NVvLG

Nederlandse Vereniging voor
Lucht- en Ruimtevaartgeneeskunde

Opsporing en behandeling van asymptomatische cliënten met coronairlijden

Resultaten van de SUSPECT studie

drs. Erik Frijters
Senior Vliegerarts, AME, DAvMed

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CardioExpert Symposium Luchtvaart Cardiologie

Potentiële belangenverstrengeling	Geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Koninklijke Luchtmacht FXT Medical Services NVvLG
Sponsoring of onderzoeksgeld Honorarium of andere (financiële) vergoeding Aandeelhouder Andere relatie, namelijk …	Geen vermeldingen

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Sprekersinformatie

Erik Frijters

2008 – heden: Vliegerarts Koninklijke Luchtmacht
Vliegmedische keuringen MIL/CIV
Consultatie
Onderwijs
Aeromedevac, Search and Rescue (2012-2016)
Aircraft Accident Investigation
Research (AEOLUS / F-35 / NATO HFM / PhD)

Academische Opleidingen:
2008: Erasmus Medisch Centrum Rotterdam
2018: MSc Aerospace Medicine, Kings College London
2022 - heden: PhD kandidaat UMCU

Uitzendingen: 2011 Afghanistan, 2015 Mali, 2016 Mali

Nederlandse Vereniging voor Luchtvaartgeneeskunde

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Contents

- Rationale
- SUSPECT Study Design
- Methods
- Subjects
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- Case Reports
- Military Policy Change
- Discussion

Rationale

Why… SUSPECT

Screening for Coronary Artery Disease USing Primary Evaluation with Coronary CTA in Aviation Medicine

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Rationale

- 1973 Ian Anderson (Director of Civil Aviation Medicine Canada) presented a paper to the Aerospace Medical Association (AsMA)

- The risk of medical, in-flight incapacitation in pilots should be no greater than 1% per annum (for two pilot, civil aviation commercial operations)

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- Accepted airworthiness targets at that time were approximately 1 aircraft accident per 10 million flying hours (10^7) hrs, due to mechanical failure

- Anderson proposed that pilot aeromedical failure could be assessed in the same way and provide an objective method of assessing fitness for medical certification

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→ Cardiovascular Risk vs. Fitness to Fly

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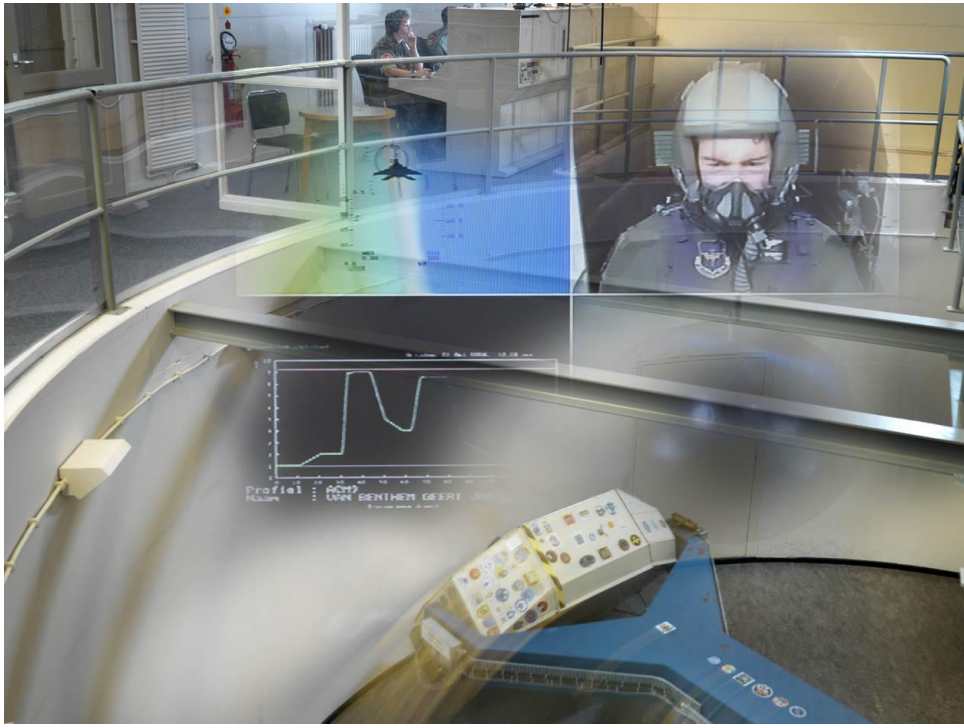
Rationale

- What about military fighter pilots..?

Rationale

- G-Forces!



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Rationale

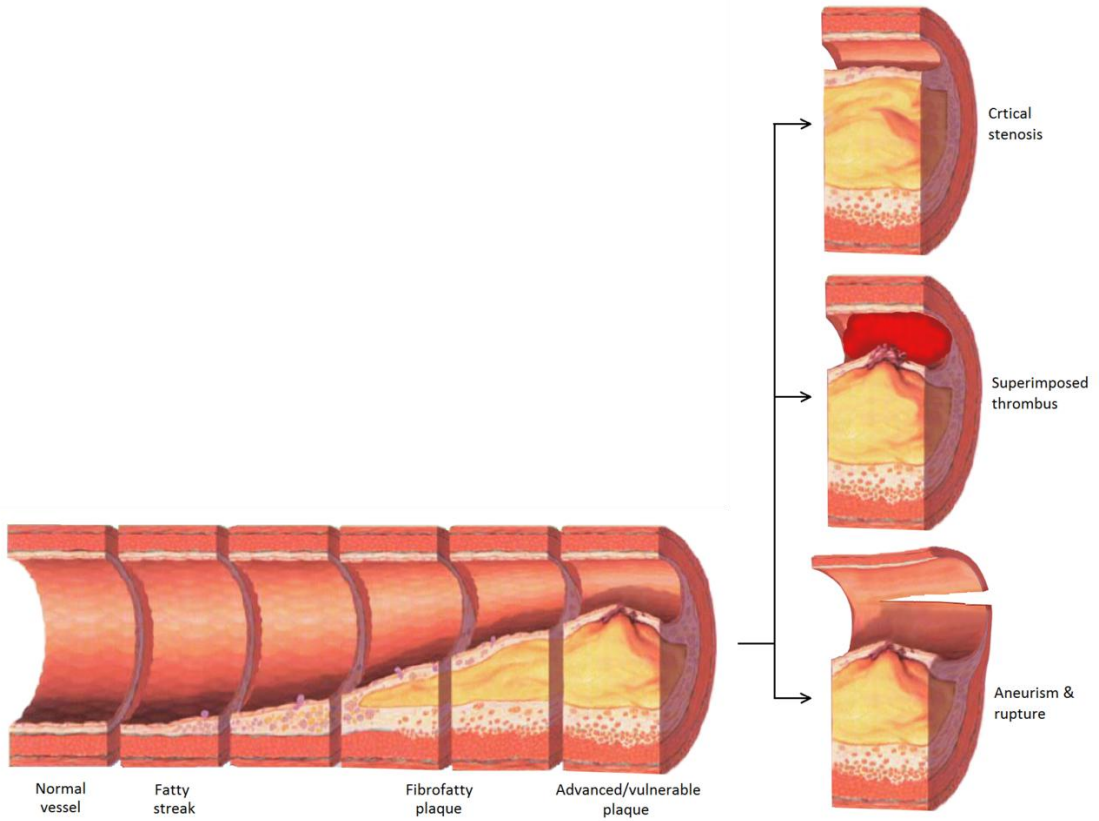
- G-Forces!

Rationale – Coronary Artery Disease (CAD)

➢In 25% of cases, myocardial infarction/sudden death is the first symptom of CAD!

