Accuracy of prospectively ECG-triggered very low-dose coronary dual-source CT angiography using iterative reconstruction for the detection of coronary artery stenosis: comparison with invasive catheterization

Christian Layritz1*, Jasmin Schmid1, Stephan Achenbach2, Stefan Ulzheimer3, Wolfgang Wuest4, Matthias May4, Dieter Ropers1, Lutz Klinghammer1, Werner G. Daniel1, Tobias Pflederer1, and Michael Lell4

1Department of Internal Medicine 2 (Cardiology), University of Erlangen, Ulmenweg 18, D-91054 Erlangen, Germany; 2Department of Internal Medicine 1 (Cardiology), University of Giessen, Giessen, Germany; 3Siemens Healthcare, Forchheim, Germany; and 4Department of Radiology, University of Erlangen, Erlangen, Germany

Received 17 March 2014; accepted after revision 13 May 2014; online publish-ahead-of-print 17 June 2014

Objective
To evaluate the image quality and diagnostic accuracy of very low-dose computed tomography (CT) angiography (CTA) for the evaluation of coronary artery stenosis.

Background
Iterative reconstruction (IR) has shown to substantially reduce image noise and hence permit the use of very low-dose data acquisition protocols in coronary CTA.

Methods
Fifty symptomatic patients with an intermediate likelihood for coronary artery disease underwent coronary CTA (heart rate: 59 ± 5 bpm, prospectively ECG-triggered axial acquisition, 100 kV, 160 mAs, 2 × 128 × 0.6 mm collimation, 60 mL contrast, 6 mL/s) prior to invasive coronary angiography. CTA images were reconstructed using both standard filtered back projection (FBP) and a raw data-based IR algorithm [Sinogram Affirmed Iterative Reconstruction (SAFIRE), Siemens Healthcare]. Subjective image quality (four-point Likert scale from 0 = non-diagnostic to 3 = excellent image quality), image noise, signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR), as well as the presence of coronary stenosis
50% were independently determined by two observers.

Results
The mean dose–length product was 46.8 ± 3.5 mGy cm (estimated effective dose 0.66 ± 0.05 mSv). IR led to significantly improved objective image quality compared with FBP (image noise: 41 ± 12 vs. 49 ± 11 HU, P < 0.0001; CNR: 16 ± 8 vs. 12 ± 4, P < 0.0001; SNR: 13 ± 7 vs. 10 ± 3, P < 0.0001). Four coronary segments were not evaluable on FBP data, whereas all segments showed diagnostic image quality with IR. To detect significant coronary stenosis, sensitivity, specificity, positive predictive value, and negative predictive value were 69% (11/16), 97% (175/180), 69% (11/16), and 97% (175/180) per vessel with FBP data sets, respectively. With IR data sets, the corresponding values were 81% (13/16), 97% (178/184), 68% (13/19), and 98% (178/181). These differences were not statistically significant (P = 0.617).

Conclusions
Raw data-based IR significantly improves image quality in very low-dose prospectively ECG-triggered coronary dual-source CTA when compared with standard reconstruction using FBP.

Keywords
Coronary CT angiography • Low dose • Iterative reconstruction

* Corresponding author. Tel: +49 9131 85 35000; Fax: +49 9131 85 35532. E-mail: christian.layritz@uk-erlangen.de

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2014. For permissions please email: journals.permissions@oup.com.
Introduction

There is ample evidence that coronary computed tomography angiography (CTA) can accurately rule out coronary artery stenosis in patients with chest pain. The method’s major advantage is its high negative predictive value. Coronary CTA can be used to avoid invasive angiography in symptomatic patients with a low pre-test likelihood of having a haemodynamically significant stenosis. Since its advent, the frequency of coronary CTA has increased and in centres with an established programme, the rates of invasive coronary angiography without intervention have decreased.

Radiation exposure associated with coronary CTA is a relevant concern and dose-reduction strategies are therefore an area of active research.

