JIFA January 31th 2014

HDL and Arterial Wall

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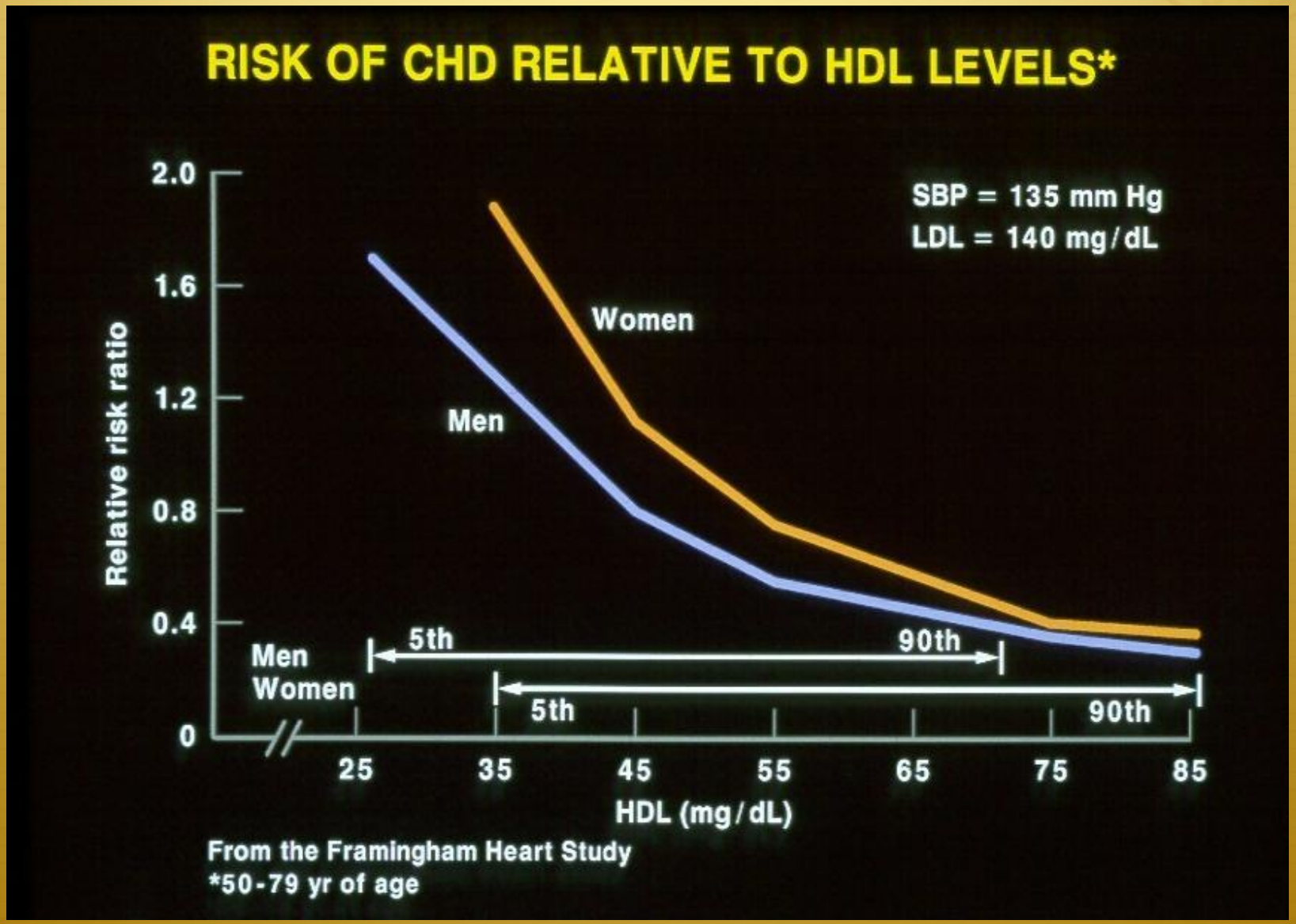
Conflict of Interest

- M'Ath intellectual property owner
- Involvement in R & D for atherosclerosis software developments

