COST-COST MODEL FOR RULING OUT CORONARY ARTERY DISEASE IN SYMPTOMATIC PATIENTS WITH ULTRA-SENSITIVE PHONOCARDIOGRAPHY IN THE GERMAN AMBULATORY SECTOR

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¹St. Bernward GmbH, Hamburg, Germany
²Herzklinik Ulm, Ulm, Germany
³Analytic Systems, Munich, Germany
The issue (inpatient data only)

Decreasing frequency of ACS

<table>
<thead>
<tr>
<th>Year</th>
<th>Instable AP</th>
<th>STEMI</th>
<th>NSTEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>165.780</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>106.931</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>131.785</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>145.202</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>124.133</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>103.600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>80.690</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>81.936</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>70.521</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2008: 342.632
2016: 319.323 -6.8%

Increasing coronaryography + PCI

<table>
<thead>
<tr>
<th>Year</th>
<th>Coro with measurements</th>
<th>Only diagnostic coro</th>
<th>PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>220.595</td>
<td>362.195</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>470.150</td>
<td>480.617</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>565.144</td>
<td>621.379</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>1.179.287</td>
<td>1.530.695 +29.8%</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
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<td>2011</td>
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<td>2012</td>
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<td>2013</td>
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<tr>
<td>2014</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Patient with chest pain**

- Diagnoses of 1,212 patients (age ≥ 35 y), who consulted their GP for chest pain

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest wall syndrome</td>
<td>565</td>
<td>46.6</td>
</tr>
<tr>
<td>CAD</td>
<td>135</td>
<td>11.1</td>
</tr>
<tr>
<td>Psychogenic disturbance</td>
<td>115</td>
<td>9.5</td>
</tr>
<tr>
<td>Infection respiratory tract</td>
<td>98</td>
<td>8.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>48</td>
<td>4.0</td>
</tr>
<tr>
<td>ACS</td>
<td>44</td>
<td>3.6</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>42</td>
<td>3.5</td>
</tr>
<tr>
<td>Trauma</td>
<td>39</td>
<td>3.2</td>
</tr>
<tr>
<td>Benigne stomach disease</td>
<td>26</td>
<td>2.1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>25</td>
<td>2.1</td>
</tr>
<tr>
<td>COPD/Asthma</td>
<td>23</td>
<td>1.9</td>
</tr>
<tr>
<td>Other</td>
<td>52</td>
<td>4.3</td>
</tr>
</tbody>
</table>

Bösner Dtsch Arztebl 2010; 107(38): A-1812
Table I3  Clinical pre-test probabilities in patients with stable chest pain symptoms

<table>
<thead>
<tr>
<th>Age</th>
<th>Typical angina</th>
<th>Atypical angina</th>
<th>Non-anginal pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>30-39</td>
<td>59</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>40-49</td>
<td>69</td>
<td>37</td>
<td>38</td>
</tr>
<tr>
<td>50-59</td>
<td>77</td>
<td>47</td>
<td>49</td>
</tr>
<tr>
<td>60-69</td>
<td>84</td>
<td>58</td>
<td>59</td>
</tr>
<tr>
<td>70-79</td>
<td>89</td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td>&gt;80</td>
<td>93</td>
<td>76</td>
<td>78</td>
</tr>
</tbody>
</table>

2016 KBV Guidelines

<table>
<thead>
<tr>
<th>&lt;15%</th>
<th>15%&gt; Intermediate risk &lt;85%</th>
<th>&gt;85%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No further testing</td>
<td>CTA</td>
<td>CAG</td>
</tr>
<tr>
<td>15%&lt; X-ECG&lt;30%</td>
<td>&gt;50% SPECT, C-MRT, D-MRT, X-Echo</td>
<td></td>
</tr>
</tbody>
</table>

Diamond GA, Forrester JS: Analysis of probability as an aid in the clinical diagnosis of coronary artery disease, NEJM 24 (1979); 300:1350-7; ESC Guidance 2013
Nationale VersorgungsLeitlinie Chronische KHK 4. Auflage, 2016 Version 1 AWMF-Register-Nr.: nvl-004
### ESC SCAD guidelines 2013

<table>
<thead>
<tr>
<th>Characteristics of tests commonly used to diagnose the presence of coronary artery disease</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress ECG</td>
<td>45-50</td>
<td>85-90</td>
<td>93%</td>
</tr>
<tr>
<td>Stress Echo</td>
<td>80-85</td>
<td>80-88</td>
<td>97%</td>
</tr>
<tr>
<td>Stress SPECT</td>
<td>73-92</td>
<td>63-87</td>
<td>95%</td>
</tr>
<tr>
<td>Dobutamin Stress Echo</td>
<td>79-83</td>
<td>82-86</td>
<td>97%</td>
</tr>
<tr>
<td>Dobutamin Stress MRI</td>
<td>79-88</td>
<td>81-91</td>
<td>97%</td>
</tr>
<tr>
<td>Vasodilatator Stress Echo</td>
<td>72-79</td>
<td>92-95</td>
<td>96%</td>
</tr>
<tr>
<td>Vasodilatator Stress SPECT</td>
<td>90-91</td>
<td>75-84</td>
<td>98%</td>
</tr>
<tr>
<td>Coronary CT</td>
<td>95-99</td>
<td>64-83</td>
<td>99%</td>
</tr>
<tr>
<td><strong>CADScore</strong></td>
<td><strong>81-90</strong></td>
<td><strong>45-53</strong></td>
<td><strong>97%</strong></td>
</tr>
</tbody>
</table>


