Computed Tomography of the Coronary Arteries: Developmental and Prognostic Investigations

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To Anna

“Always pass on what you have learned.”

Yoda

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ABSTRACT

Computed tomography (CT) is an increasingly used modality for investigations of patients with suspected coronary artery disease (CAD). Technical advances could improve diagnostic accuracy and lead to clinical workflow improvements. Also, more prognostic information can optimize clinical follow-up strategies and treatments.

The general aim of this thesis was to explore the use of CT for CAD investigations. Three studies aimed to examine new technologies, including the evaluation of an on-site, computed tomography-based fractional flow reserve (CT-FFR) software (study I), the evaluation of an AI-based, calcium scoring computed tomography (CSCT) software (study III), and the evaluation of a photon-counting detector (PCD)-CT (study IV). One study aimed to evaluate the long-term prognostic value of coronary computed tomography angiography (CCTA) in symptomatic patients with no history of CAD (study II).

The software evaluation studies (study I and III) and the prognostic study (study II) utilized CT data from clinical patients, while the PCD-CT evaluation study (study IV) used CT data from cadaveric specimens. The performances of both software programs were compared with standard references, being represented by fractional flow reserve (FFR) measurements (study I), and coronary artery calcification (CAC) scores from a semi-automatic software (study III), respectively. The PCD-CT performance on CAC quantification was compared with corresponding results from an energy integrating detector (EID)-CT, using micro-CT as the standard reference (study IV). The prognostic study merged registries to identify major adverse cardiac events (MACE), having a follow-up time of up to 7.5 years (study II).

The CT-FFR and CSCT software correlation and agreement to corresponding standard references were good and excellent, respectively. Also, both software programs had time-saving potential (study I and III). The CAC quantification was more accurate using PCD-CT than EID-CT (study IV). The prognosis was excellent in patients with normal coronary arteries, and progressively impaired in non-obstructive and obstructive CAD (study II).

The results in this thesis convey developmental, technical CT technology advances for CAD investigations. In addition, prognostic follow-up data is communicated. The results may benefit patients by an increased accuracy in the CT evaluation of CAD and can contribute to improve clinical follow-up strategies. Furthermore, the results suggest possibilities to improve the workflow in clinical radiology, which potentially could impact health care costs.

SAMMANFATTNING PÅ SVENSKA

Datortomografi (DT) är en kliniskt använd modalitet för utredning av misstänkt kranskärlsjukdom. För att förbättra framtida diagnostik, klinisk effektivitet och uppföljningsstrategier är det av stor vikt med teknisk vidareutveckling, och att erhålla relevant prognostisk information.

Syftet med denna avhandling var att studera användandet av DT vid misstänkt kranskärlssjukdom. Tre studier syftade till att utvärdera nya tekniker, vilket innefattade utvärderingar av två nya mjukvaror samt en utvärdering av fonträknar-DT (FR-DT). En studie syftade till att utvärdera det prognostiska värdet av DT kranskärl.

Det första delarbetet utvärderade en mjukvara, som använde data från DT kranskärl för att beräkna tryckfall över misstänkta kranskärlsstenoser. Tiden för att erhålla tryckfallsmätningarna registrerades också. Resultaten av tryckfallsmätningarna jämfördes med en standardreferens, vilken utgjordes av invasiva, kateterburna tryckfallsregistreringar. Det andra delarbetet undersökte prognosen för patienter med olika fynd vid DT kranskärl. Genom registersamkörning erhöles data om kranskärlsrelaterad sjukdom med uppföljningstid på upp till 7.5 år. Det tredje delarbetet utvärderade en AI-mjukvara som utförde automatiska mätningar av kranskärlskalk, baserat på kliniskt utförda DT-undersökningar för detta ändamål (calcium scoring). Tiden för att erhålla mätningarna registrerades också. Resultaten jämfördes med en standardreferens, vilken utgjordes av en konventionell, semi-automatisk metod. Det fjärde delarbetet utvärderade förmågan att kvantifiera kranskärlskalk från avlidna med FR-DT. Bilder från både FR-DT och DT användes för kvantifiering av kalkvolym och jämfördes med en standardreferens, vilken utgjordes av micro-DT.

Korrelationen och överensstämmelsen mellan mjukvarorna och standardreferenserna var god för tryckfallberäkningarna över kranskärlsförträngningar, och mycket god för AI-baserad mätning av kranskärlskalk. Båda mjukvarorna hade tidsbesparande potential. För patienter med normala kranskärl var prognosen utmärkt, men den försämrades med ökad grad av kranskärlssjukdom. Användande av FR-DT bidrog till en bättre noggrannhet än DT vid kvantifiering av kranskärlskalk.

Avhandlingen förmedlar värdet av teknisk utveckling vid utredning med DT för misstänkt kranskärlssjukdom. Dessutom presenteras nya, prognostiska data. Resultaten kan gynna patienten genom skärpt diagnostik och mer effektiva utredningar, vilket kan ge framtida ekonomiska effekter. Därtill kan de prognostiska resultaten bidra till förbättrade, kliniska uppföljningsstrategier.

LIST OF PAPERS

I Jakob De Geer, Mårten Sandstedt, Anders Björkholm, Joakim Alfredsson, Magnus Janzon, Jan Engvall, Anders Persson

Software-based on-site estimation of fractional flow reserve using standard coronary CT angiography data

Acta Radiologica. 2016;57(10):1186-1192.

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II Mårten Sandstedt, Jakob De Geer, Lilian Henriksson, Jan Engvall, Magnus Janzon, Anders Persson, Joakim Alfredsson

Long-term prognostic value of coronary computed tomography angiography in chest pain patients

Acta Radiologica. 2019;60(1):45-53.

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III Mårten Sandstedt, Lilian Henriksson, Magnus Janzon, Gusten Nyberg, Jan Engvall, Jakob De Geer, Joakim Alfredsson, Anders Persson

Evaluation of an AI-based, automatic coronary artery calcium scoring software

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IV Mårten Sandstedt, Jeffrey F. Marsh, Kishore Rajendran, Hao Gong, Shengzhen Tao, Shuai Leng, Anders Persson, Cynthia McCollough

Improved Coronary Calcification using Photon-Counting-Detector CT: An ex-vivo Study in Cadaveric specimens

Manuscript was submitted to European Radiology (13 August, 2020).

An abstract is accepted (19 August, 2020) for a virtual, oral presentation at RSNA, 29 November to 5 December, 2020.

AN INTRODUCTIONAL OVERVIEW OF THE THESIS

An introductional overview of the thesis				
Study	Aim	Study design	Material & methods	Main conclusion
I	Evaluate the performance of an on-site CT-FFR software, using FFR as the standard reference.	Observational, cross-sectional study with prospectively collected data, retrospectively analysed.	In total 23 arteries from 21 patients were used for comparison.	Good correlation and agreement between methods.
II	Evaluate the long-term prognostic value of CCTA in symptomatic patients with no previous history of CAD.	Observational cohort study with prospectively collected data, retrospectively analysed.	In total 1205 CCTA patients had normal findings, non-obstructive CAD or obstructive CAD. Merged registries identified MACE over 7.5 years.	Excellent prognosis for patients with normal coronary arteries, which was progressively impaired for non-obstructive and obstructive CAD.
III	Evaluate an AI-based, CAC scoring software, using a conventional software as the standard reference.	Observational, cross-sectional study with prospectively collected data, retrospectively analysed.	In total 315 CSCT scans were used for comparison.	Excellent correlation and agreement between methods.
IV	Compare the accuracy of coronary calcification quantification, imaged from a PCD-CT and an EID-CT, using micro-CT as the standard reference.	Observational, cross-sectional study with prospectively collected data, retrospectively analysed.	The volumes from in total 13 cadaveric coronary calcifications were quantified. The quantification was based on the three imaging methods.	More accurate CAC quantification using PCD-CT than EID-CT.

Figure I. Thesis overview.

AI: artificial intelligence; CAC: coronary artery calcifications; CAD: coronary artery disease; CCTA: coronary computed tomography angiography; CSCT: calcium scoring computed tomography; CT: computed tomography; CT-FFR: computed tomography-based fractional flow reserve; EID: energy integrating detector; FFR: fractional flow reserve; MACE: major adverse cardiac event; micro-CT: micro-computed tomography; PCD: photon counting detector

AUTHOR CONTRIBUTIONS

- Study I** Software-based on-site estimation of fractional flow reserve using standard coronary CT angiography data
- Study II** Long-term prognostic value of coronary computed tomography angiography in chest pain patients
- Study III** Evaluation of an AI-based, automatic coronary artery calcium scoring software
- Study IV** Improved Coronary Calcification using Photon-Counting-Detector CT: An ex-vivo Study in Cadaveric Specimens

Study	I	II	III	IV
Idea/hypothesis/design	P	L	L	L
Project planning	P	L	L	L
Projekt management/operation	L	L	L	L
Analysis	P	L	L	L
Assembling the results	P	L	L	L
Manuscript writing	P	L	L	L
Correspondence with journal(s)	S	L	L	L
Revision	P	L	L	L

L: Lead

P: Participated

S: Supporting

ABBREVIATIONS

3-D	Three-Dimensional
ACS	Acute Coronary Syndrome
AI	Artificial Intelligence
ANN	Artificial Neural Networks
AS	Agatston Score
CAC	Coronary Artery Calcification
CAD	Coronary Artery Disease
CBA	Calcium Blooming Artifacts
CCS	Chronic Coronary Syndrome
CCTA	Coronary Computed Tomography Angiography
CFD	Computational Fluid Dynamics
CI	Confidence Interval
CMIV	Center for Medical Image Science and Visualization
CR	Class of Recommendation
CSCT	Calcium Scoring Computed Tomography
CT	Computed Tomography
CT-FFR	Computed Tomography-based Fractional Flow Reserve
CTP	Computed Tomography Perfusion
CT-SCAAR	Computed Tomography-Swedish Coronary Angiography and Angioplasty Registry
CV	Cardiovascular
DNN	Deep Neural Networks
EBCT	Electron Beam Computed Tomography
ECG	Electrocardiogram
EID	Energy Integrating Detector
ESC	European Society of Cardiology
FBP	Filtered Back Projection
FFR	Fractional Flow Reserve
FOV	Field of View
HMT	Half Maximum attenuation Threshold
HR	Hazard Ratio
HU	Hounsfield Unit

ICA	Invasive Coronary Angiography
ICC	Intra-Class Correlation coefficient
IQR	Interquartile Range
kV	Kilovolt
LAC	Linear Attenuation Coefficient
LE	Level of Evidence
MACE	Major Adverse Cardiac Event
mAs	Milliampere-seconds
MDCT	Multi-Detector Computed Tomography
MI	Myocardial Infarction
micro-CT	Micro-Computed Tomography
MMA	Methyl Methacrylate
MS	Mass Score
mSv	MilliSievert
NCCT	Non-Contrast, non-gated chest Computed Tomography
NSTEMI	Non-ST Elevation Myocardial Infarction
PCD	Photon Counting Detector
PCI	Percutaneous Coronary Intervention
PET	Positron Emission computed Tomography
PTP	Pre-Test Probability
PVA	Partial Volume Averaging
RIKS-HIA	Registry of Information and Knowledge about Swedish Heart Intensive care Admissions
ROI	Region of Interest
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SCCT	Society of Cardiovascular Computed Tomography
SD	Standard Deviation
SPECT	Single-Photon Emission Computed Tomography
STEMI	ST-Elevation Myocardial infarction
SWEDEHEART	Swedish Web-based system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
UAP	Unstable Angina Pectoris
VS	Volume Score

BACKGROUND

A historical overview

The history of x-ray imaging began in 1895, when the German physicist Wilhelm Röntgen imaged a hand, subsequently described in the publication “On a New Kind of Rays” (1). The publication rendered a world-wide scientific interest, and soon led to the opening of numerous clinical x-ray rooms, which integrated the technology into medical practice. As an acknowledgement, Wilhelm Röntgen was awarded the 1901 Physics Nobel Prize “in recognition of the extraordinary services he has rendered by the remarkable rays subsequently named after him” (2).

After the first years of clinical x-ray imaging, researchers began to investigate whether this novel technique could also contribute to the formation of tomography images. The term tomography originates from the two Greek words *tomos* (slice) and *graphein* (draw) (3), and the basic idea was to obtain better diagnostic abilities by the creation of three-dimensional (3-D), cross-sectional images. A first approach towards tomography imaging was taken by the French physician André Bocage, who introduced a primary theoretical topographical concept in 1921. His inventions had several essential features of modern tomographic devices, but André Bocage never managed to obtain a workable unit. Over time, other investigators succeeded to attain topographical images in practice (3), but it took another half century until computers were powerful enough to effectively integrate relevant tomography algorithms. Eventually, in 1971, the first computed tomography (CT) scanner was introduced, being able to perform head examinations, which were reconstructed with 13 mm slices, using an 80 x 80 matrix. The scanner, named the “E.M.I.”-scanner, was designed by the English engineer Godfrey Hounsfield, while underlying mathematics was suggested by the African American physicist Allan Cormack. Subsequently, both pioneers were jointly awarded the 1979 Nobel Prize “for the development of computer assisted tomography” (4).

Over the coming years, the CT technique became iteratively improved, and the clinical use was successively expanded to include various organ systems. Due to the constant motion of the heart, CT imaging of the coronary arteries had to overcome specific temporal resolution challenges. There were some early attempts to use intravenous contrast for visualisation of the coronary arteries already in the 1980s (5), but the technical prerequisites at that time were not yet sufficient for a clinical implementation. Nonetheless, in 1990, the American cardiologist Arthur Agatston used electron beam computed tomography (EBCT) to quantify coronary artery calcifications (CAC) (6). The quantification method, the Agatston score (AS), was independent of the use of intravenous

contrast and with no attempts to assess any coronary artery stenosis. The EBCT technique used for this purpose obtained a radiation fan by the deflection of an electron beam towards tungsten rings and led to a good temporal resolution. However, the EBCT technology was later replaced by the multi-detector computed tomography (MDCT) technique, which had better spatial resolution and could be used for wider purposes (7, 8). The first truly feasible MDCT system for assessment of the coronary arteries with intravenous contrast is considered to be a 16-detector row scanner, introduced in 2001 (9). Thereafter, several technical advancements have facilitated the development of up to 384-detector row, dual energy MDCT scanners, with the ability to investigate the coronary arteries with an excellent spatial resolution, along with the capability to scan the heart in less than one second. Also, three decades after its introduction, the AS technique remain largely unchanged, and the technique is today endorsed for cardiovascular (CV) risk prediction by clinical guidelines worldwide (10, 11).

