Optimised detection, visualisation and quantification of the coronary artery plaque: which pathway?

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In this thesis detection, visualisation and quantification of coronary artery plaque using different imaging methods was investigated. First, preclinical studies were performed to assess the effectiveness of improving coronary artery calcium scoring using both calcium scoring CT (CSCT) and coronary CT angiography (CCTA). Second, the ability of low-dose CT (LDCT) to detect coronary artery calcium was evaluated in conjunction with myocardial perfusion PET. Furthermore, the improvement in major adverse cardiac events prediction based on coronary artery calcium (CAC) derived from LDCT scans was examined. Third, coronary artery plaque analysis was performed in patients from the highest cardiovascular risk group. Fourth, a prospective study was proposed in which both invasive and non-invasive methods will be applied to differentiate between ischemia caused by aortic stenosis and coronary artery stenosis.

Low risk patients

CAC scoring follows the strictly defined Agatston method, which was developed on electron beam tomography. Interestingly, despite the introduction of novel CT technology, including multidetector CT scanners, spectral CT systems, or photon counting CT (PCCT), the CAC scoring method has remained unaltered since 2007. This conservative approach might be explained by the fact that the Agatston score was extensively validated in large longitudinal cohort studies and has demonstrated its predictive value for future cardiovascular events. Nevertheless, the Agatston score is susceptible to be influenced by acquisition parameters, including tube voltage, radiation dose, and temporal resolution, as well as reconstruction parameters such as kernel and slice thickness. These factors can potentially lead to misclassification of cardiovascular risk in patients. Therefore, there is an urgent need to improve the calculation of the Agatston score to incorporate current technological advancements.

Iterative reconstruction

As a first step, we explored the factors that influence the calculation of CAC score from CSCT scans, including reconstruction methods, motion artefacts, and radiation dose reduction. Traditionally, for CT scan reconstruction a filter-back projection method was used. In terms of reconstruction methods, iterative reconstruction (IR) has replaced the traditional filter-back projection method. Nevertheless, as IR creates high-quality images by reducing noise, application of IR in calcium scoring remained questionable. The main concern of IR utilisation in clinical practice was decreased calcium detectability due to decreased noise levels. As demonstrated in our phantom study, each of the four examined reconstruction methods reduced the detectability of small calcifications by up to 22%. However, these findings were not reflected in a patient study, which aligns with the findings of Schindler et al., who also found no difference in the detectability of small calcifications between iterative reconstruction and filter-back projection. This might be explained by the fact that in the patients' study the total Agatston score was investigated, in which small calcifications play a minor role. An upcoming challenge is calcium scoring on photon-counting CT scan.

It is important to note that CAC remains the most significant negative predictor of cardiovascular diseases, as demonstrated by the MESA study. Therefore, we should exercise caution when applying IR to calcium scoring scans, as these reconstruction methods may lead to missed detection of small calcifications and

improper classification of patients into the zero Agatston score risk group.

Motion artefacts

The next step was to examine the impact of heart rate and motion artefacts on CAC scoring. It is widely recognised that coronary artery velocities can exceed 90 mm/s, which is dependent on the artery segment and heart rate. As observed by Johnson et al, despite targeting a heart rate of 60 beats per minute (bpm), 50% of the scans were conducted at heart rates exceeding 70 bpm, which corresponds to velocities of 30 mm/s or higher. Taking everything into consideration, despite the ECG-triggering of CSCT scans, motion artifacts continue to pose a significant challenge in a large number of CT scans. Previous studies have primarily focused on enhancing CAC quantification through the utilisation of machine learning methods, in an attempt to mitigate the influence of motion artifacts. Zhang and colleagues presented coronary calcium classification based on convolutional neural networks (CNN) corrected images, which reduced the variation of calcium scores to 3.7%. In our study, our focus was not on improving CAC scoring, but rather on accurately recognising motion artifacts using CNN. As demonstrated, the CNN achieved a high accuracy of 90% in classifying motion-contaminated images into the appropriate calcium scoring risk category, regardless of various influential technical factors, such as iterative reconstruction, radiation dose reduction, and coronary artery velocity. Therefore, the precise recognition of motion artifacts through this approach may further enhance CAC scoring.