*not in guideline*
Diagnosing CAD by noise?
Hypersensitive phonocardiography

Case Reports 1967 and 1973

A Diastolic Murmur Arising in a Stenosed Coronary Artery*

William Dock, M.D. and Smil Zoneraich, M.D.
Brooklyn, New York

In a man with heart failure due to hypertension and ventricular aneurysm, a diastolic murmur was recorded in a sharply localized area, and only when he was erect. This high pitched murmur seemed to have arisen in a stenosis (occluded thombus) of the descending branch of the left coronary artery.

2003 M. Akey:
Stenosal murmurs of coronaries:

- Most of the time not audible
- Up to 1000 times softer than other heart sounds

**Difference:**
Heart sound and coronary murmurs

**Todays goal of auscultation:**
Detection of defective heart valves:

In all arteries stenosis cause turbulences.
Those develop different flow sounds.
The signal is soft, but can be traced and illustrated by use of specific techniques.

Master thesis 2005,
Claus Graff & Samuel Schmidt

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The CADScor® Algorithm

The CADScor® system for diagnosing CAD risk using acoustic properties

- The CADScor® System consists of a disposable patch and reusable sensor/touch-screen interface
- The product is based on the concept that atherosclerosis in coronary vessels will produce unique murmurs detectable by advanced acoustic equipment during diastole

- Minimal training requirements
- Measurement takes <10 min.
- Noninvasive
- No patient exposure to radiation or contrast dye
- High negative predictive value
- Relatively low capital and consumable costs

Hansen J, Zimmermann H, Schmidt SE, Hammershøi D, Struijk JJ: System for Acquisition of Weak Murmurs Related to Coronary Artery Diseases, Computing in Cardiology 2011;38:213-216
Company information from Acarix AB
Main clinical studies

Registration study
AC003SH
2013

N=228
Symptomatic, no CAD diagnosed
One center (DK)

CE Mark August 2015

N=2,000
New algorithm
five centres (DK)
PEP: Superior DF

Started 01/18
Dan-NICAD II

Dan-NICAD
2014-2016

N=1,675
Symptomatic, no CAD diagnosed
Two centers (DK)

VALIDATE
2016

N=231
Symptomatic, scheduled for CAG
Two centers (GER)

German outpatient
Start Q1/19
Ulm

N=500
Symptomatic
German pathway

SCREENING STUDIES

N=231
Symptomatic,
scheduled for CAG
Two centers (GER)

BACC
2016/2019

CHF, N=200
Two centers

Screening studies

DK, Diabetes,
UKE Hamburg

Diagnostic performance of an acoustic-based system for coronary artery disease risk stratification

Simon Winther,1 Louise Nissen,1 Samuel Emil Schmidt,1 Jelson Sybreng Wieten,1 Laust Dupont Rasmussen,1 Lars Lyhne Knudsen,1 Lene Helleskov Madsen,1 Jane Kirk Johansen,1 Bjørn Skogstad Larsen,1 Johannes Jan Struijk,1 Lars Frost,1 Niels Ramsing Holm,1 Esvald Høj Christensen,2 Hans Erik Bøker,3 Morten Bøttcher4

Original Research Article

Aktuelle klinische Forschung zur nicht-invasiven
KHK Diagnostik: VALIDATE

Thorsten Rau

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2Department of Cardiology, Herlev University Hospital, Denmark
3Department of Cardiology, Gentofte University Hospital, Denmark
4Department of Cardiology, Herlev University Hospital, Denmark

1Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Denmark
2Department of Cardiology, Herlev University Hospital, Denmark
3Department of Cardiology, Gentofte University Hospital, Denmark
4Department of Cardiology, Herlev University Hospital, Denmark
Registration study

Patients referred to CCTA or ICA
For CAD diagnostics

Excl.: Pregnancy, diastolic murmur, heart surgery, arrhythmias, etc.

n=255

CADScore®

n=228

Calcium Score

n=109

Coronary-CT

n=10

n=119

Catheter

Exclusion protocol violation:
- n=3 CADScore® not performed
- n=3 Catheter not performed

Algorithm violation:
- n=7 Arrhythmias
- n=14 Side noise and similar

Registration study

Patients with obstructive CAD (n=63)
Patients with non-obstructive CAD (n= 41)
Patients with non-CAD (n=124)

A CAD-score ≤ 20 rules out CAD with 93% NPV in a patient cohort with 28% prevalence.

The sensitivity in this patient group was 90%.

