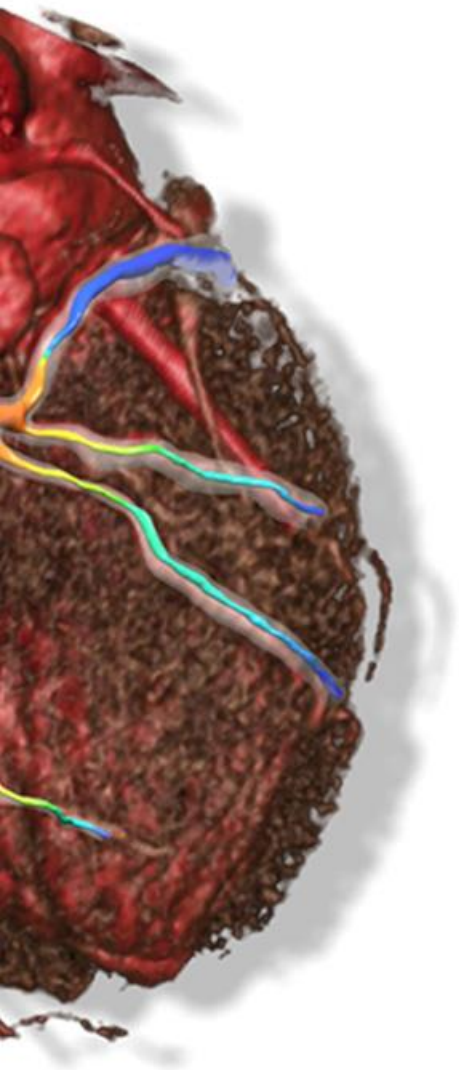
A SMARTool project workshop

CAD RISK PREDICTION AND STRATIFICATION: THE ICT APPROACH



SMARTool clinical and biohumoral results

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Tuesday 6th November 2018

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Horizon 2020
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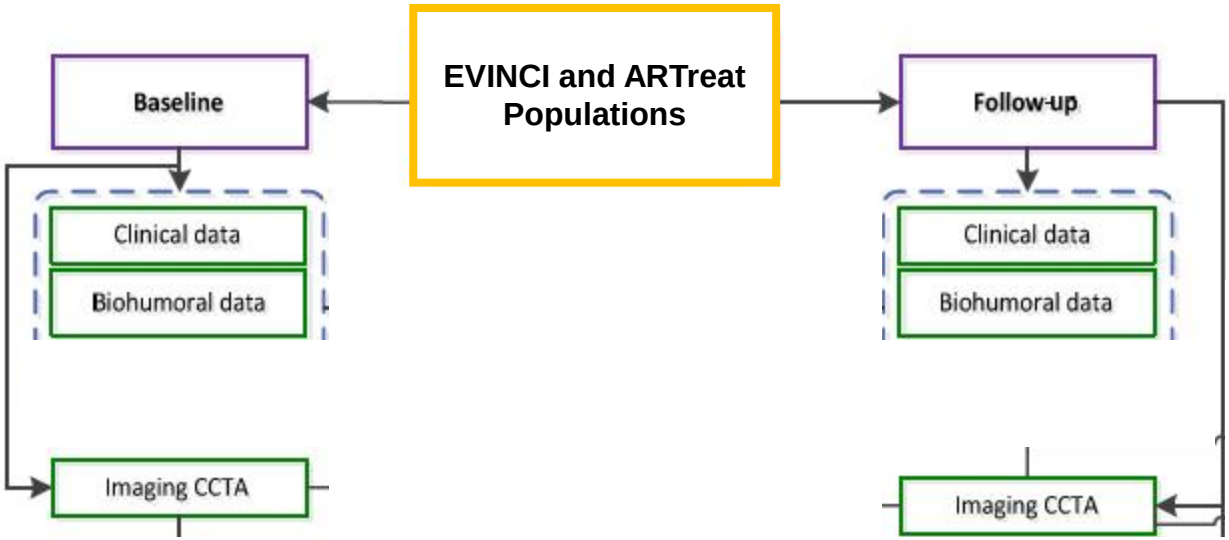
SMARTool Flow chart



SMARTool: WP1 and WP2

WP1 Objective:

•To collect retrospective EVINCI clinical and imaging data from 515 patients;
•To select SMARTool patients (N=300-350) from existing EVINCI and ARTReat clinical/imaging data;
•To submit enrolled SMARTool patients to non-invasive CCTA testing.