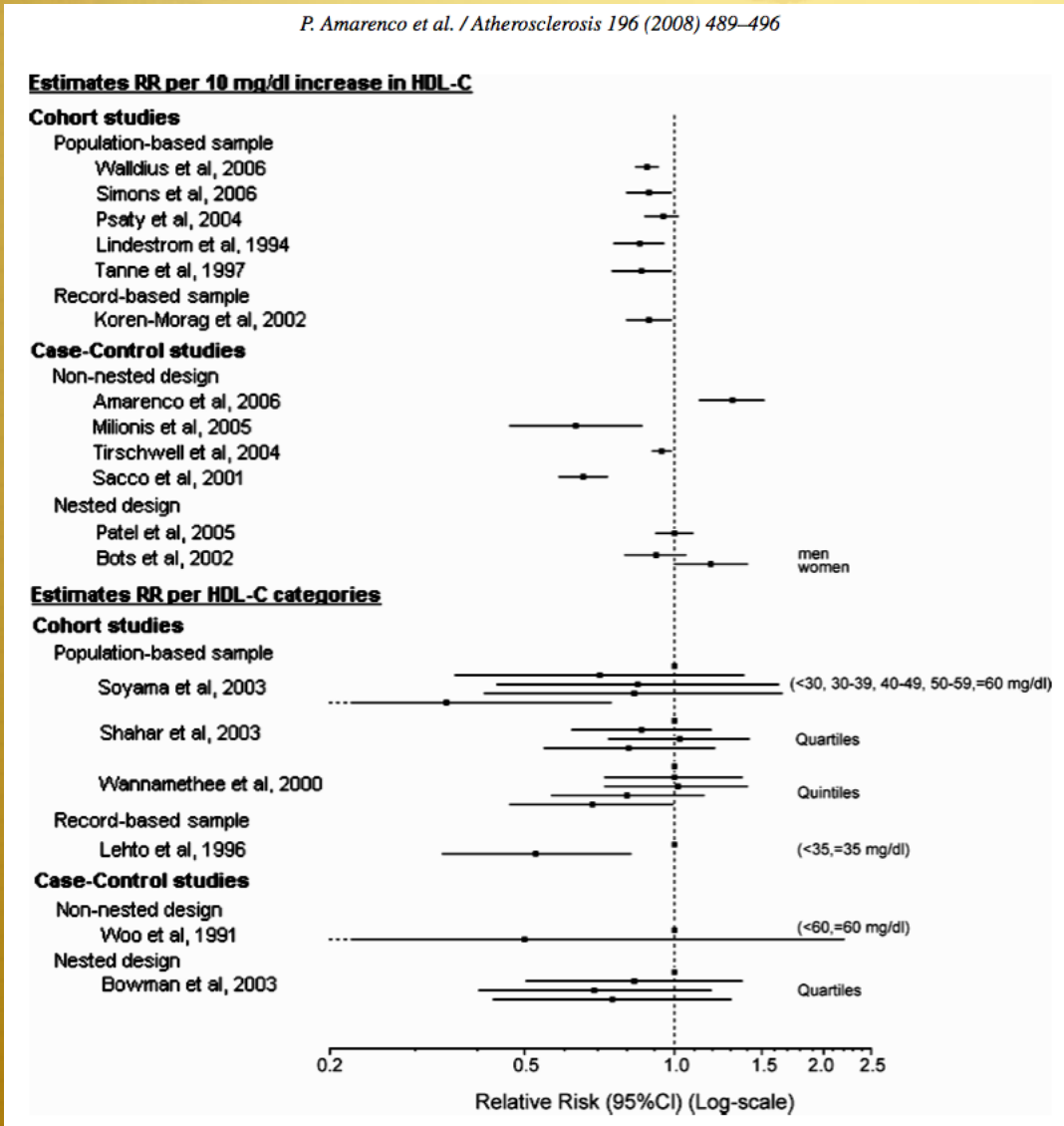
HDL-C as a marker

- HDL-C , LDL-C & CCA-IMT are independent markers of future CVE.
- LDL lowering is associated with CVE incidence reduction
- Epidemiological association between HDL C , triglycerides levels and risk of CV disease.

HDL-C and CHD


RISK OF CHD RELATIVE TO HDL LEVELS*
SBP = 135 mm Hg
LDL = 140 mg/dL
Relative risk ratio
2.0
1.6
1.2
0.8
0.4
0
Women
Men
Men
Women
5th
90th
5th
90th
25
35
45
55
65
75
85
HDL (mg/dL)
From the Framingham Heart Study
*50-79 yr of age

HDL and Stroke Risk : Systematic Review



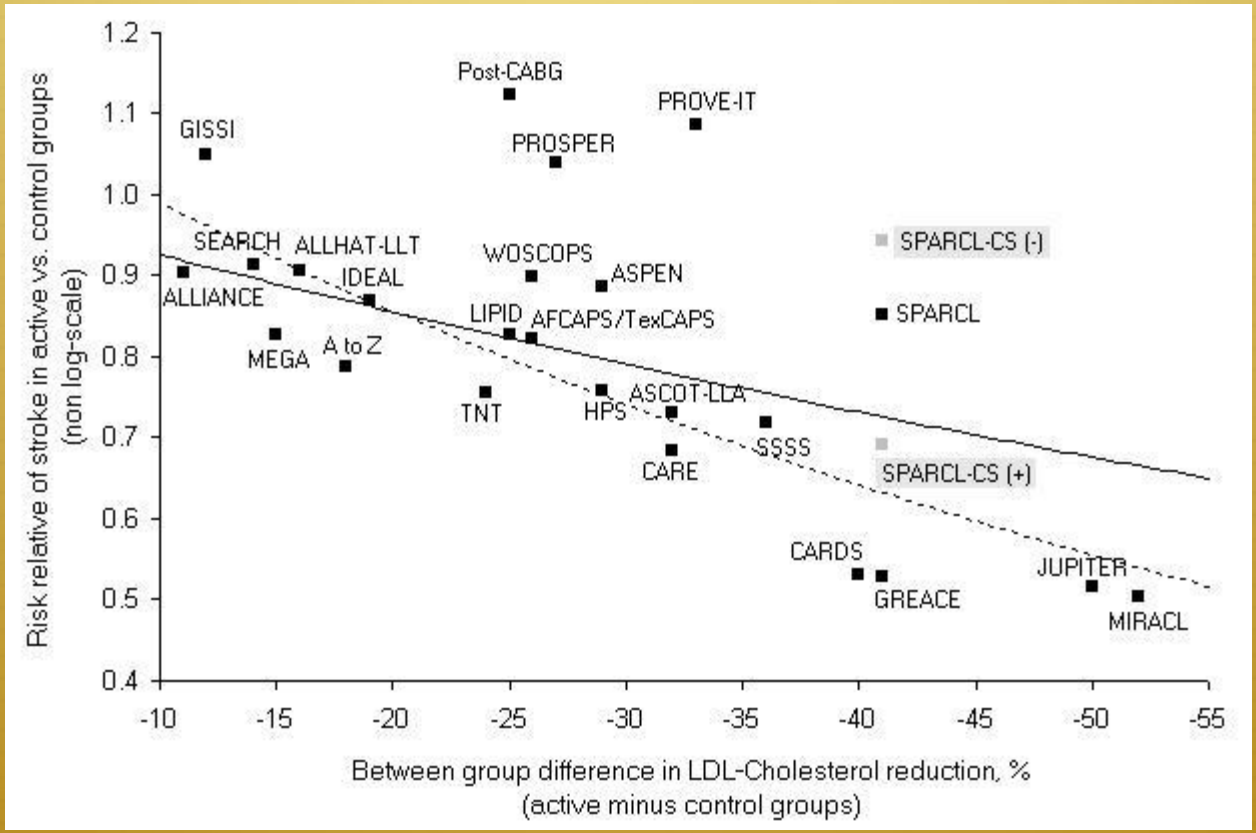
10 Prospective cohort studies (n=238,739) : 11 to 15% decreased stroke risk per 10 mg/dL increase in HDL-C

Amarenco et al. Atherosclerosis. 2008;196:489-96

Stroke Risk and LDL Lowering

Each 1 mmol (39 mg) LDL-C reduction reduced the risk of stroke by 21% (95% CI 6.3 to 33.5%, p<0.001)