Coronary artery disease

The presence of coronary artery disease (CAD) is accompanied by atherosclerotic narrowing of the coronary arteries, which can cause a supply-demand mismatch in myocardial blood perfusion. The CAD can result in different clinical presentations and is clinically categorized as either chronic coronary syndrome (CCS) or acute coronary syndrome (ACS) (10). In the CCS, an inadequate oxygen supply can lead to myocardial ischemia, which is typically recognized as chest discomfort. The ACS is usually caused by thrombus formation due to an erosion or rupture of an atherosclerotic plaque (10) and is often presenting with chest discomfort or chest pain (12, 13).

The ACS is clinically classified as non-ST elevation myocardial infarction (NSTEMI), ST-elevation myocardial infarction (STEMI) and unstable angina pectoris (UAP) (12, 13). A myocardial infarction (MI) is either a STEMI or NSTEMI, and is defined as the presence of acute myocardial injury detected by significantly increased cardiac biomarkers, preferably troponins, in the setting of typical symptoms and/or evidence of acute myocardial ischemia (12). While both a STEMI and NSTEMI diagnosis require elevated troponin, the conditions are being distinguished based on electrocardiogram (ECG) characteristics (12), since a STEMI presents with a persistent ST segment elevation, while a NSTEMI may or may not have other ECG characteristics indicative of ischemia. An UAP event is considered to be present in patients with ACS symptoms, with or without ECG changes indicative of ischemia, but without elevated troponin over the decision limit. Thus, a NSTEMI and an UAP differ primarily in if the myocardial ischemia is severe enough to result in elevated troponins (13).

A CCS is associated with recurrent symptoms indicative of ischemia, and such a diagnosis may be based on a typical patient history, assessment of CV risk factors and physical examination. If a CCS diagnosis needs to be verified,

pre-test probability (PTP) models can be applied. Such models estimate the PTP of obstructive CAD, thereby supporting the clinical decision whether to proceed with further non-invasive imaging or invasive coronary angiography (ICA). Guidelines from the European Society of Cardiology (ESC) recommend the PTP model to be based on age, sex and nature of symptoms (10), whereas U.S. guidelines use more than one PTP model (14). While the ACS is caused by an epicardial arterial obstruction mechanism, some CCS may be caused by microvascular disease, which can be difficult and complex to diagnose with conventional methods (15). The manifestations of CAD may be stable for long periods of time, such as in CCS, but a plaque rupture or erosion may provoke an acute presentation such as in an ACS. Therefore, CAD is to be considered a dynamic process, which may cause various clinical presentations over time (10).

The CAD is not only complex and changeable in its nature, but also constitutes the leading cause of death in the world (16), posing significant challenges for health care personnel to provide optimal diagnostics and treatments. Preventive care is to be specifically considered, since at least 25% of all individuals that experience sudden cardiac death do not have foregoing symptoms (17), and more than half of all sudden cardiac deaths are not preceded by an established CAD diagnosis (18). Moreover, CAD is a major economic issue for countries in the European Union (19) and in the United States (20), which emphasizes the importance of cost effective utilization of health care resources.

Techniques and concepts in computed tomography imaging

The generation of X-rays for computed tomography imaging

The induction of a current through an x-ray tube cathode releases electrons (thermionic emission) and a tube voltage causes the electrons to be accelerated towards the positively charged anode plate. The tube current is usually expressed in milliamperere-seconds (mAs) which indicates the quantity of electrons released over time, and the tube voltage is expressed in kilovolt (kV), which denotes the electrical potential between the anode and the cathode. There are two main interactions that lead to x-ray production. One type of interaction occurs when accelerated electrons collide with the anode, thereby ejecting inner shell electrons in the anode material. An outer shell electron then drops to fill the vacancy, and the excess energy is simultaneously emitted as a photon. This process renders characteristic radiation, which is element specific. The second type of interaction occurs when accelerated electrons are redirected by a positively charged anode material nucleus. The loss of electron kinetic energy causes emission of photons, creating breaking radiation, bremsstrahlung. The generated x-ray beam is thereby constituted by a combination of x-ray energies with

narrow characteristic radiation spikes and a continuous breaking radiation spectrum (21).

The interaction with matter

An x-ray beam reaching a patient can either penetrate the tissues to reach the detector elements or become attenuated. The attenuated x-ray beams may interact by photoelectric absorption, Compton effect, pair production or scattering. The photoelectric effect is initiated by a photon hitting an inner shell electron, thereby transferring its energy, and causing the electron to be ejected. The electron vacancy is filled by an outer shell electron, and a characteristic x-ray photon is simultaneously emitted. Compton effect is initiated by a photon hitting an outer shell electron, leading to scattering of the photon, while the outer shell electron is deflected (22, 23). Pair production and scattering are not relevant in clinical radiology, and therefore not further described.

The attenuation refers to the reduction of x-ray photon energies as they pass through a material and may be quantified by linear attenuation coefficients (LAC) or Hounsfield units (HU). The LAC describes the photons absorbed by unit thickness of a material (22). The HU is used for CT and is derived from a linear transformation of the LAC (24).

Energy integrating detector-computed tomography

The energy integrating detector (EID)-CT image generation technology encompasses x-ray tubes, filters, collimators and detectors, as schematically outlined in Figure 1. The polychromatic x-ray beam produced in the x-ray tube initially passes through a metal filter, which removes low energy photons that would not contribute to the resulting image. This reduces the patient radiation dose and leads to a more monochromatic beam (22). The collimator is located between the filter and the patient and is typically made of lead or tungsten. It narrows and focuses the x-ray beam to the area of interest, thereby diminishing x-ray scatter and additionally reduces the patient's dose. The CT detectors measure the transmission of x-rays passing through the patient. Until the 1990s, a single slice CT technology was used, which detectors were consisting of only one detector element row. Today, MDCT systems are equipped with several detector element rows (25, 26). Modern, commercially available MDCT systems use EID-CT detectors that are based on the indirect conversion technique, where incident photons are converted to light by scintillator materials. The light is then transformed to an electric signal, which is proportional to the total energy deposited by all photons being absorbed by the scintillator during a finite time period. To avoid light leakage (cross-talk) between neighboring detector elements, septal layers of reflecting material are separating each detector element.

Since the septal layers occupy detector area, they restrict the detector's geometric dose efficiency and thereby limit high resolution technology improvements for clinical CT examinations (27).

In conventional EID-CT, one x-ray tube with one peak energy generates an x-ray beam, received by one detector. In dual energy EID-CT, an additional peak energy is utilized, which enables material decomposition and the creation of virtual monoenergetic images (28).

Figure 1. A schematic illustration of the main components in an energy integrating detector- computed tomography system.

Photon counting detector-computed tomography

Photon counting detector (PCD)-CT is a novel technique which has the potential to improve several aspects of the currently clinically used EID-CT technology. The PCD-CT technology employs an x-ray tube, filter, collimator and detector, similarly to an EID-CT system. However, EID-CT systems have detectors that integrate all photon energy deposited over a finite time period to produce a signal. The PCD-CT systems apply another detector technology, counting each incident x-ray photon energy.

Every photon that hits the detector in a PCD-CT enters a semiconductor, where it generates negative and positive charges. The most commonly used semiconductor materials are cadmium telluride or cadmium zinc telluride, but other materials have also been utilized for this purpose (29, 30). An electric field

applied to the semiconductor makes the negatively charged electrons drift towards the anode, where a signal proportional to the energy of the photon is generated. In this direct conversion technique, incident photons are thus converted to electric signals without the use of scintillators, and septal layers are thereby not needed. Detector elements can therefore be made smaller than in the EID-CT, which enables an improved spatial resolution and geometric dose efficiency. Every photon that reaches the detector deposits its energy into the detector material, which gives rise to a proportional electrical signal. Based on the magnitude of the electrical signal from each photon, all counts are categorized in user-defined, energy threshold bins. The electronic system can be set to exclude any electrical signals smaller than a pre-set threshold, thereby reducing electronic image noise. Since individual photons are being counted, low energy photons can be given a larger weight than in the EID-CT, and it is thus possible to obtain an increased image contrast and improved iodine contrast to noise ratio. Unlike the EID-CT dual energy technique, a single tube-potential is used, yet the PCD-CT still provide energy resolved image data at every scan. This renders possibilities for advanced image data processing, such as material decomposition and mono-energetic image synthesis. In addition to the aforementioned possible PCD-CT technology benefits, the radiation dose is shown to be less than in conventional EID-CT systems (27-30).

Micro-computed tomography

The micro-computed tomography (micro-CT) technology has the ability to generate images with very high spatial resolution, near histological levels of details. The technique is traditionally used for studies on small animals and biological specimens (31), but is also applied in archeology and industrial non-destructive precision engineering (32, 33). The fundamental technology is similar to traditional EID-CT, with an x-ray tube emitting photons towards the object of interest, and detectors with photodiodes using light conversion. Contrarily to an EID-CT, the micro-CT may use a stationary x-ray tube and detector, while the examined object is rotating. After imaging, reconstruction techniques are applied, including conventional settings such as field of view (FOV) and filtered back projection (FBP) (33).

The process of image formation

The first step in CT image formation is patient scanning. In this process, the gantry-enclosed x-ray tube, filter, collimator and detector rotate, while the table and the patient move. The MDCT pitch is a measure of overlap of the acquired data during scanning and characterized by the table movement per one 360° gantry rotation divided by the width of all simultaneous acquired slices (34).

The second step in CT image formation, the reconstruction, converts raw data to readable digital images. This process defines the FOV, matrix size and

slice thickness, all of which affect the voxel volume. Reconstruction algorithms are usually FBP or an iterative reconstruction technique. The FBP image quality is generally limited by noise and streak artefacts, as these cannot be improved unless an increase of the radiation dose is made. With developments in computer processing power, iterative reconstructions have therefore become increasingly used. Iterative reconstructions perform repetitive comparisons between assumed and measured data until convergence is reached, improving image quality and thus allowing for radiation dose reductions (35).

The third step is the transformation of digital information into a displayed image, which then is available for reader optimizations, such as window adjustments.

The concept of image quality

The CT image quality is influenced by factors such as the spatial resolution, the image noise and the contrast resolution. Also, for CT imaging of the coronary arteries, the image quality is affected by the temporal resolution.

The spatial resolution measures how close two objects in an image may be located and still be determined as separate, and can be quantified in line-pairs/cm. Also, spatial resolution may be evaluated qualitatively, using grading of blurring (36). Blurring decreases the visibility of small objects which leads to a reduced ability of detail imaging (37). The CT spatial resolution is impacted by patient motion and is additionally influenced by several factors in image acquisition and image reconstruction. Also, in a post-processed image, magnification decreases spatial resolution. For more than 10 years, the EID-CT pixel sizes at the isocenter has remained 0.5-0.6 mm, limited by detector element septations. However, PCD-CT detector pixels sizes can be made smaller, corresponding to a pixel size 0.25 mm at isocenter, which improves the spatial resolution (29).

The CT image noise originates from quantum noise or electronic noise. The quantum noise is due to a random photon distribution at the detector level and varies according to the number of incident photons. The electronic noise originates from electronic circuits in the CT system. The image noise is represented by an unwanted attenuation variation between voxels in an otherwise homogeneous image. The CT image noise appears as a granular pattern, and induces a decreased visibility of low-contrast objects (37). An image noise quantification can be obtained by the standard deviation (SD) of attenuation measurements (e.g. using HU or LAC) in a region of interest (ROI). Image noise is often increased in large patients, since fewer photons reach the detector, but can also be influenced by several other factors in image acquisition and image reconstruction. Image noise may be decreased using iterative reconstructions (38) and PCD-CT imaging (29).

The contrast resolution is the ability to distinguish attenuation intensity variations and is affected by x-ray penetration variations in adjacent tissues and by the image noise. To increase contrast resolution by photoelectric effect, iodine may be added, or tube voltage decreased. Image contrast resolution may also be enhanced using energy resolved images (29).

The temporal resolution is the ability to resolve fast moving objects and is determined by the time needed for data acquisition of the CT (39). In cardiac CT, significant temporal resolution improvements have been made with the introduction of dual source CT scanners (39, 40).

Partial volume averaging and calcium blooming artifacts

Cardiac CT imaging of the coronary arteries is vulnerable to a wide spectrum of artifacts, which may impair the diagnostic ability.

The partial volume averaging (PVA) artifact is highly undesired in coronary CT imaging and occurs when tissues with heterogeneous attenuation are encompassed within one voxel. Since each voxel's attenuation becomes an average of all tissue attenuations embodied in a voxel, the PVA becomes most pronounced when widely different material densities are represented. The voxel attenuation average may lead to blurring at interface and size misrepresentation of the represented tissues (41). In CAC imaging, PVA is associated with inter-scan variability in both CSCT and non-contrast, non-gated chest computed tomography (NCCT) (42-44). An important subset of PVA is calcium blooming artifacts (CBA), which makes calcifications appear larger than their true size (41), leading to limitations in coronary computed tomography angiography (CCTA) specificity (45). Smaller CT detector pixel sizes can improve the spatial resolution, thereby reducing the PVA and CBA.

Other undesired CT artifacts in cardiac imaging are motion artifacts and beam hardening artifacts (41).

Morphological assessment of the coronary arteries

Calcium scoring computed tomography

The presence of CAC is a specific feature for CAD, and the extent of CAC is demonstrated to be proportional to the degree of CAD (46, 47). A quantification of CAC can be performed with a non-contrast enhanced, ECG-triggered, calcium scoring computed tomography (CSCT) examination. The CSCT method has been used for several years, and considered a clinically reliable predictor of future CV events for asymptomatic individuals (48, 49). Also, a CSCT is often performed together with a CCTA, to optimize image acquisition and support CCTA interpretation.

The indication for a CSCT scanning among asymptomatic individuals is determined by pre-test CV probability risk assessments, which can be provided by various tests. European (ESC) guidelines recommend the Systematic Coronary Risk Estimation, SCORE (10, 50) (predicts the 10-year CV death risk), while U.S. guidelines endorse the Pooled Cohort Equations (11) (predicts the 10-year atherosclerotic CV disease event), but other well-known pre-test CV probability risk assessment tests also exist, such as the Framingham risk score (51). While the conventional pre-test CV probability models can provide a population-based CV risk assessment, the CSCT-derived CAC score constitute a CV risk assessment based on the individual's CAC burden.