Non Modifiable Risk Factors:

- Age
- Sex (M>F)
- Family History
- Ethnic Background



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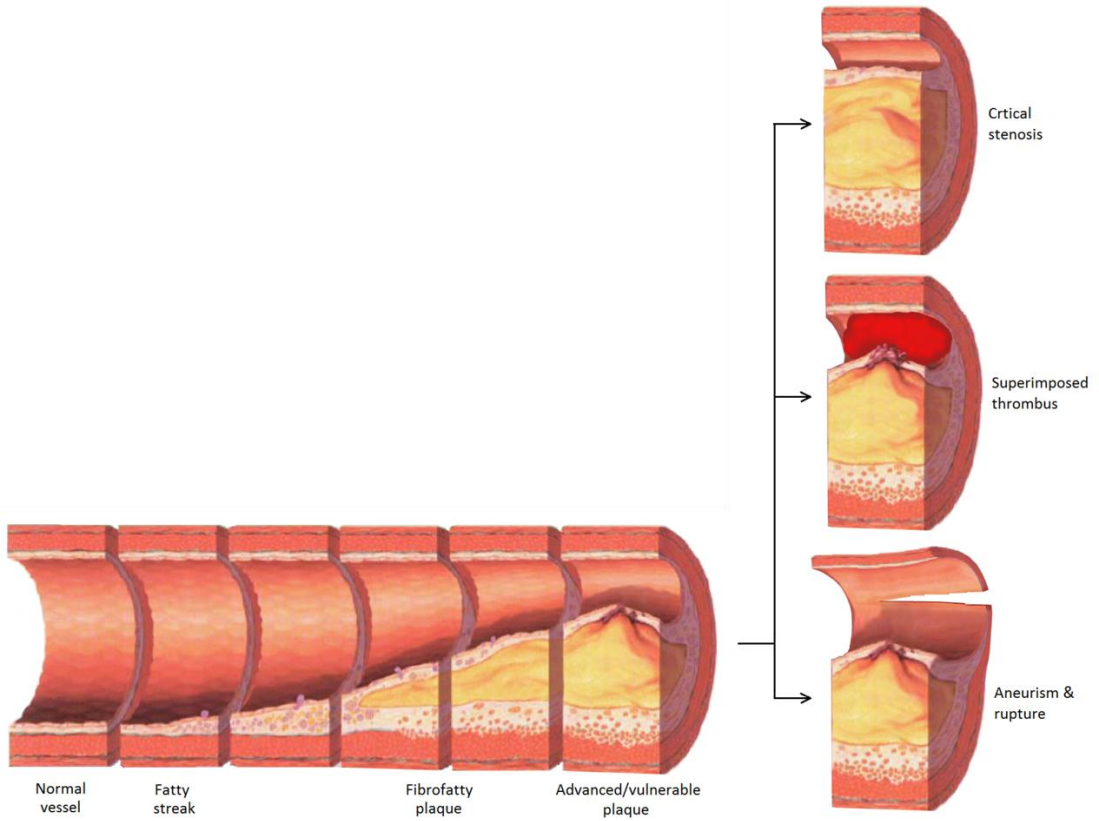
Non Modifiable Risk Factors:

- Age
- Sex (M>F)
- Family History
- Ethnic Background

Modifiable Risk Factors:

- High Cholesterol
- High Blood Pressure
- Smoking
- Diabetes
- Obesity
- Poor diet
- Physical Inactivity
- Psychosocial (stress)



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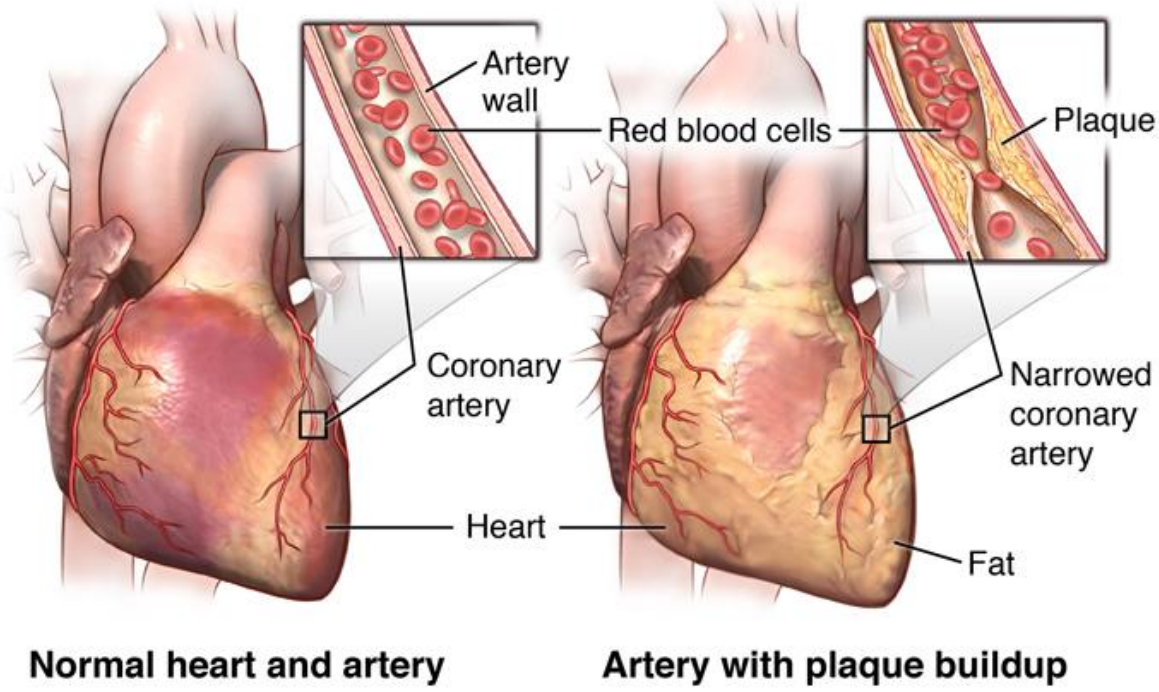

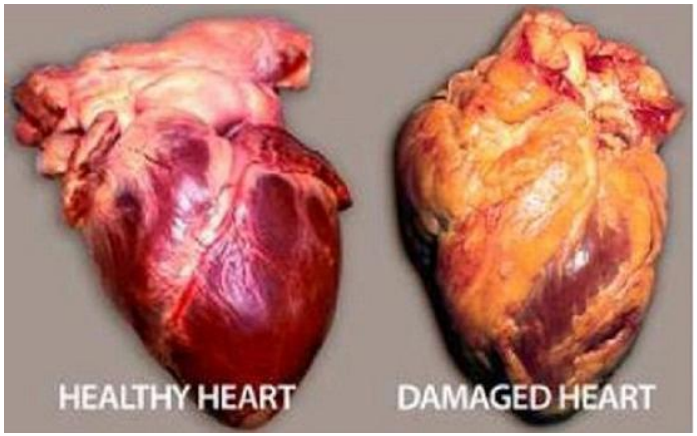

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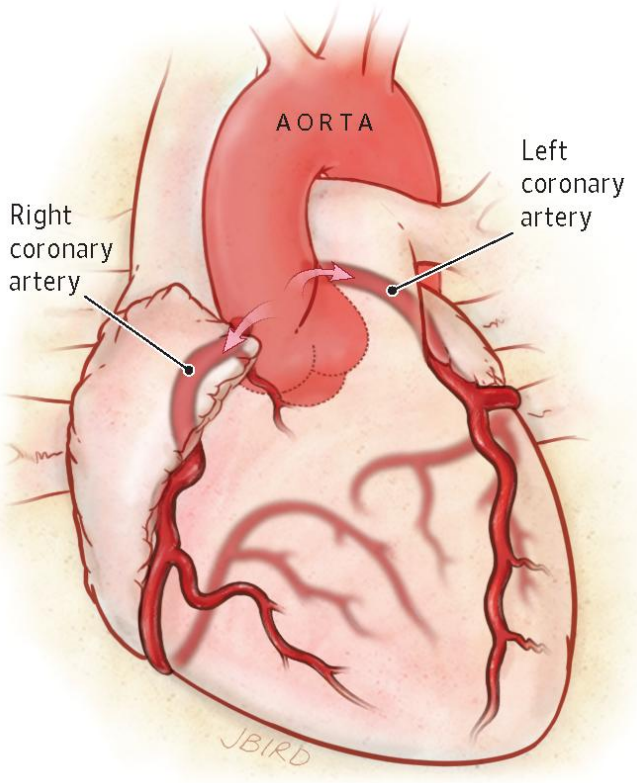
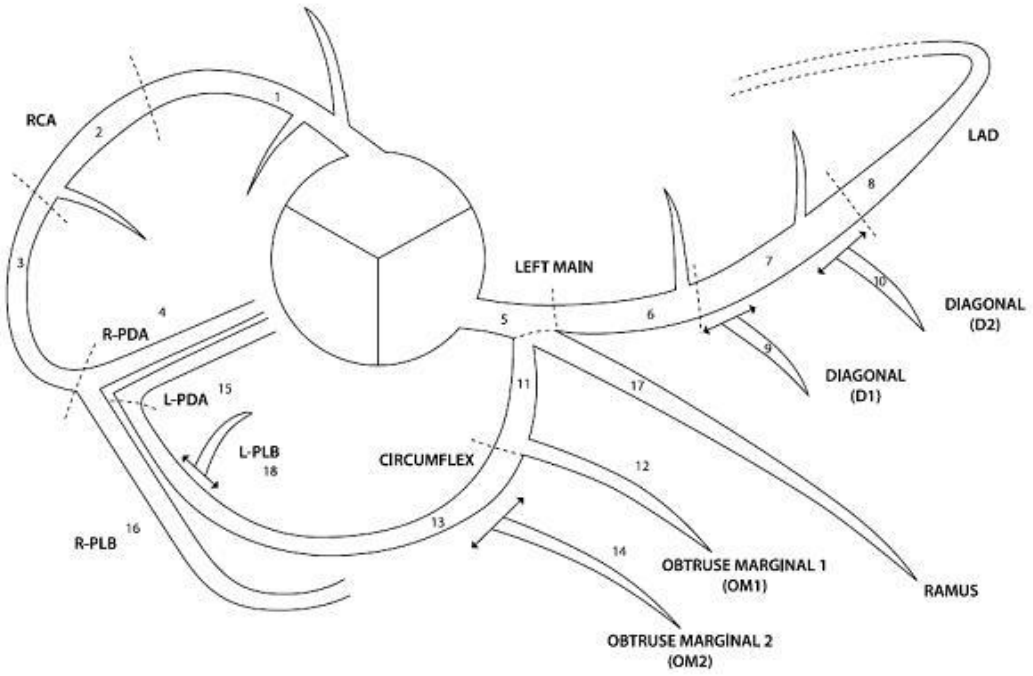
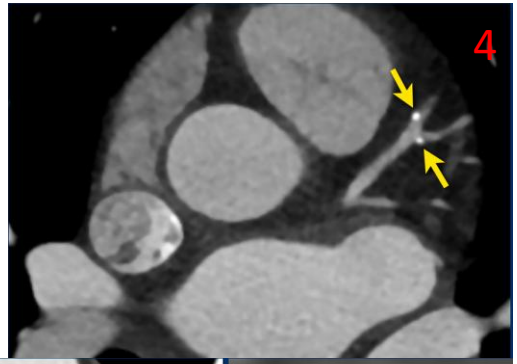