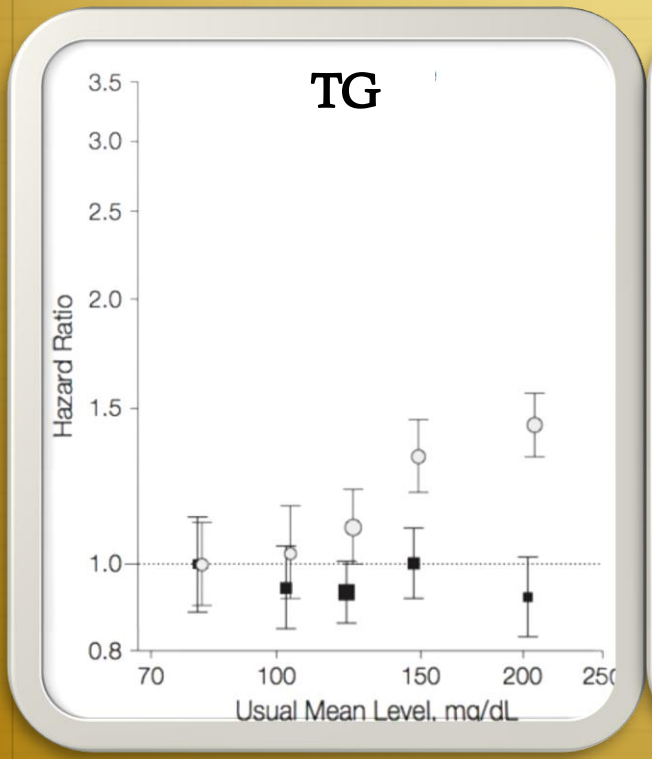
Total n=165,732

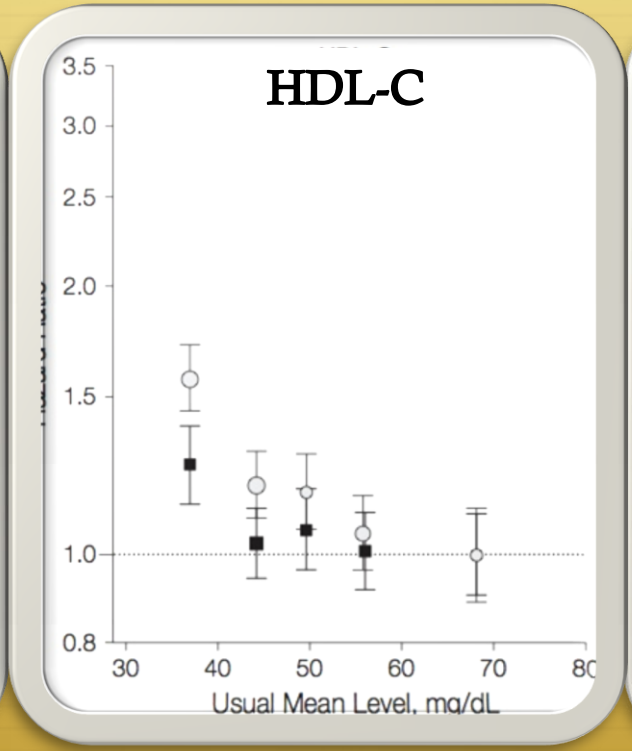


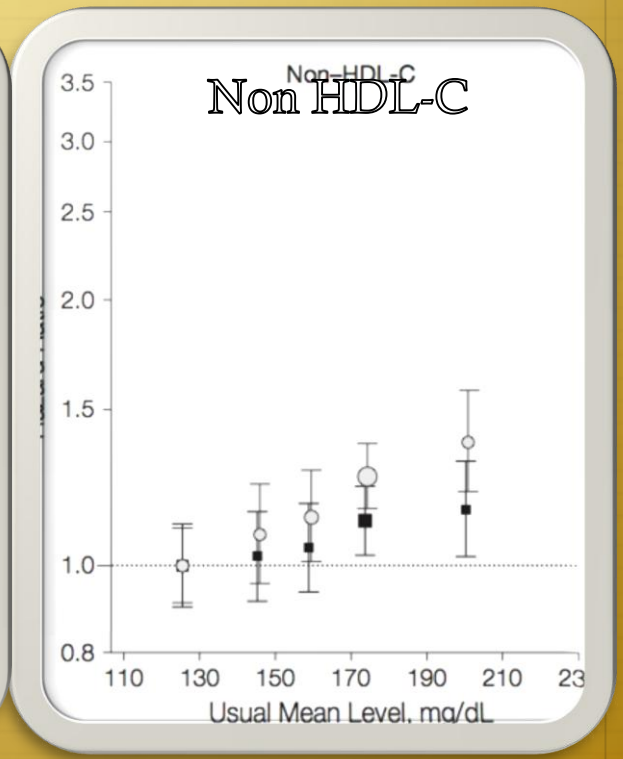
Amarenco P, Labreuche J. Lancet Neurol. 2009; 8:453-63

