

# **CVON ARGUS**

AlgoRithm for the exclusion diaGnosis of coronary vascUlar diSease

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#### **Overview**

- Who are we?
- What is ARGUS?
  - Background
    - Biology
    - Epidemiology
  - Rationale and aim
  - Place of hackathon within programme
- ARGUS / ABN AMRO hackathon
  - Data
  - Imaging techniques
  - Text mining in CT and MRI reports



#### Who are we?



**Sophie Bots, MSc**PhD student, background in Epidemiology and Statistics



**Floor Groepenhoff, MD**PhD student, background in Medicine



**Klaske Siegersma, MSc**PhD student, background in Technical Medicine



**Enja Blasse, BSc**Data manager, background in Physics



**Thuur Peeters, BSc**Master student Biology of Disease

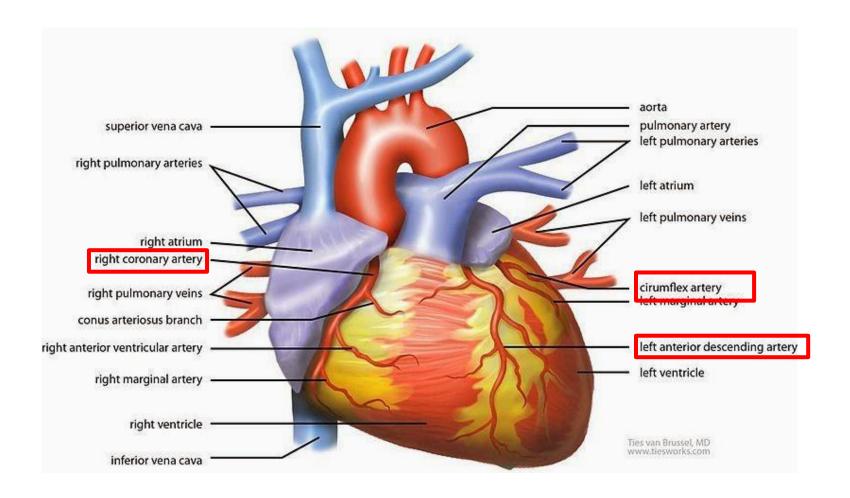




# What is ARGUS?

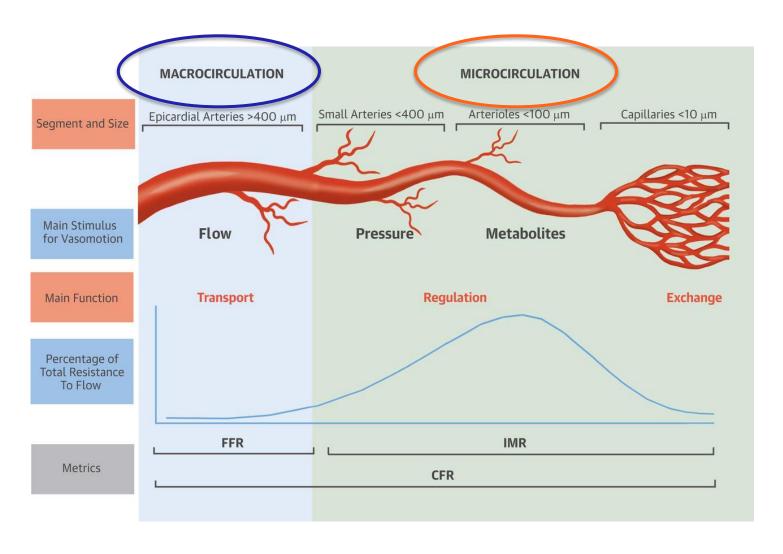
Sophie

# **Biology: heart and vasculature**



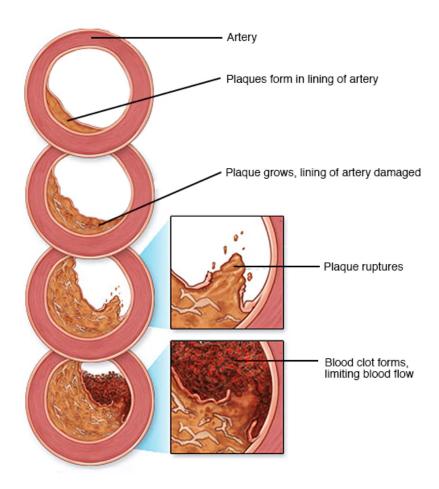


# **Biology: macro- and microvasculature**

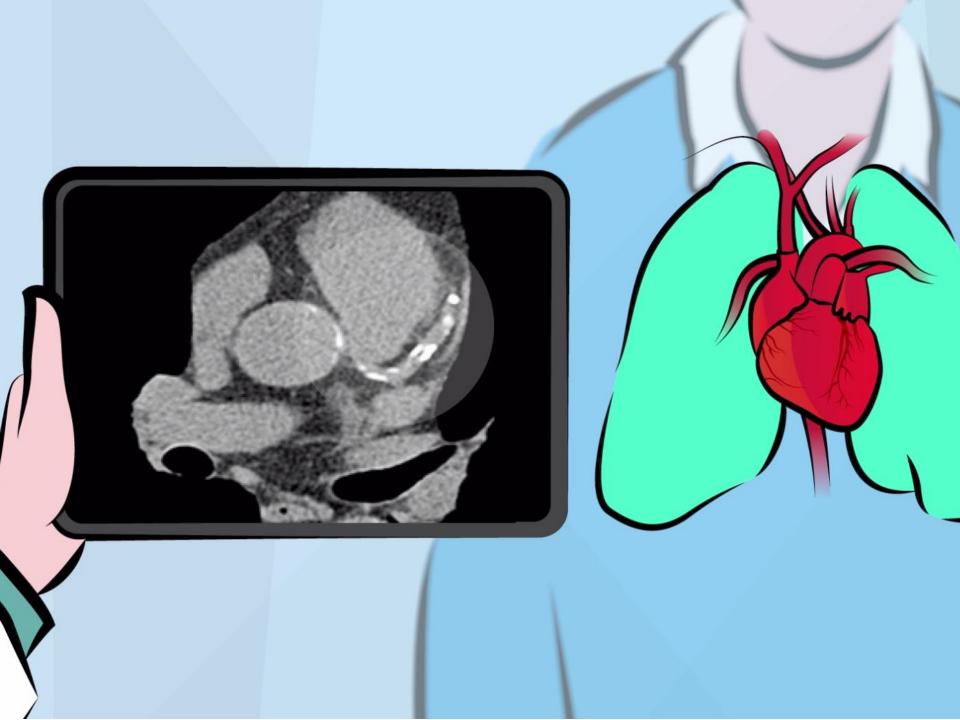




# **Biology: Obstructive CAD**







## **Biology: non-obstructive CAD**

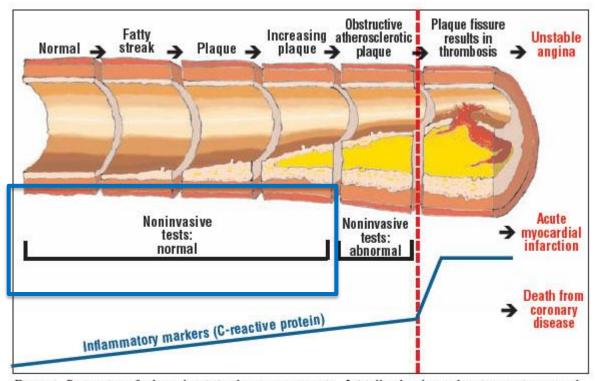
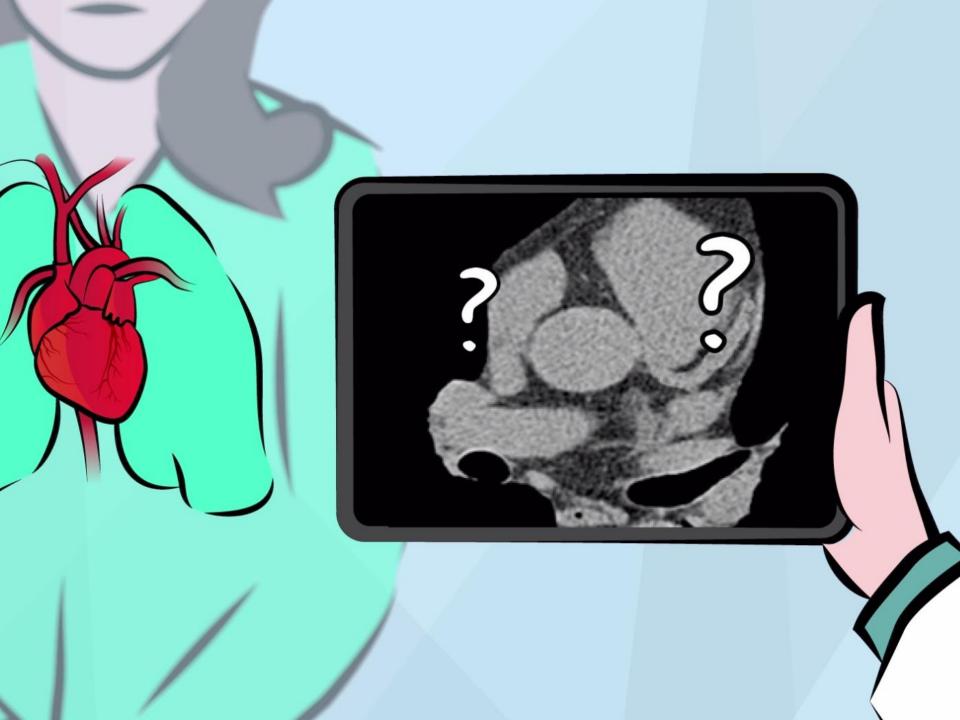
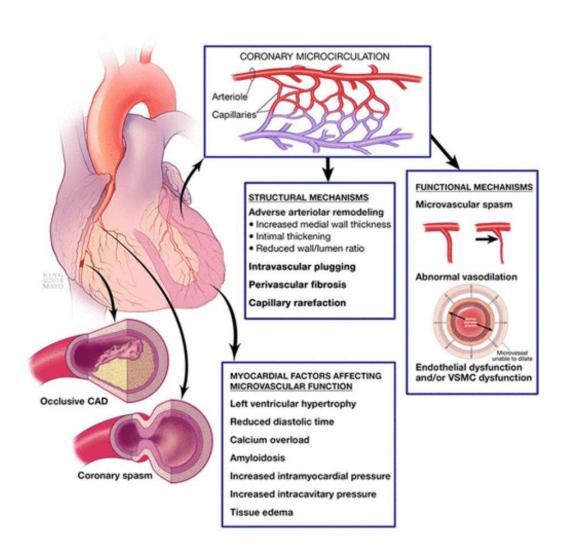