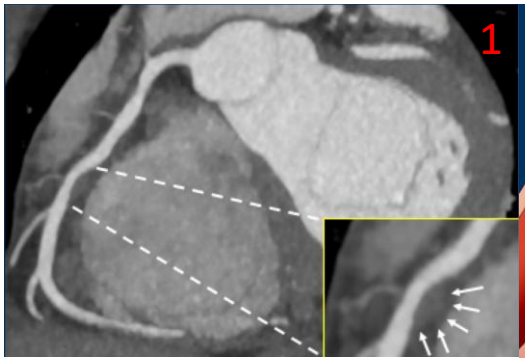


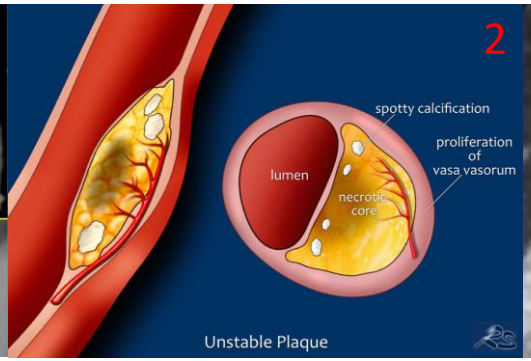
Coronary Artery Disease - Reporting and Data System (CAD-RADS)

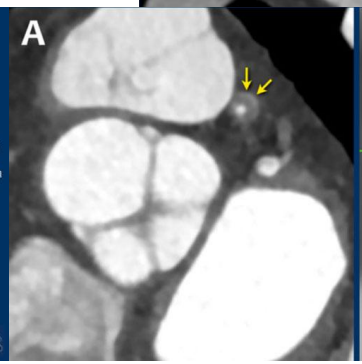
High Risk (Vulnerable) Plaque Criteria

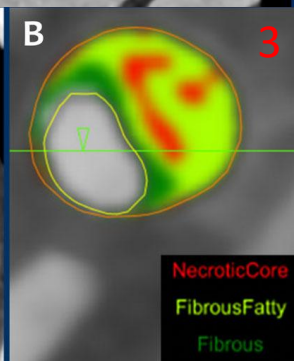
1. Low-attenuation plaque, average density <30 HU
2. Positive remodeling
3. Napkin-ring sign
4. Spotty calcification











HU: Hounsfield Units

Adapted from Radiology Assistant,
Csilla Celeng, Richard Takx, Robin Smithuis and Tim Leiner

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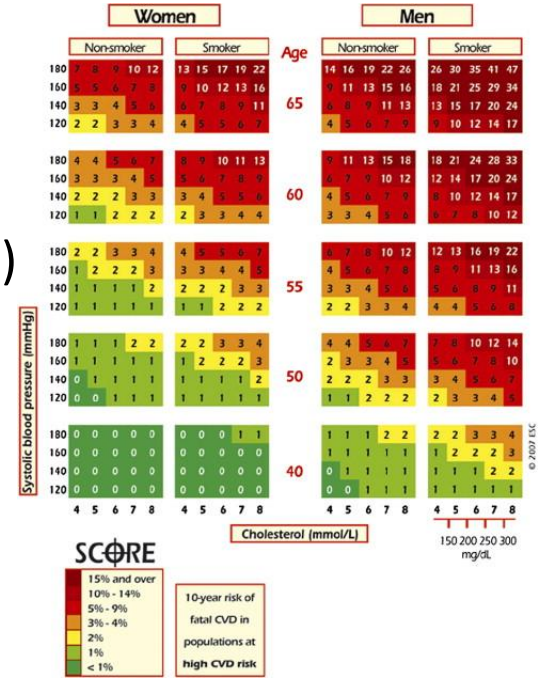
Rationale – Screening Methods

- Risk for medical incapacitation must be <1%

- Military regulations (MAR-FCL 3.140)
  Cardiovascular system – Coronary Artery Disease (CAD)
  - ➢ Screening required from age 40
  - ➢ Clinically relevant CAD: stenosis ≥ 50%

- Every Aeromedical Exam: physical exam,
  resting ECG, lab, Framingham Risk Score*

- xECG (since 2009): >40yr: xECG every 3 years
  >50yr: xECG yearly



- HOWEVER... xECG lacks diagnostic accuracy screening in low risk population

* in 2014

SUSPECT Study design

- Study started in November 2014 (IRB approval)

- Research aim:

Assess the value of cardiac CT for clinically and "aeromedically" relevant CAD in asymptomatic Dutch military aircrew aged ≥ 40 years, *compared to the current cardiac screening protocol, which includes an exercise ECG*

1. Primary endpoint: relevant CAD, defined as a composite of a coronary stenosis ≥50% and/or CACS >100 Agatston Units
2. Secondary endpoints, the prevalence of:
    1. mild coronary stenosis: defined as 25-49% stenosis
    2. vulnerable (high risk) plaque features
    3. "aeromedically significant CAD": defined as a left main stenosis of >30%, any luminal stenosis ≥50%, and/or an aggregate coronary stenosis of ≥120%

SUSPECT Study design

UMC Utrecht

- Study started in November 2014 (IRB approval)
- Coronary CTA - Voluntary basis
- Inclusion:
  - Royal Netherlands Air Force Military Air Crew ≥ 40 years old, who are required to undergo cardiac screening at Aeromedical Examination
- Exclusion:
  - Symptomatic, prior revascularization therapy, CT-related contra indications, pregnancy (…)
- Estimated CCTA sensitivity 92%, specificity 85%
- Assuming a prevalence of CAD >30% in 25% → 250 inclusions are needed

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CCTA: Coronary Computed Tomography Angiography
CAG: Coronary Angiography
CACS: Coronary Artery Calcium Score

Methods

- Aeromedical Exam:
  - Audiogram
  - Pulmonary Function Testing
  - Labs, incl cholesterol
  - Resting ECG
  - Ophtalmological Exam
  - Physical Exam

- Exercise ECG with VO_2max

- CT scan @ University Medical Center Utrecht:
  - 128/256 Slice CT with contrast (low radiation dose: ~3mSv)