Task 1.1 Clinical and imaging (CCTA) data collection and selection
(retrospective/baseline collection and acquisition at follow-up)
(Leader FTGM, Participating partners CNR, LUMC, UTU, UZH, B3D)

WP2 Objective:

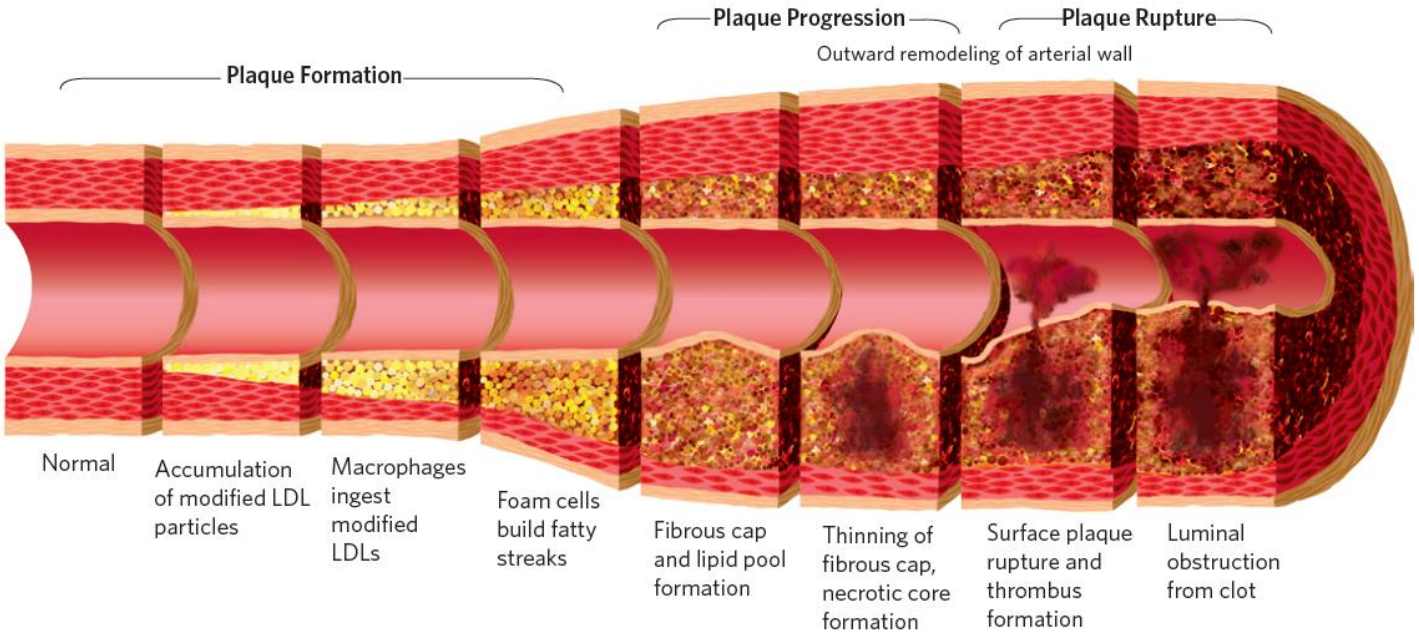
•To collect the non-imaging (clinical, biohumoral, molecular) data from baseline and follow-up samples

Task 2.1: Biohumoral data collection and analysis at baseline and at follow-up
(Leader CNR , Participating partners FTGM, UTU, UZH)

Clinical features

	CLINICAL FEATURES	Baseline n= 263	Follow up n= 263	P value Baseline vs Follow up
DEMOGRAPHICS	Age (yrs)	61 ± 9	67 ± 9	<0.0001
	Gender (males)	165 (63)	165 (63)	---
RISK FACTORS	Increased prevalence/recognition of Risk Factors			
PHARMACOLOGICAL TREATMENT	Increased treatment of Risk Factors and Ischemia			
CURRENT SYMPTOMS	Decreased Symptoms			