Emerging Risk Factor Collaboration

Risk of Stroke

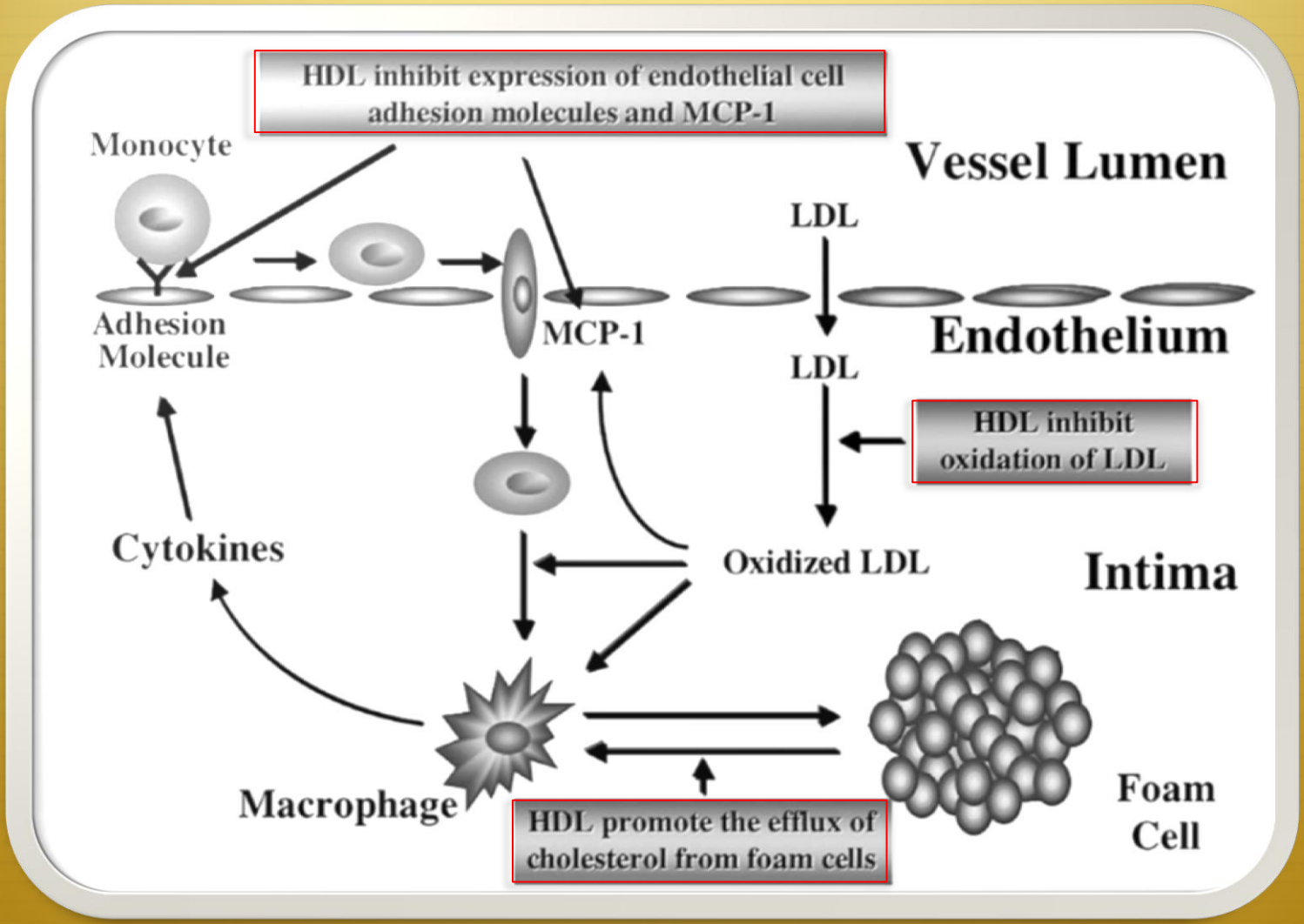






JAMA. 2009;302:1993-2000

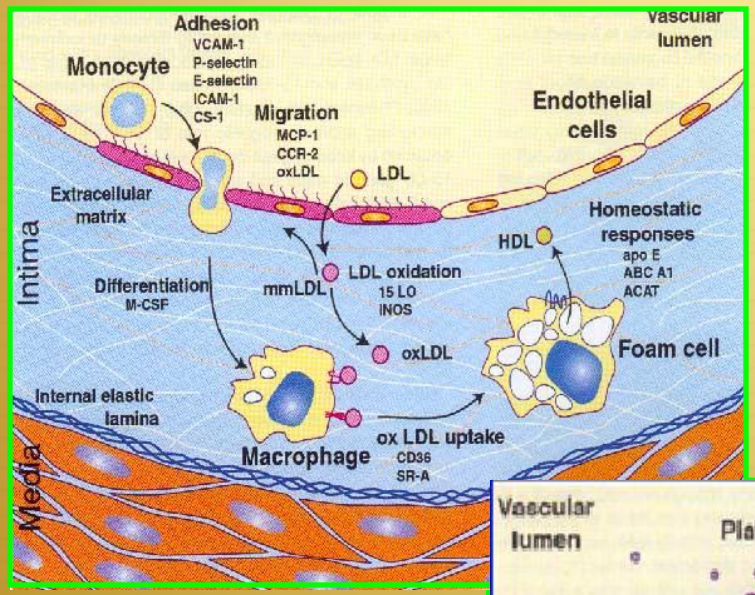
Anti-Atherosclerotic effect

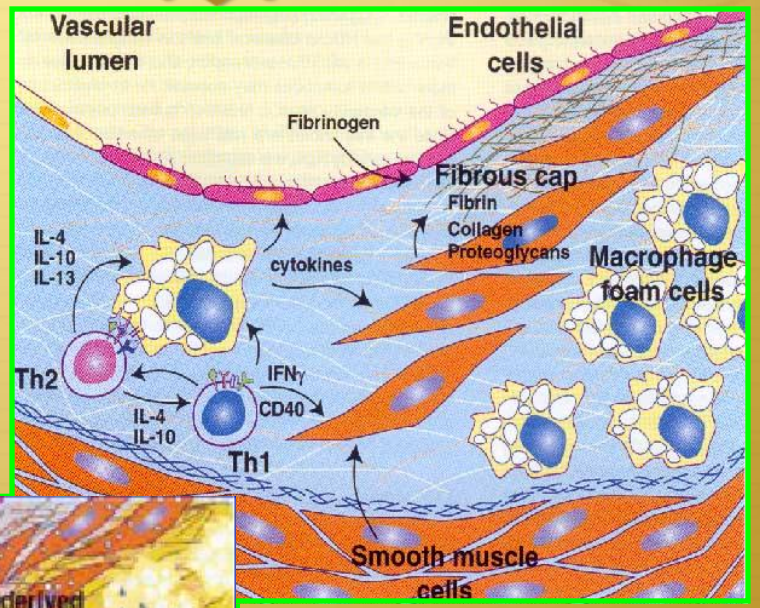


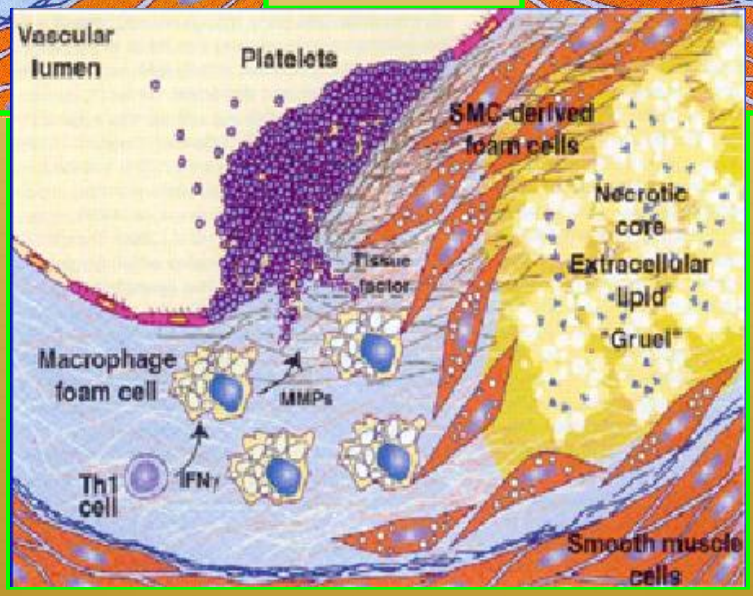
Atherogenesis

Endothelial dysfunction & IMT

Foam Cells -→ Plaque







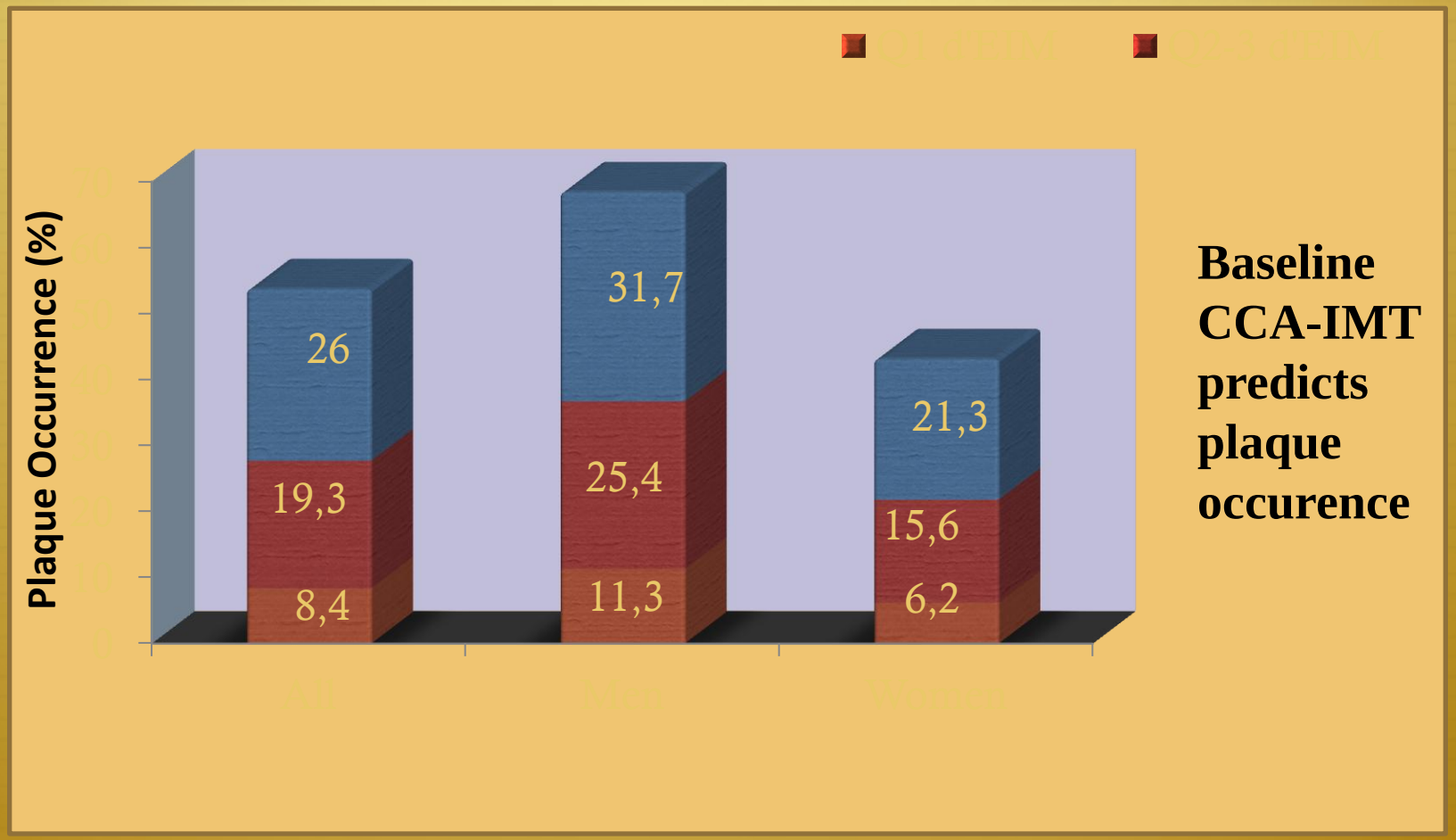
Thrombus

Glass , Cell 2001,104:503-516

HDL-C and vascular protective properties

- Promote cholesterol efflux from macrophages in the artery wall
- Anti-oxidant
- Anti-thrombotic
- Anti-inflammatory
- Improve endothelial function & repair
- Improve diabetic control
- Others

IMT & Plaque : the EVA Study



Baseline CCA-IMT predicts plaque occurence

C Bonithon Kopp P-J Touboul ATVB 1996

IMT and Plaque : EVA Study

TABLE 4. ORs and 95% CIs for Carotid Plaque Occurrence During Follow-Up Associated With Quartiles of Baseline CCA-IMT According to Presence of Carotid Plaques at Baseline

Presence of Carotid Plaques at Baseline	Quartile 1	Quartiles 2–3	Quartile 4
No			
n	197	461	156
Plaque occurrence, %	7.6	16.5	18.6
Age- and sex-adjusted OR	1	2.43 (1.35–4.36)†	2.66 (1.36–5.19)†
Multivariate-adjusted OR*	1	2.29 (1.27–4.12)†	2.43 (1.23–4.78)†
Yes			
n	29	100	67
Plaque occurrence, %	13.8	32.0	43.3
Age- and sex-adjusted OR	1	3.24 (1.03–10.20)‡	5.06 (1.56–16.41)†
Multivariate-adjusted OR*	1	3.28 (1.00–10.27)‡	5.24 (1.51–18.26)†