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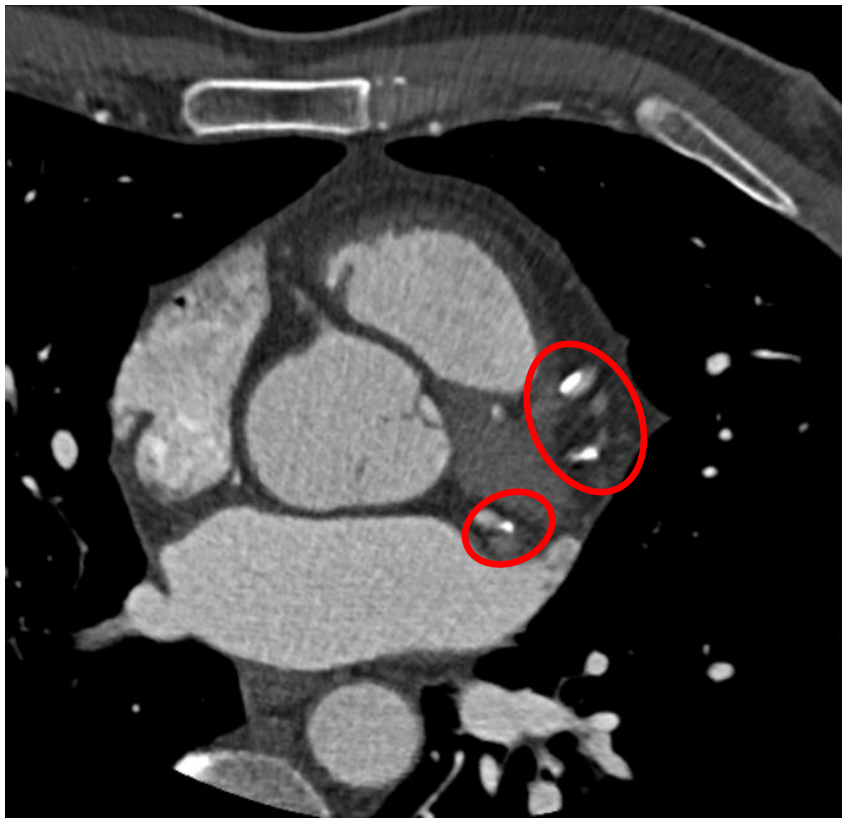
pikabu.ru



	Scoring Results : Agatston Score Protocol			
	LAD	LCX	RCA	Total Coronaries
Score	360.25	38.38	178.61	577.24
#ROI's	15	5	16	36
AreaSq (sq.mm.)	95.61	16.5	60.64	172.75

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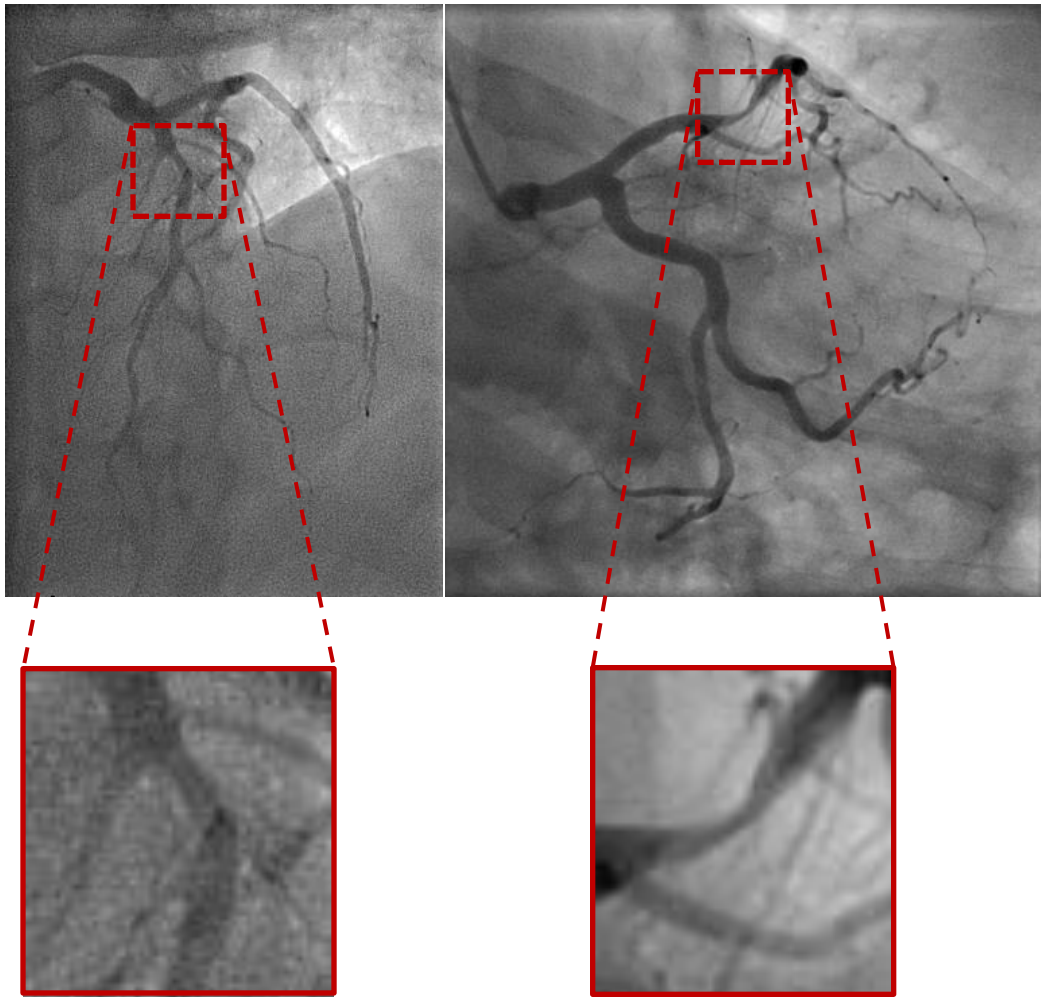
Coronary CT Angiography (CCTA)

Coronary Angiography (CAG)



Methods & Aeromedical Consequences

After scan:
SUSPECT team discusses CTA scan (and tx options based on best clinical judgment)

- No stenosis and CACS 0 = keep up the good work!
- CACS 1-99 AU or single luminal stenosis <25% → Lifestyle advice, statins if indicated
- CACS 100 – 399 AU, a single luminal stenosis 25-49% (CADRADS 2) or vulnerable plaque (≥ 2 features) → Lipid lowering therapy (e.g. statins) and life style advice / and referral to cardiologist
- CACS ≥400 AU, Left main >30 %, or any stenosis ≥50 % → DNIF & further evaluation by cardiologist
- Aeromedically relevant CAD → Lipid lowering therapy and lifestyle advise, results discussed with aeromedical specialist (AMS) of the military aviation authority of the RNLAF / and referral

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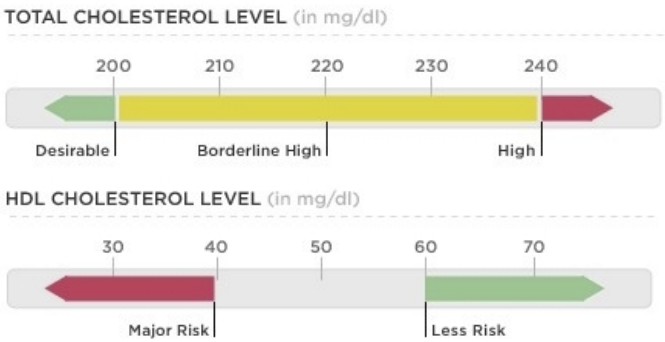
Characteristics	N=211
Age (years)	48.5 (5.3)
Male	207 (97.7%)
Hypertension, treated	13 (6%)
Hypercholesterolemia, treated	13 (6%)
Diabetes	2 (1%)
Current smoker	24 (11%)
Former smoker	61 (28%)
Positive Family History of CAD	54 (25%)
Alcohol use >5 units per week	76 (38%)
Physical activity (hour/week)	3.5 (2.2)
Performed Exercise ECG	200 (94%)
Normal Exercise ECG	193 (96.5%)
Average VO_2 max (ml/kg/min)	36.0 (6.3)*
Body mass index (kg/m²)	26.1 (2.9)
Resting heart frequency	62 (10)
Systolic blood pressure (mmHg)	136 (13)
Diastolic blood pressure (mmHg)	84 (8)
Pulse pressure (mmHg)	52 (9)
Total cholesterol (mmol/L)	5.0 (0.9)
Triglycerides (mmol/L)	1.6 (0.9)
LDL-cholesterol (mmol/L)	2.9 (0.8)
HDL-cholesterol (mmol/L)	1.3 (0.3)
eGFR (mL/min/1.73m²)	126 (24)



* Performed xECG with VO2max: n=111

Preliminary Results (men)

Cardiac CT findings:	N=207
CACS 0 AU	130 (62.8%)
CACS > 0 - <100 AU	56 (26.4%)
CACS 100 - 399 AU	15 (7.2%)
CACS ≥ 400 AU	6 (2.8%)