Guidelines in Europe and in the United States assign a class of recommendation (CR) IIb with level of evidence (LE) B, for the performance of CSCT in asymptomatic patients, typically with an intermediate pre-test CV probability, prior to preventive statin treatment (10, 11, 50).

The risk stratification benefits of a CSCT in an asymptomatic population need to be balanced against the risk of radiation exposure, and a dose of 1.0-1.5 millisievert (mSv), not exceeding 3 mSv, is recommended (52). However, a recent study demonstrated the median CSCT radiation dose to be as small as 0.5 mSv (53).

A CSCT scan is typically performed using a prospectively ECG-triggered, sequential scan or a high-pitch (Flash) spiral scan with image acquisition in mid to late diastole, tube voltage 120 kV and mAs varying with body habitus. Reconstructions are normally performed using a FOV only covering the heart, slice thickness 3 mm and FBP (54, 55).

The most commonly used CAC scoring technique is the AS, introduced in 1990 (6), and applied in most risk stratification studies. The AS is obtained by multiplying the calcified area with a maximum attenuation factor (130-199 HU, factor 1; 200-299 HU, factor 2; 300-399 HU, factor 3; and ≥ 400 HU, factor 4), using a lower threshold of 130 HU (6). The AS technique is considered gold standard, but demonstrates a limited inter-scan reproducibility (56). Both the Volume score (VS) and the Mass score (MS) have better inter-scan reproducibility than the AS but are largely confined to research settings. The VS is reported in cubic millimeters and is the sum of all coronary artery voxels with HU more than 130. The MS represents the mineral mass, in milligrams (57).

A clinically established method to interpret the AS is by a classification of the absolute AS values into predefined risk categories (58). Likewise, the AS can be analysed along with age, gender and ethnicity in risk estimation distribution percentiles.

The CAC score reporting is based on quantification of CAC in axial images, traditionally using semi-automatic software programs. The CAC scoring is generally not considered very difficult, but it requires expert reader interaction to manually identify and mark all calcifications. Recent studies have demonstrated

excellent performance of artificial intelligence (AI) applications in radiology, for example in lung cancer CT diagnostic (59). International guidelines support the use of CSCT, and the usage of this method is predicted to increase. Therefore, more automated clinical methods are warranted, and CAC scoring may be a suitable candidate for AI development in the radiology clinics.

In addition to CAC scoring in CSCT, guidelines in the United States recommend the evaluation and reporting of CAC on all NCCT, regardless of scan indication, assigned a CR I. The CAC evaluation should preferably be estimated as none, mild, moderate or severe, but the guidelines also suggest that it is reasonable to evaluate the CAC on an ordinal scale, or by using the AS (60).

Coronary computed tomography angiography

While the ICA prevails as the gold standard for CAD diagnostics in symptomatic patients with a high PTP for obstructive CAD, its invasive nature is a concern. Therefore, in patients with low-intermediate PTP for obstructive CAD, non-invasive methods are more appropriate. The exact definition of intermediate PTP in this setting is rather arbitrary. In European (ESC) guidelines, PTP >15% is applied, having no specified upper limit, yet 65% has been used historically. The U.S. guidelines apply a range of PTP 10%-90% (14).

The 2019 European (ESC) guidelines for the diagnosis and management of CCS downgrade the PTP for obstructive CAD. In most patients with a low (<15%) PTP, testing is not recommended. If obstructive CAD cannot be excluded clinically, evaluation may be performed with non-invasive functional imaging or CCTA, both assigned a CR I, LE B. The decision of which initial non-invasive test to choose depends on the patient's characteristics, local resources and test availability, but CCTA is generally to be preferred in the lower range of clinical likelihood for obstructive CAD (10, 14). Guidelines in the United States, issued in 2012, primarily recommend a non-invasive, functional testing for patients with intermediate-high PTP for obstructive CAD, assigned a CR IIa, LE B-C. The use of CCTA is primarily reserved for patients with intermediate PTP for obstructive CAD, who have previously performed functional testing (inconclusive results or ongoing symptoms) or cannot perform functional imaging testing, assigned CR IIa, LE C. Also, for patients with intermediate PTP, an exercise ECG is usually recommended (see below, page 24) (14, 61).

At the time for performing the prognostic study in this thesis (study II), very few studies had evaluated the long-term prognostic value of CCTA (62, 63). Still, this is important information to improve decision-making regarding further clinical management, especially for patients with non-obstructive CAD.

Contrary to a CSCT scan, a CCTA scan is performed with intravenous contrast, which brings the ability to visualise the coronary arteries, and to assess coronary artery stenoses. In order to decrease the heart rate and increase coronary artery vasodilation, beta blockers and nitroglycerin may be administered

prior to the examination. Depending on the CT scanner available and the patient's characteristics, such as age, heart rate and heart regularity, a CCTA scan can be prospective or retrospective. In a prospective, ECG-triggered, sequential scan, the x-ray beam is activated during predetermined cardiac phases. The image acquisition is repeatedly performed until the whole heart is imaged. As the CT scanner moves the table between the sequences of image acquisition, this technique is sometimes called a "step-and-shoot scan" (38). If the heart rate is irregular or fast, an ECG-triggered retrospective, spiral scan may be preferred. This technique renders images from the whole cardiac cycle, using a low pitch, and makes it possible to freely choose any cardiac phase for image reconstructions. Also, a multiphase reconstruction can be performed. However, the retrospective scan requires a relatively high radiation dose (38). A prospective, ECG-triggered, high-pitch, spiral (Flash) scan is possible in dual source CT systems. With this technique, two simultaneously, overlapping spiral scans acquired at a pitch >3 allow for the imaging of the whole heart in one heartbeat (38). In order to obtain an adequate image quality, the scan needs to take place during diastole, and it is therefore required that the patient has a heart rate below 65-70 beats per minute.

During the last years, the CCTA radiation dose has decreased significantly, recently reported to generate a median of 0.6 mSv, 1.3 mSv and 4.8 mSv for high-pitch protocols, sequential protocols and retrospective protocols, respectively (53).

The CT equipment is recommended to have a fast gantry rotation (≤ 350 ms) and a minimum of 64-slice MDCT (55). Traditionally, the standard tube voltage has been 100-120 kV. However, modern CT equipment applies automated tube potential selection and also automated tube current modulation. Both the automated tube potential and the automated tube current modulation adapts to the scout-image based signal to noise ratio and help to reduce the radiation dose along with optimizing the image quality. In retrospective CCTA, an ECG-based tube current modulation may also be applied, decreasing radiation dose in systole when cardiac motion is greater (38, 55). Reconstructions are performed with FBP or iterative reconstruction techniques. A FOV only including the heart, thin axial slices (0.5-0.6 mm), increment 50% of slice width and 512 x 512 matrix is normally used (55).

For CCTA reporting, images can be interpreted using multiplanar reconstructions but other techniques, such as curved multiplanar reconstructions may also be employed.

A CCTA scan with adequate image quality provides an excellent sensitivity for detection of a coronary artery stenosis and an excellent negative predictive value to rule out a coronary artery stenosis (64). Nevertheless, the specificity and positive predictive value is moderate, the former being closely linked to cal-

cifications and CAD overestimation (45). Possible strategies to improve specificity include computed tomography-based fractional flow reserve (CT-FFR), computed tomography perfusion (CTP) imaging and the use of improved spatial resolution.

Invasive coronary angiography

For symptomatic patients with high PTP for obstructive CAD, it is generally reasonable to proceed with an ICA. European (ESC) guidelines recommend an ICA for symptomatic patients with a high likelihood of obstructive CAD, CR I, LE B (10). U.S. guidelines do not provide any formal recommendations in this particular setting (14).

An ICA is performed using a fluoroscopy guided catheterization of the coronary ostia, with subsequent iodine contrast agent injection, during which fluorography images are acquired from varying cardiac angles. The fluoroscopy and fluorography have x-ray beams emitted continuously, allowing for a dynamic visual assessment. Fluoroscopy is mainly viewed on a monitor in the catheterization laboratory, while fluorography images usually are viewed after x-ray exposure. If a significant stenosis is present, percutaneous coronary intervention (PCI) can be performed in the same session, using a balloon to dilate the narrowed part of the artery. A metal stent may then be inserted to uphold the arterial wall diameter over time, sometimes coated with medication (drug eluting stent), which blocks cell proliferation to prevent restenosis.

The risk of adverse side effects during an ICA is relatively small, but can be serious, such as cerebrovascular events, coronary artery dissection, arrhythmias and MI (65, 66). Also, the radiation dose is a concern, since the reported average radiation dose for a diagnostic ICA is 7 mSv (67).

Functional assessment of the coronary arteries

The exercise electrocardiogram

The exercise ECG evaluates the CV system response to physical stress and has, both in Europe and in the USA, traditionally been an initial test in the work-up of suspected obstructive CAD. In such a setting, the test is mainly based on an ST segment depression as a sign of myocardial ischemia.

Due to a limited sensitivity and specificity to detect ICA-verified, significant CAD (68), the 2019 European (ESC) guidelines downgrades recommendations to a diagnostic alternative if imaging tests are not available, assigned a CR IIb and LE B. Instead, in the 2019 ESC guidelines, the exercise ECG is suggested to be used as a complement to clinical assessment and to obtain prognostic information (10). Notably, the diagnostic performance of exercise ECG has never been systematically compared to findings of significant CAD verified with ICA

in conjunction with FFR (68). In U.S. guidelines, the exercise ECG is endorsed as an initial method for most patients with suspected CAD, particularly for those with intermediate PTP for obstructive CAD that can exercise and have an interpretable ECG, assigned a CR I and LE A (61).

Fractional flow reserve

During an ICA, the significance of intermediate coronary artery stenoses may be difficult to assess by visual estimation alone (69). In such cases, the hemodynamic significance of a stenosis can be explored by using the fractional flow reserve (FFR), assigned a CR I, LE A and CR IIa, LE A, by European (ESC) and U.S. guidelines, respectively (10, 70).

The FFR is defined as the maximum blood flow ratio between catheter-based measurements from distal to the coronary artery stenosis ($Flow_s$) and from the aorta ($Flow_a$).

$$FFR = \frac{Flow_s}{Flow_a}$$

Adenosine is administered to induce vasodilation (i.e. maximal flow), prior to measurements. Since the flow is the pressure difference in the coronary vascular system divided by the resistance, it may be rewritten as:

$$FFR = \frac{(P_d - P_v) / R_s^{max}}{(P_a - P_v) / R_n^{max}}$$

P_a : pressure in aorta; P_d : pressure distal to stenosis; P_v : venous pressure; R_s^{max} : resistance in myocardium in stenotic region in vasodilation; R_n^{max} : resistance in normal myocardium in vasodilation

Considering that measurements are obtained under vasodilation, resistances are very small and similar, therefore left out. Also, venous pressure is very low compared to arterial pressure, and can be neglected. The basis for a FFR calculation is therefore:

$$FFR = \frac{P_d}{P_a}$$

Thus, in practice, the FFR is based on a pressure ratio, based on measurements in the aorta and distal to the coronary artery stenosis. An FFR of 0.6 means that the local, maximum myocardial flow distal to the stenosis is 60% of

its normal value (71). An FFR of ≤ 0.75 is usually associated with myocardial ischemia (72-74), while 0.75-0.80 is considered to be in a “grey zone” regarding its significance (70). The FFR is clinically widely used and enables the interventionist to correctly identify which stenoses to treat with PCI. However, in patients which have a microvascular disease, a pathological hyperemic response may yield false FFR values (75).

Computed tomography-based fractional flow reserve

Advances in computational fluid dynamics (CFD) have led to the development of CT-FFR, which is a non-invasive technique to determine the hemodynamic significance of CAD based on CCTA data. The CFD utilize the Navier-Stokes equations, which describe the flow of incompressible fluids. For the CT-FFR estimation, the patient’s blood pressure is processed in conjunction with CT data and computerized in several consecutive algorithms.

First, the coronary artery anatomy needs to be segmented, and a 3-D anatomical model is generated. Thereafter, the resting state total coronary artery blood flow (milliliters/minute) is predicted, based on calculations from the myocardial mass (automatically segmented from CCTA images), which utilize allometric scaling laws that describe the relationship between the dimension of an organ and the corresponding blood supply needed.

As a next step, the resting state total coronary artery blood flow is distributed on the 3-D anatomical model, based on the diameter of the coronary arterial branches diameters.

Subsequently, to simulate the resting state blood flow, the Navier-Stokes equations are applied on the 3-D anatomical model. In this process, several simultaneously applied algorithms integrate local characteristics, such as turbulence, viscosity and stenosis length, with the patient’s blood pressure and pulse. Lastly, to resemble an adenosine induced hyperemic state, a virtual reduction of microvascular resistance is performed (76, 77).

Other functional imaging tests

For patients with intermediate PTP of obstructive CAD, if testing is needed, European (ESC) and U.S. guidelines recommend non-invasive functional imaging or anatomical imaging with CCTA (10, 61). Recommendations by guidelines are described above, page 22.

The non-invasive functional imaging tests being used to evaluate obstructive CAD are single-photon emission computed tomography (SPECT), positron emission computed tomography (PET), stress echocardiography, or stress cardiac magnetic resonance imaging. The functional imaging methods have different optimal performance ranges for sensitivity and specificity to detect obstructive CAD, which are impacted by the PTP test, but also depending on if a comparison is made with ICA or ICA in combination with FFR (68).

In SPECT and PET examinations, myocardial blood perfusion defects visualised on tomographic images after injecting radioactive tracer molecules are indicative of myocardial ischemia. In stress echocardiography and stress cardiac magnetic resonance, myocardial wall movement abnormalities are indicative of myocardial ischemia.

Non-invasive functional imaging methods have shown excellent prognostic value to predict CV events (78, 79) and a recent meta-analysis comparing negative results on functional imaging tests, stress ECG and CCTA showed that all methods yielded an excellent prognosis (80). However, in symptomatic patients with no previous CAD, a comparative study over a short to median follow-up time has shown that CCTA had better prognostic information for non-obstructive CAD than functional imaging tests (81).

