

# Feasibility of cardiovascular population-based CT screening

Vonder, Marleen

10

# Summary

# Feasibility of cardiovascular population-based CT screening

One of the challenges in cardiovascular population-based CT screening is to secure imaging biomarker validity to perform proper risk stratification on one hand, while screening large populations at a radiation dose as low as possible on the other hand. The aim of this thesis is to determine the feasibility of radiation dose reduced cardiovascular population-based CT screening in order to increase the health benefits of screening.

## PART I - Design of population-based CT screening

The prevalence and disease burden of cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD) and lung cancer is high. Population-based low-dose CT screening followed by early treatment for these three diseases (Big-3) has high potential to cure the disease or to delay or to stop progression of the disease. In **Chapter 2**, the current evidence and CT protocols for early detection of the Big-3 diseases with low dose chest CT are discussed. Imaging biomarkers are analyzed on these low dose CT scans: Lung nodule management based on nodule volume measurements can be performed, CVD risk stratification based on coronary artery calcium (CAC) score is feasible, and quantification of emphysema shows potential for early diagnosis of COPD. Currently, quantification of the different imaging biomarkers is based on different scans each optimized and validated for one of these specific imaging biomarkers. Although using validated conventional CT protocols for the three biomarkers is most convenient, radiation dose may exceed the maximum dose for a screening examination (2.3 mSv, with maximum dose of 5 mSv). Multiple options for combining the acquisition protocols for quantification of all three imaging biomarkers are available [Chapter 2: *Figure 4*]. However, there is a sublte balance in maintaining imaging biomarker validity of the Big-3 protocol and reducing the total radiation dose of such an acquisition. Screening for COPD and CVD in addition to lung cancer may significantly improve cost-effectiveness of low-dose lung cancer screening in the future. Studies are needed to confirm this hypothesis. Eventually, smoking cessation remains the most effective measure for decreasing disease burden from the Big-3 diseases.

Nonetheless, before Big-3 screening can be implemented, a prospective randomized study that can show the risk and benefit in CVD risk stratification based on CAC scoring should be performed. In **Chapter 3**, the rationale and technical considerations in developing a robust and standardized CAC imaging protocol are described and a

detailed protocol that can be implemented for CAC imaging for screening purposes is presented. The imaging protocol includes a fixed tube voltage, individually tailored tube current setting, mid-diastolic Electrocardiographic (ECG) triggering, fixed field-of-view, fixed reconstruction kernel, fixed slice thickness, overlapping reconstruction and no iterative reconstruction (IR) [Chapter 3: *Table 2* and *3*]. Analysis of the scans should be performed with one type and version of CAC scoring software, by dedicated researchers experienced in CAC scoring. Altogether, the protocol results in scans with good image quality for evaluating CAC, at a low radiation dose, from which reliable CAC scores can be derived and CVD risk stratification can be determined. The data management protocol in chapter 3 describes the organization of data handling between the coordinating center, participating centers and analyzing center [Chapter 3: *Figure 2*]. The described imaging protocol is optimized for second generation dual-source CT (DSCT) and detection of CAC. Before this protocol can be used for other CT systems/generations, validation is needed. The described protocols and methods were applied in the large-scale population based cardiovascular screening trial ROBINSCA.

Continuous efforts to further optimize the CAC imaging protocol can be valuable to provide a cutting-edge imaging protocol to the market when CVD screening has been proven ready for wide-scale implementation. A way to optimize the protocol is to use the high-pitch spiral mode not only in participants with a low heart rate (≤65 bpm) but also in participants with a high heart rate (>65 bpm), to potentially reduce the radiation dose. Nevertheless, the use of high-pitch spiral mode in participants with high heart rates should first be validated. In **Chapter 4**, we found that high-pitch spiral mode instead of sequential mode can be used for CAC risk stratification in participants (n=1,990) with a regular high heart rate, resulting in 48% radiation dose reduction. A similar number of zero scores was found for high-pitch spiral and sequential mode CAC scanning regardless of the heart rate. The Agatston score was slightly lower based on high-pitch spiral mode scanning compared to sequential mode scanning for both the low and high heart rate group. However, the difference in Agatston score between high-pitch spiral and sequential mode scans was similar for the high heart rate group and the reference low heart rate group. Moreover, risk categorization based on the Agatston score showed almost perfect agreement for both scan modes in the high heart rate group (κ=0.927) and low heart rate group (κ=0.946) [Chapter 4: *Table 1* and *2*]. Thus, radiation dose can potentially be halved when the high-pitch spiral mode is used instead of the sequential mode in participants with a regular high heart rate.