*Adjusted for sex and baseline age, history of smoking, hypertension (3 categories as in Table 2, 2 dummy variables), diabetes (3 categories as in Table 2, 2 dummy variables), hypercholesterolemia, and personal history of CHD.

†$P \leq 0.01$ and ‡$P \leq 0.05$.

Zureik, Ducimetiere, Touboul, et al. ATVB 2000;20:1622-1629

Rationale for the HDL/IMT evaluation

- Association between HDL-C reduction and CV events
- Prooven association between LDL increase and CV events
- Statistical association between LDL level decrease and risk of stroke.
- Inverse association between IMT values and stroke in prospective studies

Methods

- Data from 6 cross sectional Ultrasound studies
- All observational , 5 published and one stopped
- Same ultrasound methodology to minimize variability :
  - Following same IMT definition (Mannheim consensus)
  - Edge detection IMT measurement
  - Same training of all investigators involved in these studies
  - Image acquisition done on the same software
  - Data were processed at the same core lab (Intelligence in Medical Technologies ®)

Methods (II)

Risk factors definition :

- BP : > 140-90 mmHg or current bpld treatment

- Dyslipidemia : LDL-C > 160mg/dL (Friedewald formula) or current lld treatment.
- Diabetes Blood glucose > 126mg/dL or current treatment for Diabetes (I or II)

- Family history of MI (< 55 y-o for men , <65 y-o for women)

- Early menopausis (<40 y-o)

- Lipid parameters all obtained at inclusion time.