Dose reduction can be achieved by lowering the tube current. Tube current and dose are linearly correlated, so that 20% tube current reduction will result in a 20% dose reduction. Dose and image noise are also correlated, and image noise is proportional to 1/square root (tube current). Image noise is critical for the assessment of the coronary arteries and increased image noise may render an examination non-diagnostic, especially in the presence of massive calcifications.

More elaborate techniques such as automatic exposure control, ECG-based tube current modulation, prospectively ECG-triggered acquisition, and low-kV scanning have been introduced, which aim to reduce dose while maintaining the noise level.

CT image reconstruction has traditionally used filtered back projection (FBP). However, with FBP, increased spatial resolution is directly associated with increased image noise, which is usually compensated by higher X-ray tube output and subsequently higher radiation exposure.

Iterative reconstruction (IR) techniques have been proposed for over three decades to improve image quality by reducing quantum noise and artefacts, but only recently this computationally intensive technology could be translated into clinical practice in CT due to the improvement of computational power.

High-pitch dual-source CT has demonstrated that radiation exposure could dramatically be reduced to a level of < 1 mSv. High-pitch and fast table speed allow performing image acquisition for the entire volumetric data set of the heart within a single cardiac cycle. Radiation exposure is low since no slice overlap is used.

The aim of this study was to test the feasibility of a very low-dose CTA protocol in symptomatic patients with an intermediate risk of coronary artery disease (CAD) by combining prospectively ECG-triggered high-pitch acquisition with low tube current and iterative image reconstruction and to compare the results with invasive catheterization.

Methods

Patient population

Fifty consecutive patients with an intermediate likelihood for CAD were included in this prospective, IRB-approved study. All patients were symptomatic and either referred from the emergency department or from cardiologists outside the hospital because of first presentation of angina pectoris. Clinical data are provided in Table 1.

There was no previously known CAD in all patients. Only patients without a previous diagnosis of CAD were included; patients with previously coronary interventions or coronary artery bypass grafts, renal failure (estimated glomerular filtration rate < 60 mL/min), known allergy to iodinated contrast material, hyperthyreosis, atrial fibrillation, heart rate > 65 bpm after pre-medication with beta-blockade, and body weight > 100 kg were excluded. The last two criteria were chosen to homogenize the patient group. Following coronary CTA, all patients underwent invasive catheterization as the gold standard for CAD within 1 day.

Written informed consent was obtained from each patient.

Coronary CTA

Imaging was performed with a dual-source CT system (SOMATOM Definition Flash, Siemens AG, Healthcare Sector, Forchheim, Germany) using a prospectively ECG-triggered axial acquisition at 70% of the R wave to R wave interval. Detector configuration was 2 × 128 × 0.6 mm, gantry rotation time 0.28 s, tube voltage 100 kV, and tube current 160 mAs. All examinations were performed in deep inspiration. A test bolus was used to individually determine the contrast transit time. About 10 mL of contrast material (iopromide 350 mg I/mL; Imeron, Bracco, Milan, Italy) followed by 50 mL of saline solution were injected at a flow rate of 6 mL/s, and the time-to-peak enhancement in the ascending aorta was measured using a series of axial scans (1 slice every 2 s), with the first image being acquired 16 s after the start of injection. For coronary CTA, 60 mL of contrast agent were injected, followed by 60 mL of flush consisting of 80% saline and 20% contrast material, both at a flow rate of 6 mL/s. Two seconds were added to the time to peak of the test bolus as the delay for CTA.

Images with 0.6-mm slice thickness and a temporal resolution of 75 ms were reconstructed every 0.4 mm. Two sets of images were reconstructed: one with the standard method, FBP, using a medium soft kernel (B26f), and the other with an IR technique [Sinogram Affirmed Iterative Reconstruction (SAFIRE), Siemens Healthcare, Forchheim, Germany], using a medium soft reconstruction kernel (I26f S3), which is the IR kernel equivalent to the B26f.

The effective radiation dose (mSv) was estimated using the dose-length product (DLP) multiplied by a conversion coefficient for the chest as the investigated anatomical region (k = 0.014 mSv mGy cm).