## PART II - Dose reduction as a function of imaging biomarker validity

One of the challenges in population-based CT screening is to secure imaging biomarker validity to perform proper risk stratification on one hand, while screening large populations at radiation dose as low as possible on the other hand. So far, efforts for dose reduction were mainly focused on coronary CT angiography and have not been systematically implemented for CAC scoring. In **Chapter 5**, we systematically reviewed the dose reduction techniques in CAC imaging for their impact on Agatston score and CVD risk stratification. In total, 27 studies were included of which in 81% of the studies, the radiation dose was reduced ≥50% with CT dose index ($CTDI_{vol}$) ranging from 0.6 to 5.5 mGy [Chapter 5: *Figure 2* and *3*]. Dose was reduced with tube voltage reduction, tube voltage reduction and IR, tube current reduction, tube current reduction and IR, and with tin-filter spectral shaping. The different dose reduction techniques had varying impact on Agatston scores and CVD risk stratification. Tube voltage reduction led to high agreement for Agatston score but with a systematic under- or overestimation of the Agatston score even when the HU-threshold was adapted for dose reduced protocol of 0.6 to 1.2 mGy [Chapter 5: *Table 1*]. Contrary to only tube voltage reduction, tube voltage reduction with IR showed similar results for Agatston score at a radiation dose of 0.4 to 1.6 mGy (Chapter 5: *Table 2*]. Likewise, studies evaluating tube current-optimized and tube current-reduced protocols reported similar Agatston scores or a high agreement of Agatston scores [Chapter 5: *Table 3*]. Tube current reduction combined with high IR levels showed an underestimation of the Agatston score, whereas low and moderate levels of IR showed similar Agatston scores at a radiation dose of 0.8-3.9 mGy [Chapter 5: *Table 4*]. Spectral shaping with tin-filtration resulted in substantial dose reductions in CAC imaging (total dose: 0.6-1.3 mGy), but resulted in underestimated Agatston scores [Chapter 5: *Table 5*]. Twelve studies reported reclassification rates for CVD risk stratification, of which eight studies reported reclassification rates for tube current reduction with IR. Lower levels of IR tended to result in less reclassification, but a wide range of reclassification was reported: 3% up to 21% across all types of IR. Specific dose reduced protocols, including either tube current reduction and IR or spectral shaping with tin filtration, that showed low reclassification rates may potentially be used in CAC scanning and in future population-based screening for CVD risk stratification.

Any new dose reduced acquisition protocol to be implementable in clinical practice should give comparable CVD stratification results as the conventional protocol. Therefore, in chapter 6 and chapter 7 the impact of dose reduction techniques on CAC

quantification is examined to warrant the validity of CAC as an imaging biomarker for CVD at ultra-low dose CT. On third generation DSCT, radiation dose reduction for CAC scanning might be feasible by combining low tube voltages with a modeled based iterative reconstruction algorithm at different strengths. In **Chapter 6** the CAC detectability and score of thirty different combination protocols with tube voltage ranging from 70 to 110 kVp and IR levels 1 to 5 were determined in a thoracic phantom study and compared to the reference protocol of 120 kVp, 90 ref mAs with filtered-back projection (FBP). For protocols that yielded similar detectability and calcium scores as the reference protocol, additional scans were acquired at reduced tube currents ranging from 18 to 72 mAs. Moreover, additional scans were also acquired for those protocols for two larger thoracic phantom sizes. The detectability and calcium scores decreased at increasing IR levels ($\tau_b$<-0.825, p<0.001) and increasing tube voltage ($\tau_b$<-0.679, p<0.001) [Chapter 6: *Figure 2*]. The combination of a tube voltage and IR of 90kVp-IR3 and 100kVp-IR1 resulted in similar Agatston scores as determined by the conventional acquisition at 120kV-FBP without the necessity to change the calcium HU threshold (p>0.206). For these protocols, lower tube currents did not affect the detectability and Agatston score (p>0.206) [Chapter 6: *Figure 4*]. In addition, by lowering the tube current for these protocols, it was feasible to acquire coronary calcium scans of small, medium and large patient sizes with similar results for detectability and Agatston score with a dose reduction up to 60.6% compared to the reference protocol of 120kVp-FBP [Chapter 6: *Table 3*]. The 100kVp-IR1 protocol with 52-74 ref mAs also showed similar results for calcium volume and mass score as the reference protocol for all patient sizes. Nevertheless, variability of the Agatston score was slightly higher for the dose reduced protocols. Future in vivo studies should demonstrate whether this impacts CVD risk stratification or not.



