12	<50% lesion, plaque thickness >0.5mm (non-PCI lesion)	72 / 70.6	Atorvastatin	No change
			32	66.4	20			66.1 / 73.7	No	Progression (p<0.01)
35- Tardif *et al*. 2003(46)	RCT	Pre and post-PCI (stable)	61	61.1	44	6	5mm, centered on the most normal-looking cross section, 5 to 12 mm proximal to the PCI site	100.2 / 97.5	No	No difference between groups
			60	58.2	53			111.2 / 109	Probucol	
			59	58.9	46			88 / 85.5	AGI-1067 (modified Probucol) 70mg	
			64	58.8	51			112.2 / 104.9	AGI-1067 140mg	
			61	57.4	46			100 / 96.9	AGI-1067 280mg	
36- Kovarnik *et al*. 2012(47)	RCT	SA, post-PCI	42	63.5	33	12	Non-culprit vessel, 20–50% stenosis, no indication for either PCI or CABG, plaque length >20 mm	413.9 / 401.9	Atorvastatin+Ezetimibe	No change
			47	65.1	31			420.5 / 423.3	Atorvastatin	No change
37- Yano *et al*. 2012(48)	RCT	MI, post-PCI (for culprit lesion)	58	61	49	12	≤50% non-PCI lesion, ≥10 mm from the culprit lesion, 10mm most diseased segment.	88.5 / 82.7	Captopril	No change
			58	59	50			93.2 / 89.9	Captopril+Valsartan	No change
38- Hong *et al*. 2012(49)	Non-RCT	Non-culprit, non-target lesions, post MI	32	64	24	8,3	From >10mm beyond to a point >10 mm proximal to the lesion	88 / 90	A: Pitavastatin	
			62	63	44			106 / 102	B: Pitavastatin	Progression in A vs regression in B (<0.001)
39- Lee *et al*. 2012(50)	RCT	Undergoing PCI for SA or ACS	143	57.6	117	6	20% to 50% lesion, >10 mm (non-PCI lesion)	215 / 205	Atorvastatin	Regression (p<0.001)
			128	55.3	106			229 / 210	Rosuvastatin	Regression (p<0.001)
40- Tani *et al*. 2012(51)	Non-RCT	SA, undergoing PCI	114	61	94	6	From side branch to side branch, ≥20mm away from PCI site	57.3 / 55.1	Pravastatin	Regression (p<0.001)
41- Nicholls *et al*. 2011(52)	RCT	Undergoing Cath (stable)	519	57.9	386	26	20% stenosis on angiography, <50% lesion on target vessel	144.2 / 138.5	Atorvastatin	Regression
			520	57.4	379			144.1 / 135.7	Rosuvastatin	Regression
42- Nozue *et al*. 2012(53)	RCT	SA or UA, undergoing PCI	58	66	52	7,5	<50% lesion on distal and proximal sides of the culprit lesion.	244.6 / 239.2	Pitavastatin	Regression (p=0.03)
			61	67	47			203.1 / 200.3	Pravastatin	No change

RCT: randomized-controlled trial; PCI: percutaneous coronary intervention; ACS: acute coronary syndrome; LAD: left anterior descending artery; LCX: left circumflex artery; LMCA: left main coronary artery; UA: unstable angina; MI: myocardial infarction; SA: stable angina; N/P: not provided; ACAT: cholesterol acetyltransferase; AGI-1067: succinobucol; CABG: coronary artery bypass graft.

Table 2: Univariate regression analyses between selected variables and %PVC:

Variable	β - coefficient	CI Lower	CI Upper	p value
FU Time*	-0.38	-1.71	0.94	0.56
Statin	-3.85	-6.57	-1.13	0.008[a]
LDL_1	-0.042	-0.097	0.012	0.12
Plaque volume 1	0.83	-0.31	1.98	0.15
ΔLDL%	2.24	0.84	3.63	0.002[a]
Control Arms*				
Variable	**β - coefficient**	**CI Lower**	**CI Upper**	**p value**
FU Time*	1.01	-0.10	2.12	0.072
LDL_1	0.11	0.03	0.18	0.008[a]
Plaque volume 1*	-0.59	-2.31	1.13	0.48
ΔLDL%*	-1.14	-4.08	1.80	0.42

*Models adjusted with Box-Cox transformation. CI: confidence interval; LDL_1: baseline low-density lipoprotein; FU: follow up; Plaque volume 1: baseline plaque volume; DF: degrees of freedom; ΔLDL%: LDL percent change. [a] $p < 0.05$.