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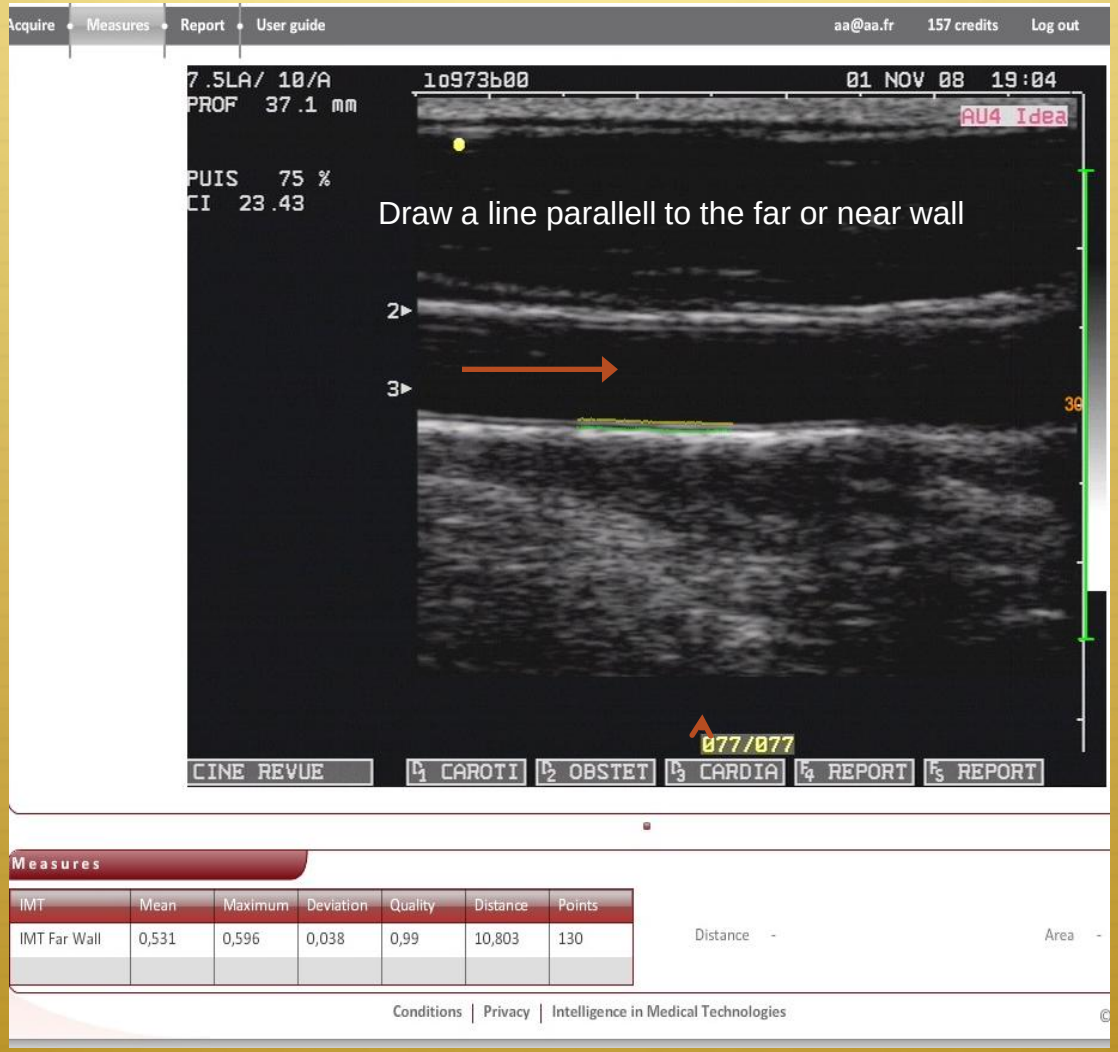
IMT Measurement



Methods (III)

Ultrasound:

- CCA IMT on both CCA far walls
- Angle with the best view
- 10mm lenght in a region free of plaque
- QI > or = 0.5
- Mean of right and left CCA IMT was computed.

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Populations

haracteristics from the six cross-sectional studies contributing to the current meta-analysis.

	CARMELA [10] (n = 10,415)	PARC [19] (n = 5264)	PARC-AALA [20] (n = 2328)	PI2 (n = 554)	REMEMBER [22] (n = 606)	VITA [21] (n = 2420)
Age, y	44.7 ± 11.3	60.6 ± 11.6	49.8 ± 8.3	56.3 ± 7.5	66.8 ± 8.3	54.0 ± 4.5
Male	4852 (46.6)	2999 (57.0)	1123 (48.2)	278 (50.2)	286 (47.2)	1073 (44.3)
Body mass index, kg/m^2	27.3 ± 4.8	25.8 ± 4.1	26.3 ± 4.5	26.9 ± 4.2	27.9 ± 4.2	25.7 ± 4.0
Diabetes	566 (5.4)	657 (12.5)	171 (7.4)	86 (15.5)	110 (18.2)	108 (4.5)
Current smokers	3312 (31.8)	795 (15.1)	206 (8.9)	126 (22.7)	101 (16.7)	567 (23.4)
Antihypertensive treatment	1198 (11.5)	2022 (38.7)	600 (25.8)	266 (48.0)	258 (42.6)	398 (16.5)
Systolic blood pressure, mmHg	120 ± 18	136 ± 16	138 ± 22	133 ± 16	140 ± 19	138 ± 18
Diastolic blood pressure, mmHg	77 ± 11	80 ± 9	86 ± 13	79 ± 10	80 ± 10	83 ± 9
Lipid-lowering treatment	233 (2.2)	2077 (39.6)	168 (7.2)	226 (40.8)	69 (11.4)	1980 (81.8)
Total cholesterol, mg/dL	198 ± 42	215 ± 42	209 ± 44	214 ± 39	223 ± 40	234 ± 38
LDL-C, mg/dL	121 ± 35	134 ± 37	133 ± 40	129 ± 34	137 ± 34	161 ± 35
HDL-C, mg/dL	46 ± 13	56 ± 17	50 ± 13	60 ± 16	61 ± 14	49 ± 13
LDL-C/HDL-C ratio	2.8 ± 1.0	2.6 ± 1.1	2.9 ± 1.3	2.3 ± 0.9	2.3 ± 0.7	3.5 ± 1.2
Triglycerides, mg/dL	132 (90–195)	107 (77–150)	133 (88–186)	110 (81–149)	108 (81–149)	103 (76–147)
Personal history of CHD	432 (4.2)	1450 (27.6)	150 (6.4)	1 (0.2)	95 (15.8)	27 (1.1)
Familial history of CHD	1378 (13.2)	802 (15.4)	201 (8.6)	109 (19.7)	99 (16.4)	216 (8.9)
CCA-IMT, mm	0.668 ± 0.105	0.751 ± 0.123	0.692 ± 0.114	0.786 ± 0.090	0.761 ± 0.103	0.668 ± 0.078
Carotid plaques	1077 (10.5)	NA	492 (22.8)	8 (1.4)	399 (65.8)	12.6 (304)

/alues are mean ± SD, number (%) or median (IQR). CARMELA indicates Cardiovascular Risk Factor Multiple Evaluation in Latin America; PARC, Paroi Artérielle et Risque :ardiovasculaire; PARC-AALA, Paroi Arterielle et Risque Cardiovasculaire in Asia, Africa/Middle East and Latin America; PI2, Plaque Intima-media Inflammation; REMEMBER, :egistry Evaluation Memory in Buttrio e Remanzacco; VITA, Vicenza Thrombophilia and Atherosclerosis; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density ipoprotein cholesterol; CHD, coronary heart disease; CCA-IMT, common carotid artery intima-media thickness; SD, standard deviation; IQR, interquartile range; NA, not vailable.