Figure 1. Progression of atherosclerosis in the coronary arteries. Initially, the plaque deposits remain external to the lumen. As the amount of plaque increases, it begins to intrude into the lumen, decreasing the diameter of the coronary artery and causing obstruction. The resulting plaque fissure or erosion leads to angina.

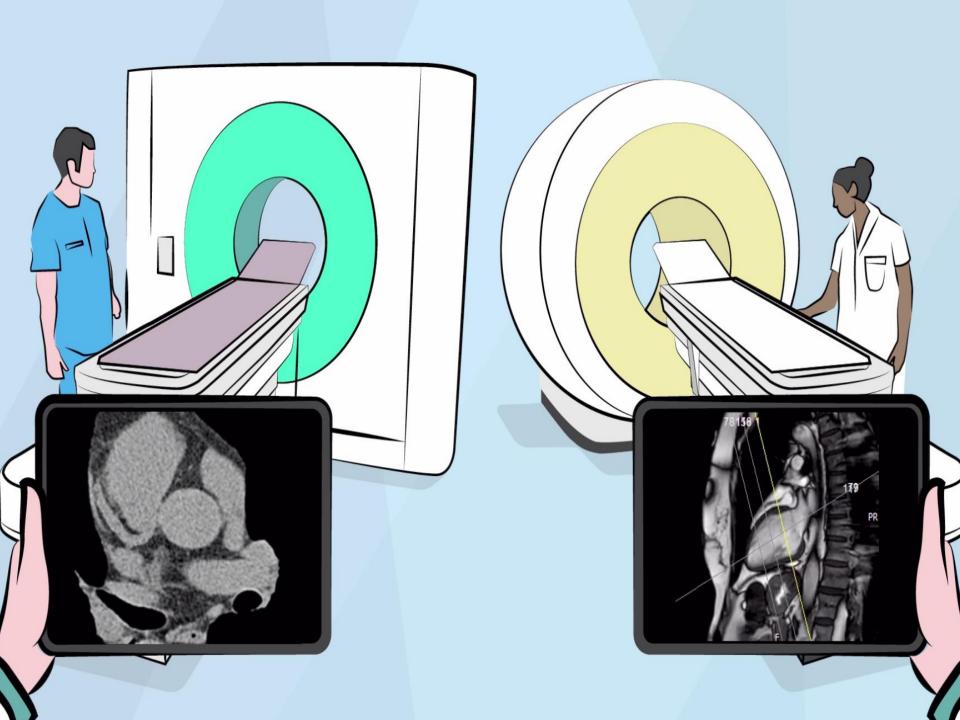




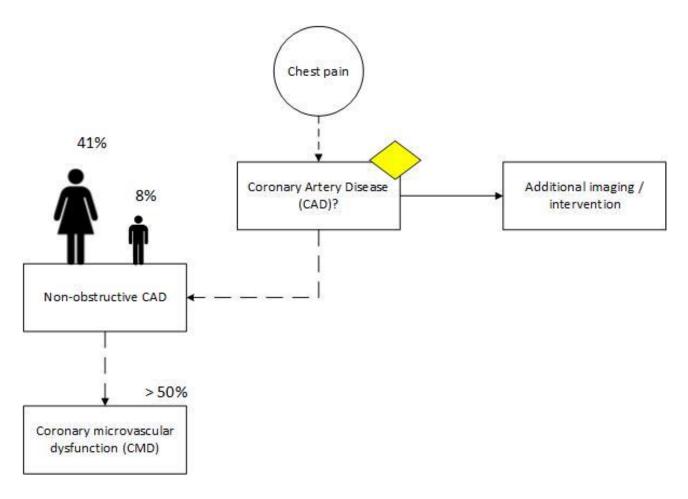
# **Biology: perfusion defects**





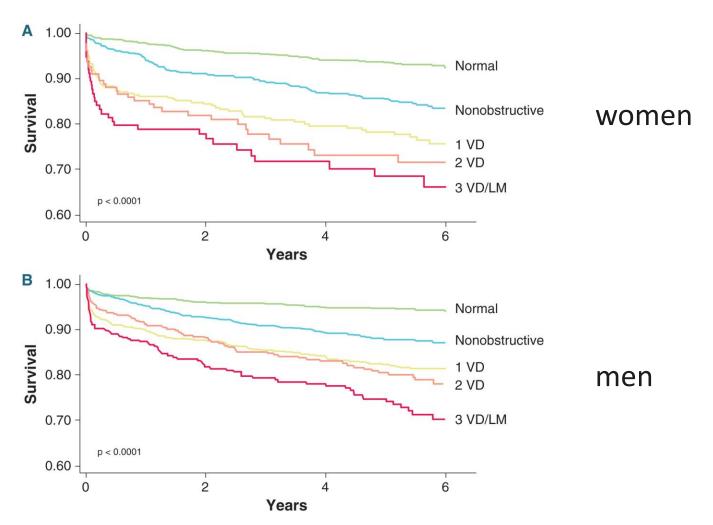


# **Epidemiology: relationship between chest pain and (non-) obstructive CAD**



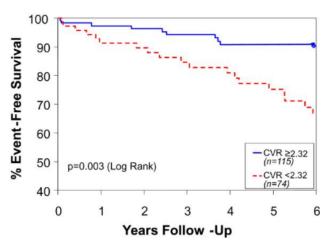


# **Epidemiology: prognosis of (non-)obstructive CAD**

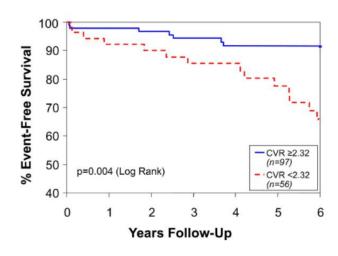


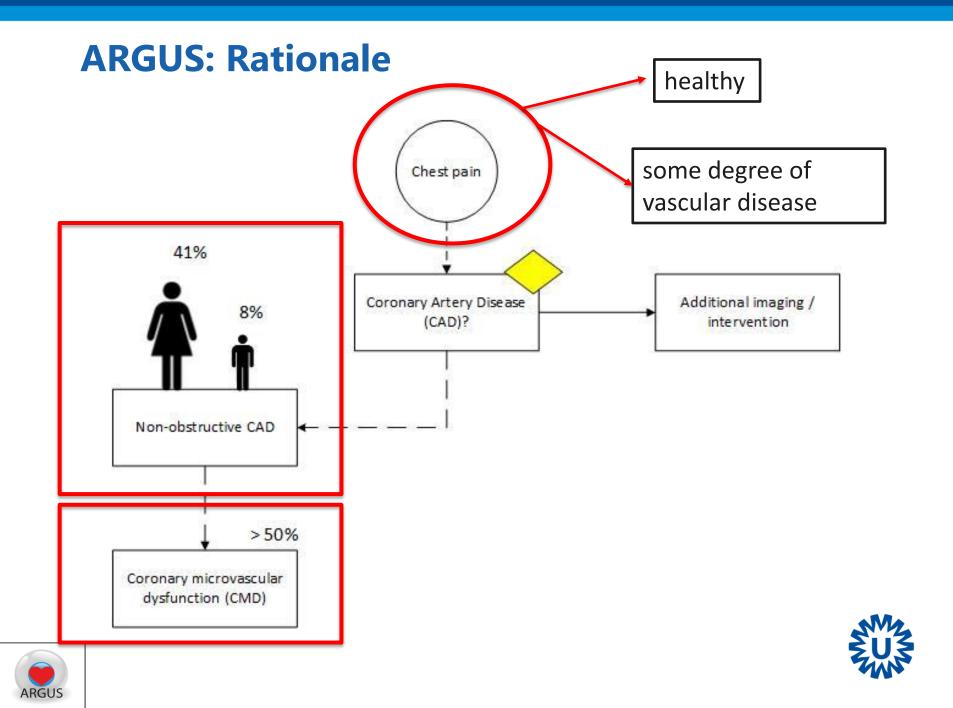
# **Epidemiology: (Non-)obstructive CAD and cardiac perfusion**