Artificial intelligence and its applications for computed tomography imaging of the coronary arteries

AI refers to the capability of a machine to imitate human behavior (82), and encompasses several technologies.

Machine learning is a subset of AI, which learns how to recognize data patterns to make predictions. The initial step in traditional machine learning is feature identification and extraction. Thereafter, model-based algorithms are applied to make assumptions on data. For example, supervised machine learning algorithms can predict a class for a given input (classification), and unsupervised machine learning algorithms can predict clustering (83).

Artificial neural networks (ANN) is a subset of machine learning, developed to employ neural networks with an input layer, one or more intermediate layers, and an output layer, illustrated in Figure 2. The input layer receives input data, the intermediate layers process data from the previous layer, and the output layer yields the resulting prediction. The processing is, thus, a mathematical mapping from image data to a prediction. Each node receives input from a number of nodes of the previous layer and combines them into an output to pass forward. The output layer is commonly binary. The training process consists of iteratively adjusting, for each node, how its many input signals are weighted together. Deep neural networks (DNN) is an ANN, with many intermediate layers. The training process for DNN is called deep learning. For ANN and DNN, no separate steps with feature identification and extraction are required, since it is already part of the deep neural network process.

Figure 2. An artificial neural network with two intermediate layers.

Convolutional neural networks are a subset of DNN networks, used frequently in medical image analysis, where the layer-wise processing consists of data feature extraction by convolution kernels (83, 84).

The development of an AI system can be divided into training, validation and testing. In training, the algorithm learns according to some given goal, often in the form of maximizing prediction performance for known examples (supervised learning). In validation, the AI model is evaluated using unseen data, which provides feedback to further optimize the model through additional training rounds. In testing, data not used in the training-validation cycles are used to independently evaluate the algorithm.

In radiology, AI has demonstrated an increasing ability to handle tasks normally performed by human readers. The potential benefits are several. AI can work continuously on tasks that normally would require expert readers, which may decrease subjectivity and reduce clinical workload. Also, reproducibility can be improved. Moreover, AI applications could save the expert reader time to spend on more complex, or rare, cases.

In CT imaging of the coronary arteries, AI may be used in several applications. The potential use of AI for combined detection and segmentation can be exemplified by the use of CSCT post-processing techniques (85, 86). Another possible employment of AI can be illustrated by a recent AI based, deep learning algorithm applied on CCTA, which automatically detects significant stenoses

based on the left ventricle texture (87). An additional area for AI development in CT imaging of the coronary arteries is outcome prediction (88).

The rationale for this thesis

As CAD is the leading cause of death and a major economic issue worldwide, it presents a large challenge for health care personnel to optimize diagnostic tools, follow-up and treatments. During the last decade, the use of CT has been increasingly endorsed for patients with suspected CAD. While a CSCT scan can contribute to a CV risk stratification, an actual visualisation of coronary artery stenoses has become possible with CCTA, and the employment of both methods are expected to increase.

Despite several major advances in CT technology, there is still a great potential for additional modality explorations and developments, which could benefit CAD patients and improve the workflow in radiology units. The endorsement and increasing usage of CT in CAD investigations also warrants prognostic follow-up data. While such information is relatively well studied for CSCT, more studies are needed to define the long-term prognostic value of CCTA.

AIMS

The overall aim of this thesis was to explore the use of CT for CAD investigations, looked upon from different clinical perspectives. Three studies evaluated novel techniques and one study analysed the long-term prognostic value of CCTA.

The specific aims for each of the four studies are stated below.

- Study I** To evaluate the performance of an on-site CT-FFR software, using FFR as the standard reference.
- Study II** To evaluate the long-term prognostic value of CCTA in symptomatic patients with no previous history of CAD.
- Study III** To evaluate an AI-based, CAC scoring software, using a conventional software as the standard reference.
- Study IV** To compare the accuracy of coronary calcification quantification of cadaveric specimens imaged with a PCD-CT and an EID-CT, using micro-CT as the standard reference.

MATERIAL AND METHODS

Ethics

For all work in this thesis that encompassed real-life patients (study I-III), the Swedish Web-based system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) (89), was used for patient identification and to retrieve data. All patients were informed regarding their partaking in a registry and the right to decline participation and to have data removed. According to the Swedish legislation, written consent is not needed in such settings. In one study, human cadaveric coronary vessel specimens were used (study IV). There was no cadaveric identity information accessible for the researchers working directly with the specimens. The analyses in this thesis were only performed on anonymised data.

A regional ethical board permit was obtained for each study in this thesis. Ethical permit for study I was issued by the regional ethical review board, Linköping (Dnr M6-09 with amendment 2013/278-32). Ethical permit for study II was issued by the regional ethical review board, Linköping (Dnr M6-09 with amendments Dnr 2013/278-32 and Dnr 2015/112-32). Ethical permit for study III was issued by the regional ethical review board, Linköping (Dnr M6-09 with amendment 2013/278-32, Dnr 2015/112-32 and Dnr 2018/535-32). The AI-based algorithm training data was acquired by the developer, obtaining ethical approval and/or patient consent, when required. Ethical permit for study IV was issued by the Mayo Clinic Institutional Review Board, Biospecimen Subcommittee, Rochester, Mn, USA (Dnr 15-004275).

Study design

Study I, III and IV were all observational, cross-sectional studies with prospectively collected data, retrospectively analysed. Study II was an observational cohort study with prospectively collected data, retrospectively analysed.

Patient and cadaveric specimen inclusions

The inclusions in this thesis were either patients scanned in the clinic, or cadaveric specimens scanned for the sole purpose of research, as illustrated in Figure 3.

Figure 3. The thesis inclusions. Three studies included computed tomography data from clinical patients. One study included image data from cadaveric coronary vessel specimen.

CCTA: coronary computed tomography angiography; CMIV: Center for Medical Image Science and Visualization; CSCT: calcium scoring computed tomography; CT-FFR: computed tomography-based fractional flow reserve; PCD-CT: photon counting detector-computed tomography

An overview of the patient inclusions and cadaveric specimens used in this thesis is presented in Figure 4. In study I-III, clinical patients referred for a CCTA scan were considered for inclusion. All referrals were initiated by cardiologists in the work-up of suspected CAD, and according to a relevant clinical indication. The CT examinations were performed according to clinical routine at Center for Medical Image Science and Visualization (CMIV), Linköping. The patients included in study I were examined 1 September 2009 - 1 March 2012 due to various scanning sub-indications and had subsequently undergone an ICA with FFR within 120 days. The patients included in study II and III were examined 1 July 2007 - 31 December 2014 and 1 December 2017 - 31 January 2019, respectively, all being referred due to chest pain (or occasionally due to other symptoms indicative of CAD), with a low-intermediate PTP for obstructive CAD. The CCTA scans at CMIV are routinely performed in conjunction with a CSCT. While study I and II used CCTA data, study III instead utilized CSCT data. Also, in

study III, 13 out of the initially excluded 27 CSCT scans were readable and represented an independent dataset, as illustrated in Figure 5. The final study sample in study I, II and III consisted of 21, 1205 and 315 patients, respectively. In study IV, six coronary arteries and one coronary venous graft were resected from three human cadavers, subsequently being separately embedded in methyl methacrylate (MMA). In total, 13 calcifications were included for the subsequent analyses.

Figure 4. Thesis inclusions and exclusions. The patient studies are indicated in red and blue. The calcium scoring computed tomography scan dataset which was used for an independent analysis is indicated in green. The cadaveric study is indicated in purple.

a: number of arteries; CCTA: coronary computed tomography angiography; CMIV: Center for Medical Image Science and Visualization; CSCT: calcium scoring computed tomography; FFR: fractional flow reserve; n: number of patient CT scans

Figure 5. Flowchart for the independent calcium scoring computed tomography (CSCT) dataset in study III. Out of the initially 27 excluded CSCT scans, seven CSCT scans could not be interpreted. Out of the remaining 20 CSCT scans, in total 13 were readable and represented an independent dataset.

CSCT: calcium scoring computed tomography

Image acquisition and reconstruction

For the image acquisition in this thesis, four EID-CT scanners, one PCD-CT scanner and one micro-CT scanner were used.

All clinical patient image acquisition was performed at CMIV, Linköping, using four Siemens CT scanners. Between July 2007 and September 2009, a Somatom Definition was used. Between September 2009 and March 2012, a Somatom Definition Flash was used. Between March 2012 and October 2014, a Somatom Definition Flash with Stellar Detector was used. Between October 2014 and January 2019, a Somatom Force was used. For all patients, nitroglycerine (≤ 1.2 mg) was administered. Also, beta blockers (≤ 10 mg Metoprolol) were routinely administered, if there was a heart rate above 65 beats per minute.

The cadaveric coronary specimen image acquisition with EID-CT and PCD-CT was performed in September 2019 at the Mayo Clinic, Mn, USA, using a Siemens research PCD-CT platform, Somatom CounT. Prior to this scanning, a cadaveric coronary specimen image acquisition was also performed with an in-house micro-CT.

Clinical image acquisition was performed by three radiographers in study I and II, while eight radiographers performed the image acquisition in study III. All radiographers had special training in cardiac CT imaging. The image acquisition of the cadaveric coronary specimens was performed by the author of this thesis, together with a dedicated PCD-CT research engineer.

The most relevant CT image acquisition and reconstruction parameters applied in the studies encompassed in this thesis are summarized in Table 1 and Table 2. All clinical patient scanning (study I-III) was performed according to established techniques and according to clinical routines. However, the scanning of the cadaveric coronary specimens (study IV) followed less well-known methods, therefore more extensively described below.

The coronary cadaveric specimens were positioned in a 30 cm water phantom to emulate the attenuation from a human thorax. The specimens were scanned on a research PCD-CT platform, which contains two separate systems, one EID and one PCD. For both systems, the radiation dose, image acquisition parameters and reconstructions were closely matched. In the PCD system, image resolution and the number of energy thresholds can be varied by four different modes of detector operation, Macro, Chess, UHR and Sharp (29). The Sharp mode was selected, using a collimation of 48 x 0.25 mm, energy threshold settings 25 and 65 keV, and effective detector pixel sizes of 0.25 and 0.5 mm for the low and high energy thresholds, respectively. The isocenter and detector pixel dimensions are illustrated in Figure 6. The low energy threshold images (25-120 keV) were used for the subsequent data analysis. Reconstructions for the EID-CT and PCD-CT data were performed with a D50 kernel. The PCD-CT data were additionally reconstructed with a D60 kernel, which was not available for EID-CT. The three reconstructed image sets are referred to as “EID-D50”, “PCD-D50”, and “PCD-D60”. Further reconstruction parameters for EID-CT and PCD-CT were including FOV 120 x 120 mm and slice thickness 1 mm, with resulting voxel dimensions of 0.23 x 0.23 x 1 mm.

Study		Study I		Study III		Study IV	
CT system		EID-CT				EID-CT	PCD-CT
Scanner		Somatom Definition Flash		Somatom Force		Somatom Definition Flash	Somatom Count
Scan mode		Spiral, retrospective	Spiral, prospective, Sequence*	Spiral, prospective, Flash**		Spiral	Spiral
Channels		2 x 128	2 x 128	2 x 128	2 x 192	128	48
Tube potential (kV)		qref 100	qref 100	qref 100	120	120	120
Tube current-time product (mAs)		qref 306	qref 324	qref 324	qref 40	138	116
Pitch		0.17-0.38***	n/a	3.4	3.2	0.5	0.5
Collimation (mm)		128 x 0.6	128 x 0.6	128 x 0.6	192x0.6	128x0.6	48x0.25
Rotation time (s)		0.28	0.28	0.28	0.25	0.5	0.5
Reconstruction technique		WFBP & SAFIRE****	WFBP & SAFIRE****	WFBP & SAFIRE****	WFBP	WFBP	WFBP
Kernel/Noise reduction level		B26f/-, I26f/3	B26f/-, I26f/3	B26f/-, I26f/3	Qr36	D50	D50, D60
Slice thickness (mm)		0.75	0.75	0.75	3	1	1
Increment (mm)		0.3	0.3	0.3	1.5	1	1
Reconstruction FOV (mm)		Adjusted for heart size	Adjusted for heart size	Adjusted for heart size	Adjusted for heart size	120	120
Image matrix size		512 x 512	512 x 512	512 x 512	512 x 512	512x512	512x512
Automated tube potential selection		Yes	Yes	Yes	No	No	No
Automated tube current modulation		Yes	Yes	Yes	Yes	No	No
ECG-modulated tube current		Yes	n/a	n/a	n/a	n/a	n/a

Table 1. Computed tomography image acquisition and reconstruction parameters for study I, III and IV.

* Patients with heart rate 60-70 beats/min, images acquired at 70% of cardiac cycle, or, patients with heart rate 70-80 beats/min, images acquired at 35-75% of cardiac cycle.

** Patients with heart rate ≤60 beats/min, images acquired at 60% of cardiac cycle.

*** Depending on heart rate.

**** Weighed filtered back projection was used until October 2011.

EID-CT: energy integrating detector-computed tomography; FOV: field of view; kV: kilovolt; mAs: milliAmpere- seconds; PCD-CT: photon counting detector-computed tomography; qRef: quality reference; WFBP: weighed filtered back projection

Study II						
	Somatom Definition	Somatom Definition Flash & Somatom Definition Flash with Stellar detector		Somatom Force		
Scanner	Spiral, retrospective	Spiral, retrospective	Spiral, prospective, Sequence*	Spiral, prospective, Flash**	Spiral, Retrospective	Spiral, prospective, Flash***
Channels	2 x 64	2 x 128	2 x 128	2 x 128	2 x 192	2 x 192
Tube potential (kV)	<90 kg: 100 >90 kg: 120	qref 100	qref 100	qref 100	qref 100	qref 100
Tube current-time product (mAs)	<90 kg: qref 380, >90 kg: qref 310	qref 306	qref 324	qref 324	qref 276	qref 290
Pitch	0.2-0.44****	0.17-0.38****	n/a	3.4	0.15-0.34****	3.2
Collimation (mm)	64 x 0.6	128 x 0.6	128 x 0.6	128 x 0.6	192 x 0.6	192 x 0.6
Rotation time (s)	0.33	0.28	0.28	0.28	0.25	0.25
Reconstruction technique	WFBP	WFBP, SAFIRE*****	WFBP, SAFIRE*****	WFBP, SAFIRE*****	ADMIRE	ADMIRE
Kernel/Noise reduction level	B26f/-	B26f/-, 126f/3	B26f/-, 126f/3	B26f/-, 126f/3	Bv36d/4	Bv36d/4
Slice thickness (mm)	0.75	0.75	0.75	0.75	0.5	0.5
Increment (mm)	0.3	0.3	0.3	0.3	0.3	0.3
Reconstruction FOV (mm)	Adjusted for heart size	Adjusted for heart size	Adjusted for heart size	Adjusted for heart size	Adjusted for heart size	Adjusted for heart size
Image matrix size	512 x 512	512 x 512	512 x 512	512 x 512	512 x 512	512 x 512
Automated tube potential selection	No	Yes	Yes	Yes	Yes	Yes
Automated tube current modulation	Yes	Yes	Yes	Yes	Yes	Yes
ECG-modulated tube current	Yes	Yes	n/a	n/a	Yes	n/a

Table 2. Computed tomography image acquisition and reconstruction parameters for study II.