Bio-humoral markers



LIPIDS
Total cholesterol
LDL and HDL cholesterol
Triglycerides

INFLAMMATION
hs CRP
Interleukin-6

CARDIAC DAMAGE
hs cTnT

HEPATIC FUNCTION
AST, ALT
ALP, GGT

THYROID FUNCTION
TSH
fT3, fT4

METABOLISM
Glucose
Creatinine
Leptin

ENDOTHELIAL ACTIVATION
sICAM
sVCAM

CARDIAC FUNCTION
NT-proBNP

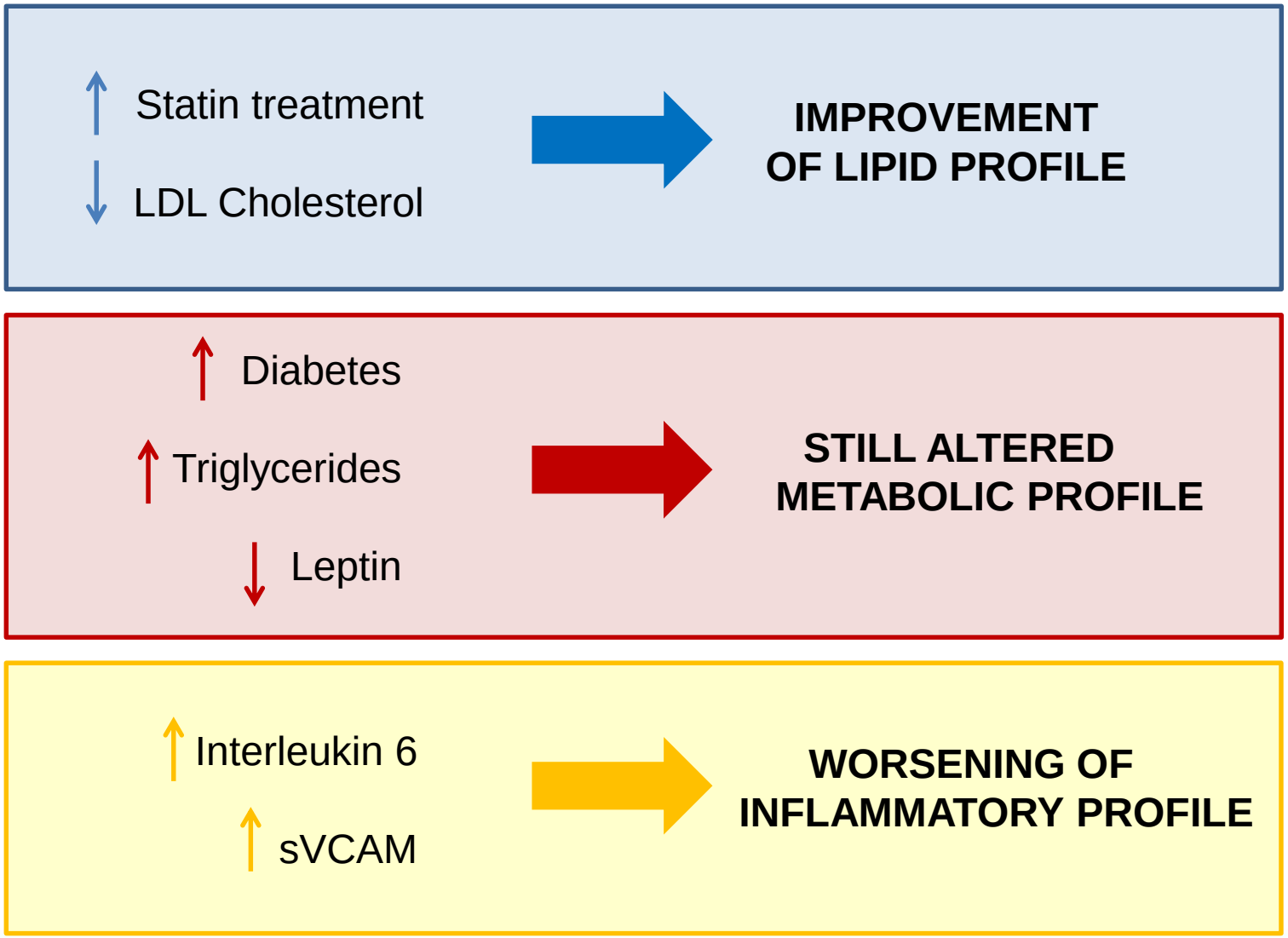
VASCULAR REMODELING
MMP2
MMP9

Biohumoral Profile

Pathway	BIOMARKER	Baseline N=263	Follow up N=263	P value Baseline vs Follow up
LIPIDS	Total cholesterol (mg/dL)	186 ± 49	180 ± 43	ns
	LDL (mg/dL)	111 ± 41	96 ± 37	<0.0001
	HDL (mg/dL)	53 ± 16	56 ± 16	<0.0001
	Triglycerides (mg/dL)	117 ± 60	144±90	<0.0001
METABOLISM	Leptin (ng/mL)	9.44 ± 9.11	5.68 ± 6.72	<0.0001
	Glucose (mg/dL)	108 ± 26	108 ± 27	ns
	Creatinine (mg/dL)	0.86 ± 0,20	0,.86 ± 0,22	ns
INFLAMMATION/ ENDOTHELIAL ACTIVATION	hs CRP (mg/dL)	0.36±0.64	0.31±0.47	ns
	Interleukin-6 (pg/mL)	1.09±1.33	1.71±3.44	<0.0001
	sVCAM (ng/mL)	543.89±167.09	618.58±329.39	<0.0001
	sICAM (ng/mL)	200.32±77.16	196.60±75.80	ns