Radiation dose reduction

Due to the capabilities of state-of-the-art Photon Counting CT (PCCT), it is now possible to reconstruct images at different energy levels independently from tube potential. This advancement enables the feasibility of calcium scoring from images acquired with lower tube potentials, potentially leading to reduced radiation dose. Van der Werf and colleagues demonstrated a 50% reduction in radiation dose for low keV levels; however, this was only achievable for medium and high density calcifications. As demonstrated in our study, we achieved a reduction of over 19% in radiation dose, regardless of calcification size and density, phantom size, or heart rate, by utilising a tube voltage of 100kV with tin filtration. Given the significant burden of cardiovascular disease, which results in a high number of CSCT scans, there is a need to reduce the radiation dose associated with these scans. Moreover, in response to the call for randomised clinical trials investigating the potential of CAC in risk classification, a decreased radiation dose may further facilitate the planning of follow-up CSCT scans.

The next step in reducing radiation dose involves performing CAC scoring from CCTA scans using a single acquisition procedure. As demonstrated by Schwarz and colleagues, CAC scores calculated from CCTA scans acquired on dual energy CT system and reconstructed with virtual non-contrast (VNC) were consistently underestimated. Similar findings were presented by Gassert and colleagues, who analysed scans acquired on a dual-layer CT system and observed a CAC underestimation of up to 75%. In our study, despite notable underestimation, CAC calculated from CCTA scans acquired on a photon counting CT system and reconstructed with the virtual non-iodine method (VNI) showed moderate agreement in patients' cardiovascular risk classification. While acknowledging the limitations of CAC calculated from CCTA scans acquired on PCCT, this method is deemed feasible, although further validation is required.

Vendor-independent Agatston score

As highlighted by Willemink and colleagues, one of the main limitations of CAC is the lack of reproducibility and discrepancies in CAC quantification observed between different vendors, which can result in significant misclassification of patients' risk. Therefore, we developed a calibration factor that resulted in a vendor-independent Agatston score (vendor-neutral Agatston score, vnAS, figure 1). Based on our analysis, when the calibration factor was applied, 11% of MESA participants were reclassified from the low to the high calcium group. Among these reclassified individuals, 15.3% experienced a coronary heart disease (CHD) event, and 23.5% experienced an atherosclerotic cardiovascular disease (ASCVD) event. This represents a difference of 8.3% and 5.3% compared to the low calcium group, respectively. According to AHA and ESC guidelines, asymptomatic individuals with CAC > 100 should be considered candidates for lipid lowering therapy. Based on our analysis, 11% of MESA individuals who experienced more CHD events, would be reclassified to the lipid-lowering therapy group. Considering that the majority of medical centres worldwide use CT scanners with lower temporal resolution compared to electron beam tomography, the percentage of reclassified patients may be even higher than what our analysis indicates. Therefore, the implementation of vnAS, which is a cost-effective and straightforward step towards achieving a unified Agatston score, can significantly improve risk stratification and provide prognostic information for specific medical treatments.

Intermediate risk patients

The proliferation of different CAC scoring methods from LDCT scans has not led to a consensus on