Image analysis

Data sets were evaluated on a workstation (Syngo Via, Siemens Healthcare). To assess image quality, all identifying data on the examinations were removed and replaced by a code. CT data sets were analysed per vessel in a random order by three investigators blinded to each others’ results, and the results from invasive catheterization. FBP data sets were evaluated by one investigator, and iterative reconstructed data sets by two other investigators. A high-grade stenosis was defined as a coronary lesion exceeding >70% lumen obstruction. FBP and IR data sets were evaluated by three readers in consensus. FBP and IR data sets

---

Table 1: Patient and scan characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>50</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>19 (38%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64 ± 10.5</td>
</tr>
<tr>
<td>Mean heart rate (bpm)</td>
<td>59 ± 5</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28 ± 2.9</td>
</tr>
<tr>
<td>Scan length (mm)</td>
<td>135 ± 8</td>
</tr>
<tr>
<td>Dose–length product (mGy cm)</td>
<td>46.8 ± 3.5</td>
</tr>
<tr>
<td>Estimated effective dose (mSv)</td>
<td>0.66 ± 0.05</td>
</tr>
</tbody>
</table>

All values are denoted as mean ± SD or n (%).
were presented in a random order, and two matching data sets (identical patient) were evaluated with a delay of at least 1 month. Cath angio was evaluated by two independent observers.

Subjective image quality was evaluated using a four-point Likert scale for the entire data set and for each individual coronary artery (from 0 = non-diagnostic to 3 = excellent image quality).

To obtain objective parameters of image quality of the proximal coronary arteries, image noise, attenuation, and contrast of the proximal coronary arteries as well as signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) were measured for each data set as reported previously. Image noise was defined as the standard deviation of CT density in a region of interest (ROI) placed in the aortic root. To account for anatomical differences between patients, the ROI was chosen to be as large as possible while carefully avoiding inclusion of the aortic wall to prevent partial volume effects. In a standardized fashion, the ROI was placed immediately cranial to the left coronary ostium (Figure 1). Attenuation within the lumen of the proximal coronary arteries was measured by placing the ROIs centrally in the coronaries. The sizes of the ROIs were chosen as large as possible without including parts of the coronary vessel wall. To determine vessel contrast enhancement, CT attenuation was measured in the pericardial fat tissue next to the right ventricle and subsequently determining the difference in CT attenuation between the vessel lumen and the fat tissue. SNR was determined by dividing this difference in attenuation by image noise, and CNR was determined by dividing contrast values by image noise. The measures were done in an identical manner for both reconstruction protocols.

Invasive catheterization

Invasive catheterization was performed in a catheterization laboratory according to the current guidelines. Ten percentage of patients were investigated using a femoral approach, and 90% had a radial approach. In 14% of all cases, sheath size 5 Fr and in 86% sheath size 6 Fr were used. Imeron (iopromide 350 mg I/mL; Bracco, Milan, Italy) was applied as a contrast agent.

Statistical analysis

All variables are expressed as mean value ± standard deviation. Statistical analyses were performed using the commercially available software (SPSS, Inc., New York, USA, version 20.0). Observed distributions were tested against hypothesized normal distribution (Kolmogorov–Smirnov test). Not normally distributed variables are expressed as median and interquartile range.

Quantitative data were analysed using a paired, two-tailed Student’s t-test after testing for normal distribution. The Wilcoxon signed-rank test was used comparing image quality scores and non-normally distributed parameters. For comparing the image quality score, Cohen’s Kappa was calculated. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the detection of significant stenosis (≥50% lumen narrowing) were calculated for both the FBP and IR technique. The diagnostic accuracy of each reconstruction algorithm (FBP and IR) was calculated using invasive catheterization as the reference method. The diagnostic accuracy of FBP and IR was compared with the use of a McNemar test. Statistical significance was assumed for a level of <0.05.

For evaluating the diagnostic accordance between two independent investigators, analysing IR reconstructed data sets Cohen’s Kappa was calculated.