Table 3: Multivariate regression model (response variable: %PVC):

Variable	β -coefficient	CI Lower	CI Upper	p value
Sex (% male)	-7.89	-31.06	15.29	0.49
Hypertension	-4.83	-20.40	10.75	0.53
Diabetes *mellitus*	-7.04	-16.41	2.33	0.13
Smoking	-3.51	-14.96	7.94	0.53
Statin[a]	-5.10	-9.41	-0.79	0.022*
FU Time	0.35	-1.48	2.18	0.696
ΔLDL%[a]	2.05	0.15	3.94	0.035*
Control arms:				
Sex (% male)	1.91	-66.55	70.37	0.95
Hypertension	-4.23	-60.77	52.32	0.85
Diabetes *mellitus*	4.79	-160.73	170.31	0.78

Smoking	19.04	-7.76	45.83	0.13
FU Time	1.96	-4.37	8.29	0.37
ΔLDL%	-0.85	-36.09	34.40	0.81

CI: confidence interval; FU: follow up; ΔLDL%: LDL percent change. [a] Statin and ΔLDL% (pooled arms): in the absence of ΔLDL%, Statin had a β = -7.08 (CI: -10.37 - -3,79, p < 0.001), and in the absence of Statin, ΔLDL% had a β = 0.33 (CI: 1.82 – 4.84, p < 0.001). *p < 0.05

Table 4: Meta-regression model (response variable: ΔPV):

Variable	β -coefficient	CI Lower	CI Upper	p value
FU time	-0.12	-0.67	0.44	0.67
ΔLDL%	0.12	0.006	0.24	0.039*
Male	-5.56	-25.75	14.64	0.58
Hypertension	-6.80	-18.57	4.57	0.25
Diabetes *mellitus*	1.09	-6.54	8.72	0.78
Smoking	8.45	-1.34	18.24	0.089
[Statin = No]	12.86	-25.84	51.56	0.51
[Statin = Yes][a]	11.77	-27.66	51.19	0.55

CI: confidence interval; FU: follow up; ΔLDL%: LDL percent change. [a]In the absence of ΔLDL%, Statin = 1 had a β = -3.51, CI: -6.07 – -0.95, p = 0.008.

Figure legends:

Figure 1: Article selection flowchart.

Figure 2: Distribution of absolute plaque volume change (ΔPV) across follow up (FU) times, stratified by statin use.

Figure 1:

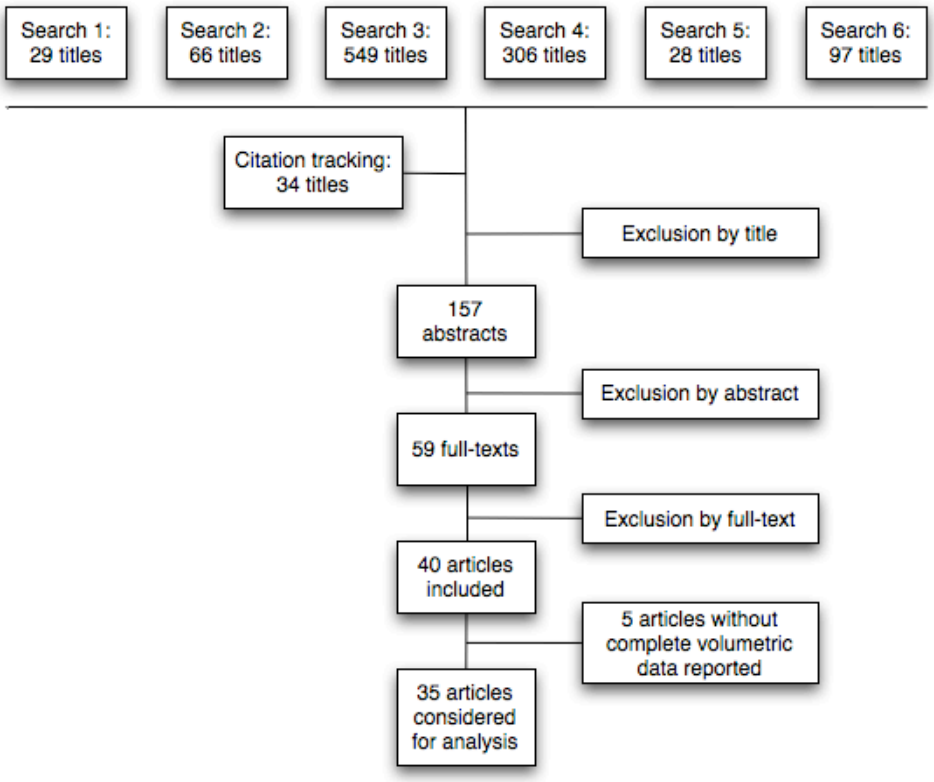
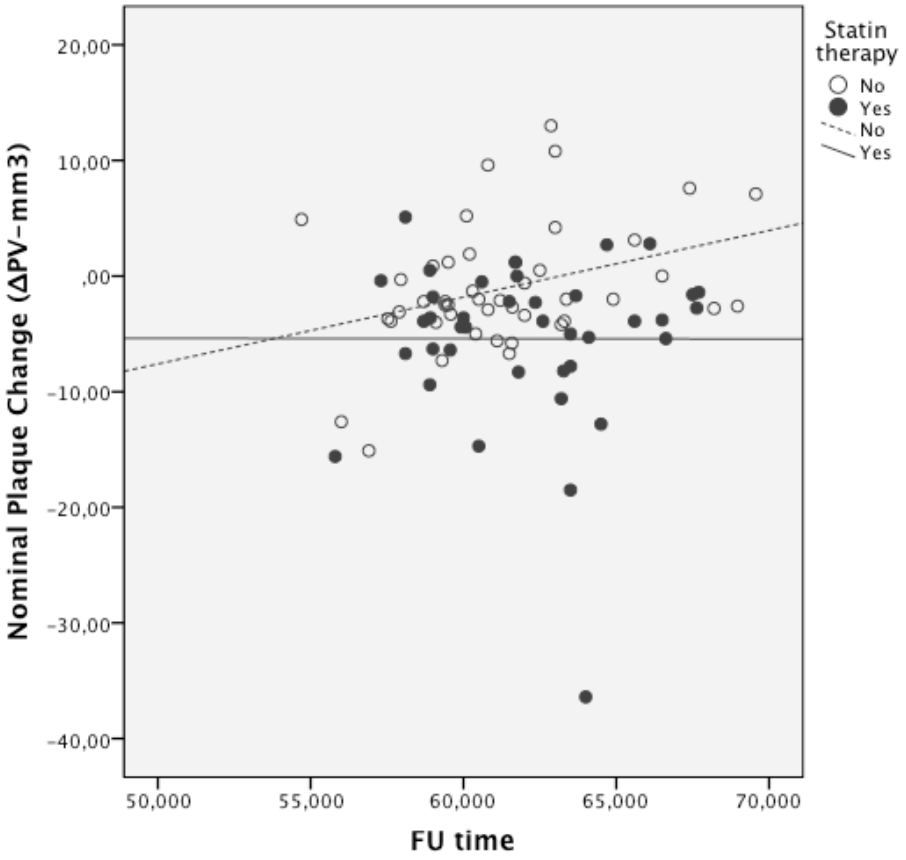