#### All Women



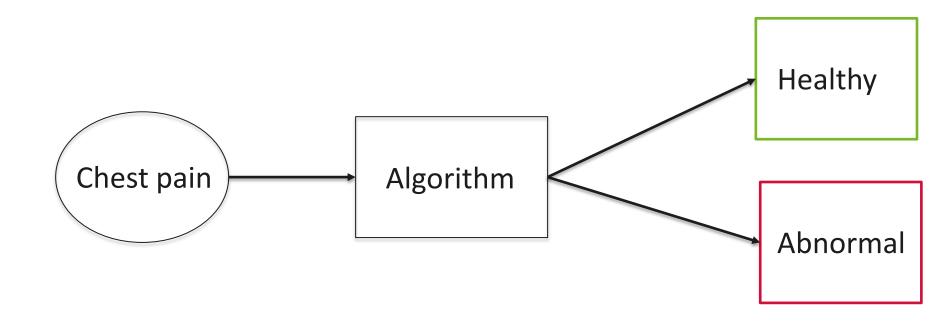
#### Women without CAD





#### **ARGUS: Aim**

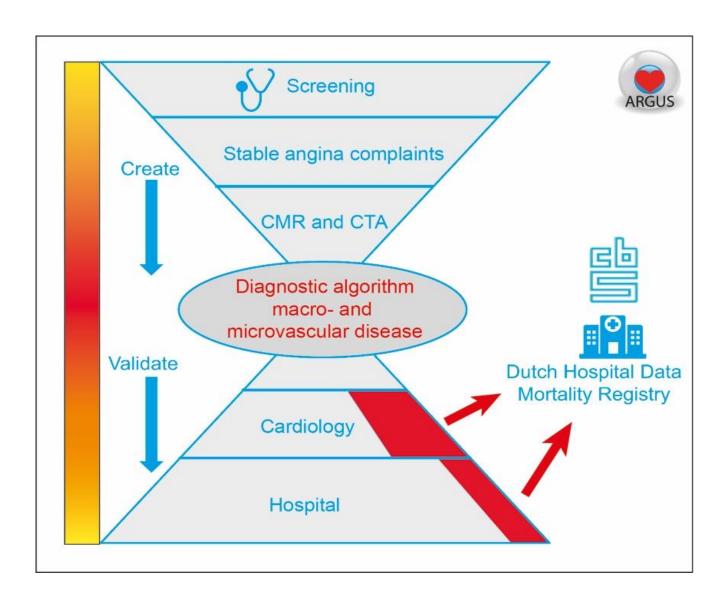
Develop and validate algorithm that accurately excludes both macro- and microvascular disease





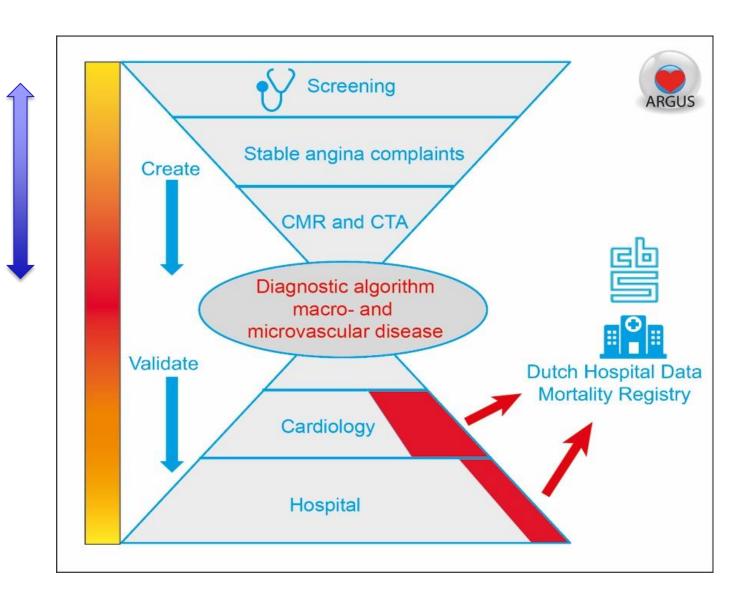


# **ARGUS: Overall set up**





# **ARGUS: Place of hackathon within programme**







# ARGUS / ABN AMRO hackathon: The data

Enja

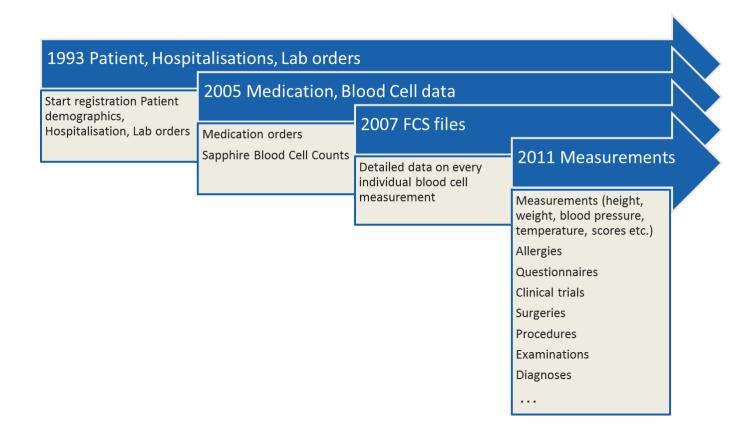
#### **Overview**

- What is UPOD?
- ARGUS Hackathon Patient selection
- ARGUS Hackathon The dataset
- Examples of imaging reports



- Utrecht Patient Oriented Database
- Established in 2003 by the Laboratory of Clinical Chemistry and Haematology
- Focus on patient care and diagnostics
- Team consists of physicians, epidemiologists, specialists in laboratory medicine, and data experts.







| <b>UPOD Database Entity</b>      | Total       |
|----------------------------------|-------------|
| Patients (unique)                | 2.300.000   |
| Clinical Patients (unique)       | 600.000     |
| Hospitalizations                 | 1.500.000   |
| Lab orders                       | 12.000.000  |
| Lab tests                        | 110.000.000 |
| Medication orders (clinical)     | 6.000.000   |
| Medication orders (policlinical) | 4.500.000   |
| Blood Cell Counts                | 2.400.000   |
| Measurements                     | 75.000.000  |
| Procedures treatments            | 97.000.000  |
| Diagnose Treatment Combinations  | 3.500.000   |
| (DBC, in Dutch healthcare)       |             |

- A database of real-world data
  - Formed with expert knowledge
  - Consisting of 'frequently asked data'
  - Enriched for 'specific requests'
  - Linked for collaborations
- A research companion
  - Data design support
  - Epidemiological support
  - Clinical support
- Data access based on scientific collaborations only