AU: Agatston units
CACS: coronary artery calcium score

Preliminary Results

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CACS 0 AU	130 (62.8%)
CACS > 0 - <100 AU	56 (26.4%)
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CACS ≥ 400 AU	6 (2.8%)
No stenosis	122 (57%)
Non-significant stenosis	81 (38%)
Significant stenosis (>50%)	8 (3.7%)
Aggregate stenosis >120%	22 (10.3%)

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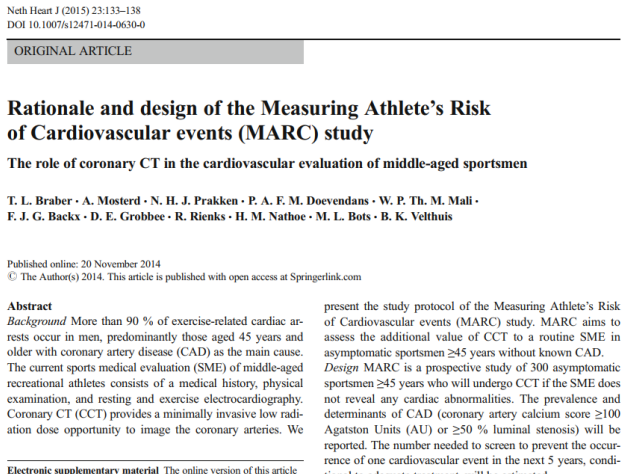
AU: Agatston units
CACS: coronary artery calcium score

Preliminary Results

Cardiac CT findings:	SUSPECT n=207	MARC n=284
CACS 0 AU	130 (62.8%)	151 (47.5%)
CACS 1-99 AU	56 (26.4%)	115 (36.2%)
CACS 100-399 AU	15 (7.2%)	29 (9.1%)
CACS ≥400 AU	6 (2.8%)	23 (7.2%)

MARC: Measuring Athlete's Risk of Cardiovascular Events (2014)



Neth Heart J (2015) 23:133–138
DOI 10.1007/s12471-014-0630-0

ORIGINAL ARTICLE

Rationale and design of the Measuring Athlete's Risk of Cardiovascular events (MARC) study

The role of coronary CT in the cardiovascular evaluation of middle-aged sportsmen

T. L. Braber · A. Mosterd · N. H. J. Prakken · P. A. F. M. Doevendans · W. P. Th. M. Mali · F. J. G. Backx · D. E. Grobbee · R. Rienks · H. M. Nathoe · M. L. Bots · B. K. Velthuis

Published online: 20 November 2014

Abstract
Background More than 90 % of exercise-related cardiac arrests occur in men, predominantly those aged 45 years and older with coronary artery disease (CAD) as the main cause. The current sports medical evaluation (SME) of middle-aged recreational athletes consists of a medical history, physical examination, and resting and exercise electrocardiography. Coronary CT (CCT) provides a minimally invasive low radiation dose opportunity to image the coronary arteries. We present the study protocol of the Measuring Athlete's Risk of Cardiovascular events (MARC) study. MARC aims to assess the additional value of CCT to a routine SME in asymptomatic sportsmen ≥45 years without known CAD.
Design MARC is a prospective study of 300 asymptomatic sportsmen ≥45 years who will undergo CCT if the SME does not reveal any cardiac abnormalities. The prevalence and determinants of CAD (coronary artery calcium score ≥100 Agatston Units (AU) or ≥50 % luminal stenosis) will be reported. The number needed to screen to prevent the occurrence of one cardiovascular event in the next 5 years, condi-

Electronic supplementary material The online version of this article

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Coronary CT angiography, no atherosclerosis	122 (57%)	117 (36.8%)
Coronary CT angiography, significant stenosis (≥50%)	8 (3.7%)	17 (5.3%)
Coronary artery disease (CACS ≥100 AU and / or 50% stenosis)	25 (12.1%)	60 (8.9%)
Aeromedically Significant CAD	27 (13.1%)	NA

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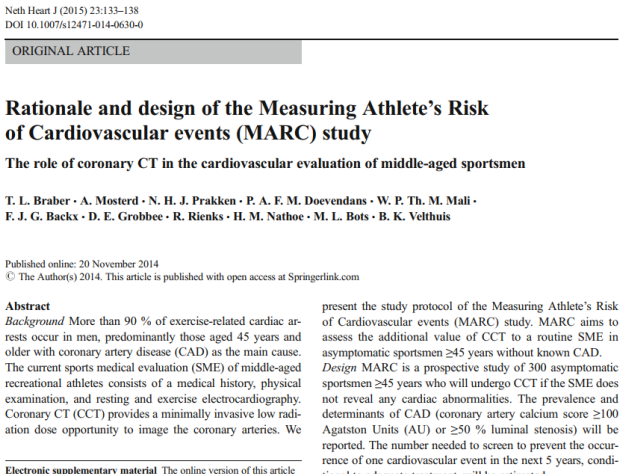

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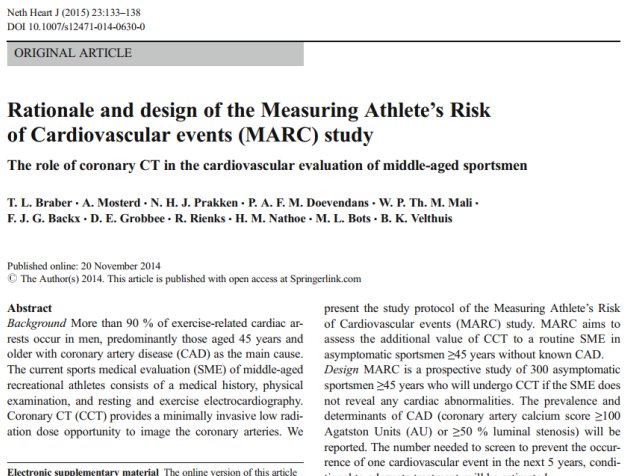

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Preliminary Results

AGE	SMOKING STAT	ANTI_HT	FAM	BMI	BP	CHOL	TG	HDL	LDL	WATT	METS	VO2MAX	CACS	Cornonary CT	Framingham
51	never	no	no	24.3	136/86	6.3	0.9	1.7	4.2	322	11.9	41.8	292	Stenosis <30%	9.6
53	never	yes	no	30.4	127/84	4.8	2	1.1	2.8	286	8.77	30.7	243	Stenosis 30-50%	13.7
52	no, quit	no	no	25.2	123/83	4.6	1.9	1	2.7	270	10.2	35.6	155	Stenosis 30-50%	9.2
54	never	no	no	21.3	140/85	5.6	1	1.5	3.6	242	10.2	35.8	577	Stenosis 30-50%	11.5
50	never	no	no	26.5	150/80	5.4	1.7	0.7	3.9				2189	Stenosis >50%	19.3
50	no, quit	no	yes	29.8	139/81	5.6	1.6	1.5	3.4	284	8.4	24.4	2.2	Stenosis >50%	8.8
50	never	no	yes	26.3	147/83	4.8	1.4	1.4	2.8	334	9.49	33.2	449	Stenosis 30-50%	9.2
52	no, quit	no	yes	28.8	142/84	4.1	1.1	0.8	2.8	373	10.4	36.3	152	Stenosis <30%	13.1
55	yes	no	no	25.7	115/80	5	2	1.1	3	269	7.17	25.1	160	Stenosis 30-50%	17.7
49	never	yes	no	25.1	130/85	5	1.9	1.4	2.7				130	Stenosis 30-50%	9.8
55	no, quit	no	no	26.5	124/85	5.5	0.7	1.9	3.3	222	20.2	35.6	239	Stenosis 30-50%	7.7
55	never	no	yes	23.4	135/85	5.7	0.7	1.6	3.8	339	11.4	40	189	Stenosis 30-50%	10.7
51	yes	no	yes	26.4	136/90	4	1.7	0.8	2.4	247	7.03	24.6	251	Stenosis <30%	20.2

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*Significant CAD: CACS ≥100 and/or stenosis ≥50%