Results

The investigated patients had a mean age of 64 ± 10.5 years, 38% were female. The mean body mass index (BMI) was 28 ± 2.9 kg/m² and the mean heart rate 59 ± 5/min. Sixty-six percentage of patients received oral beta-blockade. The mean scan range was 135 ± 8 mm (range: 102 – 138 mm) and mean DLP was 46.8 ± 3.5 mGy cm (range: 35–59 mGy cm), resulting in a mean effective radiation dose of 0.66 ± 0.05 mSv. For further details, see Tables 1 and 2.

Comparison of image quality

IR led to significantly improved objective image quality. Image noise was significantly reduced by IR (41.1 ± 12 vs. 49.1 ± 11.1

Figure 1: Determination of image noise: measurement of the standard deviation (arrows) of the attenuation [HU] within a ROI in the aortic root. (A) Example of image noise (56.7 HU) after traditional FBP reconstruction. (B) Example of image noise (40.7 HU) using IR.
HU; P < 0.0001), resulting in a significantly higher SNR ratio (SNR: 13.4 ± 7.3 vs. 10.4 ± 3.4; P < 0.0001) and CNR ratio (CNR: 16.1 ± 8.4 vs. 12.5 ± 3.8; P < 0.0001) (Figure 2 and Table 3). The image quality score, a measure of subjective image quality, was 2.68 ± 0.35 for IR and 2.56 ± 0.48 for FBP (κ = 0.49 [0.29;0.68]; Table 4).

Two hundred coronary arteries were evaluated, four segments were not evaluable with FBP reconstruction, whereas all segments had diagnostic image quality with IR.

**Invasive coronary angiography**

Catheter angiography was performed in all cases. Mean procedural time was 31.2 ± 10.3 min, and mean contrast agent volume was 76.8 ± 27.4 mL. No procedural complications occurred. Sixteen high-grade coronary stenoses were detected.

In coronary CTA with FBP, 11 of 16 coronary artery stenoses were correctly detected (sensitivity 69%). In five cases, CT was false-negative [two stenoses in the left circumflex coronary artery (LCX) and three stenoses in the left anterior descending coronary artery (LAD)]. False-positive results were found in five cases using FBP (three stenoses in the LAD, one of them was correctly evaluated on IR data sets; and two stenoses of the LCX, one of them was also correctly evaluated by IR).

In data sets obtained by IR, 13 critical stenoses were correctly detected (sensitivity 81%). In three cases, CT was false-negative (three stenoses in the LAD, and two stenoses of the LCX that were missed on FBP data sets were detectable on IR data sets).

There were six false-positive results using IR: two in the LCX, one of them was also false-positive on FBP data sets, the other one was not evaluable on FBP due to non-diagnostic image quality; there were three false-positive stenoses in the LAD, two of them were also false-positive on FBP data sets, and one was not evaluable; there was one false-positive in the right coronary artery (RCA), and this segment was also not interpretable using FBP. Cohen’s Kappa for the detection of coronary stenoses between the two observers using IR was 0.89 [0.78;0.99].

Sensitivity, specificity, PPV, and NPV of low-dose FBP-CTA to detect significant coronary artery stenosis were 69% (11/16), 97% (175/180), 69% (11/16), and 97% (175/180) on a per vessel-based analysis, respectively. Overall accuracy was 95% (186/196). With IR, values improved (P = 0.617): sensitivity, specificity, PPV, and NPV were 81% (13/16), 97% (178/184), 68% (13/19), and 98% (178/181), respectively. Accuracy was 96% (191/200, P = 0.69 when compared with FBP; Table 5 and Figures 3 and 4).

<table>
<thead>
<tr>
<th>Table 2: Clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>APCCS 0</td>
</tr>
<tr>
<td>APCCS 1</td>
</tr>
<tr>
<td>APCCS 2</td>
</tr>
<tr>
<td>APCCS 3</td>
</tr>
<tr>
<td>NYHA 0</td>
</tr>
<tr>
<td>NYHA 1</td>
</tr>
<tr>
<td>NYHA 2</td>
</tr>
<tr>
<td>NYHA 3</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hypercholesteremia</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Smoker</td>
</tr>
<tr>
<td>Family predisposition</td>
</tr>
</tbody>
</table>

All values are denoted as n (%).

