Implementation and extended use of computed tomography coronary angiography

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General discussion and future perspectives

PART I. IMPLEMENTATION OF CTCA

As summarized, **Part I** of this thesis showed that implementation of CTCA in the Netherlands is possible due to the availability of all requirements, such as high national coverage of CTCA services and the availability of modern scanners. Furthermore, **Part I** showed that local implementation of CTCA is feasible and results in a drastic reduction of CAG. However, to fully implement CTCA in the Netherlands, a substantial increase in CTCA capacity will be necessary during the following years to facilitate the recommendations of the 2019 ESC guidelines on the use of CTCA for chronic coronary syndromes. This transition will not only require a transformation in the organization of the healthcare related to CAD, but also induce an extra burden on CT-provision and cardiac imagers. Hospitals may have to increase CTCA capacity and invest in additional CTCA-capable CT-scanners or cardiovascular imaging experts. But much more important for the implementation of CTCA, this transition may also result in a shift in workflow. Therefore, not all stakeholders may be willing to implement CTCA as principal diagnostic modality. The increase in CTCA scans could lead to a decrease in diagnostic CAG's with subsequent adjustments in reimbursements for CAD related healthcare. Even more importantly, it reduces the number of invasive diagnostic procedures performed by cardiologists and may question the validity for catheterization laboratories in which only diagnostic CAG are performed. If a CTCA is performed upfront in the diagnostic work-up, patients with obstructive lesions should ideally be referred directly to a PCI centre or cardiothoracic surgical centre. In the Netherlands, this would concern 36 hospital organizations. Furthermore, the reduction of diagnostic procedures may jeopardize clinical licenses of the individual cardiologists for performing these invasive procedures.

However, such a production shift will also lead to opportunities. Both time and other resources can be re-allocated to other, clinically valuable interventional procedures. Taken together, this healthcare transition is so complex, that it will need to be managed by all involved stakeholders at a national level. This will offer the opportunity to implement CTCA with optimal conditions for both patients and health care professionals.

Apart from the barriers in healthcare organization, the differences in image quality are inseparably linked to different experiences with CTCA and therefore, linked to the adoption or rejection of this diagnostic modality. Therefore, updated national standards are necessary for CTCA equipment and protocols to provide high image quality with minimal ionizing radiation dose and minimal use of contrast material. Lastly, CTCA findings reporting and communication should be standardized and of high quality to guarantee adequate corresponding patient management. Only with all mentioned requirements in place, we will be able to implement CTCA and deliver the promising results from clinical trials to daily clinical care (1,2).

The successful local implementation of CTCA in **chapter 2**, resulted in a large (83%) reduction of the number of CAG in the diagnostic work-up for non-coronary cardiac surgery, cardiomyopathy, heart failure and ventricular arrhythmias. These results are in line with previous similar studies in patients with chest pain (87.9%) or patients referred for TAVI (76.4%) (3–5). By reducing diagnostic CAG, we avoid the risk for catheter-induced complications and avoid hospital admission (6). Furthermore, patients that undergo CAG have to endure pain and are advised to withhold physically demanding labour or activities for three to five days. Therefore, a CAG procedure purely as a diagnostic procedure has too much impact and should be withheld from patients if possible. Even though a reduction of 83% is promising, the number of diagnostic CAG can potentially further be reduced. Ideally, CTCA should be followed by non-invasive functional testing, instead of CAG, if CTCA shows signs of obstructive coronary lesions. This non-invasive stepwise approach is sufficient to rule out obstructive CAD and to select patients by CTCA and rule-in clinically relevant ischemia by non-invasive functional tests in patients with an indication for PCI or CABG, without diagnostic CAG. Future trials are warranted to investigate the impact of the combination of CTCA and non-invasive imaging for myocardial ischemia on the risk of ischemic cardiovascular events, quality of life and angina symptoms as well as the impact on the cost-effectiveness. Currently we are preparing a nationwide randomized clinical trial (CLEAR- CAD) with all partners and together with 'Zorg Evaluatie en Gepast Gebruik' (ZE&GG) aiming to evaluate both clinical and cost effectiveness of such a combined approach.

PART II. THE EFFECT OF CONTRAST ADMINISTRATION ON IMAGE QUALITY OF CTCA

In **part II** of this thesis we studied adjustments in contrast delivery to adjust the IDR and achieve an adequate, pre-specified arterial attenuation value range of 300 to 500 HU. This range ensures accurate assessment of the coronary vessel lumen and vessel wall, and therefore allows accurate evaluation of coronary artery pathology (7–13). In contrast to previous studies, the IDR in the presented studies was adjusted by diluting the contrast medium, keeping the injection rate constant (14-18). The reasoning for diluting the contrast material instead of altering the injection speed was that with dilution, the total volume of the contrast bolus is the same for all patients and therewith the influx into the right atrium. Changing the injected volume may influence the blending of inflows from the vena cava superior and inferior. Furthermore, it may alter the preload of the heart and consequently may affect ventricular stroke volume and increase the contractility of the heart.