Preliminary Results

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52	no, quit	no	no	25.2	123/83	4.6	1.9	1	2.7	270	10.2	35.6	155	Stenosis 30-50%	9.2
54	never	no	no	21.3	140/85	5.6	1	1.5	3.6	242	10.2	35.8	577	Stenosis 30-50%	11.5
50	never	no	no	26.5	150/80	5.4	1.7	0.7	3.9				2189	Stenosis >50%	19.3
50	no, quit	no	yes	29.8	139/81	5.6	1.6	1.5	3.4	284	8.4	24.4	2.2	Stenosis >50%	8.8
50	never	yes	yes	26.3	147/83	4.8	1.4	1.4	2.8	334	9.49	33.2	449	Stenosis 30-50%	9.2
52	no, quit	no	yes	28.8	142/84	4.1	1.1	0.8	2.8	373	10.4	36.3	152	Stenosis <30%	13.1
55	yes	yes	no	25.7	115/80	5	2	1.1	3	269	7.17	25.1	160	Stenosis 30-50%	17.7
49	never	no	yes	25.1	130/85	5	1.9	1.4	2.7				130	Stenosis 30-50%	9.8
55	no, quit	no	no	26.5	124/85	5.5	0.7	1.9	3.3	222	20.2	35.6	239	Stenosis 30-50%	7.7
55	never	no	yes	23.4	135/85	5.7	0.7	1.6	3.8	339	11.4	40	189	Stenosis 30-50%	10.7
51	yes	no	yes	26.4	136/90	4	1.7	0.8	2.4	247	7.03	24.6	251	Stenosis <30%	20.2

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*Significant CAD: CACS ≥100 and/or stenosis ≥50%

Case Reports

#1 - 50 yo pilot

Coronary artery calcium score (CACS)
Agatston score: 449 (98th MESA percentile)



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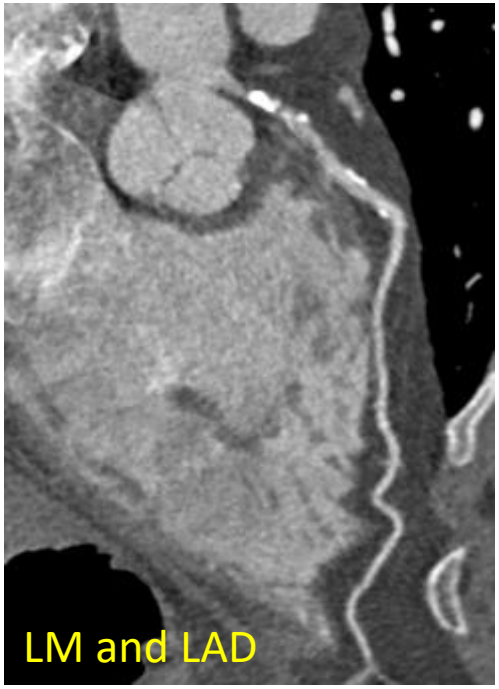
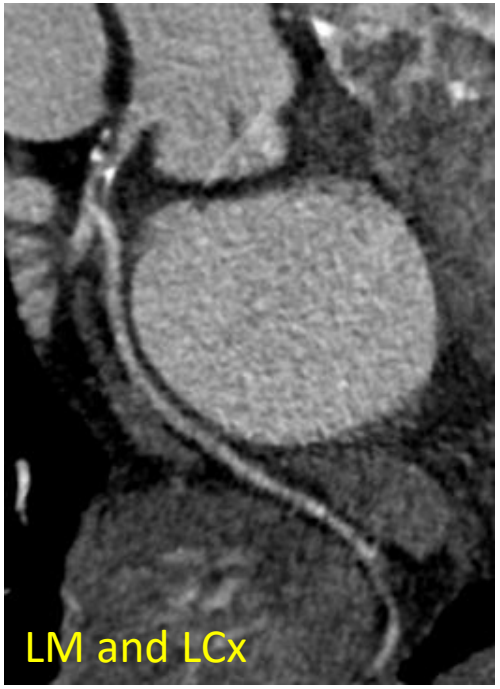
#1 - 50 yo pilot

Coronary CT angiography
Atherosclerosis distal LM and LAD with LAD stenosis





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#1 - 50 yo pilot

- Coronary CT angiography:
  - Atherosclerosis distal LM and LAD with 70% LAD stenosis

- CAG:
  - 30% stenosis distal LM, 70% stenosis LAD (Fractional flow reserve 0.72)
  - 2 overlapping stents LM and LAD

→ Return to Fly (Multi-pilot) after 6 months

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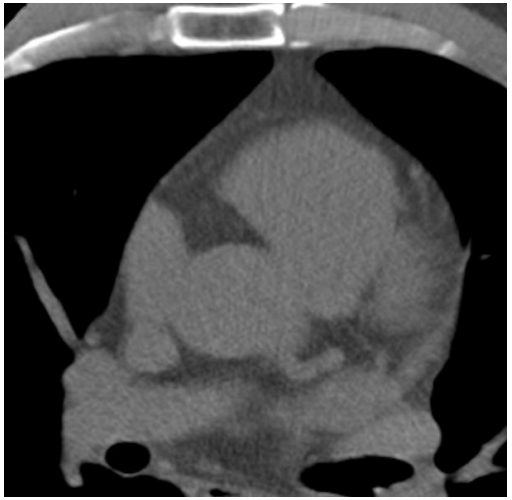
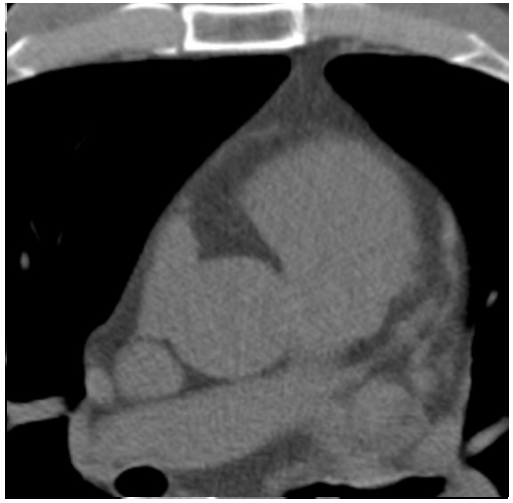
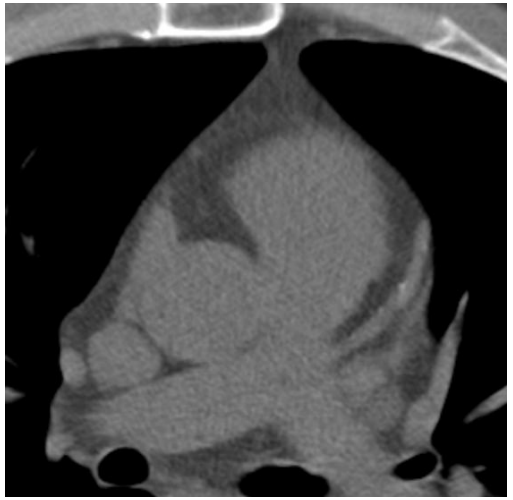
#2 - 49 yo pilot

Coronary artery calcium score (CACS)
Agatston score: 2,15 (64th MESA percentile)

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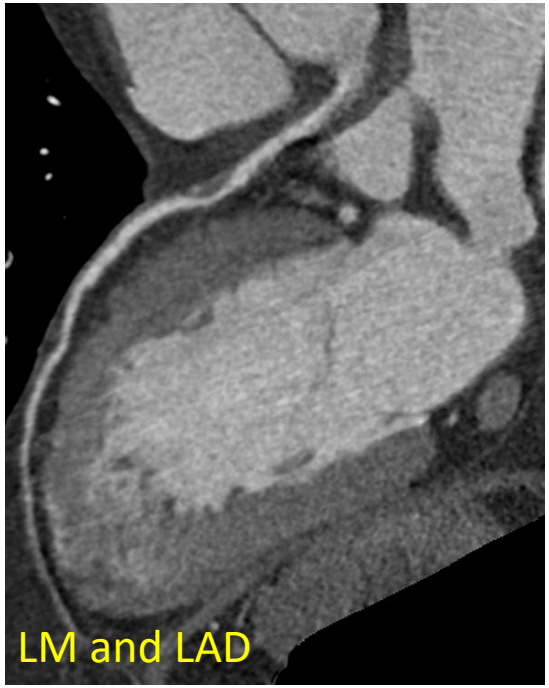
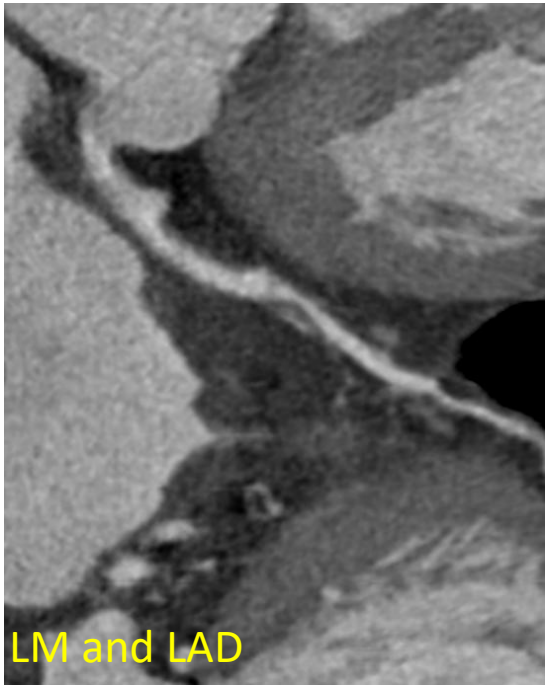
#2 - 49 yo pilot