**Figure 2:** Comparison of objective image quality parameters between FBP and ITR showing statistically significant improved parameters for noise (A), SNR ratio (B), and CNR ratio (C) for IR.
Coronary plaque

Four coronary segments were not interpretable for the detection or exclusion of coronary plaque using FBP, and all IR data sets were evaluable. Coronary plaque was detected in 115 coronary vessels using FBP data sets and in 134 vessels using IR. Plaque detection showed a good agreement between the two investigators using IR ($\kappa = 0.748 \ [0.648;0.848]$). When comparing FBP data sets and IR data sets, Cohen’s Kappa was $0.586 \ [0.47;0.70]$. Four segments could not be assessed by FBP for coronary plaque.

**Discussion**

During the last decade, there have been intense efforts to reduce radiation exposure in coronary CTA. They have mainly been driven by

---

**Table 3** Comparison of objective image quality between FBP and IR

<table>
<thead>
<tr>
<th>Comparison of objective image quality</th>
<th>Filtered back projection</th>
<th>Iterative reconstruction</th>
<th>Significance P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noise [HU]</td>
<td>49 ± 11</td>
<td>41 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SNR</td>
<td>10.4 ± 3.4</td>
<td>13.4 ± 7.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CNR</td>
<td>12.5 ± 3.8</td>
<td>16.1 ± 8.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

All values are denoted as mean ± 1 SD. SNR, signal-to-noise ratio; CNR, contrast-to-noise ratio.

**Table 4** Comparison of subjective image quality between FBP and IR

<table>
<thead>
<tr>
<th>Comparison of subjective image quality</th>
<th>Filtered back projection</th>
<th>Iterative reconstruction</th>
<th>Overall significance $\kappa = 0.49$</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQ 0</td>
<td>3 (6%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>IQ 1</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>IQ 2</td>
<td>23 (46%)</td>
<td>21 (42%)</td>
<td></td>
</tr>
<tr>
<td>IQ 3</td>
<td>23 (46%)</td>
<td>28 (56%)</td>
<td></td>
</tr>
</tbody>
</table>

All values are denoted as n (%). Differences were not statistically significant (n.s.).

**Table 5** Diagnostic accuracy for the detection of coronary artery stenosis after reconstruction using FBP and IR compared with invasive catheterization

<table>
<thead>
<tr>
<th>Accuracy</th>
<th>Filtered back projection</th>
<th>Iterative reconstruction</th>
<th>Vessel-based analysis $P = 0.617$</th>
<th>Sensitivity % (n), [95% CI]</th>
<th>Specificity % (n), [95% CI]</th>
<th>PPV % (n), [95% CI]</th>
<th>NPV % (n), [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel-based analysis</td>
<td></td>
<td></td>
<td>$P = 0.617$</td>
<td>69 (11/16) [41–89]</td>
<td>97 (175/180) [94–99]</td>
<td>69 (11/16) [41–89]</td>
<td>97 (175/180) [94–99]</td>
</tr>
<tr>
<td>Sensitivity % (n), [95% CI]</td>
<td></td>
<td></td>
<td></td>
<td>81 (13/16) [54–96]</td>
<td>97 (178/164) [93–99]</td>
<td>81 (13/16) [54–96]</td>
<td>97 (178/164) [93–99]</td>
</tr>
<tr>
<td>Specificity % (n), [95% CI]</td>
<td></td>
<td></td>
<td></td>
<td>68 (13/19) [43–87]</td>
<td>97 (178/181) [95–100]</td>
<td>68 (13/19) [43–87]</td>
<td>97 (178/181) [95–100]</td>
</tr>
</tbody>
</table>

FBP vs. IR: no significant differences according to McNemar’s test. FBP, filtered back projection; IR, iterative reconstruction; PPV, positive predictive value; NPV, negative predictive value.