- * Patients with heart rate 60-70 beats/min, images acquired at 70% of cardiac cycle, or, patients with 70-80 bpm, images acquired at 35-75% of cardiac cycle.
- ** Patients with heart rate ≤60 beats/min, images acquired at 60% of cardiac cycle.
- *** Patients with heart rate ≤60 beats/min, images acquired at 65% of cardiac cycle.
- **** Depending on heart rate.
- *****Weighed filtered back projection was used until October 2011.

FOV: field of view; kV: kilovolt; mAs: milliampere-seconds; qRef: quality reference; WFBP: weighed filtered back projection

Figure 6. The Sharp detector mode. In this thesis photon counting detector-computed tomography evaluation, the low-energy data (25-120 keV), was used for analyses. The low-energy data had an isocentre pixel size of $0.25 \times 0.25 \text{ mm}$ and detector pixel size of $0.45 \times 0.45 \text{ mm}$. The low-energy data detector pixel size is indicated with a yellow circle.

The micro-CT image acquisition was performed by the Mayo Clinic X-ray Imaging Research Core. The coronary specimens were scanned one at the time, using an almost monochromatic x-ray spectrum around 17 keV. Reconstructions were performed with an FBP algorithm and a voxel size of $0.02 \times 0.02 \times 0.02 \text{ mm}$.

An overview related to the evaluated software programs

The first CT-FFR solution was developed at Stanford University and subsequently commercialized by HeartFlow, Inc, which applied the CFD technology on the coronary arteries by the use of a super-computer. An initial evaluation was published in 2011 (90), and following work showed the CT-FFR to improve specificity, when compared with CCTA alone (91). The HeartFlow, Inc CT-FFR technique is currently clinically available in many parts of world. Nevertheless, this solution is based on a remote service, which requires transfer of data, and

has therefore been associated with a turnaround time of about 24 hours. Also, the analysis is linked to significant costs (77).

A subsequently emerged CT-FFR solution, developed by Siemens Healthcare, was designed with another approach, applying a reduced order algorithm on the normal coronary artery segments, and a full order algorithm on the segments with suspected obstructive CAD (92). This CT-FFR model presumes that the pressure alterations within normal segments are small, and extensive data processing is therefore not necessary. Since the need for computational power is considerably diminished, the technique can be applied on-site, at a conventional workstation. The CT-FFR software using this hybrid design was evaluated in three parallel studies (93-95) which were published 2014-2016, including the work presented in this thesis.

A first approach to automatic CAC scoring was presented in 2007 (96), subsequently followed by other work (86, 97-99). In 2016, a standardized evaluation of (semi-) automatic CAC scoring methods was performed in the orCaScore framework (100), with 40 patients from four different risk categories, examined on CT scanners from four different vendors. One software in the orCaScore framework study evaluated CSCT scans without any guidance of a CCTA, and this software was additionally evaluated in a separate study (85), showing a runtime of 41 s. In 2017, another novel automatic CSCT system for AS was evaluated, with an even faster runtime, being <30 s (101).

The training of the AI-based, automatic software evaluated in this thesis was performed on 2000 CSCT datasets using data from multiple hospitals, vendors and scanners from anonymous routine CSCT scans. During the model training, a heart-centric coordinate system with territory maps was used to locate the coronary arteries. The territory maps were later used to predict if voxels belonged to coronary arteries. No training datasets were used for the evaluation performed in this thesis. The model prototype consisted of two AI-algorithms: one deep-learning algorithm for spatial-based features and one machine learning algorithm for image-based features. The deep learning-based model first crop the heart region in a specific heart-centric coordinate system. The coronary territories are then predicted based on the size and form of the heart. Calcium candidate voxels inside the pericardium are subsequently extracted, using a threshold of 130 HU. Each voxel >130 HU is then extracted along with a surrounding image patch. The image patch represents the location in the heart-centric coordinate system, the prior likelihood to belong to the coronary territory map and the local image spatial characteristics. Thereafter, a machine learning-based model determines the likelihood of each candidate voxel belonging to a coronary artery. Previous work already used a similar heart-centric coordinate system for spatial features, combined with different solutions to extract calcium candidate voxels (85, 86, 96-99). At the time of this study, no previous AI-model had combined information from the heart-centric coordinate

system with a coronary territory map and local peri-voxel image information around an image patch.

Methods for data retrieval and image analysis

Some of the studies encompassed in this thesis had similarities, for example in patient identification and study design, yet a wide span of methodologies were applied, summarized below.

Retrieval of computed tomography-based fractional flow reserve measurements and comparison with the standard reference.

For study I, the CCTA datasets with diastolic, 0.75 mm thin slices were transferred to a conventional workstation, where the CT-FFR prototype was implemented. The blood pressure data from the time of the ICA was manually inserted. A default, reduced order software algorithm generated a 3-D model with arterial centerlines and luminal contours. Two readers, working in consensus, made manual model adjustments on the 3-D model. All suspected stenoses were also manually defined. A combination of the full- and reduced order algorithm was applied to generate a color-coded CT-FFR map. A PCI specialist used the images depicting the FFR pressure guidewire location to determine the equivalent location on the CT-FFR map. Subsequently, the corresponding CT-FFR and FFR measurements were compared. The workflow, along with corresponding brief CFD explanations, is illustrated in Figure 7. The time used for the CT-FFR process was evaluated in 11 independent CCTA datasets. For inter- and intra-observer agreement analysis, the smallest diameter in 10 stenotic segments were measured.

Both radiologists performing CT-FFR measurements had >5 years' experience as specialists in radiology. The interventionist had experience of >5000 PCIs.

Classification of coronary artery findings and merging of registries

According to clinical routine, CCTA data was registered to the Computed Tomography-Swedish Coronary Angiography and Angioplasty Registry (CT-SCAAR), which is a local section of the SWEDEHEART registry. In this process, coronary artery findings were classified as either normal coronary arteries/non-obstructive CAD or obstructive CAD. For the purpose of study II, one radiologist reviewed the images with normal coronary arteries/non-obstructive CAD to perform a sub-classification into normal coronary arteries and non-obstructive CAD.

Figure 7. The workflow for the computed tomography-based fractional flow reserve evaluation, and short corresponding computational fluid dynamics explanations.

3-D: three-dimensional; CCTA: coronary computed tomography angiography; CT-FFR: computed tomography-based fractional flow reserve; FFR: fractional flow reserve; ICA: invasive coronary angiography

After reclassification, the data was merged with two additional parts of SWEDEHEART: the Swedish Registry of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) and the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). RIKS-HIA contains information on hospitalizations due to MI and SCAAR contains data on revascularizations. The resulting dataset was thereafter merged with the National Board of Health and Welfare Patient Registry and the National Board of Health and Welfare National Cause-of-death Registry, which holds information on hospitalizations and on causes of death, respectively. The primary endpoint was major adverse cardiac events (MACE), defined as a composite of MI, UAP, revascularizations (PCI or coronary by-pass surgery) and CV death. In agreement with previous, similar prognostic studies (62, 102-104), only revascularizations performed >90 days after the CCTA was counted. In this manner, inclusion of revascularizations as a direct consequence of CCTA were prevented. The workflow is illustrated in Figure 8.

Figure 8. The workflow for the prognostic study.

CAD: coronary artery disease; CCTA: coronary computed tomography angiography; CT-SCAAR: Computed tomography-Swedish Coronary Angiography and Angioplasty Registry; MACE: Major Adverse Cardiac Event; NBHWNCR: National Board of Health and Welfare National Cause-of-death Registry; NBHWPR: National Board of Health and Welfare Patient Registry; RIKS-HIA: Registry of Information and Knowledge about Swedish Heart Intensive Care Admissions; SCAAR: Swedish Coronary Angiography and Angioplasty Registry

In a separate analysis, the costs for CCTA and ICA investigations was explored. First, the costs in a clinical scenario where 100% of patients are examined with an ICA was investigated. This was compared to the costs in a clinical scenario where 100% of patients are examined with a CCTA, and some patients additionally examined with an ICA. The calculations were based on data from the current study, where 18.1% of CCTA patients also underwent an ICA.

All CCTA scans were reported on by specialized readers. Out of the originally included 1370 CCTA scans examined due to chest pain of unknown origin, in total 1158 (84.5%) were reported on by three radiologists, all of them having experience of CCTA reading since 2003. Two additional readers, one radiologist and one cardiologist, reported on in total 212 examinations (15.5 %), both having experience of CCTA reading since 2011.

The creation of a calcium scoring standard reference, retrieval of the automatic calcium scoring data, and the classification into risk categories

In order to create a CSCT post-processing standard reference for study III, all 315 CSCT scans were interpreted using a previously validated (105), semi-automatic, post-processing software. All CSCT scans were interpreted by two radiologists in consensus. For the first reader, the time to report on each examination was registered. As originally described, any calcified objects in the coronary arteries with a HU of more than 130 and an area of at least 1 mm² was included (6). After manual identification and annotation of coronary calcification candidates, the AS, VS, MS and number of calcified lesions were derived. All CSCT scans were categorized into pre-defined risk groups, based on the AS values (58).

- CAC 0: No identifiable plaque, very low CV.
- CAC 1–10: Minimal plaque burden, low CV risk.
- CAC 11–100: Mild atherosclerotic plaque burden, moderate CV risk.
- CAC 101–400: At least moderate atherosclerotic plaque burden, moderately high CV risk.
- CAC >400: Extensive atherosclerotic plaque burden, high CV risk.

The most challenging 62 CSCT scans were targeted for a second opinion evaluation, performed by a radiologist and a cardiac imaging radiographer, working in consensus. To obtain an inter-reader agreement analysis, in total 106 CSCT scans were randomly chosen and distributed to two independent radiologists, both blinded to previous results. In total 71 CSCT scans were designated to one radiologist, and 35 CSCT scans to the other radiologist.

After creation of the standard reference, all 315 CSCT scans were also analysed in the AI-based, automatic software. The total AS, VS, MS, number of calcified coronary lesions, automatic run-time, and the time to double-check the automatic results were registered. For every automatically interpreted CSCT scan, a 3-D, visual feedback showed a color-coding of all included calcifications. The automatic CSCT scoring results were, similarly to in the semi-automatic procedure, classified into risk groups. The workflow is illustrated in Figure 9.

The independent dataset with 13 CSCT scans were interpreted by two radiologists in consensus and subsequently analysed in the automatic software.

The readings performed to create a standard reference for the 315 CSCT scans and the separate 13 CSCT scans were accomplished by in total three thoracic radiologists, all having more than 10 years' experience of cardiac CT. The second opinion evaluation was performed by a thoracic radiologist and a cardiac imaging radiographer, having 20 years' and two years' experience of cardiac CT and cardiac CT research reading, respectively. The CSCT scans for inter-reader

agreement were allocated to two radiologists with one year and 16 years' experience of cardiac CT, respectively.

Figure 9. The workflow for the artificial intelligence-based, calcium scoring computed tomography post-processing software evaluation.

AI: Artificial Intelligence; CV: cardiovascular

Calcification segmentation, calcification volume computation and noise measurements

In study IV, in the EID-D50, PCD-D50, PCD-D60 and micro-CT reconstructions, in each CT image of the 13 calcifications, one circular ROI was applied in the calcification and another circular ROI in the adjacent MMA. The mean attenuation measured in the ROIs was employed in a half maximum attenuation threshold (HMT) technique, to identify the boundary between the two materials.

The calcification ROIs were applied in the zone with highest attenuation, having identical size and location for all corresponding CT images in the EID-D50, PCD-D50 and PCD-D60 reconstructions. The calcification ROIs in the micro-CT reconstruction images were independently applied in the zone with highest attenuation. The MMA ROIs applied had identical size and location for

all corresponding CT images in the EID-D50, PCD-D50 and PCD-D60 reconstructions. The MMA ROIs in the micro-CT reconstruction images were independently applied. To obtain identical, corresponding ROIs in the EID-D50, PCD-D50 and PCD-D60 data, all ROIs were generated in PCD-D50, then positioned identically to corresponding images. The ROI areas were always ≥ 9 pixels. All ROIs in the EID-D50, PCD-D50 and PCD-D60 reconstructions obtained the mean CT number. All ROIs in the micro-CT reconstructions obtained the mean LAC. The open-source Image J software was used for ROI generation and for attenuation measurements.

For the EID-D50, PCD-D50, PCD-D60 and micro-CT reconstructions, in each of the 13 calcifications, in each CT image, the HMT was determined by:

$$\text{HMT} = \frac{\text{mean attenuation in the central calcification} + \text{mean attenuation in the MMA}}{2}$$

The computations were processed in an in-house Matlab algorithm (MATLAB, year 2018, Version b Natick, Massachusetts: The MathWorks Inc.), which yielded the number of segmented HMT voxels in each CT image. For each separate calcification, the number of segmented HMT voxels in every CT image were summated. The total number of HMT voxels in each calcification was multiplied with the corresponding voxel volume, which yielded the segmented HMT volume in cubic millimeters, subsequently defined as the calcified volume measurement. The workflow is illustrated in Figure 10.

In 5/170 (2.9%) separately localized EID-CT and/or PCD-CT images, the calcifications were too small for adequate measurements. For calcification segmentation in those five images, the adjacent, more centrally image HMT was applied. Any part of a calcification too small for measurements in >1 contiguous image was not included.

Finally, the 13 calcified volume measurements corresponding to the EID-D50, PCD-D50, PCD-D60 and micro-CT reconstruction were volumetrically compared.

