# CORONARY CT ANGIOGRAPHY IN PATIENTS SUSPECTED OF STABLE CORONARY ARTERY DISEASE. INTERNATIONAL GUIDELINES, COST-EFFECTIVENESS AND EXPERIENCES FROM DENMARK

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Non-invasive coronary computed tomography angiography (cCTA) possesses an impressive accuracy in excluding coronary artery disease (CAD) and coronary stenosis (1). The absence of CAD by cCTA is associated with an excellent prognosis and obviates the need for any further diagnostic workup (2). Therefore, together with the worldwide ever-expanding access to CT, cCTA has emerged as a diagnostic alternative to functional testing in patients suspected of stable CAD.

The radiation dose associated with cCTA has been an important issue in the discussion on whether it should be incorporated into clinical practice. However, based on the introduction of low-dose protocols today the mean radiation dose associated to cCTA should not exceed 1-3 mSv per examination, which is less than the radiation burden associated with both myocardial perfusion SPECT and invasive coronary angiography (ICA), respectively.

Limitations related to the diagnostic specificity of cCTA should be acknowledged. First of all, the correlation between stenosis severity when compared to ICA is poor (in general, cCTA tends to overestimate the stenosis severity) (3), and the hemodynamic significance of a stenosis cannot be assessed (4). Secondly, the presence of artifacts (e.g. motion, misalignment, calcification-induced blooming) may result in inconclusive examinations or be misinterpreted as coronary stenosis, hence adds to the risk of false-positive results. Therefore, there is ongoing debate as to whether cCTA will improve patient management and outcome or merely will lead to increased downstream utilization of unnecessary diagnostic procedures and revascularization of non-ischemic CAD (5,6).

As physiology trumps anatomy for clinical outcome, current guidelines for the management of stable CAD recommend non-invasive functional testing as the first line test. However, according to the recent ESC guidelines on the management of stable CAD, cCTA may be considered as an alternative to functional testing for ruling out CAD in symptomatic patients with intermediate pre-test likelihood of significant CAD, after a non-conclusive functional testing result, or in patients with contra-indications to functional testing (evidence level, IIa) (7). Importantly, it is highlighted in the guidelines that patients should be referred to cCTA only if a fully diagnostic image quality can be expected. Cardiologist referring patients to cCTA thus should be familiar with the most important factors influencing image quality (e.g. heart rate, tolerability of heart rate reducing agents, body size, patient cooperation, nitroglycerin, and coronary calcification), and thus the diagnostic performance of the test (7,8).

Knowledge about cost-effectiveness of cCTA vs conventional functional testing in mainstream clinical practice is sparse. In an observational study of patients suspected of stable CAD from this center, a strategy of frontline diagnostic testing

with cCTA incurred lower costs associated with downstream diagnostic testing, and was associated with fewer subsequent serious cardiac events when compared to a strategy of exercise-ECG testing (9). In a large US registry study, frontline diagnostic testing with cCTA were associated with a 26% reduction in downstream costs when compared to a strategy of SPECT, however, with comparable clinical outcomes (10). In contrast, in another registry study of more than 200.000 US Medicare beneficiaries with suspected stable CAD, total as well as CAD-related subsequent costs were higher in patients diagnosed by cCTA as compared to patients diagnosed by SPECT, exercise-ECG or stress echocardiography (11). In the latter study, mortality rates across diagnostic groups were comparable, however, downstream hospitalisation for acute myocardial infarction were lowest in the cCTA group. Differences in cost-effectiveness between studies may be explained by crucial determinants of outcome, e.g. different risk profiles of study cohorts, differences in diagnostic strategies, differences in technology and observer experience. Ongoing statistically well-powered, multicenter, prospective, and randomized studies assess cost-effectiveness of frontline non-invasive functional testing vs anatomic cCTA testing in patients suspected of CAD. In Denmark cCTA has been used as an alternative primarily to exercise-ECG, SPECT and ICA for assessment of patients suspected of CAD since 2007. Of note, the use in Denmark of stress echocardiography, cMR, or PET as frontline diagnostic tests in CAD are limited. In 2008 it was mandated by the Danish health authorities that cCTA could not be performed without simultaneous reporting of relevant data (regarding pre-test risk profile, CT acquisition characteristics including radiation dose, test quality and result, as well as information on the clinical consequence) into one of two central databases (West-Danish Heart Registry and WebPADS). Currently, cCTA is practiced in 21 Danish hospitals (min-max annual production, 60 - 2100 exams), and more hospitals are in the process of implementing the method for assessment of CAD. In three centers (Rigshospitalet, Vejle, and Skejby) cCTA is performed in cardiology departments and interpreted by cardiologists only, whereas in the rest of the centers the test is performed as collaborations between cardiology and radiology or nuclear medicine. The annual number of cCTA exams in Denmark for assessment of stable CAD (>90% of all cardiac CT studies) seems to be continuously increasing, and passed in 2012 11.000 examinations (figure 1). What do we know about the consequences in Denmark of the implementation of cCTA on patient's diagnostic management? My personal impression (nationwide registries not existing) is that the introduction of cCTA has led to a dramatic decrease in the use of exercise-ECG testing for frontline assessment of CAD. Moreover, a modest fall in the use of SPECT has been observed (12% relative reduction from 2009 until 2011). In contrast, since 2008 until 2011 the annual number of ICAs on the indication stable CAD has increased by 20% (Figure 1). It is important to acknowledge, however, that causality between the nationwide implementation of cCTA and the simultaneous increase in ICAs cannot be documented, neither can we at this point estimate the proportion of ICA referrals based on prior cCTA testing. Other potential explanations of the increasing use of ICA may be a higher political/societal awareness with regard to diagnostic assessment of patients with chest pain of unknown origin. Notably, in Denmark as in other western countries the prevalence of CAD is increasing (however