**Figure 3**: RCA without detectable stenosis. Multiplanar reconstructions of coronary DSCT angiography data sets after FBP (A) and ITR (B and C) without detectable stenosis confirmed by invasive catheterization (D).
technical advances in the scanner hardware, which in turn permitted modification of data acquisition protocols. In addition, since computational power has improved, more elaborate image reconstruction techniques, so called ‘iterative reconstruction’, can be implemented. First results in chest,21 abdominal,22 body,23 and cardiac CT4,9,12,24,25 suggest that IR may compensate for increased image noise in low-dose scan protocols. In a group of 50 consecutive patients, with an intermediate risk of coronary artery stenosis, a typical clinical setting, in which the use of coronary CTA may be considered, we could demonstrate that a very low-dose data acquisition protocol with a mean effective dose of 0.66 mSv is feasible. IR led to significantly improved objective image parameters (SNR and CNR), while there was only a moderate agreement in subjective image quality evaluation. Similar to our results, Renker et al.26 described an improved image quality score with IR that was explained by a reduction in blooming artefacts and decreased image noise with IR. Moscariello et al.12 could not find a statistically significant improvement of subjective image quality, but they also detected a lower image noise for IR. Bittencourt et al.9 showed that applying standard imaging parameters in conjunction with an IR algorithm led to a reduction in image noise of 26 ± 10%, which is comparable to our study with an image noise reduction of 17%. In another study comparing image quality using IR and FBP, Park et al.27 found a reduction of image noise from 26.3 ± 5.6 HU for FBP to 19.9 ± 4.5 HU using IR (P < 0.001). Their values for noise were substantially lower than ours. This is the consequence of a higher radiation dose when compared with our study.

Unfortunately, sensitivity as well as specificity for the detection of coronary stenoses was not satisfactory and lower when compared with reports obtained with higher radiation exposure.28 There

Figure 4: RCA with high-grade stenosis. Multiplanar reconstructions of coronary DSCT data sets after FBP (A) and ITR (B and C) with detectable stenosis confirmed by invasive catheterization (D).
were five significant coronary lesions missed using FBP that lead to revascularization. Only three of these stenoses were missed using IR, the reason for that was small vessel size ($n = 1$) and dense coronary calcifications ($n = 2$) (Figure 5). Stenoses that were not detected by CT using FBP were cases with a subjective image quality score of 0 in three cases and of 1 in one case as well as 2 in another case. The lost stenoses using IR were one case with a subjective image quality score of 1 and two cases with a subjective image quality score of 2. Beyond that, all patients with a missed significant coronary lesion were patients with a BMI above 30 kg/m², so that obesity seems to be a major problem for accuracy when using very low-dose acquisition protocols in coronary CTA. The negative predictive value for ruling out significant coronary artery stenosis was very high using FBP (97%) and IR (98%) in these very low-dose scan protocols, comparable to previous studies;¹ still the sensitivity for the detection of coronary artery stenosis was lower compared with standard radiation dose protocols (Hu et al.²⁹).

**Limitations**

Our study has several limitations. We did use a fixed low-dose scan protocol and did not examine the effect on different radiation dose levels.

We only included patients with an intermediate likelihood of CAD. As a consequence of that there were only 16 significant lesions in invasive catheterization leading to a low prevalence of critical coronary artery stenosis in our patient population. Patients with >100 kg body weight, and patients with a heart rate above 65 bpm—even after optimal beta-blockade—were excluded from this study, which may introduce some bias.

In summary, we could confirm that IR techniques reduce image noise in low-dose coronary CTA data sets when compared with data sets obtained by traditional FBP. However, subjective image quality is not improved and the accuracy for stenosis detection was lower than typically found in publications that use higher radiation exposure. Hence, before the use of very low-dose image acquisition
protocols is endorsed, it must be realized that measuring image noise is not a sufficient surrogate to ensure equal diagnostic accuracy and consequently, diagnostic performance must be re-evaluated for very low-dose protocols before their widespread implementation.

Conflict of interest: M.L. has received research grants from Siemens Healthcare and Bayer HealthCare, T.P. has received speaker honoraria from Siemens Healthcare, and S.A. has received research grants from Siemens Healthcare and Bayer HealthCare.

Funding
This study was supported by the German Government, Bundesministerium für Bildung und Forschung (01EX1012B, ‘Spitzencluster Medical Valley’).

References