HEPATIC FUNCTION	AST (U/L)	24 ± 10	24±7	ns
	ALT (U/L)	20 ± 11	22±10	0.0146
	ALP (U/L)	50 ± 18	52±19	0.0263
	GGT (U/L)	35 ± 18	32±20	0.0001
CARDIAC MARKERS	hs cardiac Troponin T (ng/mL)	7.54± 5.39	7.94 ± 5.35	ns
	NT-proBNP (ng/mL)	113.56 ± 9.67	nd	…
THYROID FUNCTION	TSH (μUI/mL)	1.79± 1.10	nd	…
	fT3 (pg/mL)	2.60 ± 0.35	nd	…
	fT4 (pg/mL)	11.10± 2.33	nd	…
VASCULAR REMODELING	MMP2 (ng/mL)	163.09±57.36	nd	…
	MMP9 (ng/mL)	138.72±200.30	nd	…

Summing Up 1

BASELINE vs FOLLOW UP

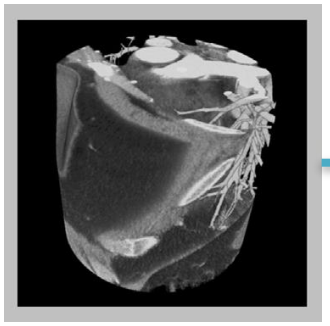


Coronary Artery Disease at CCTA

		Baseline	Follow up	P value Baseline vs Follow up
N=263	Increased Coronary ATS Burden			
N=211				

LEIDEN RISK SCORE

A



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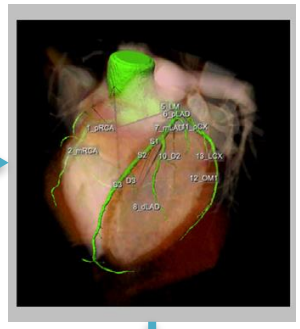

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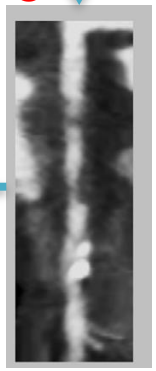

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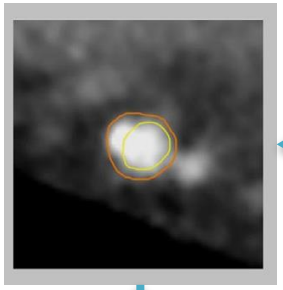

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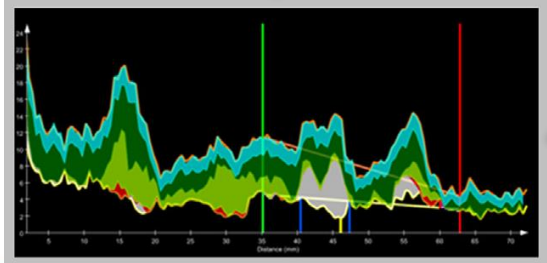