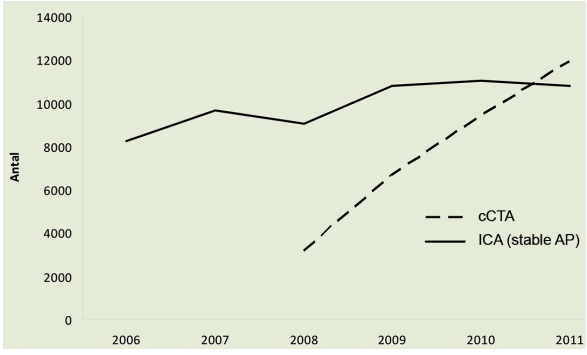


*Figure 1. cCTA and ICA*

in general, cCTA is not indicated in patients with known CAD), whereas the incidence is falling. Rather than focusing on the use of ICAs per se the more relevant question is: Has the implementation of cCTA in Denmark changed patient management and outcome in CAD? It is well known from clinical practice, that (despite prior non-invasive testing) up to 60% of subjects suspected of CAD and referred for ICA do not have obstructive disease (12). Another indicator (although not perfect) of the "appropriateness" of ICA in patients suspected of stable CAD is the proportion of ICAs followed by revascularization. Rather surprisingly, the proportion of "unnecessary" ICAs (as defined by ICAs without intervention) in Danish patients suspected of stable CAD is increasing (Figure 2). Again, causality between the latter and the nationwide implementation of cCTA cannot be documented based on these numbers. However, despite a widespread and still increasing implementation of cCTA in Denmark, we cannot at this point show any reduction in the number of ICAs or the proportion of "unnecessary" ICAs. The most important question as to whether the implementation of cCTA has changed the clinical outcome in CAD cannot be answered at this point. Danish national registries including data from >35.000 cCTA patients together with data on the use of downstream medication, ICA, coronary interventions, and outcomes from other national registries are under investigation.

In conclusion, cCTA has very high diagnostic accuracy with regard to exclusion and detection of CAD, and thus in the recent ESC guidelines on assessment of stable CAD has been assigned a level 2a indication as an alternative to functional testing for ruling out CAD in symptomatic patients with intermediate pre-test likelihood of CAD, and in whom a diagnostic CT image quality can be expected. The diagnostic performance of coronary CTA may be hampered by the presence of image artifacts, as well as suboptimal accuracy with regard to quantification of CAD. Thus, non-invasive anatomic assessment with cCTA alone is not the ideal pathway to ICA or revascularization. Other factors potentially decreasing the diagnostic specificity of cCTA are the presence of CT image artifacts, low observer experience, and scanning of patients beyond the intermediate pre-test risk range, respectively. In order to avoid compromising artifacts, adherence to official recommendations regarding cCTA acquisition (8) is essential. In the event of a positive test result, the diagnostic specificity of cCTA may potentially be improved by interpolating functional testing before decision making on ICA. Moreover, recent data convincingly have demonstrated improved diagnostic specificity when compared to cCTA of non-invasive fractional flow reserve (FFRct) which is computed from standard acquired cCTA images without the need of additional radiation, patient preparation or medication (13). The cost-effectiveness of cCTA relative to conventional functional testing is under investigation in large registry studies and prospective randomized trials.

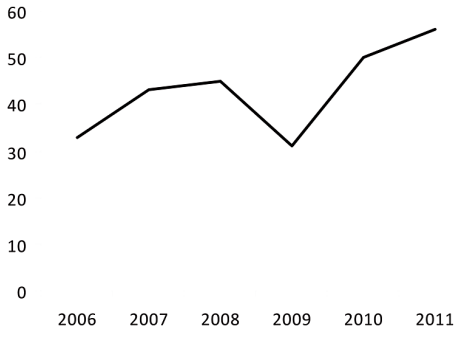


*Figure 2. Per cent "unnecessary" ICA for the indication stable cornary disease*

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