Figure 10. The workflow for the cadaveric coronary calcification volume quantification, which applied image data from an energy integrating detector-computed tomography, a photon counting detector-computed tomography and a micro-computed tomography.

EID-CT: energy integrating detector-computed tomography; HMT: half maximum attenuation threshold; HU: Hounsfield unit; LAC: linear attenuation coefficient; micro-CT: micro-computed tomography; MMA: methyl methacrylate; PCD-CT: photon counting detector-computed tomography; ROI: region of interest

The image noise was obtained from the CT number SD measurements in the water ring phantom. For measurements, a circular ROI with diameter 100 voxels (23.4 mm) was applied in each of the 258 images in the EID-D50, PCD-D50, and PCD-D60 stacks. The computation was processed in a separate in-house Matlab algorithm (MATLAB, year 2018, Version b Natick, Massachusetts: The MathWorks Inc.).

To obtain a morphological description, all calcifications were reviewed and organized into three morphological classes, each having two categories. The review and organization were performed by a thoracic radiologist having more than 10 years' experience of cardiac CT.

Statistics

This thesis converges to comparative technology evaluations and prognostic analyses, yet several different statistical methods were utilized. The statistical methods are listed in Table 3 and summarized below.

Statistical test	Study I	Study II	Study III	Study IV
Shapiro Wilks test			X	X
Spearman's rank correlation coefficient analysis	X		X	
Intra-Class correlation coefficient analysis	X		X	
Bland Altman plot	X		X	
Weighted kappa analysis			X	
Wilcoxon signed-rank test			X	
Sensitivity, Specificity, Positive predictive value, Negative predictive value	X			
Friedman test and post hoc pairwise Wilcoxon signed rank test with Bonferroni correction				X
Repeated measures ANOVA test and post hoc pairwise comparison with Bonferroni correction				X
Kruskal Wallis test		X		
Chi square test		X		
Fisher's exact test		X		
Kaplan Meier estimate		X		
Log rank test		X		
Cox proportional regression multivariable analysis		X		

Table 3 Statistical methods used in this thesis.

Continuous variables were presented as mean and SD (study III and IV), median and interquartile ranges (IQR) (study II, III and IV) or mean, median and min/max range (study I). Categorical, nominal variables were presented as numbers and percentages (study II and III).

Analyses for correlation between two methods (study I and III) were performed using the Spearman's rank correlation coefficient (ρ).

Analyses for agreement between two methods (study I and III) were performed using the intra-class correlation coefficient (ICC) and a Bland Altman plot with 1.96 SD upper and lower limits of agreements. Also, for agreement across categories, a weighed kappa analysis was performed (study III).

Analyses of agreement between two readers was performed using the ICC (study I and III). Analyses for correlation between two readers was performed using the Spearman's rank correlation coefficient (ρ) (study III).

Analyses for sensitivity, specificity, negative predictive value and positive predictive value was employed for a software validation (study I), applying two-by-two tables.

Analyses to study differences between groups were applied at several occasions. Baseline characteristics differences between groups were analysed with the Kruskal-Wallis test and the Chi square test (study II). The differences in three-year incidence between patients were analysed with the Chi square test and Fishers exact test (study II). The differences in time between methods were analysed with the Wilcoxon signed-rank test (study III). The differences in repeated calcified volumes measurements between three groups were analysed with a Friedman test and a post hoc pairwise Wilcoxon signed rank test with Bonferroni correction (study IV). The differences in repeated image noise measurements between three groups were analysed with repeated measures ANOVA test and a post hoc pairwise comparison with Bonferroni correction (study IV).

Epidemiological and survival analyses were (except for analyses of the three-year incidence which is stated above) confined to a Kaplan Meier curve with log rank tests and a cox regression multivariable analysis (study II). The cox regression multivariable analysis assessed the importance of non-obstructive CAD and obstructive CAD after adjustments for differences in age, gender, diabetes, smoking, hypertension and hyperlipidemia. For this analysis, hazard ratios (HR) with 95% confidence intervals (CI) were expressed.

In all studies, a $p < 0.05$ was considered significant. Statistical analyses were performed with IBM SPSS version 22.0, 23.0, 24.0 and 26.

MAIN RESULTS

The most important patient baseline characteristics for the studies using patient CT scans (study I-III) is summarized in table 4.

Clinical patient study	I	II	III
Number of patients (n)	21	1205	315
Age	59 (40-74)*	56 (48-64)**	58 (± 11.5)***
Males (n)	10	512	144
Women (n)	11	693	171
Body mass index (kg/m ²)	26.3 (17.6-37.9)*	26.0 (23.7-29.0)**	27.3 (± 4.7)***
Diabetes (%)	14.3	7.0	8.3
History of smoking (%)	57.1	50.2	47.3
Hyperlipidemia (%)	Not analysed	36.5	27.3
Hypertension (%)	Not analysed	46.6	52.1

Table 4. Patient baseline characteristics.

- * Median and range
- ** Median and inter-quartile ranges
- *** Mean and standard deviation

In the CT-FFR software evaluation, the mean CT-FFR and FFR was 0.81 and 0.84, respectively. The correlation between CT-FFR and FFR was analysed with Spearman's rank correlation coefficient, showing $\rho=0.77$ ($p<0.001$). The agreement between CT-FFR and FFR, analysed with ICC, was 0.73 ($p<0.001$). A Bland Altman plot with 1.96 SD limits of agreements for CT-FFR and FFR on a per-stenosis basis was -0.18 to 0.12. The CT-FFR sensitivity, specificity, positive predictive value, negative predictive value and accuracy to detect significant stenoses, using $\text{FFR} \leq 0.75$ and $\text{FFR} \leq 0.80$ as the cut-off values for the reference standard, is shown in Table 5. The mean and median time to load the CCTA data into the prototype, apply the reduced order algorithm and make the manual adjustments was 45 and 46 min (range 34 -61 min), respectively. The mean and median run-time using the full order algorithm was 4 min 16 s and 3 min 28 s

(range 2 min 10 s -12 min 30 s), respectively. The intra-reader agreements, analysed with ICC, was 0.994 and 0.996 (both with $p<0.001$), respectively. The inter-reader agreement, analysed ICC, was 0.966 ($p<0.001$).

Results for CT-FFR to detect coronary artery stenoses, defined as FFR ≤ 0.80 and ≤ 0.75				
	FFR ≤ 0.80 Per stenosis (n=23)	FFR ≤ 0.80 Per patient (n=21)	FFR ≤ 0.75 Per stenosis (n=23)	FFR ≤ 0.75 Per patient (n=21)
Sensitivity	0.83	0.83	0.80	0.80
Specificity	0.76	0.80	0.89	0.88
Positive predictive value	0.56	0.63	0.67	0.67
Negative predictive value	0.93	0.93	0.94	0.93
Accuracy	0.78	0.81	0.81	0.86

Table 5. The table is pertaining to study I, showing the sensitivity, specificity, negative predictive value and positive predictive value for the computed tomography-based fractional flow reserve software, to detect coronary artery stenoses.

CT-FFR: computed tomography-based fractional flow reserve; FFR: fractional flow reserve

In the prognostic study, the maximum and median follow-up time was 7.5 years and 3.1 years, respectively. In total 668 (55.4%) patients had normal coronary arteries, 360 (29.9%) had non-obstructive CAD and 177 (14.7%) had obstructive CAD. In a Kaplan Meier curve over 7.5 years, a MACE was registered in five (1.0%), nine (4.6%) and 34 (20.7%) patients having normal coronary arteries, non-obstructive CAD and obstructive CAD, respectively. A log rank test with pairwise comparisons demonstrated significant differences for the occurrence of MACE comparing non-obstructive CAD with normal coronary arteries ($p= 0.023$), and obstructive CAD with normal coronary arteries ($p<0.001$), respectively. A Cox proportional regression multivariable analysis, adjusting for clinical characteristics and CV risk factors, demonstrated non-obstructive and obstructive CAD to be the only significant predictors of MACE with a HR of 3.48 (95% CI=1.13–10.67, $p=0.029$) and a HR of 29.26 (95% CI=10.86–78.83;

$p < 0.001$), respectively, using normal coronary arteries as reference. The three-year incidence of MACE in 655 patients with normal coronary arteries, non-obstructive CAD and obstructive CAD was 1.1%, 2.5% and 20.7% ($p = 0.289$ for non-obstructive CAD compared with normal coronary arteries and $p < 0.001$ for obstructive CAD compared with normal coronary arteries, respectively). The three-year incidence of hospitalization due to unspecific chest pain in patients with normal coronary arteries, non-obstructive CAD and obstructive CAD were 6.7%, 7.0%, and 14.6% ($p = 0.912$ for non-obstructive CAD compared with normal coronary arteries and $p = 0.018$ for obstructive CAD compared with normal coronary arteries). The three-year incidence of hospitalization due to stable angina pectoris in patients with normal coronary arteries, non-obstructive CAD and obstructive CAD was 0.8%, 2.5%, and 9.8% ($p = 0.136$ for non-obstructive CAD compared with normal coronary arteries and $p < 0.001$ for obstructive CAD compared with normal coronary arteries). The estimated costs of an ICA strategy and a CCTA strategy were € 1458 and € 778, respectively.

In the AI-based, automatic CSCT software evaluation, the correlation between the semi-automatic software and the automatic software for the AS, VS, MS and the number of calcified lesions was analysed with Spearman's rank correlation coefficient, showing $\rho = 0.935$, 0.932 , 0.934 , and 0.903 , respectively ($p < 0.001$). The agreement between the semi-automatic software and the automatic software for the AS, VS, MS and the number of calcified lesions was analysed with ICC, showing 0.996 , 0.996 , 0.991 and 0.977 , respectively ($p < 0.001$). A Bland Altman plot for the AS, VS and MS showed mean differences and 1.96 SD limits of agreements -8.2 (-115.1 to 98.2), -7.4 (-93.9 to 79.1) and -3.8 (-33.6 to 25.9), respectively. The AS subdivision into five risk categories was plotted in a confusion matrix, depicted in Table 6. For risk category assessment, the automatic software had an accuracy of 89.5% and $\kappa = 0.919$ ($p < 0.001$). In 27 CSCT scans the risk was overestimated, while in 6 CSCT scans the risk was underestimated with the automatic software. For the semi-automatic software, the median time to interpret a CSCT scan was 59 s (IQR 35-100). For the automatic software, the median run-time was 9 s (IQR 5-18) and the median run-time plus manually verifying the results was 36 s (IQR 29-49). A Wilcoxon signed-rank test showed significant difference between methods with regard to the time needed for a clinical report ($p < 0.001$). The inter-reader agreement and correlation between the standard reference and the two independent readers for the AS were analysed with ICC and Spearman's rank correlation coefficient, showing 1.000 and 0.968 , respectively (both with $p < 0.001$). The correlation and agreement between the semi-automatic and automatic software for the AS in the independent dataset with 13 CSCT were analysed with Spearman's rank correlation coefficient and ICC, showing $\rho = 0.939$ and $ICC = 0.956$ (both with $p < 0.001$), respectively.

Semi-automatic software	Automatic software						
	Category	0	1-10	11-100	101-400	>400	Total
	0	119	19	2	0	1	141
	1-10	4	34	3	1	0	42
	11-100	0	1	55	0	0	56
	101-400	0	0	0	43	1	44
	>400	0	0	0	1	31	32
	Total	123	54	60	45	33	315

Table 6. Confusion matrix showing the agreement in cardiovascular risk categorization between the artificial intelligence-based, automatic software and the semi-automatic software. Accuracy was 89.5% and weighed kappa analysis $\kappa = 0.919$ ($p < 0.001$). No risk category shift is indicated in bold numbers. A shift of one, two and four risk categories is indicated with yellow, green and blue markings, respectively.

In the evaluation of the PCD-CT performance on CAC quantification, in total 12/13 calcifications had calcified volume measurements which were largest in EID-D50, with a gradual decrease following the order of PCD-D50, PCD-D60 and micro-CT. In 1/13 calcifications, the calcified volume measurements were largest in PCD-D60 and PCD-D 50, with a decrease following the order of EID-D50 and micro-CT. The technique- and kernel dependent volume reduction of the segmented calcifications is illustrated in Figure 11 and Figure 12. The median calcified volume measurements in EID-D50, PCD-D50, PCD-D60 and micro-CT were 22.1 (IQR 10.2–64.8), 21.0 (IQR 9.0–56.5), 18.2 (IQR 8.3–49.3) and 14.6 (IQR 5.1–42.4) mm³, respectively. A Friedman test followed by a post hoc pairwise Wilcoxon signed rank test with Bonferroni correction demonstrated significant differences between all pairwise comparisons ($p < 0.05$). The mean image noise in EID-D50, PCD-D50 and PCD-D60 was 60.4 (± 3.5), 56.0 (± 4.2) and 113.6 (± 8.5) HU, respectively. A repeated measures ANOVA test followed by a post hoc pairwise comparison using Bonferroni correction demonstrated significant differences between all pairwise comparisons ($p < 0.01$).

Figure 11. A calcification imaged with energy integrating detector (EID)-computed tomography (CT), photon counting detector (PCD)-CT and micro-CT with the half maximum attenuation threshold (HMT) overlaid.

- a.** The HMT for EID-D50 is shown in green, representing 88 segmented calcified voxels.
- b.** The HMT for PCD-D50 is shown in red, representing 66 segmented calcified voxels.
- c.** The HMT for PCD-D60 is shown in blue, representing 55 segmented calcified voxels.
- d.** Corresponding micro-CT image.

Figure 12. The volume of each segmented calcification quantified with EID-D50, PCD-D50 and PCD-D60, depicted as a percentage of micro-computed tomography.

EID: energy integrating detector; micro-CT: micro-computed tomography; PCD: photon counting detector

DISCUSSION

The theme of this thesis was limited to CT investigations of CAD, yet the studies held a broad perspective, aiming at describing anatomical, physiological and clinical aspects. The aspiration to contribute with new data from different clinical perspectives generated variations in aims, inclusions, methods, and statistical analyses, which hopefully expanded the scientific content conveyed.

In this thesis, the CT-FFR and CSCT software programs correlation and agreement to the standard references were good and excellent, respectively. Furthermore, both software programs had time-saving potentials. The cadaver coronary calcification quantification was more accurate using PCD-CT than EID-CT. Chest pain patients with normal CCTA findings had an excellent prognosis, which became progressively impaired in non-obstructive and obstructive CAD.