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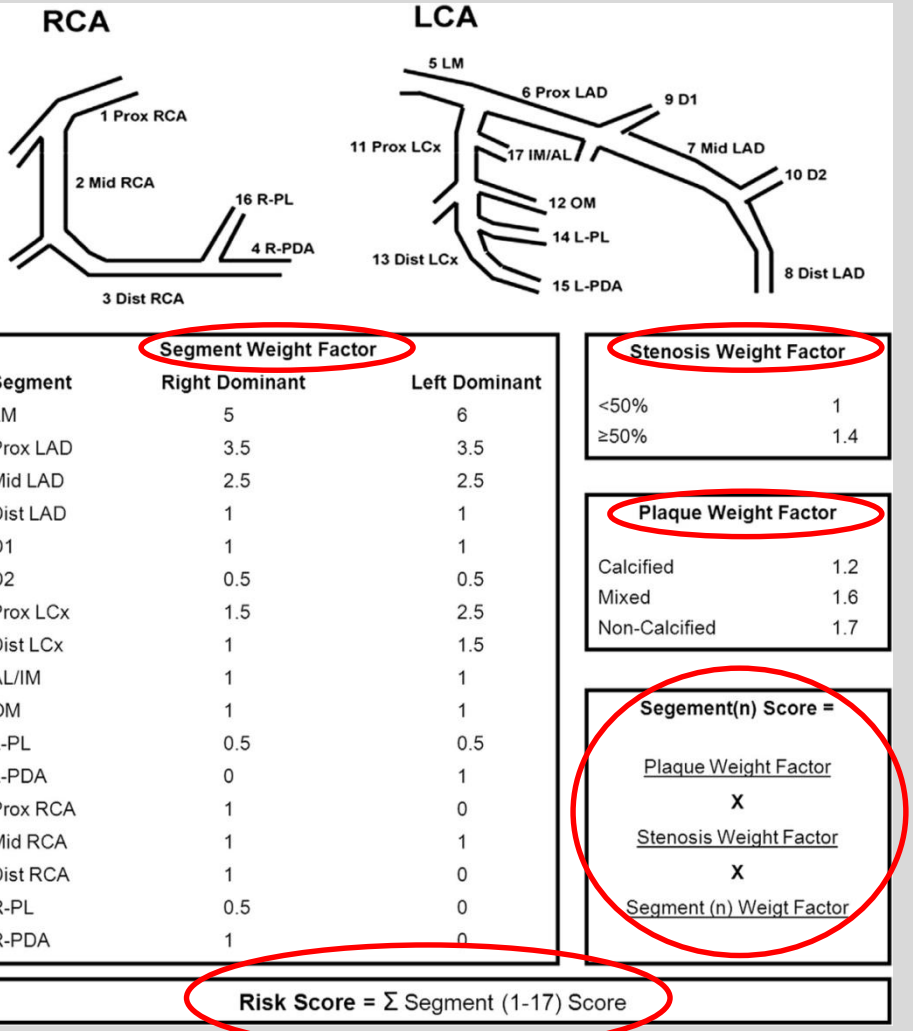


Segment Weight Factor

Segment	Right Dominant	Left Dominant
LM	5	6
Prox LAD	3.5	3.5
Mid LAD	2.5	2.5
Dist LAD	1	1
D1	1	1
D2	0.5	0.5
Prox LCx	1.5	2.5
Dist LCx	1	1.5
AL/IM	1	1
OM	1	1
L-PL	0.5	0.5
L-PDA	0	1
Prox RCA	1	0
Mid RCA	1	1
Dist RCA	1	0
R-PL	0.5	0
R-PDA	1	0