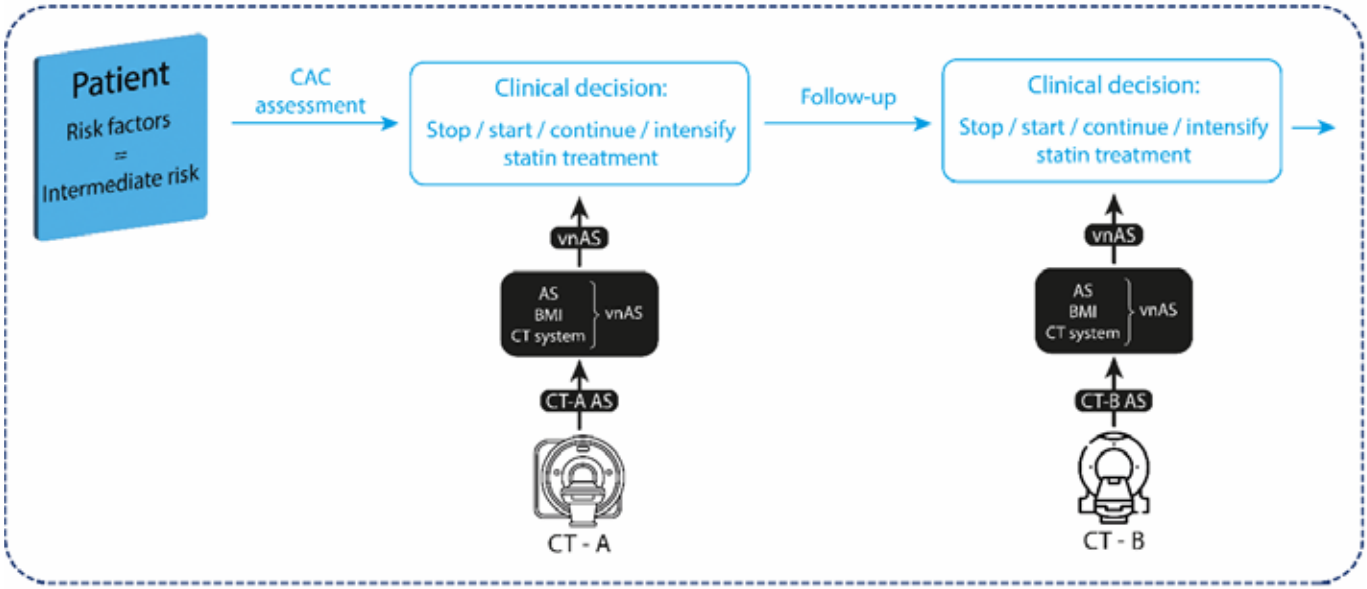

Figure 1. Schematic of vendor-neutral Agatston score calculator. Illustration of the use of the vendor-neutral Agatston score (vnAS) calculator, which converts a MDCT specific Agatston score (AS) (CT-A AS or CT-B AS) into a vnAS based on patient and CT specific parameters. The vnAS can subsequently be used for clinical decisions on statin treatment for patients at intermediate atherosclerotic cardiovascular disease risk, both initially and in follow-up assessments

which method to choose in clinical practice. However, Einstein and colleagues introduced a simple visual scoring method from LDCT, which demonstrated high agreement with CSCT scans results. This simple approach also enhanced cardiovascular risk prediction in patients referred for SPECT or PET scans. With the growing interest in AI methods, CAC scores from LDCT based on machine learning or convolutional neural networks have also been introduced. Importantly, the majority of these methods have not been validated against CSCT scans, limiting the ability to compare them with the reference standard. Recently, Pieszko et al., presented a calcium scoring method from LDCT scans acquired prior to MPI PET, which demonstrated good agreement with CAC calculated from CSCT scans. In our analysis, we compared visual and automatic methods to CSCT results, and found that visual scoring exhibited the highest agreement. Importantly, our analysis demonstrated that both visual and automatic CAC scoring from LDCT scans improve CVD risk prediction independently from MPI-PET results. Therefore, as emphasised by the Society of Cardiovascular Computed Tomography, there is a need for routine CAC scoring from LDCT scans in addition to MPI-PET scans to identify patients at high cardiovascular risk. In terms of ischemia detection, our analysis revealed that patients with reduced myocardial perfusion on 15O-water PET scans also had a higher incidence of MACE. Despite recent opinions that downplay the significance of ischemia testing, as emphasised by Ryan and colleagues, there is a need for randomised trials to determine whether outcome is influenced by the invasive intervention or the underlying disease.