Our results showed that a contrast delivery protocol adjusting for kV setting and body weight is feasible and allows for a substantial reduction of contrast medium use while

maintaining diagnostic attenuation. Simultaneously, we showed that such a contrast delivery protocol also yields adequate results over the full range of kV settings that is available on state-of-the-art CT-scanners. The modern generation CT-scanners offer a wide range of kV setting (70-120 kV), which offers the opportunity to drastically reduce ionising radiation dose, with a mean of 21% per 10 kVp (19). Especially in the low kV categories, the presented contrast delivery protocol adjusted the IDR accordingly, and did not only reduce radiation dose, but also reduced total iodine load while maintaining high image quality.

The disadvantage of these protocols is that it will require extensive knowledge of radiologists and technicians about contrast delivery systems, CT-systems potential and scan modes. This will not only increase the workload of the personnel involved, but also make CTCA less accessible for the all-round radiologist, who may only perform CTCA every now and then. However, the demand for high quality CTCA examinations is increasing and radiologists will be confronted with this technique more routinely. Therefore, my opinion is that contrast medium administration should always be personalized. Not only to reduce contrast dose and adjust coronary attenuation, but also to resolve the differences in coronary attenuation or image quality across hospitals, as discussed in **part I** of this thesis. These uniform attenuation values also may facilitate more accurate assessment of CAD and increase the precision of advanced coronary artery stenosis measurements, like FFR-CT and CT myocardial perfusion. To overcome the increase in workload and reduced accessibility, future contrast delivery protocols should be integrated in easy to use software applications, providing the optimal patient specific IDR or percentage contrast dilution before image acquisition. Build-in machine learning applications could potentially be used to further reduce variations in coronary attenuation, using patient characteristics, CT-scanner parameters and test-bolus variables, as discussed in **chapter 3** of this thesis.

PART III. THE EXTENDED USE OF CTCA IN PATIENTS UNDERGOING TAVI

Since CTA is already used in the work-up for TAVI for sizing of the valve prosthesis and the evaluation of the access route, using CTCA (i.e. including coronary assessment to the standard CTA reading) for the evaluation of CAD will not lead to additional diagnostic tests in the TAVI work-up. Therefore, the extended use of these images will create a leaner, streamlined clinical pathway. The use of CTCA as an alternative for CAG to evaluate CAD in the TAVI work-up will be beneficial for multiple reasons. Not only will it be necessary to decrease work-up time, but also will it reduce patient burden (21). An additional CAG is only necessary if there are indications of clinically relevant coronary lesions on CTCA. This thesis shows that a reduction of 37% to 70% in CAG is possible, depending on the

threshold that is used (50% DS or 70% DS) and depending on the coronary segments evaluated (all or only the proximal segments). This reduction in invasive procedures will reduce physical strain, by reducing pain and possible complications. Furthermore, it may reduce mental strain by reducing hospital admission duration and immobilization. These factors are of extra importance in this population, consisting almost exclusively of elderly, fragile patients (6,22). Therefore, CTCA should be implemented in the standard work-up for TAVI for evaluation of CAD, as these patients would strongly profit from a non-invasive diagnostic approach. In addition, using the CTCA scans for the evaluation of CAD will most probably also result in a significant cost reduction and a reduction in complications. To illustrate the difference in costs: The cost of a diagnostic CAG is over 2000 euro per procedure, taking into account the cost of personnel, material, the costs of incidental complications and hospital admission, while the costs for coronary evaluation by a radiologist on the already acquired CTCA scans will only cost around 50 euro.

As is recommended by the guidelines, an additional CAG would only be necessary if there are >70% DS lesions in proximal coronary segments on CTCA. However, this thesis shows in **chapter 5** that even if CAG confirms the presence of these lesions, treatment with subsequent pre-procedural PCI did not reduce mortality in our cohort of TAVI patients. These findings were comparable to results of previous observational studies (23,24). An explanation of this finding may be that performing a pre-TAVI PCI induces extra risks in this frail patient population, which eliminates the potential health benefit of treating the lesion with PCI. However, until results from sufficiently powered randomized controlled trials persuade the field into one direction, we should either rely on clinical rationale or insights from these observational studies. Although clinical rationale may urge cardiologists to perform a preventive PCI in TAVI patients, we believe that a more restrictive PCI policy is indicated. A staged post-TAVI PCI strategy should be considered in patients in whom angina symptoms persist despite the increased coronary blood flow and vasodilator reserve after TAVI. However, pre-TAVI PCI may be considered in patients with pharmacological refractory angina symptoms, together with significant lesions in the proximal coronary arteries. Another consideration could be to perform pre-TAVR PCI in patients in whom coronary access is thought to be compromised after the procedure.

Apart from the evaluation of CAD, CTCA may assist to predict the overall procedural risk as well as to uncover specific areas that may pose additional risk of complications. In this thesis, we showed that a higher volume of aortic valve calcification volume pre-TAVI was associated with a larger increase of white matter hyperintensity volume at MRI during follow-up, indicating chronic brain infarctions. These findings show the potential for CTCA, used for automated aortic valve calcium screening, as an imaging biomarker

to predict chronic silent brain infarctions in patients undergoing TAVI. Personalized knowledge of the post-procedural risks may assist in deciding whether to perform or withhold the procedure, as well as facilitate the decision to perform the TAVI procedure with additional preventive measurements, like a cerebral protection device. Altogether, this thesis shows that an extended use of CTCA in the work-up for TAVI will support a leaner diagnostic work-up and assist in personalizing risk assessment. Therefore, the extended use of CTCA will assist in lowering patient burden, reduce procedure related complications and improve patient outcome.

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