Stenosis Weight Factor

<50%	1
≥50%	1.4

Plaque Weight Factor

Calcified	1.2
Mixed	1.6
Non-Calcified	1.7

Segement(n) Score =

Plaque Weight Factor
X
Stenosis Weight Factor
X
Segment (n) Weigt Factor

Risk Score = Σ Segment (1-17) Score

De Graaf M et al., 2014

Association with CAD

Leiden Risk Score

		Baseline				Follow up			
		Class 0 (0-5) N=82	Class 1 (5-20) N=127	Class 2 (>20) N=48	P Value	Class 0 (0-5) N=61	Class 1 (5-20) N=131	Class 2 (>20) N=65	P Value
DEMOGRAPHICS	Age	57.9 ± 7.8	60.4 ± 8.13	63.8 ± 11.3	0.0012	64.2± 7.7	66.5 ± 8.3	70.3 ± 11.3	0.0007
	Male gender	33 (40%)	90 (71%)	38 (79%)	<0.0001	19 (31%)	87 (66%)	55 (84%)	<0.0001
METABOLISM	HDL	56.0 ± 18.6	53.3 ± 16.2	46.6 ± 10.6	0.0244	61.6 ± 18.1	56.1 ± 16.4	50.8 ± 11.2	0.0012
	Diabetes mellitus	7 (8%)	22 (17%)	17 (35%)	0.0009	9 (15%)	29 (22%)	28 (43%)	0.0009
	Creatinin	0.82 ± 0.17	0.88 ± 0.20	0.91 ± 0.20	0.0414	0.81 ± 0.17	0.85 ± 0.20	0.93 ± 0.27	0.0105
	Glucose	102.3 ± 26.2	108.7 ± 22.7	115.8 ± 28.4	0.0098	102.2 ± 20.2	106.8 ± 28.9	114.5 ± 29.72	0.0119
	Leptin	12.2 ± 9.3	8.1 ± 8.5	8.2 ± 9.9	0.0044	7.5 ± 8.1	5.6 ± 7.0	4.0 ± 4.1	0.0109
INFLAMMATION/ ENDOTHELIAL ACTIVATION	Interleukin 6	0.93 ± 0.883	1.18 ± 1.64	1.10 ± 1.04	ns	1.07 ± 0.76	1.70 ± 3.72	2.32 ± 4.28	0.0061
	sVCAM	514.3 ± 101.1	572.3 ± 213.4	525.7 ± 112.6	ns	580.7 ± 149.4	620.9 ± 440.4	649.3 ± 156.3	0.0420
CARDIAC DAMAGE	hs cTnT	5.44 ± 3.14	7.61 ± 5.82	9.06 ± 5.73	0.0003	6.12 ± 3.92	7.32 ± 4.21	10.48 ± 7.20	<0.0001

SUMMING UP 2

Predicting CAD Presence/Severity/Risk
BASELINE vs FOLLOW UP

Diabetes and biomarkers of metabolic syndrome, such as **HDL**, **glucose** and **leptin** levels, are associated with **CAD (**presence/severity/risk) at **baseline and follow up**

→ **ABNORMAL METABOLISM IS A PERSISTENT DETERMINANT OF CAD**

Biomarkers of inflammation and endothelial activation, such as **IL-6** and **sVCAM**, are associated with **CAD** (presence/severity/risk) at **follow up**

→ **INFLAMMATION IS AN ADDITIONAL DETERMINANT OF CAD**

Association with CAD Progression

N = 66 Revascularized

	Baseline Variables	Plaque Number Increase N=101/193		Leiden score Increase N=106/193		TPV Increase N=74/149	
		HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
METABOLISM	ALT	2.03 (1.26-3.25)	0.0034	2.24 (1.40-3.59)	0.0008	1.79 (1.03-3.13)	0.0401
	Leptin	0.72 (0.56-0.93)	0.0103	0.70 (0.55-0.90)	0.0055	0.68 (0.50-0.93)	0.0159
INFLAMMATION	Interleukin 6	1.63 (1.05-2.54)	0.0298	1.61 (1.03-2.49)	0.0350	1.63 (0.98-2.69)	0.0585
VASCULAR REMODELING	MMP9	1.32 (1.03-1.68)	0.267	1.29 (1.02-1.64)	0.0351	1.56 (1.19-2.05)	<0.001
THYROID FUNCTION	fT4	3.18 (1.09-9.24)	0.0337	3.31 (1.16-9.45)	0.0251	---	---