High risk patients

As demonstrated in the PROSPECT II trial, it was discovered that the composition of coronary artery plaque, rather than the severity of stenosis, served as a predictor of MACE. In this study, high risk plaques were defined using NIRS-IVUS as lesions with a maximal lipid core burden index (maxLCBI) greater than 400 and plaque burden exceeding 70%. In our study, no significant relationship between total cholesterol levels or low-density lipoproteins and plaque composition was observed, consistent with previous findings. Importantly, our study demonstrated a correlation between low concentrations of high-density lipoproteins and a high risk of lipid-rich plaques. The relation between low levels of high-density lipoprotein (HDL) and an increased risk of CAD was identified in the Framingham study. As demonstrated by Honda and colleagues, HDL levels were inversely correlated with changes in lipid plaque composition, as assessed by NIRS, regardless of statin use. This finding has been confirmed by other study groups as well. Taking everything into consideration, HDL may have a potential role in reducing the amount of lipids within artery plaques, although further investigation is required to fully understand this association.

In terms of assessing lesion stenosis severity, adenosine-dependent Fractional Flow Reserve (FFR) is considered the gold standard. Despite its clinical value, the use of hyperaemia in adenosine-dependent FFR is limited due to the diverse response to adenosine. Moreover, adenosine-induced hyperaemia may be influenced by increased heart rate or decreased blood pressure, which may require further correction, such as accounting for the rate pressure product. According to investigators of the FAVOR I and FAVOR II trials, quantitative flow reserve (QFR), a wire-free method of intracoronary flow measurement, improved the evaluation of intermediate coronary artery stenosis. Previous studies have reported cut-off values of minimal lumen area derived from IVUS measurements that predict significant stenosis. In our study, we found that minimal lumen area and minimal lumen diameter of the coronary artery, calculated using IVUS, accurately identified lesions with decreased coronary flow. Given the limitations of pressure wire assessment due to contraindications for adenosine infusion or patients' discomfort during hyperaemia, the combination of NIRS-IVUS and QFR may have a role in assessing stenosis severity in this patient population.
Among high-risk patients, those with severe aortic stenosis and concomitant CAD pose a significant challenge. As invasive coronary angiography is still considered the standard for assessing coronary artery stenosis severity in these patients, we propose a prospective pilot study in which we investigate quantitative myocardial perfusion measurement using cadmium-zinc-telluride SPECT (CZT-SPECT) or PET, in addition to invasive methods such as coronary artery flow reserve, and index of microvascular resistance to evaluate coronary artery flow. With an improved understanding of the physiological changes caused by aortic stenosis, we propose that SPECT and intravascular indices could potentially assist in guiding the decision-making process regarding revascularisation in patients with severe aortic stenosis and concomitant CAD.

Future perspectives

Fundamentally, the key to improving the diagnosis of CAD is to continue with further development of coronary artery plaque analysis techniques. It goes without saying that the aim of the diagnostic process is to be as least invasive as reasonably achievable. Therefore, due to its widespread availability, speed of image acquisition, and relatively low scanning costs, computed tomography plays a critical role. Nevertheless, as also shown in our studies, current CT still has some limitations. First of all, further improvement of IR methods is needed to increase precision in plaque visualisation and analysis. Second, in cardiac CT, a reduction in motion artefacts is essential, which can be achieved through increased temporal resolution or the application of motion correction techniques. Third, to utilise CCTA broadly in cardiac screening, further advancements are needed that help to minimise radiation dose.