The dose of chest CT imaging in third generation DSCT can be further reduced by spectral shaping of the x-ray beam due to pre-filtration by a tin-filter placed behind the x-ray tube. The potential for radiation dose reduction in lung cancer screening with this ultra-low dose chest CT was recently shown. Possibly, the advent of ultra-low-dose CT lung cancer screening may also offer the opportunity to screen at an ultra-low-dose for coronary calcifications. In **Chapter 7**, we analyzed the impact of this ultra-low-dose technique on CAC quantification based on three different CAC phantoms. Phantom inserts with 100 small and 9 large calcifications, and a moving artificial artery with 3 calcifications (speed 0 to 30 mm/s) were placed in a thorax phantom simulating different patient sizes. The phantom was scanned in high-pitch

spiral mode at tube voltage of 100 kVp with a tin-filter (Sn100 kVp) with ECG-gating, and was compared to the reference protocol with tube voltage of 120 kVp with ECG-gating. We found that the Sn100 kVp scan protocol with standard HU threshold of 130 HU, resulted in lower detectability of calcifications (9% versus 12%, p=0.027) and lower calcium scores (p<0.008) regardless of coronary movement [Chapter 7: *Table 1, Figure 2* and *3*]. Adaptation of the HU threshold to 117 HU for calcium scoring at Sn100 kVp resulted in similar detectability (p=1.000) and Agatston score (p>0.206) for small and medium patient size. Besides, the Sn100 kVp protocol led to a major decrease in radiation dose of 63% to 73% for, respectively, small to large patient size.

Methods for dose reduction are not limited to setting and techniques available on a scanner, but dose reduction can also be achieved by comparing different types of CT systems, while applying a similar CAC protocol. In large multi-center screening trials and in follow-up studies, it is often not possible to use exactly the same type of CT system. In **Chapter 8**, we compared CAC quantification between three generations of DSCT systems to determine the variability between CT systems. The same three CAC phantoms as in the former chapter were used, and were scanned with tube voltage of 120 kVp, tube current of 90 reference mAs with prospective ECG-gating at sequential and high-pitch spiral mode, for, respectively, first and second/third generation DSCT. The three DSCT generations had similar detectability of coronary calcifications with median (range) detectability of 11(8), 11(4) and 12(2) out of 100 calcifications, for first, second and third generation, respectively (p>0.272). Small variations in median Agatston score were found across the three DSCT generations, ranging from 0.5 to 6.1% for the non-moving phantom, while increasing to a maximum median differenc of 12.7% for the phantom with the moving artifical artery [Chapter 8: *Figure 3*]. Contrary, the mass score varied only by 0.5% to a maximum of 5.1%, with no significant differences between the generations for the moving coronary artery. Likewise, the variability in mass score tended to be lower than in Agatston score for all DSCT systems, with lowest Agatston variability for third generation DSCT. Median Agatston and mass score differed by no more than 12.7% and 5.6%. This indicates that CAC progression can only be concluded if the Agatston and mass score increase above this level compared to baseline.

In **Chapter 9**, the main findings of the results presented in the previous chapters are discussed in a broader perspective and recommendations for future studies are given. From the studies in this thesis it can be concluded that cardiovascular population-

based CT screening is feasible with a standardized and validated imaging biomarker protocol. Combining screening protocols, optimizing scan parameters and using latest generation of DSCT can significantly reduce radiation dose. Nevertheless, before cardiovascular population-based CT screening can be implemented, an imaging biomarker profile for CAC is needed to ensure proper use of dose-reduced protocols. Future results of the ROBINSCA trial and other large population-based studies should show whether CT screening for the Big-3 diseases should be implemented.