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Main Results of this meta analysis

Total Population : 21587 patients with complete information

Individual meta analysis

Mean age 51 , 49% men

Across the studies : mean HDL ranged from 46 to 61 mg/dl

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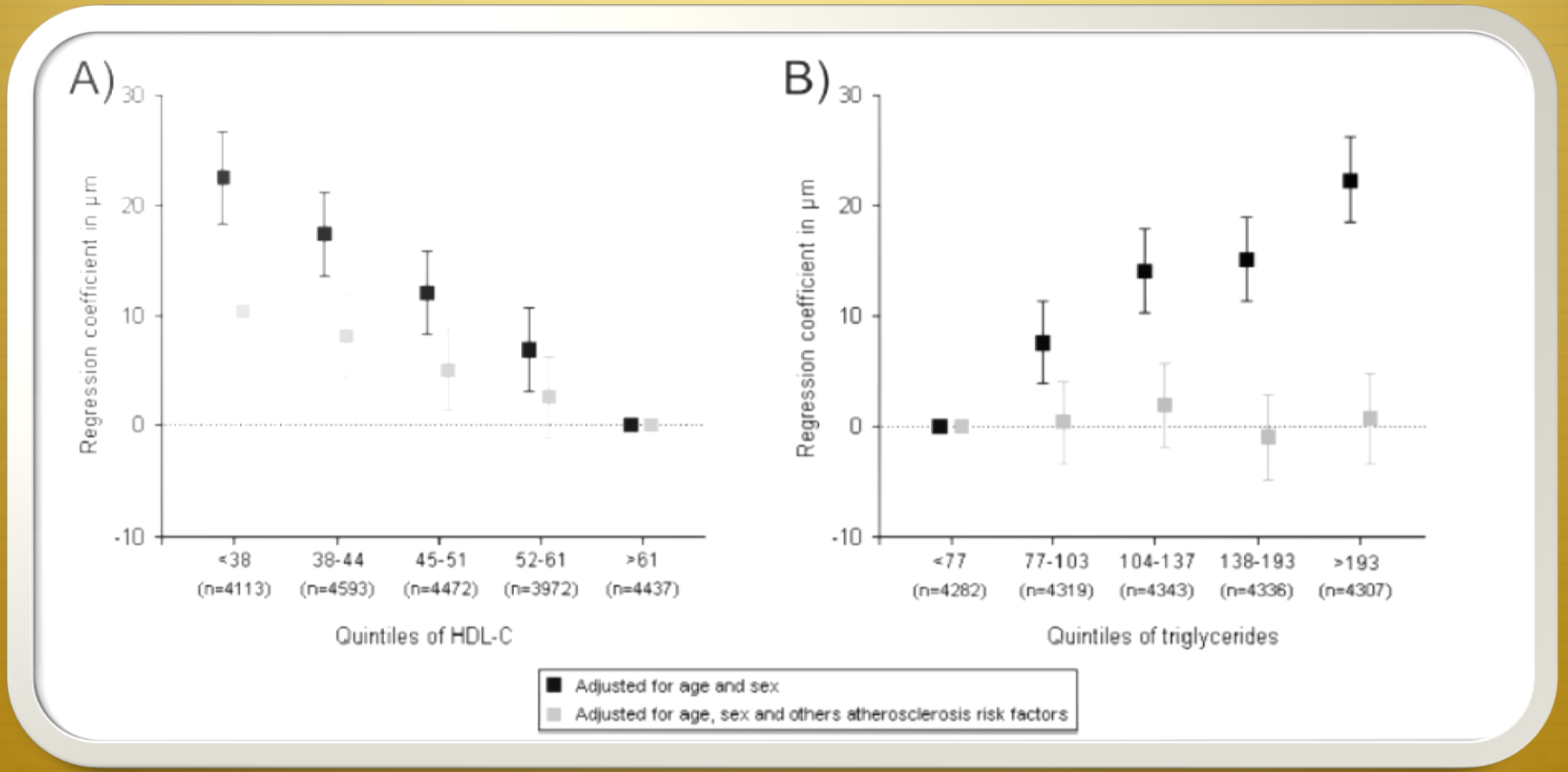
CCA-IMT and Quintiles of HDL-C ,Triglyceride levels



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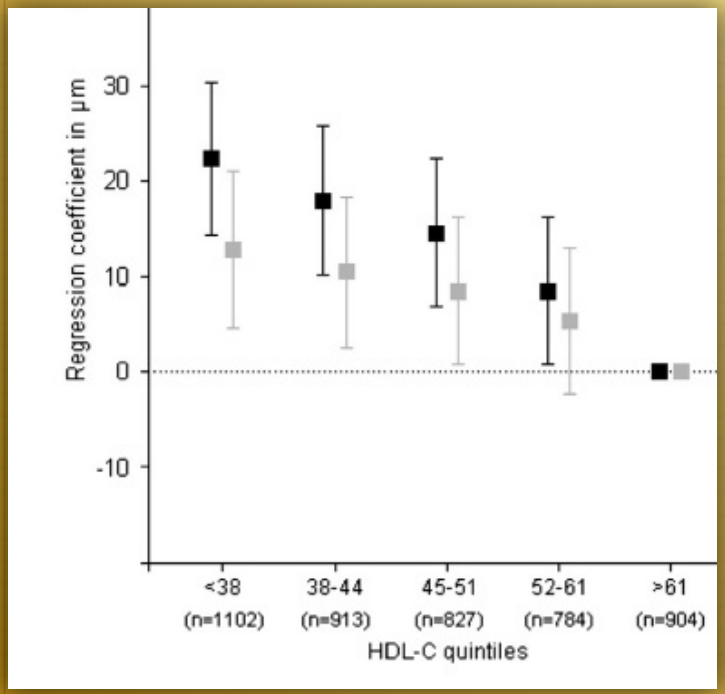
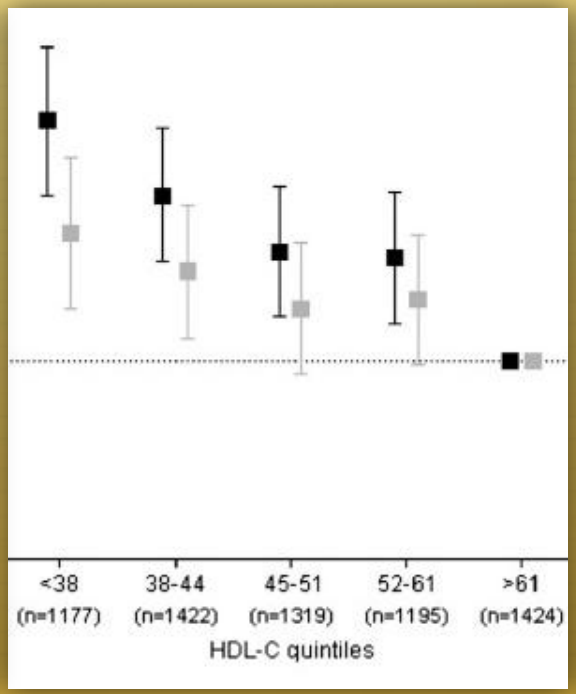
HDL/IMT associations according to LDL Levels