SUMMING UP 3

CAD PROGRESSION

ALT and **leptin**,
are associated with
CAD PROGRESSION

→ **ABNORMAL METABOLISM**

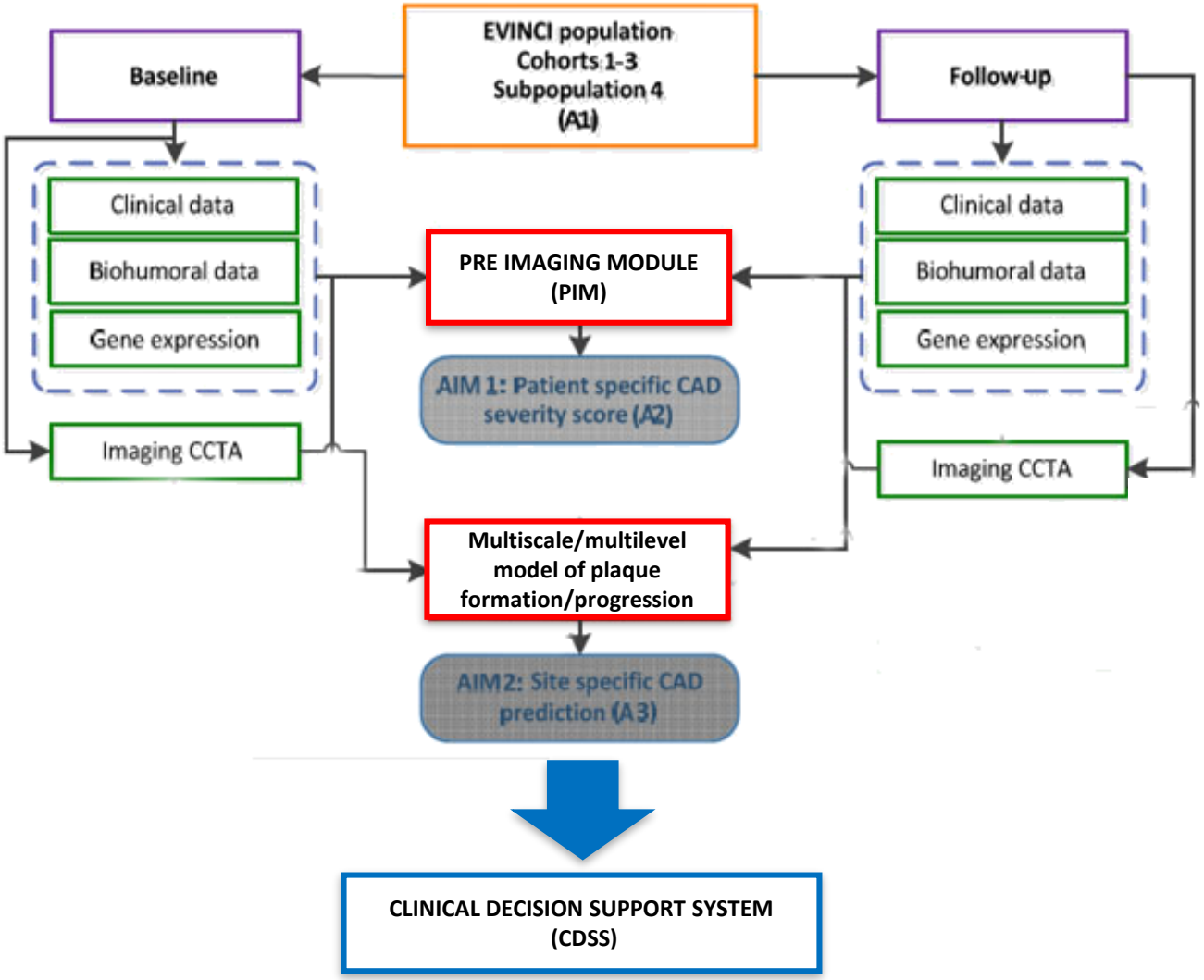
Interleukin 6
is associated with
CAD PROGRESSION

→ **INFLAMMATION**

MMP9 and **fT4**,
are additionally associated with
CAD PROGRESSION

→ **VASCULAR REMODELING AND THYROID FUNCTION**

SMARTool Flow chart



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Af — l:

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

Clinical Investigation and Reports

Plasma Concentrations and Genetic Variation of Matrix Metalloproteinase 9 and Prognosis of Patients With Cardiovascular Disease

Stefan Blankenberg, MD; Hans J. Rupprecht, MD; Odette Poirier, PhD; Christoph Bickel, MD; Marek Smieja, MD, PhD; Gerd Hafner, MD; Jürgen Meyer, MD; François Cambien, MD; Laurence Tiret, PhD; for the AtheroGene Investigators

Background—Matrix metalloproteinase (MMP)-9 secretion by macrophages and other inflammatory cells accelerates atherosclerotic progression and destabilizes vulnerable plaque in animal models. However, epidemiological data evaluating the prognostic impact of circulating concentrations and functional genetic variations of MMP-9 are lacking.