Figure 2:


Statin therapy
No
Yes
No
Yes
Nominal Plaque Change (ΔPV-mm3)
20,00
10,00
,00
-10,00
-20,00
-30,00
-40,00
50,000
55,000
60,000
65,000
70,000
FU time

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4 CONSIDERAÇÕES FINAIS:

Os artigos apresentados trazem dados relevantes sobre a aplicabilidade do IVUS em 2 situações clínicas de grande relevância na Cardiologia Intervencionista. No primeiro delas, enfatiza-se a necessidade de cautela na utilização da ALM em substituição a um método funcional invasivo para a definição de lesões hemodinamicamente significativas. Existe uma limitação do método, com grande heterogeneidade dos dados que buscaram a correlação com o FFR. A combinação da acurácia diagnóstica dos estudos até então publicados apontam para um baixo impacto do IVUS na tomada de decisões, com melhor performance – de forma semelhante aos estudos iniciais – para a exclusão de doença significativa do que para definição de lesões a serem tratadas. Os dados, entretanto, apontam para uma tendência a áreas luminais menores do que as atualmente propostas pela literatura para a predição de estenoses com repercussão funcional.

No segundo artigo, parece não haver associação linear entre o tempo e a mudança percentual ou absoluta do volume de placa (%PVC, ΔPV), mesmo quando incluídos no modelo variáveis que poderiam potencialmente alterar esta associação. A conclusão aplica-se a populações de risco moderado a alto, avaliadas em um intervalo relativamente curto. Os achados são similares para os braços controle em separado. Houve associação entre o uso de estatinas e a mudança percentual do LDL colesterol e o %PVC, em acordo com modelos fisiopatológicos e evidências publicadas[22,23]. Os achados sugerem não haver, com base nos dados publicados, um modelo linear de predição da progressão da placa coronariana, medida com o IVUS. Deve, no entanto, haver cautela na interpretação e extrapolação destes resultados pela grande heterogeneidade observada.

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5. ANEXO: ATA DE APROVAÇÃO EM DEFESA DE TESE

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DECLARAÇÃO

A Comissão Examinadora, abaixo assinada, composta pelos Professores Doutores Antônio Luiz Pinho Ribeiro, Marco Aurélio Alvim Costa (por videoconferência), Carlos Faria Santos Amaral, Enrico Antonio Colosimo, Marco Túlio Villaça Castagna e Raimundo Marques do Nascimento Neto, aprovou a defesa da tese intitulada: **"ULTRASSOM INTRA-CORONARIANO NA AVALIAÇÃO LONGITUDINAL DA PROGRESSÃO VOLUMÉTRICA DA ATEROSCLEROSE CORONARIANA E SEU VALOR DIAGNÓSTICO EM RELAÇÃO À RESERVA DE FLUXO FRACIONADA: META-ANÁLISES"**, apresentada pela doutorando **BRUNO RAMOS NASCIMENTO**, para obtenção do título de Doutor em Saúde do Adulto, pelo Programa de Pós-Graduação em Ciências Aplicadas à Saúde do Adulto – área de concentração em Ciências Clínicas, da Faculdade de Medicina da Universidade Federal de Minas Gerais, realizada em 18 de dezembro de 2012.

Prof. Antônio Luiz Pinho Ribeiro
Orientador

Prof. Marco Aurélio Alvim Costa
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Prof. Enrico Antonio Colosimo

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