# 1. Look for patients with

CT and MRI

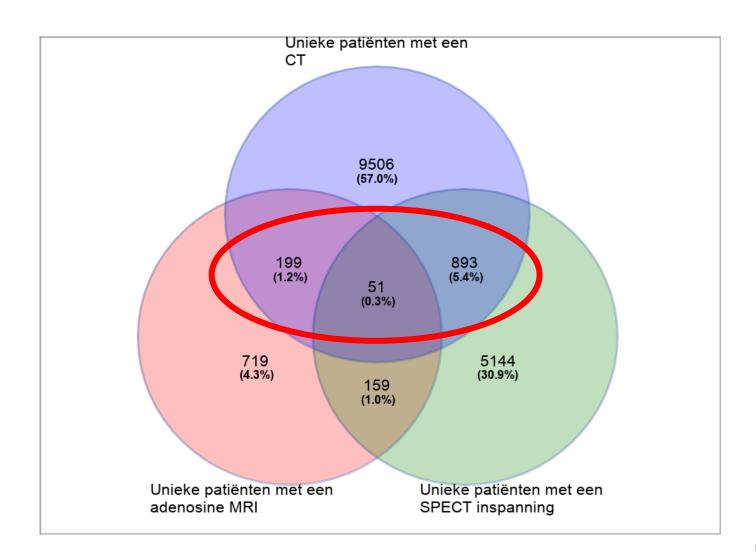
or

- CT and SPECT
- Both scans before 31nd of october 2018

### 2. Look at timeframe

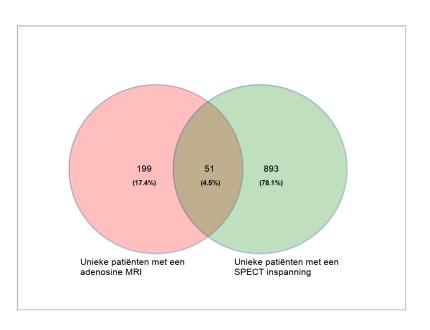
## 3. Refine patient selection

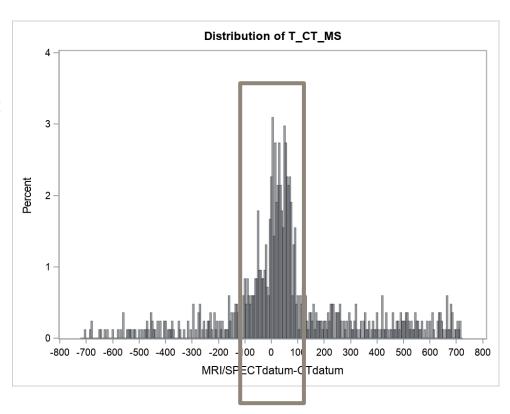






Before selection based on timeframe: 1143 unique patients





After selection based on timeframe: (max 100 days between scans)
458 unique patients

#### **Excluded:**

- Patients with more then 2 MRIs and/or SPECTs within 100 days
- Test patients
- Procedures with no report (research)

#### To be excluded:

- Patients who don't belong in ARGUS
- Based on radiology reports



### **Patient groups:**

- First database:
  - A 466 patients with CT and MRI/SPECT within 100 days
  - B 4851 patients with MRI/SPECT without CT
  - C 661 patients with CT and MRI/SPECT > 100 days apart
- Second database:
  - 10649 patients with CT without MRI/SPECT

# Multiple events per patient occur



# Relational database including:

- Patient selection
- Celldyn
- Medication
- Lab
- ECG
- Diagnoses / DBCs
- Procedures
- Measurements
- Cardiology letters
- Radiology reports



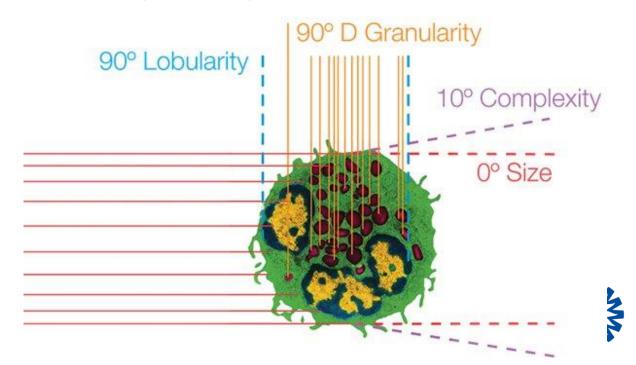
#### **Patient selection**

- St1\_pat\_tijdsel
  - Patient demographics for group A, B, C
  - Column 'type' to indicate group
  - Pateventid to link across tables
  - Verr\_date (MRI/SPECT) & CT\_date
- St1\_verr\_tijdsel
  - Patient demographics for group A, B, C including details of imaging that led to inclusion
- St1\_patsel\_ct
  - Patient demographics for CT group



# Celldyn

- Raw haematology parameters
- Based on 20k cells per sample



# Celldyn

- St2\_celldyn & St2\_CT\_celldyn
- All available haematology measurements for the included patients
- Time window: 5 year period before imaging
- Contains red & white blood cell and platelet characteristics
- Contains Suspect flags, warnings, errors...



#### Medication

- St3\_medicatie & St3\_CT\_medicatie
- All prescriptions (clinical & policlinical)
- Time window: 5 year period before imaging
- Based on electronic health records
  - Prescriptions without end date may have ended
  - Medication use without record not included
- Does not include OR / Intensive Care
- Includes ATCcodes



#### Lab

- St4\_lab & St4\_CT\_lab
- All available lab measurements
- Time window: ever
- Partly overlaps with celldyn table
- 2700+ kinds of lab tests
  - Eg CRP, Glucose, Hb, K, Leucocyt...
  - Different names for same test because of changes in UMC Utrecht software systems
- Contains units, lower/greater than, text



#### **ECG**

- St5\_ecg & St5\_CT\_ecg
- Time window: 90 day period before imaging
- 12 rows for one ECG
- As raw as it gets



### **Diagnoses / DBCs**

- St7\_dbcs & St7\_CT\_dbcs
- St7\_diagnosen & St7\_CT\_diagnosen
- Time window: ever
- To give an indication of history
- Both DBC and diagnoses registration changed over the years: from free text to codes



#### **Procedures**

- St8\_verrichtingen & St8\_CT\_verrichtingen
- Time window: 50 year period before imaging
- To give an indication of history
- Lab orders, imaging, appointments, surgeries...



### **Cardiology letters**

- St9\_cardiologie\_brieven &
   St9\_CT\_cardiologie\_brieven
- Time window: 100 day period around imaging
- Pseudonimized
- Group A, B, C: letter found for >90% of patients
- Group CT: letter found for 45% of patients



### **Radiology reports**

- St9\_radiologie\_verslagen &
   St9\_CT\_radiologie\_verslagen
- The reports that belong to the imaging that led to inclusion
- Added: all other CT, MRI, SPECT reports
- Free text, sometimes dictated



#### Measurements

- St10\_metingen & St10\_CT\_metingen
- Time window: 50 year period before imaging
- Blood pressure, length, weight, painscores, etc
- Measurements hidden in free text not included





# Imaging techniques

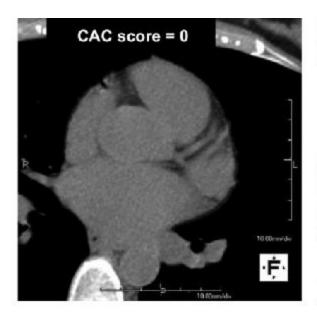
Floor & Klaske

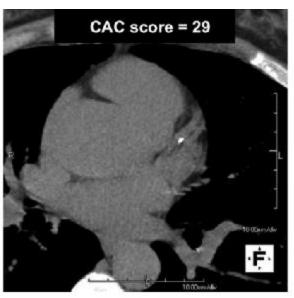
### **Outcome ARGUS = NO CAD on imaging**

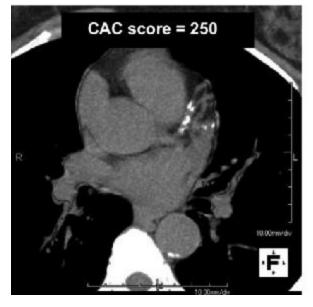
- 1. Obstructive CAD  $\rightarrow$  CT
- 2. Perfusion defects → SPECT or MRI