The thesis suggests possibilities to use novel CT techniques in the work-up of CAD, which could improve image interpretation and efficiency. Also, the prognostic data may guide clinical follow-up strategies.

Aspects on thesis patient and cadaveric specimen inclusions

For this thesis, a CCTA referral was a prerequisite for all studies employing patient CT data. While the CT-FFR software evaluation and the prognostic study used CCTA scans, the AI-based, automatic CAC scoring software evaluation applied CSCT scans.

All studies encompassing patient CT data were performed in the work-up of suspected CAD. The CT-FFR software evaluation included patients scanned for various sub-indications, which was important to include a larger number of CT-FFR measurements. The prognostic study only included chest pain patients with no previous history of CAD, since this was a prerequisite to accomplish this study's objectives. Likewise, for the CAC scoring software evaluation, chest pain patients with no previous history of CAD were included. Based on the findings in the prognostic study, such a population was known to be at a relatively low CV risk, and thereby assumed to be relatively similar to an asymptomatic population.

In both the CT-FFR evaluation and in the prognostic study, there were more exclusions than in similarly performed, comparable studies (62, 63, 93, 94, 102, 104, 106). For the CT-FFR evaluation, the relatively sizable number of exclusions could largely be explained by missing images of the ICA pressure guide-wire. For the prognostic study, the high number of exclusions was probably due to strict registry entry criteria; if any coronary artery segment was unreadable, the whole examination was documented as inconclusive. Thus, for the CT-FFR

evaluation and for the prognostic study, the relatively large number of exclusions could be considered as strengths. For the AI-based, automatic CAC software evaluation, in total 8.6% of all CSCT scans were excluded, which limits generalizability. Nonetheless, all readable, initially excluded CSCT scans were evaluated in an independent analysis. In the cadaveric study, there were relatively few calcification volumes included, yet the differences in volume measurement results between EID-CT, PCD-CT and micro-CT were statistically significant.

Aspects on thesis image acquisition and methods

All image acquisition in the patient studies was derived from clinical CT scans, reflecting real-life patients. The Society of Cardiovascular Computed Tomography (SCCT) guidelines from 2016 state that the minimum equipment requirement for CCTA scanning is a 64-slice scanner (55), yet all CCTA scans used in this thesis were performed with a 2 x 64-slice scanner or better. Thus, even though the earliest inclusions of patient CT data in this thesis are from 2007, all present technical requirements were fulfilled. Also, all CSCT scans used for the automatic CAC scoring software evaluation were acquired according to general standards (54), which follow the 2016 SCCT guidelines recommendations to prospectively apply ECG-triggered scanning (55).

For both studies in this thesis that evaluated post-processing software programs, model-specific variations were avoided by using data from only one CT scanner, and this may limit generalizability. One can therefore not rule out that multi-hospital, multi-vendor, multi-scanner CT data would have yielded different results. However, both additional studies that evaluated the same CT-FFR software program were using data from two CT scanners, yet obtained findings which were comparable to the results in this thesis (93, 94). Also, with regard to the study evaluating an automatic CAC scoring software, previous work has showed a good inter-scanner agreement for CAC scores when examined with different vendors (107). Since the prognostic study included patients over several years, in total four CT scanners were used. Even though all CT scanners were from the same vendor, imaging technology was evolving between 2007 and 2014, and this could have impacted the assessment of image findings.

It is well known that cardiac CT image acquisition is challenging. For the studies in this thesis, a limited number of radiographers performed all clinical patient CT scans, most noticeable for the CT-FFR evaluation and the prognostic study. This aspect is likely important to uphold a good image quality and could be regarded as a strength.

For the cadaveric coronary specimen study, the reconstruction parameters were not set to match a CSCT or a NCCT, but rather to maximize the PCD-CT high-resolution capability. Future studies should evaluate the PCD-CT ability for coronary calcification quantification using dedicated, clinical reconstruction

protocols. Also, for the cadaveric coronary specimen study, image data were reconstructed using FBP, while iterative reconstructions may be more coherent with today's clinical reconstruction protocols. Nevertheless, at the time for this study, FBP was the only available alternative.

If the reference standard used for comparisons is inaccurate, the subsequent results will be hampered. For the CT-FFR evaluation, the clinical FFR measurements is the reference which has the best documentation in terms of patient outcome (108). For the PCD-CT calcification volume quantification evaluation, the standard reference needed the best spatial resolution possible. Imaging was therefore performed with a micro-CT, which had voxel dimensions of $8 \times 10^{-6} \text{ mm}^3$. This is to be considered a very small image voxel size, and it is therefore reasonable to assume that this standard reference was accurate. For the AI-based, automatic, CAC software evaluation, the standard reference was represented by 315 manually annotated datasets. Even though the manual work was thoroughly performed, there is still a risk that some standard reference measurements were falsely annotated (and possibly correctly annotated in the automatic software, even though they were statistically managed as false).

All methods applied in this thesis required meticulous manual work, which necessitated strategies to counteract human errors. In the evaluation of the two post-processing software programs, errors were minimized by having two radiologists working in consensus. Moreover, for the AI-based, automatic CAC scoring software evaluation, a second opinion was performed to further minimize errors. Notably, for the AI-based CAC software evaluation, these measures probably also improved the standard reference. For both evaluations of post-processing software, reliability was assessed with inter-reader analyses. In the cadaveric study, even though the number of calcifications were limited, the image datasets yielded in total 17698 attenuation measurements and 8461 HMT calculations. To reduce the risk of errors, the measurements and calculations were aided by in-house Matlab programs.

In previous studies investigating the prognostic value of CCTA, follow-up data was mainly acquired by clinical visits, questionnaires and phone interviews, resulting in patients lost to follow-up being between 3% and 17% (63, 102, 103, 109). In one exception, there were no patients lost to follow-up (106), but this study was limited to 232 patients. In this thesis prognostic study, the nature of the Swedish health system enabled merging of registries, which only resulted in 0.2% of the patients being lost to follow-up. Those patients (in total three) were all foreign citizens. Considering the composite nature of MACE and a relatively large cohort, a follow-up of 99.8% of patients is to be considered a significant strength, adding to the external validity.

Aspects on thesis main results

In the CT-FFR software evaluation, the correlation, agreement and accuracy between the CT-FFR software and the FFR were reasonably good, and the processing time for the prototype was typically less than one hour. The results were coherent with other work that evaluated the same CT-FFR software (93, 94), thereby supporting the software's validity. The most important benefit of the CT-FFR software is probably the potential to reduce false positive CCTA scans, which thereby communicates an opportunity to improve CCTA specificity. A CT-FFR development in the clinical setting may thereby decrease the number of ICA, in this manner reducing potentially serious complications, and lessen health care costs.

While the CT-FFR can improve CCTA reading results, the PCD-CT may produce better image quality by improvements in the acquisition hardware. The most important result of the PCD-CT calcification quantification evaluation is less CBA due to higher resolution, which leads to a more accurate quantification of CAC. Such advances can improve the accuracy of CSCT- and NCCT scans, thereby reducing misinterpretations prior to clinical risk stratifications. By extension, the PCD-CT high resolution abilities to reduce CBA may also be beneficial for the interpretation of CCTA. If so, the utilization of PCD-CT could, along with CT-FFR, eventually further improve the CCTA specificity. The PCD-CT evaluation in this thesis was performed on static cadaveric specimens, without iodine contrast in the vessel lumen. To further assess the PCD performance on CSCT, NCCT and CCTA scans, future studies should explore PCD-CT imaging using motion phantoms or real patients. Furthermore, for CCTA, the CBA reduction capacity should additionally be assessed with iodine in the coronary vessel lumen. Such evaluations could preferably be performed using iterative reconstructions. The results obtained are novel and can therefore not adequately be compared with any previous work. Notably, one preceding study reports on CSCT scanning using PCD-CT, but had another approach, showing PCT-DT benefits on CSCT inter-scan variability and radiation dose-reduction (110).

In almost any clinical environment, radiologists suffer from a shortage of time, which can cause stress and decrease the quality of radiology reports. Most CT-FFR computations performed in this thesis were shown to take less than one hour. This was, at the time for this study, to be compared with the clinically available CT-FFR software, which until recently had a turnaround time of 24 hours (77). Also, the AI-based, automatic CAC scoring software was shown to be faster than a conventional method, and its run-time was faster than similar, previous automatic solutions (85, 101). Thus, both software programs had capabilities to save time in the clinics and may thereby hold the potential to improve workflow. In due course, the possibilities of the software programs to advance efficiency could impact health care costs. Moreover, the time-saving potential of the AI-based, automatic CAC software could reduce stress, which may

lead to an improved quality of the radiology reports. Nevertheless, the most important results from the evaluation of the AI-based, CAC scoring software are probably the excellent correlation and agreement with regard to the standard reference, both for numerical CAC scores and risk classifications. The results were overall congruent with other AI-based, automatic CAC scoring software evaluations (85, 86, 99), but there are several differences among the studies, which make comparisons difficult. The findings are likely demonstrating promising possibilities for a clinical implementation, yet slightly more than 10% of the automatically derived AS results led to a CV risk misclassification, the majority shifting from risk category AS 0 to AS 1-10. This is probably a drawback, since false positive CSCT scans in the lower CAC range could lead to unnecessary drug prescriptions (111, 112). The automatic results were accessible in an immediate 3-D, visual CAC scoring feedback, which could be used to double-check results, thereby minimizing possible errors. Still, future AI-development related to the AI-based, automatic CAC scoring software evaluated should probably focus on refinements in the lower range of CAC scores. Generally, AI applications have limitations with regard to CT scans that exhibit combinations of a complicated medical history, several conditions represented in an image, and a complex request from the referring clinician. However, a referral for CAC scoring is an uncomplicated request, and the method should therefore be suitable for AI development in the clinical setting. A clinical implementation could, along with the aforementioned benefits, also permit the radiologist to focus on more demanding and complex tasks.

While the studies investigating novel CT techniques are important for future development, the currently increasing clinical usage of CT for CAD investigations also warrants more clinical, prognostic patient data. The most important results in the prognostic study were related to the Kaplan Meier estimate, which showed an excellent prognosis in CCTA patients with normal coronary arteries, which became progressively impaired in patients with non-obstructive and obstructive CAD. These findings confirmed the results of previous studies (63, 102-104, 106, 109), but the length of the follow-up time (up to 7.5 years), was, at that time, only reached in one previous work (62). The study thereby added novelty with its long follow-up time, but also, as previously discussed (page 61), by having extremely few patients lost to follow-up. Results from the multivariable analysis showed that non-obstructive and obstructive CAD were the only significant predictors of MACE, also after adjusting for age, gender and classical CV risk factors. Similar findings were also described in another work, which reports on an independent association between MACE and non-obstructive CAD plus a score related to coronary plaque morphology (CT-Leaman score) (113). The results from the multivariable analysis is not too surprising, since atherosclerotic findings on a CCTA are patient-specific manifestations of CAD, while CV risk factors are not. Relevantly, the multivariable analysis was based on relatively few MACE compared to the number of included

patients. However, the prognostic study could preferably be repeated now, since it would include a much larger number of patients, along with a follow-up time of up to 13 years. Such a study would enable a stronger multivariable analysis and add even more reliable prognostic data. Nonetheless, the obtained results from the Kaplan Meier analysis and the multivariable analysis proposes that CCTA may be useful for a clinical estimation of the long-term risk for MACE, and that its data can contribute to improve clinical follow-up strategies.

While CCTA patients with normal findings usually are left without specific treatment, obstructive CAD leads to further investigations and treatment. The results in this thesis showed a less favourable prognosis also for patients with non-obstructive CAD, which indicates the need for a preventive strategy. An observational study has shown benefits of lipid-lowering agents for CCTA patients with non-obstructive CAD (114), but this has not been demonstrated in clinical trials. However, a clinical trial performed in Scotland showed that the addition of CCTA to standard care impacted decision-making, which led to more preventive strategies and improved patient outcomes (115). Even so, no specific analysis was performed to investigate the benefit of lipid-lowering agents among the included patients.

Furthermore, in the prognostic study, there was a relatively high three-year incidence of readmissions. These hospitalizations were both due to angina pectoris and unspecific chest pain, also in patients with normal findings and non-obstructive CAD. Interestingly, previous investigations have shown that a CCTA performed in an acute setting may reduce hospital readmissions (116, 117). The high readmission rate in this thesis could be due to recurrent or progressive non-cardiac chest pain, but it could also be related to doctor-patient miscommunication. Nevertheless, the results probably indicate that the work-up of patients with chest pain may be improved with a structured and informative follow-up strategy.

Notably, the results also suggested potential benefits on health costs expenditure by using a CCTA strategy, which may be important along with thinkable economic advantages generated by the CT-FFR software. Further effects of a CCTA strategy on downstream testing and associated impact on health economics should be addressed in future studies.

Ethical aspects

The studies in this thesis were conducted according to the declaration of Helsinki (118) and according to Good Clinical Practice (119). Also, the four ethical principles proposed by Beauchamp and Childress (120) - autonomy, non-maleficence, beneficence and justice - were acknowledged. In 2018, the General Data Protection Regulation substituted the Swedish Personal Data Act (121), yet this did not impact ethical or legal considerations in this thesis. All studies were approved by a regional ethical review board.

Before any clinical CT scan referral, specialized cardiologists performed individual assessments, balancing potential risks to possible benefits. The risks associated with CT were mainly limited to ionizing radiation exposure and iodine-contrast induced nephropathy, while benefits were confined to a clinically useful, accurate CAD estimation. These considerations were made in a real-world, pragmatic setting with respect for autonomy and in accordance with the principle of non-maleficence and the principle of beneficence. In conjunction with the subsequent clinical CT scans, patients were informed, in written form, regarding their participation in a national quality registry. The information included the right to deny participation and to have data removed, which is in accordance with the principle of autonomy. According to the Swedish legislation, no written consent is needed in this setting (122).