Coronary CT angiography
Atherosclerosis LAD with >50% stenosis





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#2 - 49 yo pilot

Coronary CT angiography 2015

Atherosclerosis mid LAD (segm 7) with stenosis

CAG

Moderate stenosis (70%) of LAD, FFR 0.79 (=border line)

PCSK9 inhibitor → LDL towards <=1 mmol/L and Ascal

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#2 - 49 yo pilot

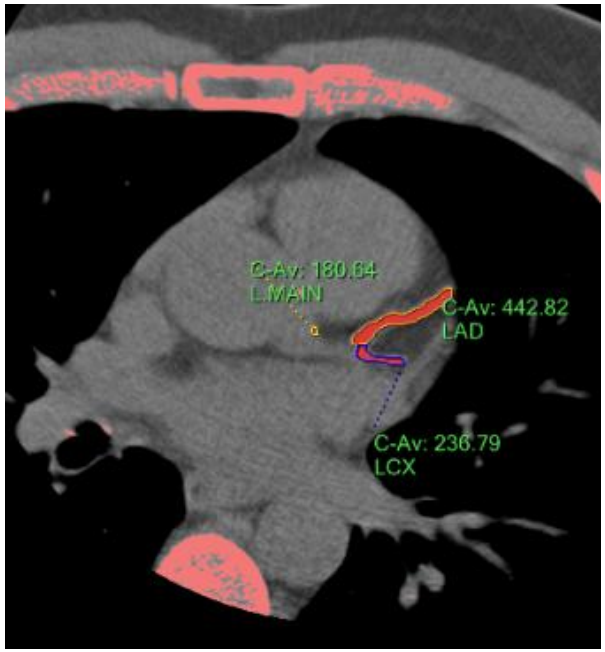
2016: CT angiography, no plaque progression or regression
2017: Cardiac MRI: no ischemia/ no infarction
2018: CT angiography, no changes
2020: Dyspnea on exertion. Cardiac MRI: septal perfusion defect basal to apical.

CAG
Progression of lesion (70%) mid LAD, FFR 0.75
Stenting 1 with drug-eluting stent

→ Return to Fly (Multi-pilot) after 6 months

#3 - 50 yo pilot

Coronary artery calcium score: 2189 AU (99th MESA percentile)



	Scoring Results : Agatston Score Protocol				
	L.MAIN	LAD	LCX	RCA	Total Coronaries
Score	4.1	970.13	453.7	760.86	2188.79
#HOTs	1	17	12	14	44
AreaSq (sq.mm.)	2.05	266.16	127.2	190.72	584.13

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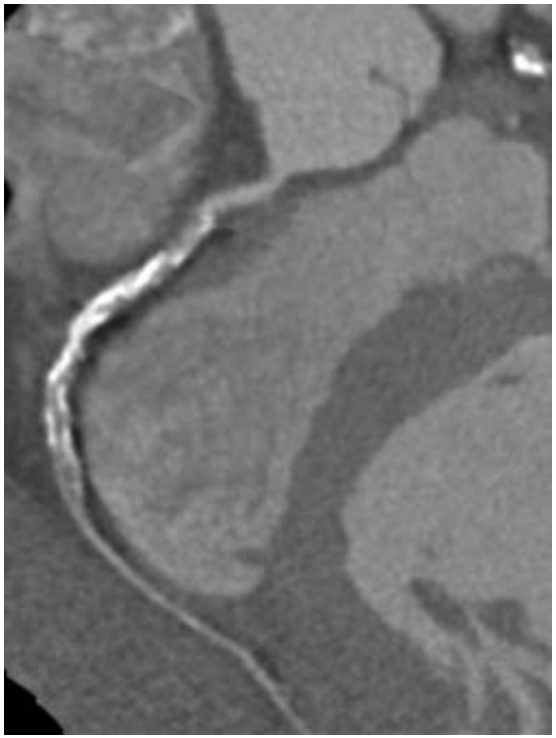
#3 - 50 yo pilot

Coronary CT angiography: Diffuse calcified atherosclerosis, stenosis grade difficult to assess



RCA

LCX-MO

LAD

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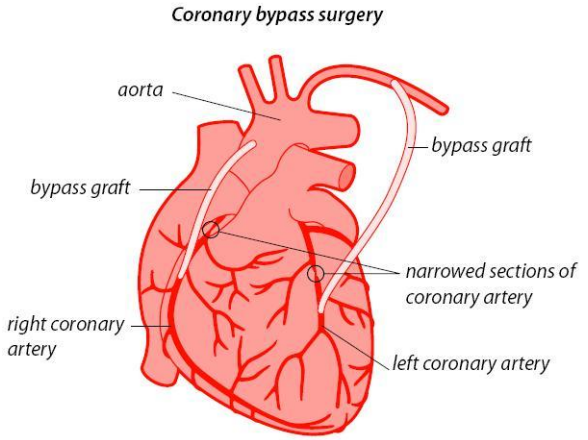
#3 - 50 yo pilot

- CAG:
  - Occlusion dominant mid RCA with distal filling via collaterals
  - 70 % stenosis mid and distal LAD and stenosis MO2

- CABG:
  - Uncomplicated RIMA – LAD; LIMA – MO2 & PRL of RCA

- 2017 Liver transplant

- Return to Fly (Multi-pilot)



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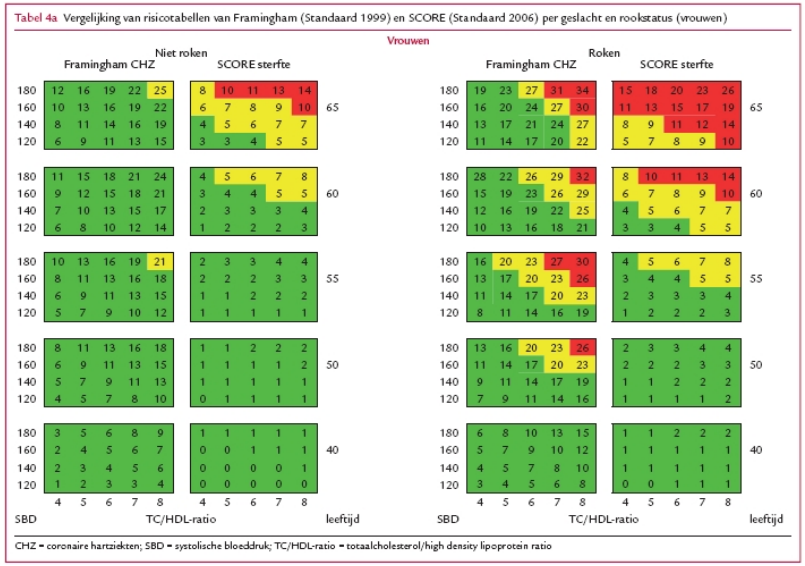
Military Regulations... after Update (2020)

- From the age of 40 an appropriate risk calculator will be used by the Flight Surgeon to estimate cardiovascular risk at every aeromedical examination. Enhanced screening shall be performed if the 10 year risk for cardiovascular events exceeds 10%. Enhanced screening can also be indicated based on clinical judgment and/or aeromedical judgment.