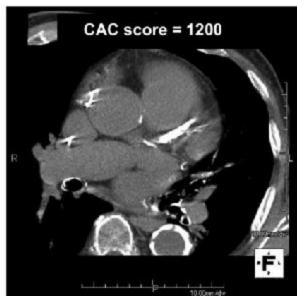


### CT









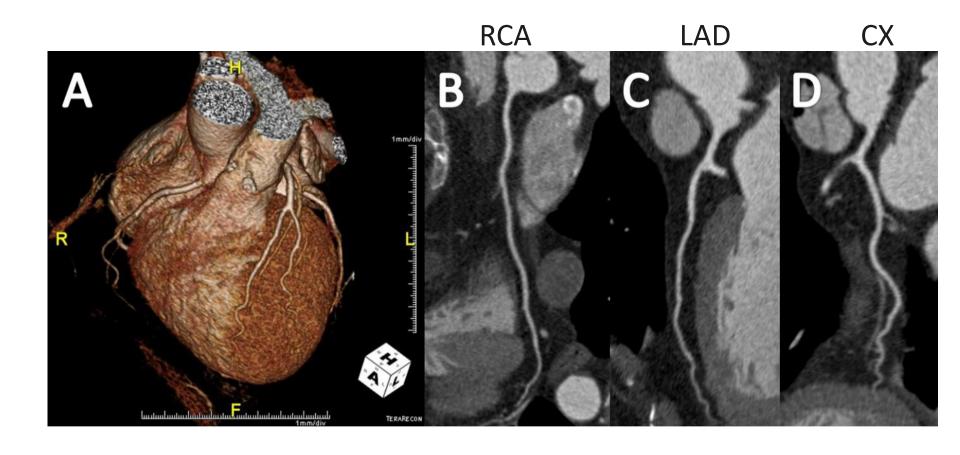


# **CT** angiography: with contrast agent



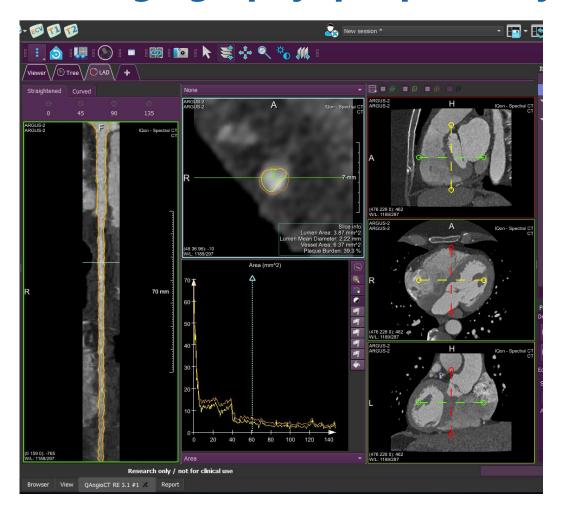


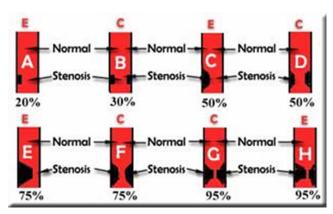
# **CT** angiography: results





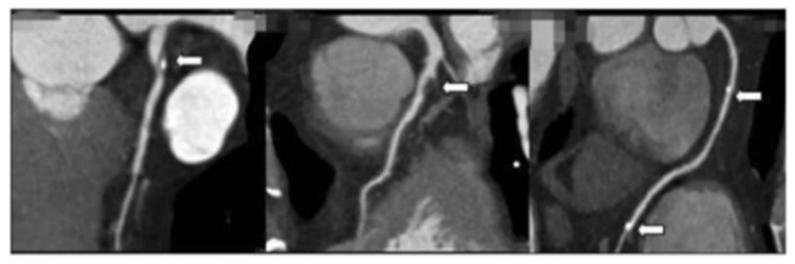
### **CT-angiography: plaque analysis**







### **Plaque types**



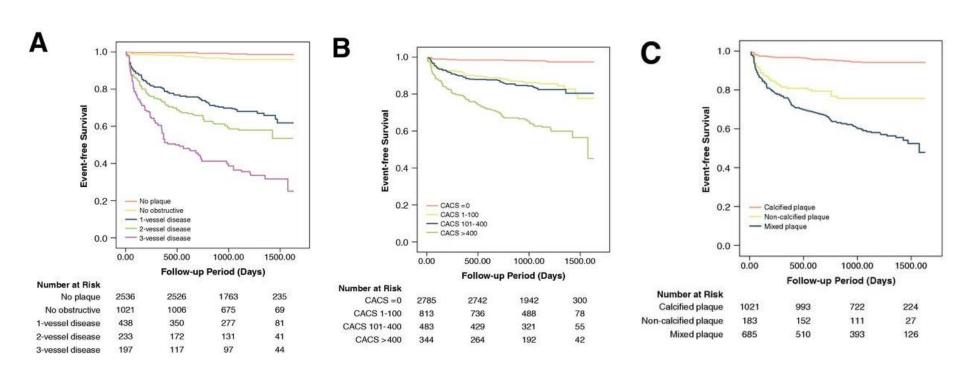
Mixed plaque

Non-calcified plaque

Calcified plaque



### **Prognosis of CT-characteristics**





#### **Perfusion defects?**

#### **Parameters**

- 17-segments model
- Ejection fraction

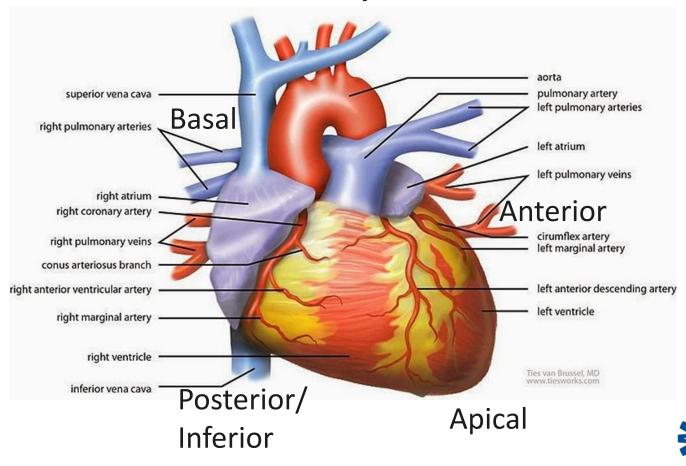
#### **Modalities**

- MRI + Adenosine stress
  - Delayed enhancement
  - Perfusion defects
- SPECT
  - Wall movement
  - Perfusion defects



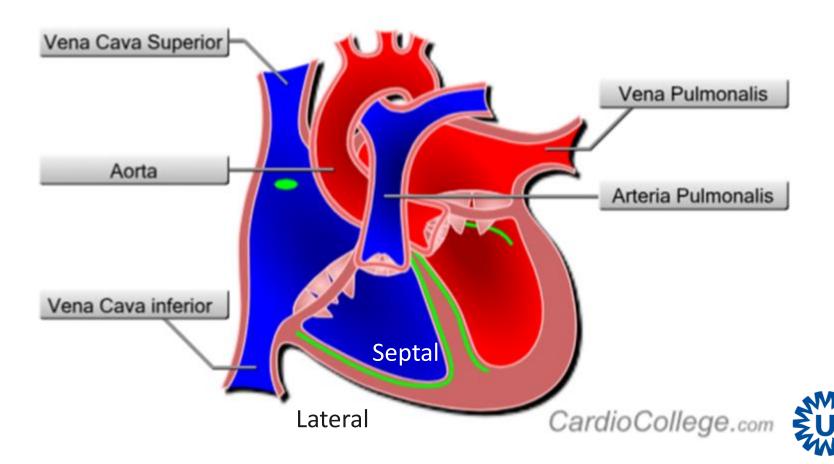
#### 17-segments model

- Structured representation of cardiac anatomy
- Basis: Perfusion areas of coronary arteries



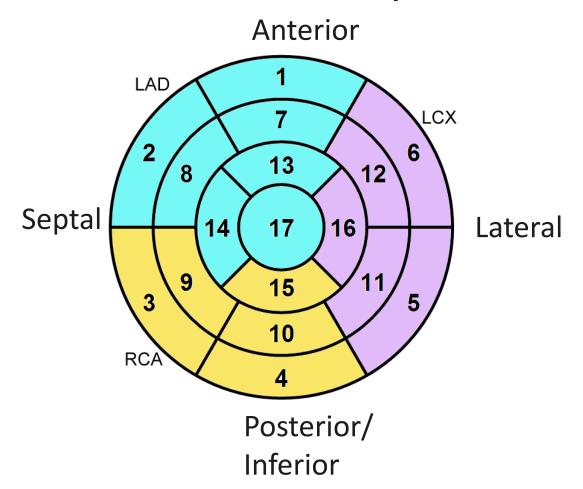
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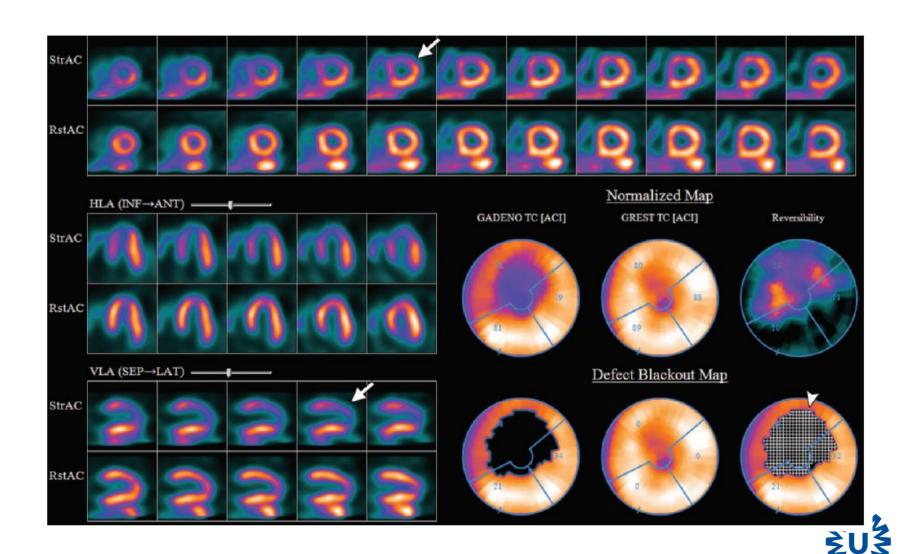


### **SPECT-imaging**

- Analysis of perfusion of the heart muscle
- Radioactive-tracer
- Primarily qualitative, currently quantitive measures are being developed.
- Stress and Rest
  - Stress: Increased perfusion of the heart muscle.