Methods and Results—In a prospective study of 1127 patients with documented coronary artery disease, we measured baseline plasma MMP-9 levels and determined the MMP-9/C-1562T and MMP-9/R279Q genotypes. During the follow-up period (mean of 4.1 years), 97 patients died from cardiovascular (CV) causes. Median concentrations of MMP-9 were significantly higher among patients who experienced a fatal CV event than among those who did not (62.2 versus 47.8 ng/mL; $P<0.0001$). The crude hazard risk ratio of CV death associated with increasing quartiles of MMP-9 was 1.4 (95% CI, 1.2 to 1.8; $P<0.0001$), and after adjustment for clinical and therapeutic confounders, it was 1.3 (95% CI, 1.1 to 1.6; $P=0.005$). Additional adjustment for highly sensitive CRP, interleukin-6, fibrinogen, and interleukin-18 revealed a hazard risk ratio to 1.2 (95% CI, 0.9 to 1.6; $P=0.15$). The T allele of the C-1562T polymorphism was associated with increased MMP-9 levels in a fairly codominant fashion ($P=0.004$). Although none of the polymorphisms was significantly related with future CV death, there was a significant association ($P=0.02$) between the R279Q polymorphism and CV events in patients with stable angina.

Conclusions—Plasma MMP-9 concentration was identified as a novel predictor of CV mortality in patients with coronary artery disease. Whether it provides independent prognostic information compared with other inflammatory markers will have to be additionally assessed. (***Circulation***. 2003;107:1579-1585.)

Key Words: metalloproteinases ■ inflammation ■ prognosis ■ coronary disease

Clinical Track

Thyroid Function and the Risk of Atherosclerotic Cardiovascular Morbidity and Mortality

The Rotterdam Study

Arjola Bano, Layal Chaker, Francesco U.S. Mattace-Raso, Aad van der Lugt, M. Arfan Ikram, Oscar H. Franco, Robin P. Peeters, Maryam Kavousi

Rationale: **Thyroid hormones have been linked with various proatherogenic and antiatherogenic processes. However, the relationship of thyroid function with manifestations of atherosclerosis remains unclear.**

Objective: **To investigate the association of thyroid function with atherosclerosis throughout its spectrum; that is, subclinical atherosclerosis, incident atherosclerotic cardiovascular (ASCV) events, and ASCV mortality.**

Methods and Results: **This population-based study was embedded within the Rotterdam Study. The risk of atherosclerosis was evaluated by measuring (1) presence of subclinical atherosclerosis, assessed by coronary artery calcification score >100 AU; (2) ASCV events, defined as fatal and nonfatal myocardial infarction, other coronary heart disease mortality, or stroke; (3) ASCV mortality, defined as death because of coronary heart disease and cerebrovascular or other atherosclerotic diseases. Associations of thyroid-stimulating hormone and free thyroxine with the outcomes were assessed through logistic regression and Cox proportional hazard models, adjusted for potential confounders, including cardiovascular risk factors. A total of 9420 community-dwelling participants (mean age±SD, 64.8±9.7 years) were included. During a median follow-up of 8.8 years (interquartile range, 4.5–11.8 years), 934 incident ASCV events and 612 ASCV deaths occurred. Free thyroxine levels were positively associated with high coronary artery calcification score (odds ratio, 2.28; 95% confidence interval, 1.30–4.02) and incident ASCV events (hazard ratio, 1.87; confidence interval, 1.34–2.59). The risk of ASCV mortality increased in a linear manner with higher free thyroxine levels (hazard ratio, 2.41; confidence interval, 1.68–3.47 per 1 ng/dL) and lower thyroid-stimulating hormone levels (hazard ratio, 0.92; confidence interval, 0.84–1.00 per 1 logTSH). Results remained similar or became stronger among euthyroid participants.**

Conclusions: **Free thyroxine levels in middle-aged and elderly subjects were positively associated with atherosclerosis throughout the whole disease spectrum, independent of cardiovascular risk factors. (*Circ Res*. 2017;121: 1392-1400. DOI: 10.1161/CIRCRESAHA.117.311603.)**

Key Words: atherosclerosis ■ coronary arteries ■ humans ■ logistic models ■ odds ratio

Sciences,
(Prof W Li F
N Gao BSc, Y Sun
Diabetes Researcl
(Prof

dence of fatal infection than was placebo. There was no significant difference in all-cause mortality (hazard ratio for all canakinumab doses vs. placebo, 0.94; 95% CI, 0.83 to 1.06; P=0.31).

CONCLUSIONS

Antiinflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering. (Funded by Novartis; CANTOS ClinicalTrials.gov number, NCT01327846.)

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THANKS FOR YOUR ATTENTION