Tabel 4a Vergelijking van risicotabellen van Framingham (Standaard 1999) en SCORE (Standaard 2006) per geslacht en rookstatus (vrouwen)

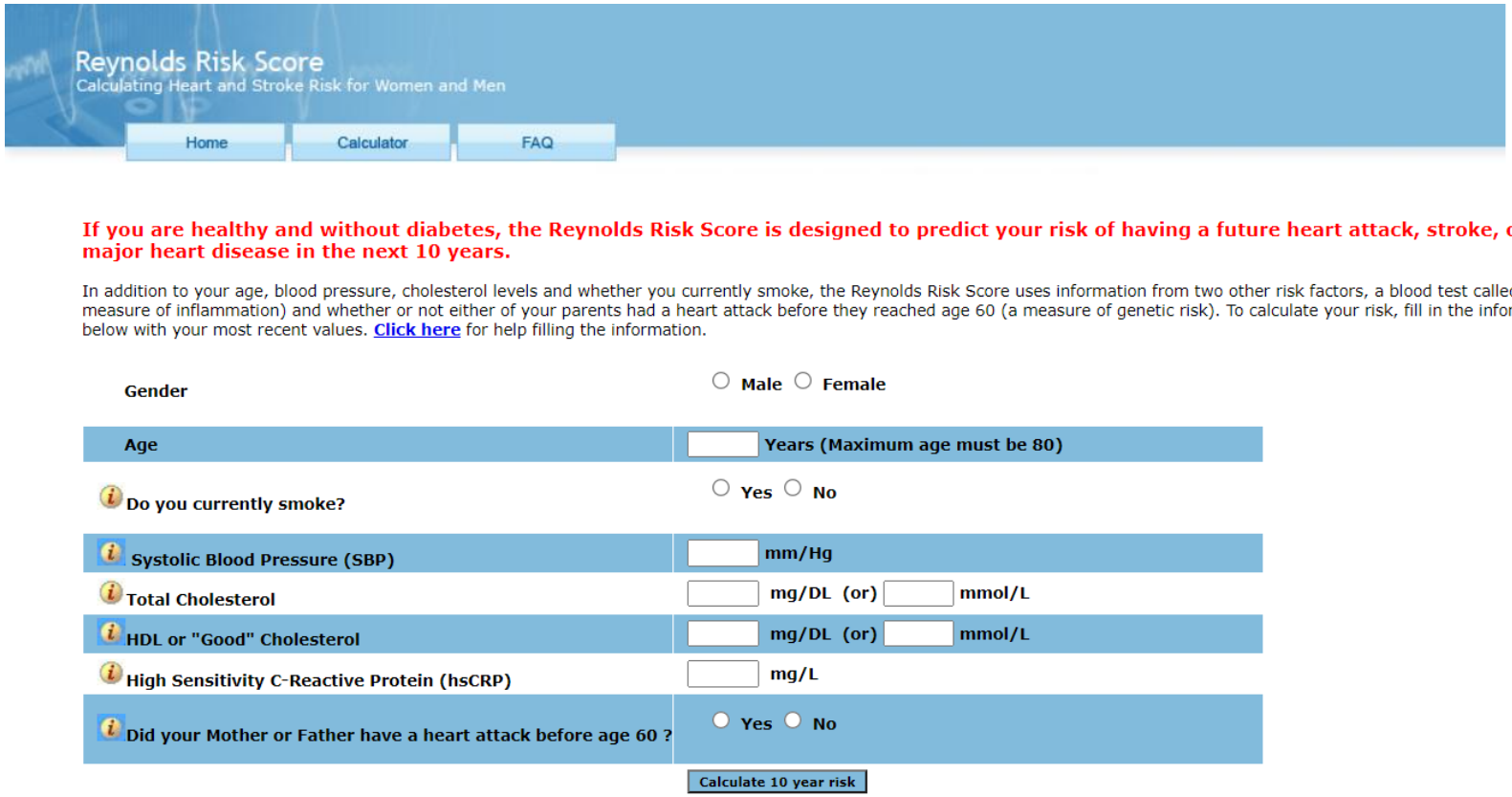
Vrouwen

	Niet roken										Roken									
	Framingham CHZ					SCORE sterfte					Framingham CHZ					SCORE sterfte				
SBD \ TC/HDL-ratio	4	5	6	7	8	4	5	6	7	8	4	5	6	7	8	4	5	6	7	8
180	12	16	19	22	25	8	10	11	13	14	19	23	27	31	34	15	18	20	23	26
160	10	13	16	19	22	6	7	8	9	10	16	20	24	27	30	11	13	15	17	19
140	8	11	14	16	19	4	5	6	7	7	13	17	21	24	27	8	9	11	12	14
120	6	9	11	13	15	3	3	4	5	5	11	14	17	20	22	5	7	8	9	10
180	11	15	18	21	24	4	5	6	7	8	28	22	26	29	32	8	10	11	13	14
160	9	12	15	18	21	3	4	4	5	5	15	19	23	26	29	6	7	8	9	10
140	7	10	13	15	17	2	3	3	3	4	12	16	19	22	25	4	5	6	7	7
120	6	8	10	12	14	1	2	2	2	3	10	13	16	18	21	3	3	4	5	5
180	10	13	16	19	21	2	3	3	4	4	16	20	23	27	30	4	5	6	7	8
160	8	11	13	16	18	2	2	2	3	3	13	17	20	23	26	3	4	4	5	5
140	6	9	11	13	15	1	1	2	2	2	11	14	17	20	23	2	3	3	3	4
120	5	7	9	10	12	1	1	1	1	1	8	11	14	16	19	1	2	2	2	3
180	8	11	13	16	18	1	1	2	2	2	13	16	20	23	26	2	3	3	4	4
160	6	9	11	13	15	1	1	1	1	2	11	14	17	20	23	2	2	2	3	3
140	5	7	9	11	13	1	1	1	1	1	9	11	14	17	19	1	1	2	2	2
120	4	5	7	8	10	0	1	1	1	1	7	9	11	14	16	1	1	1	1	2
180	3	5	6	8	9	1	1	1	1	1	6	8	10	13	15	1	1	2	2	2
160	2	4	5	6	7	0	0	1	1	1	5	7	9	10	12	1	1	1	1	1
140	2	3	4	5	6	0	0	0	0	1	4	5	7	8	10	1	1	1	1	1
120	1	2	3	3	4	0	0	0	0	0	3	4	5	6	8	0	0	1	1	1

leeftijd: 65, 60, 55, 50, 40

CHZ = coronaire hartziekten; SBD = systolische bloeddruk; TC/HDL-ratio = totaalcholesterol/high density lipoprotein ratio

Military Regulations... after Update (2020)



Reynolds Risk Score

Calculating Heart and Stroke Risk for Women and Men

Home | Calculator | FAQ

If you are healthy and without diabetes, the Reynolds Risk Score is designed to predict your risk of having a future heart attack, stroke, or other major heart disease in the next 10 years.

In addition to your age, blood pressure, cholesterol levels and whether you currently smoke, the Reynolds Risk Score uses information from two other risk factors, a blood test called hsCRP (a measure of inflammation) and whether or not either of your parents had a heart attack before they reached age 60 (a measure of genetic risk). To calculate your risk, fill in the information below with your most recent values. Click here for help filling the information.

Gender	○ Male ○ Female
Age	Years (Maximum age must be 80)
Do you currently smoke?	○ Yes ○ No
Systolic Blood Pressure (SBP)	mm/Hg
Total Cholesterol	mg/DL (or) mmol/L
HDL or "Good" Cholesterol	mg/DL (or) mmol/L
High Sensitivity C-Reactive Protein (hsCRP)	mg/L
Did your Mother or Father have a heart attack before age 60 ?	○ Yes ○ No

Calculate 10 year risk

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Military Regulations... after Update (2020)

- From the age of 40 an appropriate risk calculator will be used by the Flight Surgeon to estimate cardiovascular risk at every aeromedical examination. Enhanced screening shall be performed if the 10 year risk for cardiovascular events exceeds 10%. Enhanced screening can also be indicated based on clinical judgment and/or aeromedical judgment.

- Applicants with suspected symptomatic coronary artery disease shall be grounded pending investigation. Asymptomatic applicants with an abnormal exercise test shall be grounded pending investigation. Asymptomatic applicants with a normal exercise stress ECG, but elevated cardiovascular risk (>10% per 10 years) shall undergo enhanced screening, while maintaining flying status.

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Military Regulations... after Update (2020)

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Enhanced screening should at least comprise of CACS and CTCA.

Discussion and conclusion of the study

- CT as a one time screening tool for high risk occupations?
- Ethical considerations for treatment?
- Preliminary results, publication: WIP
- Comparison between xECG, risk scores and CT scan
- Comparison between SUSPECT, MARC study and referred (clinical) patients

➢ Results yet to be published...

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Future work...

- Analyze long term outcome of SUSPECT cohort..?
- Develop specific Risk Score / Matrix for low-risk populations with high-risk occupations, such as air crew

Aanbevolen literatuur:

- An introduction to aviation cardiology
  Nicol ED, et al. Heart. 2019. PMID: 30425080

- Assessing aeromedical risk: a three-dimensional risk matrix approach
  Gray G, et al. Heart 2019. PMID: 30425081

- Management of established coronary artery disease in aircrew without myocardial infarction or revascularization
  Davenport ED, et al. Heart 2019. PMID: 30425081

https://heart.bmj.com/content/105/Suppl_1

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Met dank aan…

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- Centrum voor Mens en Luchtvaart, Soesterberg
- Universitair Medisch Centrum Utrecht
- Centraal Militair Hospitaal, Utrecht

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Vragen?

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