### **SPECT-Imaging: Reversible perfusion defect**

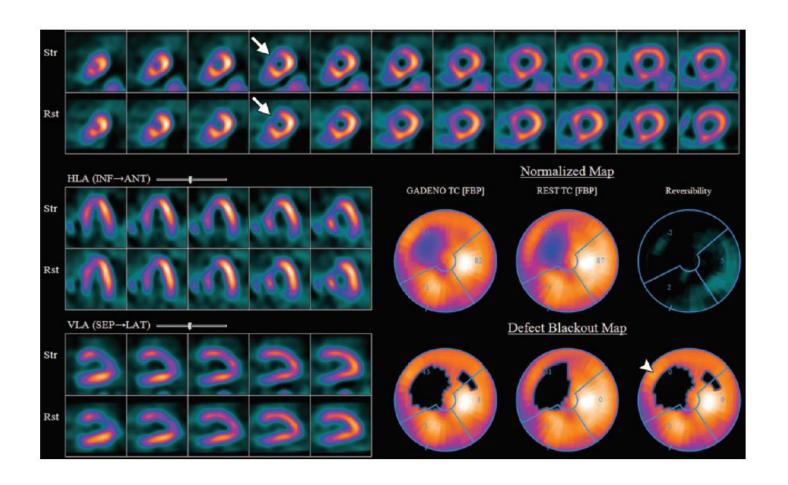


#### **SPECT-imaging: Parameters**

- Wall movement
- Perfusion defects
- Quantitative parameters:
  - SSS = Summed Stress Score
  - SRS = Summed Rest Score
  - SDS = Summed Differential Score

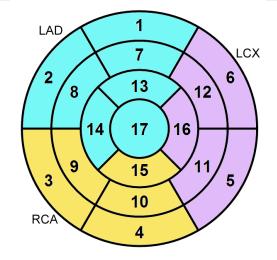


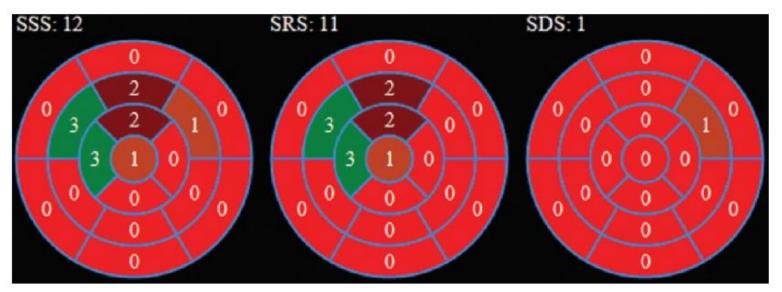
### **SPECT-Imaging: Irreversible perfusion defect**





### **SPECT: SSS, SRS and SDS**





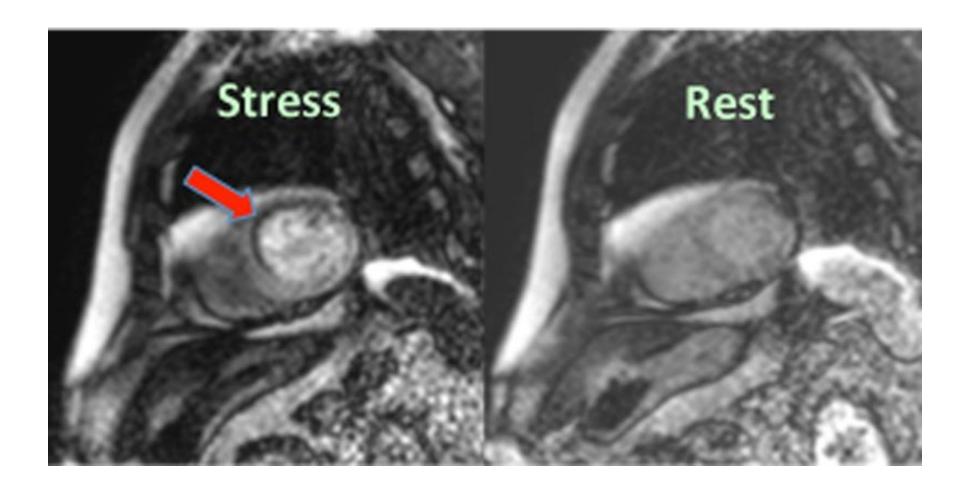


#### **MRI**

- Pharmacological stress: administration of Adenosine
- Gadolinium = contrast agent
- Terms used in report:
  - Delayed Gadolinium Enhancement
    - Retention of gadolinium contrast material → non-contracting scar or fibrotic tissue
    - ! Not specific for ischemia, could be result of other cardiac disease, check indications and conclusion of radiologist
  - Perfusion defects
  - If lucky.. 'mogelijk microvasculair lijden'

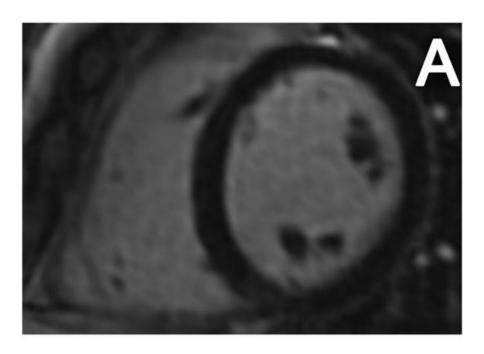


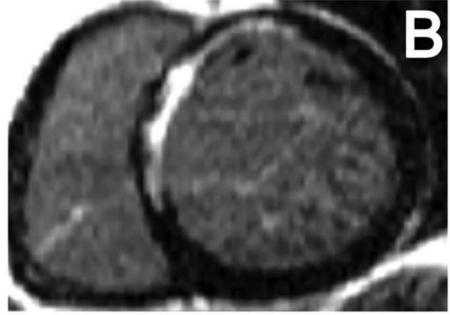
#### **Perfusion defect in stress**





# **Delayed enhancement**









# Text mining and labelling of CT and MRI reports

Thuur

#### **Data: CT reports (free text)**

#### **CT-report clean**

\_Klinische gegevens: Coronairlijden?

CT hart:

Gescand volgens het prospectief getriggerd protocol.

Kalkscore:

Agatston score 0.

CTA:

Normale origo van de coronairen. Normale cardiale anatomie. Rechts dominant coronair systeem.

Knik in de proximale RCA segment 1, waarvan significantie niet goed te bepalen op dit onderzoek. Verder geringe wandonregelmatigheden in de RCA, hoofdstam, LAD en LCX, zonder significante stenose (<50%).

Mixed plaque in de linker en rechtercoronaire cusp. In aanleg tricuspide aortaklep. Annulus calcificaties mitralisklep. Pectus excavatum met compressie op de rechterharthelft.

Hypodensiteit in de rechterleverkwab, best passend bij een cyste.

#### **Conclusie:**

#### Kalkscore: Agatston score 0.

CTA: Knik in de proximale RCA segment 1, vermoedelijk op basis van een mechanische oorzaak bij een pectus excavatum. Significantie niet goed te bepalen op dit onderzoek. Verder geringe wandonregelmatigheden in de RCA, hoofdstam, LAD en LCX, zonder significante stenose (<50%).

#### **CT report with CAC and stenosis**

Klinische gegevens: CAD. Verdenking oud infarct.

Indicatie: Kalkscore? Sign Stenose?

CT HART - CORONAIREN

Er is geen relevant onderzoek beschikbaar om mee te vergelijken.

Kalkscore:

Agatston 1294 (99ste MESA percentiel).

CTA:

Normale connecties. Tricuspide aortaklep. De RCA ontspringt op 12 uur uit de anterieure sinus van Valsalva. De hoofdstam ontspringt op 5 uur uit de linkersinus van Valsalva. Er is een rechts dominant coronair systeem. Er is een linkeratrium divertikel. Geen thrombus in het linkerhartoor.

Ostiale calcificaties zowel bij de RCA als hoofdstam, **zonder significante stenose**. Uitgebreide wandstandige calcificaties van de coronairen. **Significante stenose van de LCX segment 13, van** > **50%.** Mixed plaque in de proximale LAD, imponeert niet significant op bronbeelden. Geen andere significante stenoses.

#### Nevenbevinding:

Normale luchthoudendheid en densiteit van de longen. Geen intrapulmonale noduli. Milde degeneratieve veranderingen van thoracale wervelkolom.

#### Conclusie:

- 1. Kalkscore: Agatston 1294 (99ste MESA percentiel).
- 2. Significante stenose van LCx (segm 13) van >50%.
- 3. Geen relevante nevenbevindingen.