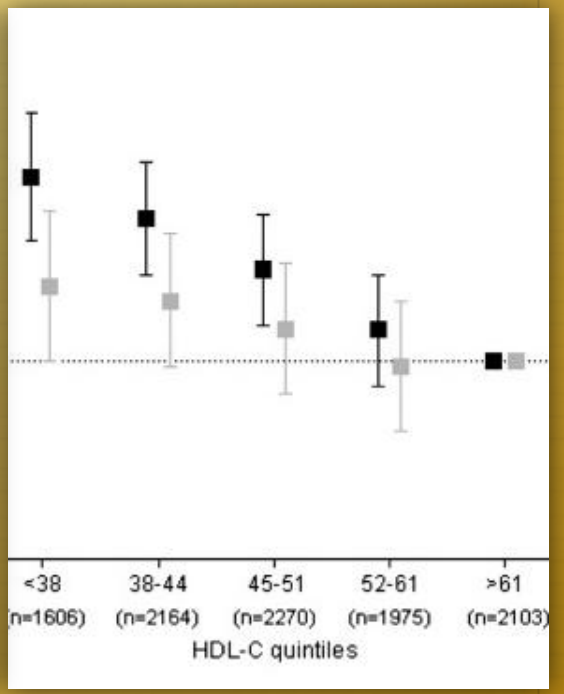
LDL-C <100 mg/dL

LDL-C 101-130 mg/dL

LDL-C >100 mg/dL







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New Trends in Atherosclerotic Evaluation

Meta-analysis of CIMT change in 48 Randomized Studies

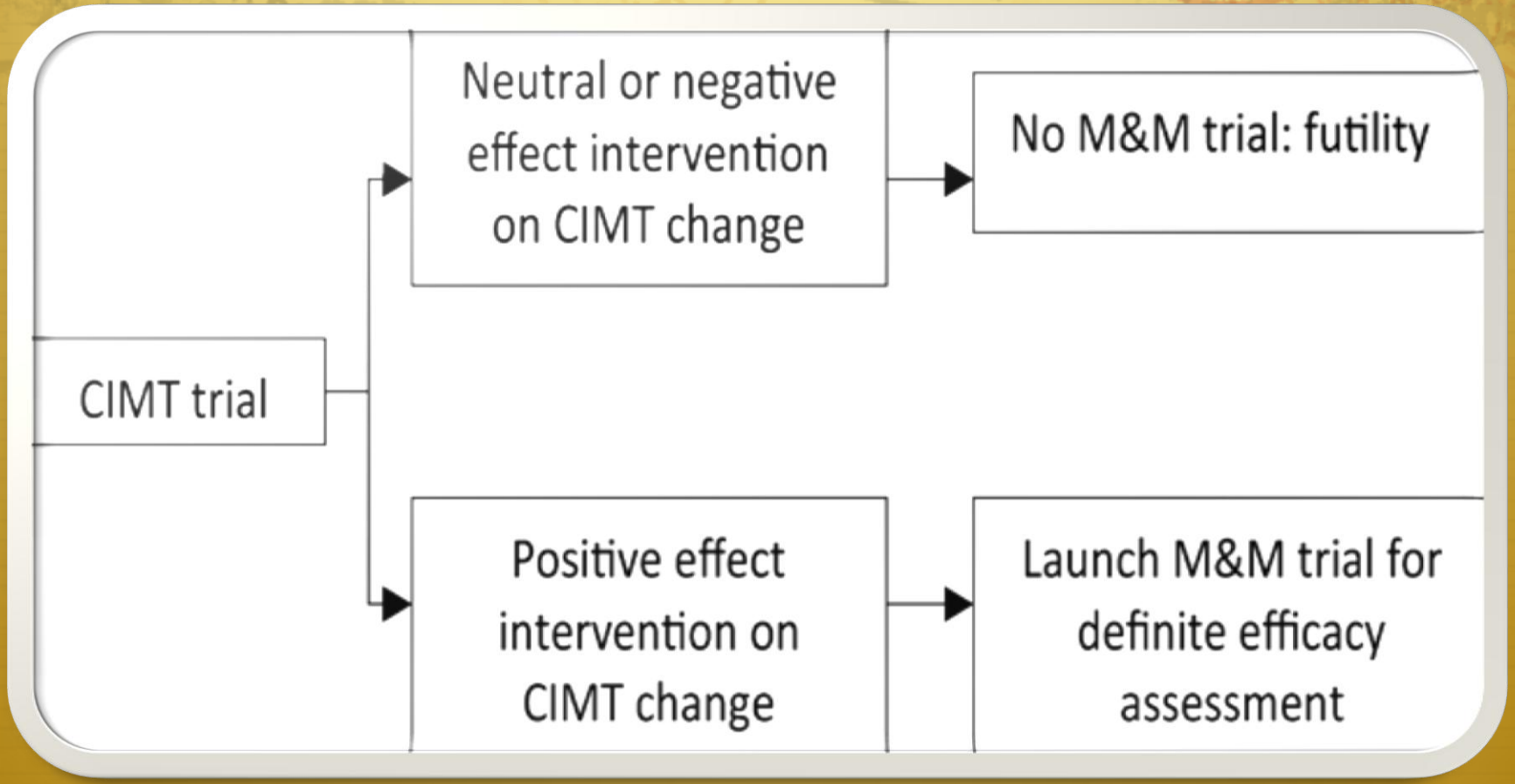
CIMT Trial as Decision Tool for Launching a Large-Scale Morbidity and Mortality Trial, Overall and for Lipid-Level Modifying Therapies and Nonlipid-Level Modifying Therapies Separately

	PPV	NPV	Sensitivity	Specificity
Lipid-level modifying	1.00 (0.77; 1.00)	0.86 (0.49; 0.97)	0.93 (0.79; 0.99)	1.00 (0.61; 1.00)
Nonlipid-level modifying	0.91 (0.62; 0.98)	0.82 (0.59; 0.94)	0.77 (0.50; 0.92)	0.93 (0.70; 0.99)
Primary prevention	0.93 (0.70; 0.99)	0.67 (0.39; 0.86)	0.78 (0.55; 0.91)	0.89 (0.57; 0.98)
Secondary prevention	1.00 (0.72; 1.00)	0.91 (0.62; 0.98)	0.91 (0.62; 0.98)	1.00 (0.72; 1.00)

CIMT indicates carotid intima-media thickness; M&M, morbidity and mortality; NPV, negative predictive value; and PPV, positive predictive value.
Values between brackets are the 95% confidence intervals.

Results From a Carotid Intima-Media Thickness Trial as a Decision Tool for Launching a Large Scale M&M Trial Circulation CV imaging 2013

New Trends in Atherosclerotic Evaluation



Results From a Carotid Intima-Media Thickness Trial as a Decision Tool for Launching a Large Scale Morbidity and Mortality Trial Circulation CV imaging 2013

Conclusion

- CCA-IMT evolution might be a powerfull endpoint for the evaluation of HDL-C raising agents.
- Longitudinal studies including prospective IMT and plaque evaluation and clinical outcome should be done to confirm these data
- IMT change and plaque occurrence might be in the future the first step to go for anti atherosclerotic drugs evaluation .

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