Until recently, all clinical CT scanners employed energy-integrating detectors, which are characterised by limited spatial resolution and limited capacity to distinguish between different tissues and materials. However, in recent years a new technology, photon counting CT (PCCT) has emerged. This advancement overcomes some limitations associated with conventional CT scanner technology and introduces new opportunities for change. PCCT is primarily recognised for its ability not only to enable data acquisition at different energy levels but also to improve spatial resolution. This enhancement allows for better differentiation between various materials and for more accurate diagnosis. However, the advantages of PCCT extend far beyond these improvements. By reducing electronic noise, PCCT enables data acquisition with thinner slices, allowing for more detailed structural analysis when applying sharp kernels. Moreover, this reduced noise permits data acquisition at lower radiation doses, without loss of information. In the field of cardiology, this presents the opportunity to analyse in-stent restenosis, even in stents deployed in small vessels - an achievement that has not always been possible until now. Moreover, material decomposition significantly enhances the ability to distinguish contrast media from tissues, which could be applied to new diagnostic tasks. One notable example is k-edge imaging, which allows for the use of contrast media materials that have not been employed in clinical settings thus far. As a result, a detailed analysis of cardiac muscle is now within grasp. It goes without saying that PCCT opened a new chapter in terms of coronary artery disease diagnosis and management, which may further improve radiologists' confidence in stating the diagnosis and decrease the need of additional diagnostic tests. However, for now, high-resolution scanning on PCCT is combined with increased radiation dose. Moreover, acquisition of spectral data from PCCT is not only unavailable from high-resolution data, but is also inextricably linked with a tube voltage of 120 kVp. Having said that, further improvement on image reconstruction is essential to fully utilise PCCT technology advancement.

Next, future studies are needed to apply the utilisation of Artificial Intelligence (AI) methods into reconstruction methods and image analysis. As underlined by Reinke et al, validation metrics used in AI methods presentation might be

chosen inadequately in relation to the clinical and research problem, and therefore overestimating the overall performance of AI. Therefore, a lot of effort should be made to raise the awareness of the importance of image analysis validation and to increase the access to relevant knowledge among researchers.

In terms of CAC scoring, to remain the importance of calcium as a risk predictor, the methodology of CAC quantification should be changed and as such adjusted to current CT technology. With the introduction of IR, which decreases noise levels, the application of smaller slice thickness became feasible. Knowing the radiation dose reduction opportunities presented by IR, in addition to increased high resolution imaging techniques, the CAC scoring acquisition can, and should, be improved. Nevertheless, due to conservative approach and years of research performed with Agatston method, this seems to be a real challenge. However, we believe that introduction of vendor neutral AS revealed the weak points of Agatston score resulting in patients risk misclassification in a real clinical scenario. Therefore, we believe that in addition to other studies reporting drawbacks of the conservative CAC score technique, they might bring a change to clinical standards in the future. Considering high risk patients, there is an increasing awareness of CT potential for planning and guiding interventions. Therefore, by overcoming the CT limitations mentioned above, we are increasing the role of CT in decision making about revascularisation.

Changing the subject to functional imaging, which is undeniable strictly combined with plaque analysis, nuclear medicine with ^{15}O-water PET has no equal in terms of perfusion analysis. Therefore, for the validation of functional imaging performed with PCCT, studies employing a reference ^{15}O-water PET should be planned. Moreover, with a great variety of nuclear tracers, like sodium fluoride (^{18}F-NaF) or fibroblast activation protein inhibitor (^{68}Ga-FAPI), further improvement in terms of tissue characterisation with PCCT is possible and should be considered.

Final conclusion

Given the wide range of diagnostic methods and technological advancements, we have proposed pathways to enhance the diagnosis of coronary artery disease in patients at low, intermediate, and high risk. Regarding calcium scoring in low risk patients, recent advancements in CT technology have enabled more accurate calcium scoring while reducing radiation dose. However, the limitations of the Agatston score highlight the need for an improved metric in calcium scoring. In patients from the intermediate-risk group who are referred for myocardial perfusion scans, utilising a simple visual assessment of CAC from low-dose CT scans may enhance cardiovascular risk prediction, potentially leading to improved patient outcomes.
In the high-risk group, where an invasive angiography is indicated, the application of IVUS, NIRS-IVUS or OCT can aid in identifying high-risk plaques, while QFR (or other computational fluid dynamic-based tools like virtual FFR) can assist in assessing coronary artery stenosis severity, thereby reducing the need for adenosine stress test. ♦

Link to full thesis: https://research.rug.nl/en/publications/optimized-detection-visualization-and-quantification-of-the-coron