# **Data: CT reports textmining**

| F                     | G                       |      |
|-----------------------|-------------------------|------|
| Stenose               | Calcium                 | I    |
| yes                   |                         | 810  |
| yes                   |                         | 3187 |
| no                    |                         | 76   |
| None                  | None                    |      |
| >50%                  |                         | 76   |
| None                  | None                    |      |
| None                  | NA                      |      |
| 0.5                   |                         | 0    |
| yes                   |                         | 111  |
| 0.5                   |                         | 127  |
| yes                   | AMBIGUOUS:0;;;101       |      |
| no                    |                         | 161  |
| yes                   | AMBIGUOUS:0;;;181;;;NA  |      |
| AMBIGUOUS:<50%;;;>50% |                         | 63   |
| yes                   |                         | 3787 |
| 0.5                   |                         | 46   |
| yes                   | AMBIGUOUS:226;;;48;;;NA |      |
| no                    |                         | 230  |



#### **Data: MRI reports (free text)**

#### **MRI** report clean

Klinische gegevens.

Blanco cardiale voorgeschiedenis. Niet bekend met hypertensie.

#### MRI hart.

Scan volgens **adenosine stress protocol**. Op de cineopnames is er een iets asynchrone contractie van de linkerventrikel met een gering verlaagde ejectiefractie. Er zijn geen akinetische dyskinetische segmenten.

Kwantificatie van de korte as: Linkerventrikel EF 45%, einddiastolisch volume 240 ml. Rechterventrikel EF 40%, eindsystolisch volume van 249 ml.

Bij perfusie onderzoek is er een goede aankleuring in alle perfusie territoria. Bij adenosine stress verandert dit niet: **Geen ischemie**.

Delayed enhancement opname laat geringe Mid myocardiale aankleuring zien aan de onderzijde bij de inserties van de rechterventrikel, aspecifieke bevinding. **Geen ischemisch substraat.** 

#### Conclusie.

Geen aanwijzen voor doorgemaakt myocardinfarct. Bij stress perfusie geen ischemie.

#### MRI report with perfusion defect

Klinische gegevens:

Mgl ooit TIA doorgemaakt. Pijnklachten abd, niet verdacht voor cardiael origine. Op echo globaal hypokinetische LV. Vader prematuur coronairlijden, geen hartfalen in familie. LVF? aanw ischaemie?

#### MRI hart:

Geen eerder onderzoek ter vergelijk. MRI hart volgens het **adenosine stress protocol.** 

#### Verslag:

Globaal lichte hypokinesie van het linkerventrikel met een licht verlaagde LVEF van 45%. Het LV lijkt basaal iets gedilateerd met een diameter van 60 mm, echter het volume van het LV is nog binnen de norm. Hypertrabecularisatie van het linkerventrikel, waarbij er in 3 van de MESA segmenten (apicale helft voorwand, laterale wand en onderwand) voldaan wordt aan de non-compactie criteria. Eveneens hypertrabecularisatie apicale helft rechterventrikel. Normale contracties en functie van het RV. Geen significant kleplijden. **Geen delayed enhancement.** 

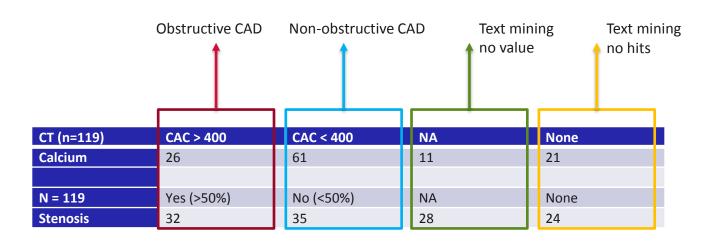
Op de adenosine stressopname wordt basaal anteroseptaal en inferoseptaal subendocardiaal **geringe hypoperfusie** gezien, kan passen bij ischemie.

#### **Conclusie:**

- Globale lichte hypokinesie LV met een licht verlaagde functie van 45%.
- Beeld van non-compactie.
- Induceerbare hypoperfusie basaal anteroseptaal en inferoseptaal, kan passen bij ischemie.



### **Data: MRI and CT manual checking results**



| MRI (n=119) | Delayed enhancement | Perfusion defect |  | Double negative    |  |
|-------------|---------------------|------------------|--|--------------------|--|
| Positive    | 39                  | 46               |  | 1                  |  |
| Negative    | 78                  | 70               |  | 55                 |  |
| No result   | 2                   | 3                |  | /                  |  |
|             |                     |                  |  |                    |  |
|             |                     |                  |  | I                  |  |
|             |                     |                  |  |                    |  |
|             |                     |                  |  | 1                  |  |
|             | ▼                   |                  |  | ▼                  |  |
|             | Perfusion defect    |                  |  | No perfusion defec |  |



#### **SPECT:** physical exercise

Myocardperfusiescintigram bij inspanning en rust m.b.v. resp. 436 en 396 MBq Tc-99m-myoview.

Klinische gegevens: pAF, nu klachten verdacht voor AP.

Vraagstelling: Ischemie?

Fietsergometrietest: Patiënt werd belast tot maximaal 60 Watt ergometrische belasting gedurende 3,5 minuten. Dit is 70% van de streefbelasting. Hartfrequentie bedroeg bij aanvang van het onderzoek 75 sl/min. De bereikte hartfrequentie was 139 sl/min., overeenkomend met 100% van maximaal beoogde hartfrequentie. De bloeddruk was bij aanvang 200/80 mmHg, bij maximale inspanning 190/80 mmHg, en in de herstelfase 150/70 mmHg. Patiënt ervoer geen klachten maar was voor starten test erg gespannen.

Liggend rust-ECG: Sinusritme 75/min, enkele PACs, intermediaire as, geleidingstijden binnen de norm, geen pathologische Qs, voltages passend bij LVH, waarbij 1-2 mm komvormige ST depressies in II, III, aVF, V4-6.

*Inspannings-ECG*: Toename van de pre-existente ST-depressies naar 2 tot 3 mm in II, III, AVF, V4 - 6, geen ritme stoornissen.

SPECT: Enige diafragma attenuatie. Activiteitsverdeling zowel in stress als in rust binnen de norm.

Gated-SPECT: Alzijdig goede kinetiek en wandverdikking na inspanning en in rust.

Poststress: LVEF 97%, waarschijnlijk overschat bij klein hart en hypertrofie.

In rust: LVEF 92%, eveneens waarschijnlijk overschat.

Rust- en inspannings-SPECT:

SSS (summed stress score; AC): 0

SRS (summed rest score; AC): 7

SDS (summed differential score; AC): 0

Lowdose-CT: Uitgebreide calcificaties in de coronairen alsmede calcificaties in de thoracale aorta. Uitgebreide calcificatie in het kraakbeen in de trachea en grotere bronchiën. Enkele 1,5 mm grote noduli onder andere in de rechter middenkwab, aspecifiek. Status na mamma-ablatie links. Dens mammaweefsel zonder noduli.

#### Conclusie:

- 1. Inspanningstest met redelijke inspanningstolerantie.
- 2. X-ECG: significante toename van pre-existente ST depressies, mogelijk nog in het kader van het strain patroon in rust.
- 3. Scintigram: geen perfusiestoornissen

### **SPECT:** pharmacological exercise

ONDERZOEK: myocardscintigram-SPECT bij rust en inspanning m.b.v. 537 en 530 Megabequerel Tc-99m myoview d.d. 27 en 28 maart 2013

KLINISCHE GEGEVENS: Voorwandinfarct. Status na PCI LAD. Afgesloten rechter collateraal gevuld door LAD.

Lengte: 176 cm. Gewicht: 75 kg.

MEDICATIE: Onder andere Metoprolol 50 mg en perindopril.

VRAAGSTELLING: Restischemie onderwand?

Patiënt kreeg nitrospray sublinguaal toegediend voor de toediening van het radiofarmacon in rust.

ADENOSINEBELASTINGSTEST. Indicatie: verminderde inspanningstolerantie.

Patiënt werd belast d.m.v. 63 mg adenosine-infusie in combinatie met maximaal 80 Watt ergometrische belasting gedurende 6 minuten.

De hartfrequentie bedroeg bij aanvang van het onderzoek 61 sl/min. bij een bloeddruk van 150/80 mmHg. Tijdens de belastingstest liep de hartfrequentie op naar maximaal 111 sl/min. bij een bloeddruk van 140/80 mmHg.

Patiënt ervoer tijdens de belastingstest niet herkenbare precordiale pijnklachten. Aan het eind van het onderzoek was de hartfrequentie 67 sl/min. en de bloeddruk 130/80 mmHg.

Er traden bijwerkingen van de adenosine op, te weten: "bonzend" gevoel in de buik, dyspnoe, duizelig, een warm gevoel en een branderig gevoel in de keel, borst en buik.

LIGGEND RUST-ECG: Sinusbradycardie, 56 slagen/min, intermediaire hartas, normale geleidingstijden, aspecifieke intraventriculaire geleidingsstoornis, trage R-progressie, kleine Q in II en AVF, vlakke repolarisatie in AVL, bifasische T-toppen in V1, enige ST-elevatie in II, AVF, V2 en V3.