All CT scans on patients included in this thesis were performed according to a relevant clinical indication. Thus, in accordance with the principle of non-maleficence, the thesis studies did not generate any extra exposure to ionizing radiation or to iodine contrast agents. However, when personal information is needed to interpret research data, patient integrity may be infringed. Consequently, in accordance with the principle of non-maleficence, strategies for an appropriate management of clinical patient data were predetermined. For the patient studies, only the necessary clinical baseline data and the most relevant image data was retrieved and analysed. Additionally, to minimize the risk of any unauthorized person identifying an individual patient, all analyses, in all studies, were performed on anonymised data. Eventually, for the studies encompassing patient data, the scientific knowledge value of the research was estimated to outweigh the potential adverse risks, an opinion which was shared with the regional ethical review board. In accordance with the principle of justice, patients in this thesis were managed on an equal basis, using predefined inclusion- and exclusion criteria. Also, patients in this thesis were observed, and thus not subjected to any study-associated diagnostic alternatives or treatment options.

The cadaveric specimen study was performed at the Mayo Clinic, Mn, USA, which has comprehensive ethical standards and regulations. Prior to the work performed as a research affiliate, an education in medical ethics was compulsory, followed by an examination. The biospecimen protocol was issued by Mayo Clinic Institutional Review Board, Biospecimen Subcommittee. The cadaveric specimen donation process was performed by the Department of Anatomy, Mayo Clinic, following ethical and legal regulations. The details regarding the donation process were not available for the author of this thesis. At the Department of Anatomy, the frozen cadavers were collected, and coronary vessel specimens resected. All cadaveric specimens were securely transported between Department of Anatomy and Department of Radiology, using a sealed container placed inside a secondary opaque container. After the scanning procedure, the

cadaveric specimens were safely stored, according to established routines. The original identities of the cadaveric specimens were not known for the researchers performing the study in this thesis. For all image acquisition, calcification quantification and analyses, the cadaveric coronary specimens were therefore labeled with an identity number (e.g. Hu 1, LAD). For obvious reasons, the cadaveric specimen's management necessitated a respectful conduct, which also was a natural part of the Mayo Clinic research atmosphere.

Further development after the thesis publications

The CT-FFR software evaluation was the earliest work in this thesis, published in 2016. Since then, the CT-FFR technique has been associated with several further advances. For example, a developmental extension of the software evaluated in this study was combined with AI in a machine-learning CT-FFR algorithm and analysed in a multicenter study. It was demonstrated to have an almost perfect correlation to CT-FFR and showed a significantly shortened processing time (123). Likewise, the currently clinically available CT-FFR software has correspondingly obtained a reduced processing time (124). To explore the clinical utility of CT-FFR, a multi-center study showed that CT-FFR altered the treatment plans (which were based on CCTA alone) in roughly 2/3 of patients having more than a 30% CAD obstruction (125). Also, the comparative efficiency of CT-FFR to diagnose CAD has been investigated, where CCTA, SPECT and PET were outperformed by CT-FFR, using FFR measurements (≤ 0.80) as the standard reference (126). When comparing CT-FFR with CTP imaging, the methods had a similar diagnostic ability, using FFR measurements (≤ 0.80) as the standard reference (127). Moreover, a prognostic study over a median of 4.7 years showed that CT-FFR < 0.80 was associated with more MACE compared with the conventional assessment of a $\geq 50\%$ CCTA stenosis (128). The CT-FFR model has also shown favourable features in the assessment of the optimal position for coronary artery stents (129). Nevertheless, even though the exploration of CT-FFR have provided new insights, studies are so far limited by being of observational nature.

The prognostic investigation in this thesis was published in 2018 and had an extraordinarily long follow-up time of maximum 7.5 years. Since then, a study on elderly, asymptomatic individuals demonstrated a follow-up time of maximum > 10 years, showing the CCTA prognostic value to be better than conventional risk assessment and CAC scoring (130). Also, a study with a follow-up time of maximum > 11 years showed prognostic CCTA data which were coherent with the results in this thesis. The results also revealed that CCTA findings had better correlation with adverse cardiac events than a clinical risk score (the Morise score) (131).

For automatic CAC scoring, a very recent study evaluates an AI-based solution which can be applied on CT examinations beyond CSCT (132). This is a ground-breaking expansion of this field, and likely to be clinically beneficial,

especially considering the permissive U.S. guidelines which are related to CAC reporting on NCCT scans (60).

FUTURE PERSPECTIVES

Ever since the introduction of the E.M.I. scanner, the CT technology has unceasingly continued its development, and today the modality is fundamental for a very large number of clinical investigations. For imaging of the coronary arteries, the CSCT- and CCTA examinations have been well integrated among the arsenal of clinical tools for cardiac investigations. Also, for both methods, there has been a steady increase in clinical requests. As European (ESC) guidelines suggest alterations in the CCS assessment (10), an additional near-future increase in clinical CCTA patients is expected, which probably mirrors the importance of further research. Future advances are difficult to predict, but the main themes for this thesis, CT-FFR, prognostic CCTA studies, AI software programs and PCD-CT may all be associated with forthcoming developments.

The CFD and CT-FFR encompass a specific area of development, which shifts the CCTA technique towards functional imaging. The CT-FFR has lately been quite extensively explored (123, 125, 128, 129) but the studies so far are limited by being observational in nature. Nonetheless, the clinical trials NCT03187639 and NCT03702244 are underway, which are designed to present clarity on the clinical utility of CT-FFR (133). Interestingly, future CFD cardiac applications are not limited to the coronary arteries, since a recent CFD algorithm is suggested to quantify cardiac chamber flow dynamics (134). Such a development could have a large clinical impact, since it nudges the cardiac CT technique further towards functional imaging, and into what is cardiac MRI imaging territory.

Among other emerging techniques for CT investigations for CAD, CTP imaging warrants to be mentioned. Since this method detects flow-limiting CAD, it may improve CCTA specificity, and combinations of CTP imaging and CT-FFR is demonstrated to further advance diagnostic performance (127).

The clinical guidelines for preventive treatment after CSCT are based on 30 years of research, while the CCTA is a newer technique. Even though the prognostic study in this thesis had a long follow-up time, data from investigations with an even longer follow-up time can further delineate the role of CCTA in the work-up of chest pain patients. Future studies should also analyse preventive strategies in non-obstructive CAD, preferably with clinical trials. Also, the incremental prognostic value of CCTA in combination with CT-FFR should be additionally addressed (128). Moreover, future studies could further explore the integration of AI to facilitate CCTA risk stratification (88).

The use of different AI applications could probably enrich various fields of future clinical radiology. For CAC scoring, the results in this thesis could guide similar research and be beneficial prior to further technical software program advances. Forthcoming AI developments related to CAC scoring should aim to

integrate supplementary imaging abilities, such as the detection and characterization of pulmonary nodules. Also, in CAC scoring, image noise can be difficult to discriminate from small calcifications. Therefore, it may be advantageous to superimpose an AI-application with the ability to detect CSCT scans that exhibit a high noise level. Such solutions could, for example, be designed to label scans with a high level of noise for a more meticulous manual review. Likewise, future AI-software programs for CAC scoring that can process examinations beyond CSCT scans are likely to gain a very large impact (60, 132). For CCTA, AI advances related to for example coronary artery plaque characterization and cardiac chamber segmentation could be beneficial.

The use of PCD-CT may be a key game-changer in future CT imaging, also for CAD investigations. The results in this thesis illustrate that the PCD-CT can reduce CBA, thereby improving CAC quantification, which is important to assess CAD. Future studies should investigate whether PCD-CT correspondingly can help to reduce CBA in in-vivo CCTA, CSCT and NCCT scans. Such findings would communicate a potential to improve not only CSCT and NCCT inter-scan variability, but also CCTA specificity. Additional conceivable advances in imaging of the coronary arteries with PCD-CT include image noise reduction and decreased radiation dose (28, 29). Furthermore, the multi-energy capabilities might help to subtract CAC, and could be beneficial to obtain both a CSCT and CCTA from only one CT scan (135). Moreover, the technique can permit the usage of more than one contrast agent, which may be useful in thoracic imaging. The combination of PCD-CT with CFD has not been explored, but can likely generate incremental improvements, both for CT-FFR and for cardiac chamber flow dynamics. Furthermore, in a broad sense, the potential of AI applications on PCD-CT data should be investigated.

In conclusion, future perspectives related to the work in this thesis could mirror combinations of PCD-CT acquisition data with AI-based, morphological and functional post-processing advances. Also, additional prognostic studies, possibly integrating AI and CT-FFR, could further define the role of CCTA in the work-up of chest pain patients.

CONCLUSIONS

The four studies in this thesis convey developmental hardware and software advances related to CT for CAD investigations and also add prognostic CCTA data.

The four studies have led to the following specific conclusions:

- Study I** The correlation, agreement and accuracy between a CT-FFR software and the FFR were reasonably good, and the prototype could be timesaving.
- Study II** Symptomatic CCTA patients with normal coronary arteries and no history of CAD had an excellent long-term prognosis, but the prognosis was progressively impaired in patients with non-obstructive and obstructive CAD. Patients with non-obstructive and obstructive CAD were independently associated with MACE.
- Study III** The correlation and agreement between an AI-based, automatic CAC scoring software and a conventional software were excellent. The AI-based risk category classification was accurate, yet with an overestimation tendency. Also, the AI-based method could be timesaving.
- Study IV** The quantification of coronary calcifications from cadaveric specimens was more accurate using the PCD-CT than EID-CT, and a dedicated PCD-CT kernel further improved the accuracy.

THE SIGNIFICANCE OF THIS THESIS

The general theme for this thesis was to evaluate new CT techniques for CAD investigations, but also to analyse the prognostic value of CCTA. However, the CT development related to CAD investigations is an extremely research-intense area, encompassing numerous new publications annually. The importance of this thesis alone should therefore not be overestimated. Nonetheless, this thesis presents novel data on technical advances and clinical follow-up, which can benefit future patients by improvements in diagnostics and work-up. Moreover, the results indicate possibilities to improve the workflow and efficiency in clinical radiology, which eventually could reduce stress among radiologists and impact health economy. Also, hopefully, the content in this thesis could spark new ideas, or be targeted for extended research, thereby ultimately adding further health care advantages.

ON THE LEARNING OBJECTIVES FOR A DOCTORAL DEGREE

While working on this thesis, several cornerstones have contributed to fulfill the 10 learning objectives for a doctoral degree.

First and foremost, the conduction of all four studies along with innumerable supervisor, co-supervisor and co-author-discussions have been essential to reach the learning objectives. Similarly, in a broad sense, the participation in several post-graduate courses provided important and useful insights. The study performed at the Mayo Clinic in Minnesota, USA, was supervised by some of the most prominent CT researchers in the world, and therefore warrants a special mention. The time spent at this extremely special research community intensively enriched the PhD training by several scientific counsels, accompanied by diverse unique learning experiences. A continuous participation in the CMIV research school contributed to incremental scientific education, mainly by scientific presentations and discussions. Also, the PhD education half-time seminar offered important scientific reflection. The participation in international conferences awarded a broader specialist comprehension. Lastly, the continuous, clinical work as a thoracic radiologist has provided clinical experience, which was integrated into the research settings.

POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Med 12 000 fall årligen är kranskärslssjukdom, åderförkalkning i hjärtats artärer, den vanligaste dödsorsaken i Sverige. I en ny avhandling vid Linköpings universitet har nya avancerade, tekniska metoder för skiktröntgen undersökts, med syftet att förbättra och förenkla utredningen av kranskärslssjukdom.

Utredning och behandling av kranskärslssjukdom fordrar stora resurser från sjukvården och skapar betydande samhällskostnader. Kranskärslssjukdom orsakar också stort lidande. För att hjälpa patienter och hantera sjukvårdens utmaningar är det oundgängligt med bra utredningsmetoder. De sista åren har skiktröntgen för misstänkt kranskärslssjukdom utvecklats explosionsartat. Metoden anses patientsäker och kostnadseffektiv, och har kapacitet att avbilda hjärtat på mindre än en sekund.

I en avhandling om skiktröntgen eftersträvar röntgenläkaren Mårten Sandstedt ytterligare förbättringar för diagnostik av kranskärslssjukdom. En av studierna genomfördes på Mayo Clinic, USA, och utvärderade kapaciteten att avbilda åderförkalkningar i kranskärlen med en ny skiktröntgenmetod. Denna teknik erhåller mycket hög bildupplösning genom att registrera energin från enskilda ljuspartiklar (fotoner) i avbildningsprocessen, och anses kunna bidra till ett framtida paradigmskifte inom skiktröntgen. Avhandlingens övriga studier, som är utförda på Linköpings universitet, har utvärderat hur artificiell intelligens och nya mjukvaror kan förbättra bildgranskning. En studie har också analyserat långtidsprognosen för patienter som undersökts med skiktröntgen på grund av bröstsmärta.

Avhandlingens resultat åskådliggör lovande möjligheter att förbättra diagnostiken av kranskärslssjukdom med skiktröntgen. Ny teknik visade potential att kunna bidra till mer korrekt diagnos, vilket kan förhindra användandet av mer riskfyllda undersökningar. Användning av artificiell intelligens för bildtolkning visade sig fungera utmärkt, och medgav möjliga tidsvinster. Därtill visade ny teknik kunna bidra till potentiella, framtida fördelar ur både en hälsoekonomisk aspekt, och ur ett arbetsmiljöperspektiv. Analyser visade också att långtidsprognos hos patienter med bröstsmärta varierar med graden av kranskärslssjukdom, vilket är viktig information för uppförande av nya, kliniska uppföljningsstrategier.

ERRATA

Study	Page	Original	Corrected
I	2/7	...ref. mAs at 185 A, and...	...q ref mAs at 324, and...
I	2/7	...sequential imaging or a high pitch FLASH protocol...	...retrospective or sequential imaging or a high pitch FLASH protocol...
I	2/7	...in total 45 patients (71%) representing 49 vessels (68%).	...in total 42 patients (67%) representing 48 vessels (68%).
II	2/7	...intermediate risk (4,7)... ...ECG is uninterpretable.	...intermediate risk (4)... ...ECG is uninterpretable (5,7)
II	2/9	Of the originally included 1396 CCTA, 1178 (84.4%) were...	Of the originally included 1370 CCTA, 1158 (84.5%) were...
II	3/9	...218 (15.6%) CCTA were...	...212 (15.5%) CCTA were...
III	3/8	Mild atherosclerotic plaque burden, moderate CV.	Mild atherosclerotic plaque burden, moderate CV risk.

Errata table: Errors are indicated in yellow. Corrections and addenda are indicated in green.

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APPENDIX (STUDY I-IV)

Papers

The papers associated with this thesis have been removed for copyright reasons. For more details about these see:

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