Dan-NICAD
Danish study of Non-Invasive testing in CAD

Study Population
1675 participants with low to intermediate CAD-risk
Admitted to Coronary-CT

When CAD was suspected, an invasive angiography with FFR was performed

Dan-NICAD
FFR determined disease

- CAD-score ≤20: negative test (rule-out CAD)
- CAD-score >20: positive test (refer for further testing)


<table>
<thead>
<tr>
<th>FFR determined (95% confidence interval)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>71% (67-76%)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>81% (73-87%)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>96% (95-98%)</td>
</tr>
<tr>
<td>Specificity</td>
<td>53% (50-56%)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>16% (13-18%)</td>
</tr>
</tbody>
</table>
The German Guidance Pathway

Nationale VersorgungsLeitlinie Chronische KHK 4. Auflage, 2016 Version 1 AWMF-Register-Nr.: nvl-004
Patient pathways (reimbursed by EBM)

• Base Case
  follows EBM reimbursement rules

• Treatment alternative
  adds CADScor® as second diagnostic step after PTP determination

* Kassenärztliche Bundesvereinigung
Key characteristics model

• Individual patient model (MS Excel)
  – to be transformed into Markov cohort model (TreeAge®)
• Payor perspective
• Simulated patients drawn from different populations
  – low prevalence to high prevalence
  – Model allows the addition of other populations.
• Germany specific cost schemes
  – for private insurers, public sick funds
• Treatment base case follows guidelines
  – CADScor® added in a separate treatment pathway
TreeAge® cohort model

Upper Branch: D-F alternative

DF strata 1-5
(<15%, ..., >85%)

Follow-up procedures

Lower Branch: CADScore(R) alternative, clone of D-F branch, different probabilities

CS<=20 stratum (obsolete in D-F branch)
Simulation setup

- Individual patient simulation using MS Excel
- 10,000 draws from the designated population
- Generate demographic and morbidity variables for each patient
- Generate patient specific pathways for base case and treatment alternative
- Store individual patient results
- Aggregate data and analyze
Measures of effectiveness

• Pretest sensitivity and specificity
  – Share of false negatives (CAD patients classified as non CAD)
  – medical consequences
    • will suffer from missing treatment
  – economic consequences
    • will show up again with the same disease

– Share of false positives (non CAD patients who have not been sorted out by the pretest)
– medical consequences
  • unnecessary radiation
– economic consequences
  • will go through unnecessary diagnostic procedures
Cost valuation schemes

• EBM (Einheitlicher Bewertungsmaßstab)
  – Stress ECG and Stress Echo are part of „specialist lump-sums“, other procedure costs are added individually

• GOÄ (Gebührenordnung der Ärzte)
  – health plans for public service employees („Beamte“);
  – No lump-sums; individual cost items for all procedures; generally higher amounts than EBM cost items

• Practice costs
  – based on treatment time and resource usage – not yet implemented

• Additional CADScor® costs
  – GOÄ: reimbursed, No. 660 of current catalogue
    EBM (assumption): not reimbursed
The German Guidance Pathway

Nationale VersorgungsLeitlinie Chronische KHK 4. Auflage, 2016 Version 1 AWMF-Register-Nr.: nvl-004
Model DE
Treatment Population: Dan-NICAD
10,000 simulations
Model DE
Treatment Population: Dan-NICAD
10,000 simulations
Results (EBM/GOÄ cost schemes)

Low prevalence (Dan-NICAD 1)  
Total cost (€), **EBM**

<table>
<thead>
<tr>
<th></th>
<th>Base</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretest + diagnostics</td>
<td>386</td>
<td>303</td>
</tr>
<tr>
<td>False Positives</td>
<td>12,1%</td>
<td>8,70%</td>
</tr>
<tr>
<td>False Negatives</td>
<td>2,71%</td>
<td>3,49%</td>
</tr>
</tbody>
</table>

**Total Cost**  
-21,5%

High prevalence  
(AC 003)  
Total cost (€), **EBM**

<table>
<thead>
<tr>
<th></th>
<th>Base</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretest + diagnostics</td>
<td>616</td>
<td>536</td>
</tr>
<tr>
<td>False Positives</td>
<td>12,6%</td>
<td>9,82%</td>
</tr>
<tr>
<td>False Negatives</td>
<td>6,22%</td>
<td>7,90%</td>
</tr>
</tbody>
</table>

**Total Cost**  
-13,0%

Low prevalence  
Dan-NICAD 1)  
Total cost (€), **GOÄ**

<table>
<thead>
<tr>
<th></th>
<th>Base</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretest + diagnostics</td>
<td>563</td>
<td>466</td>
</tr>
<tr>
<td>False Positives</td>
<td>11,6%</td>
<td>8,87%</td>
</tr>
<tr>
<td>False Negatives</td>
<td>2,24%</td>
<td>3,11%</td>
</tr>
</tbody>
</table>

**Total Cost**  
-17,1%
Summary

• Hypersensitive phonocardiography is a test to rule-out CAD in symptomatic patients
• Given the current testing landscape and payment schemes in Germany:
  – There is a reasonable probability that the test may reduce costs and invasive measurements
• Next steps:
  – Prove it in clinical reality
  – Discuss data with payors