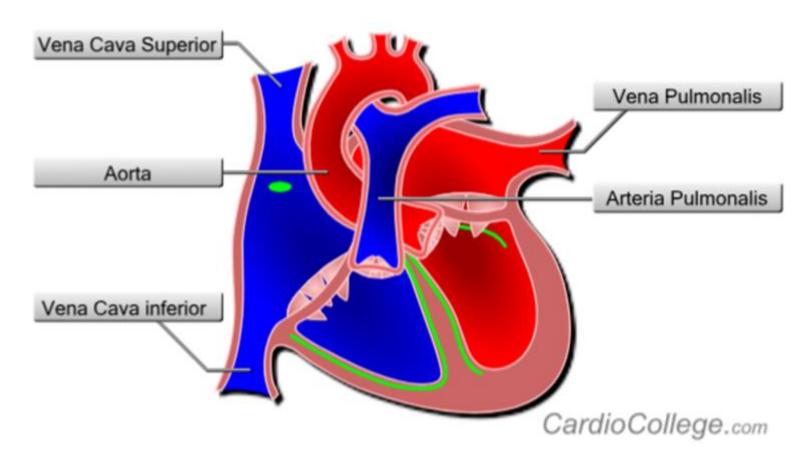
*INSPANNINGS-ECG*: In de eerste helft van de inspanningstest regelmatig een VES en kortdurend bigeminie. Maximaal 1 mm ST-depressie in afleidingen II, III, AVF en V4 tot en met V6. Reciproke ST-elevatie AVR.

SPECT: Respectievelijk 99 en 100% accepted beats. Tijdens inspanning een beperkt gebied met hypo-activiteit inferoseptaal, mid- en basoventriculair. In rust nagenoeg volledige normalisatie. Apico-anteroseptaal een beperkt gebied met persisterende hypo-activiteit. Daarnaast apical thinnin



# **Explanation of ECG data**

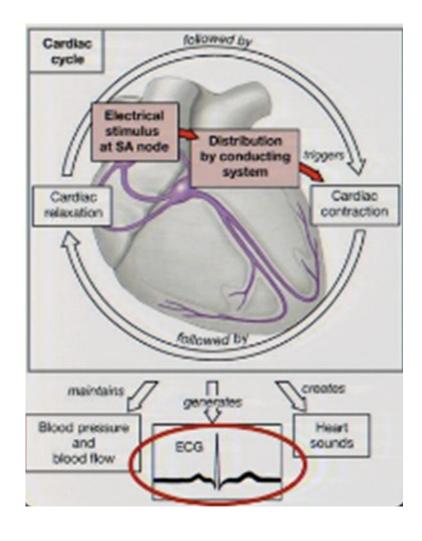
# Cardiac anatomy





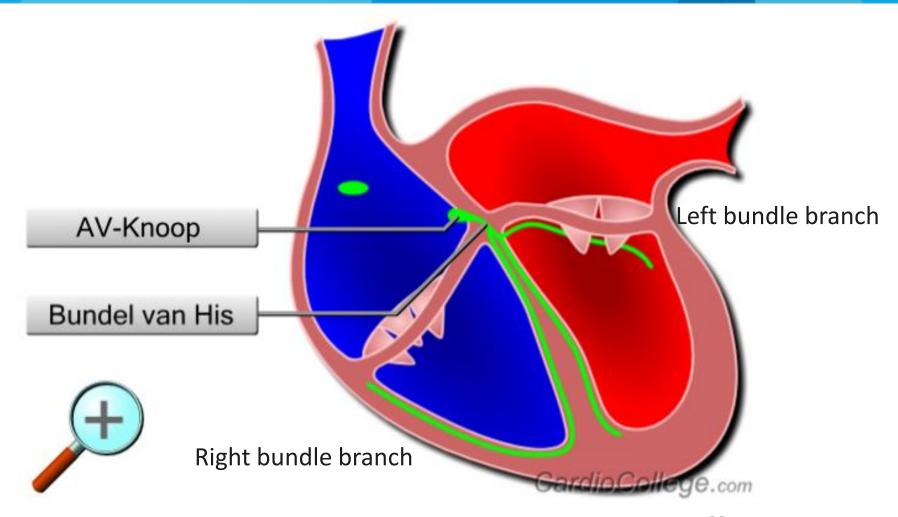
# Cardiac electrophysiology: ECG

mageuramante



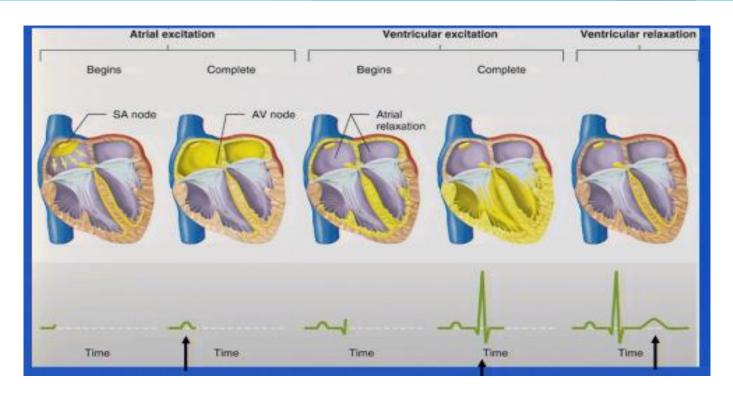


# Cardiac electrophysiology





# From cardiac cycle to ECG



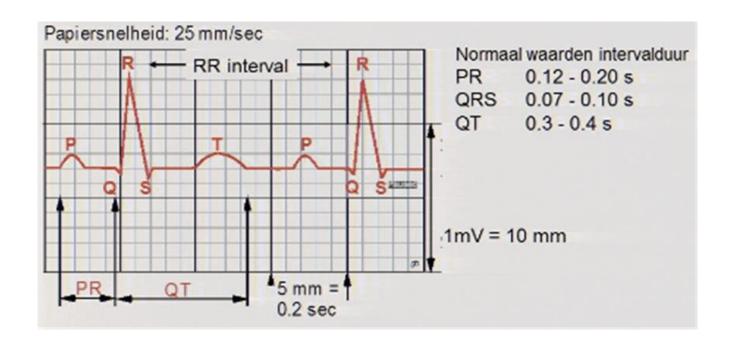
P- top QRS-complex

T-top

- P = atriale depolarisatie = atrial activation
- QRS = ventricular depolarization = ventricular activation
- T-top= ventricular repolarization = ventricular relaxation

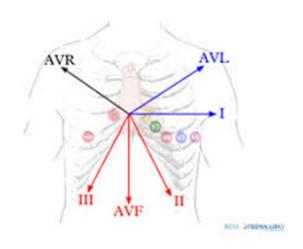


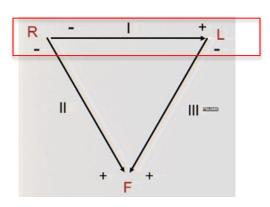
### Normal ECG

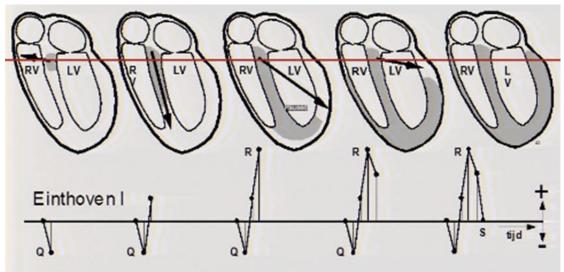




# One example of an ECG lead: Einthoven 1

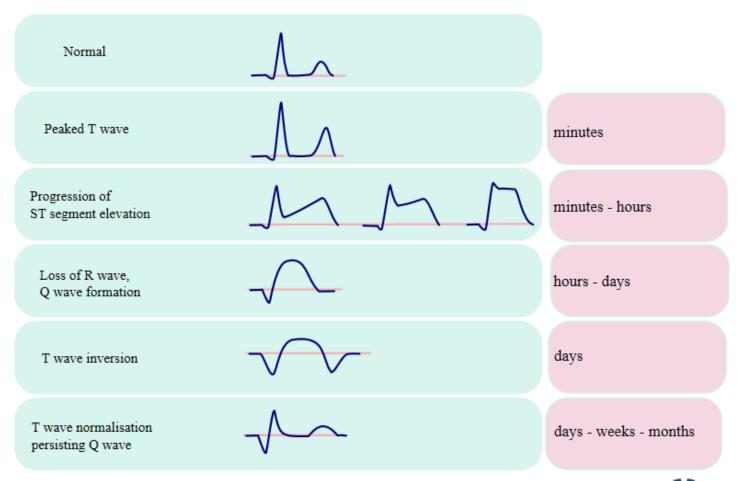








## ECG abberations indicative for ischemia







# **Questions?**