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Multimodality imaging in prevention of coronary artery disease

Ties, Daan

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General discussion

GENERAL DISCUSSION

The aim of this thesis was to explore the potential of a novel multimodality cardiac imaging strategy in prevention of acute myocardial infarction (AMI) and sudden cardiac death (SCD), with a special focus on creating synergy between existing and novel prevention strategies. Considering the still high cardiovascular disease (CVD) mortality and morbidity and the expected increase in CVD-related healthcare costs, improved strategies for AMI and SCD prevention are warranted to control the increasing CVD burden for society in the future (1).

Early identification of very-high-risk individuals and personalized powerful treatment

Professional practice guidelines for prevention of AMI and SCD currently focus on lifestyle interventions and prescription of blood pressure- and cholesterol-lowering drugs guided by risk assessment. One of the downsides of this strategy is that a high residual risk of AMI (causing irreversible myocardial damage leading to symptoms, demand for care and recurrent hospitalizations) and SCD remains present despite lifestyle modification and preventive drug therapy (2–4). Myocardial ischemia caused by obstructive coronary artery disease (OCAD) indicates very high risk of incident AMI and SCD in asymptomatic individuals and is an excellent target to identify a very-high-risk population, who may require more urgent management to prevent AMI and SCD (5). However, highly effective detection of low-prevalent subclinical OCAD in the general population is challenging. Combining the characteristics of different cardiac imaging techniques in a multimodality imaging strategy is promising to effectively identify asymptomatic individuals with critical disease in the general population (6,7).

In **Chapter 2**, the study protocol of the EARLY-SYNERGY trial is described. The EARLY-SYNERGY trial aimed to investigate a multimodality cardiac imaging approach combining non-contrast cardiac computed tomography (CT) to quantify the coronary artery calcium score (CACS) and, in selected individuals with high CACS, cardiac magnetic resonance myocardial perfusion imaging (CMR-MPI) to early diagnose subclinical OCAD and other critical disease in the general population. CT-based CACS was chosen as a primary test based on previous evidence that the CACS predicts the presence of OCAD in symptomatic patients (8). CACS of 300 or higher is associated with a 5-year event rate of approximately 10% (8). Therefore, a CACS of 300 or higher was chosen as an entry criterion in EARLY-SYNERGY to achieve sufficient statistical power to show a potential reduction in CVD event rate by early OCAD diagnosis and guideline-based treatment. The results of the first stage of the EARLY-SYNERGY trial, described in **Chapter 3**, revealed that OCAD was observed in 22.8% of asymptomatic individuals with increased CACS. Approximately 30% of these individuals had one or more critical disease requiring guideline-based management, and up to 35.6% of individuals with a CACS >1000 had OCAD. The EARLY-SYNERGY trial is the first to prove that a multimodality imaging strategy, taking CT for CACS quantification as a primary test, can increase efficiency of early critical disease detection. However, it remains uncertain whether early guideline-based treatment of subclinical OCAD results in improved clinical outcome. To date, only limited evidence on the usefulness of early detection and treatment of OCAD in asymptomatic individuals is available

(9). Large-scale randomized-controlled clinical trials comparing any early guideline-based OCAD treatment versus no early detection and no treatment at all have not yet been performed in asymptomatic individuals. Nevertheless, clinical practice guidelines currently recommend to treat myocardial ischemia caused by OCAD affecting 10% or more of the left ventricle with optimal medical therapy (OMT) and/or revascularization, irrespective of the presence of symptoms (10,11). This recommendation is largely based on data from randomized-controlled clinical trials (RCTs) reporting improved clinical outcome and reduction in ischemic size by OMT alone or in combination with revascularization in symptomatic patients (12–16). Besides potentially allowing physicians to intervene, imaging evidence of serious disease also increases the urge to act by patients, for instance by adopting lifestyle changes or adhering to preventive drug therapy, and could in this way contribute to AMI and SCD prevention (17). Whether early OCAD diagnosis and guideline-based treatment improves clinical outcome of asymptomatic individuals however remains to be determined by RCTs. The EARLY-SYNERGY trial as described in **Chapter 2** will be the first RCT to evaluate whether early OCAD diagnosis and guideline-based treatment, either by OMT and/or revascularization, improves clinical outcome in comparison to no OCAD evaluation and treatment (i.e., the natural course of coronary atherosclerosis) in asymptomatic individuals with increased CACS. Further studies evaluating the current and other multimodality imaging approaches (f.e., with lower or higher CACS entry criteria or with other cardiac imaging techniques) are warranted to enhance potential implementation of a multimodality imaging approach.

Improving the multimodality imaging strategy

It is essential to minimize the number of 'unnecessary' referrals for diagnostic tests, in order to prevent harm by undergoing these tests and subsequent unnecessary treatments caused by false positive test results. **Chapter 4** revealed that increased CACS and male sex were the only independent predictors of subclinical OCAD, whereas clinical risk factors were not associated with the presence of OCAD in these individuals. The findings of this study support the hypothesis that CT for CACS quantification is an ideal first-line test, not only to establish the need for preventive interventions as a first step, but also to guide further diagnostic work-up, for instance by CMR-MPI, to evaluate the presence of critical disease in an early stage. One way to prevent unnecessary referral is by performing an extra, preferably simple and inexpensive test to decide on performing CMR-MPI in individuals with increased CACS. To this end, the role of several conventional circulating biomarkers in referring asymptomatic individuals with increased CACS for additional diagnostic testing was investigated in **Chapter 5**. Conventional circulating biomarkers showed modest diagnostic performance for OCAD detection in the EARLY-SYNERGY population. OCAD was frequently present in individuals with low biomarker levels and was even sometimes present in individuals with biomarker levels below the limits of detection. Missing individuals with OCAD implicates a loss in benefit of multimodality imaging and less prevented AMI and SCD, reducing the benefit of such an approach. Conventional circulating biomarkers are not able to accurately guide referral to CMR-MPI for subclinical OCAD evaluation and it is therefore unlikely that circulating biomarkers could improve referral to further diagnostic testing. Future studies evaluating

other tests as gatekeepers to further diagnostic testing, for instance novel circulating biomarkers detected by proteomics, are warranted to further investigate potential improvement of a multimodality imaging strategy.

Current risk-based approaches in CVD prevention: the starting point?

Clinical practice guidelines on CVD prevention currently recommend to decide on initiation of preventive therapy based on CVD risk estimation (18,19). CVD risk assessment is based on the presence of traditional CVD risk factors collected in clinical risk prediction models (RPMs). RPMs are often developed and tested in one single population and most RPMs are not externally validated by the developing or independent researchers (20). In **Chapter 6**, the performance of a wide spectrum of RPMs for the prediction of incident CVD manifestations was external validated in three large independent cohorts. RPMs showed reasonable performance, but generally overestimated the risk of CVD manifestations on external validation. In general, RPMs ignore specific factors that contribute to individual CVD risk, such as socioeconomic status and ethnicity (21–27). RPMs are therefore often unable to accurately estimate CVD risk on an individual level. RPM performance on an individual level could be improved by specifically updating and revalidating RPMs for distinct target populations. Automated iterative feedback of clinical patient characteristics and corresponding outcomes to RPMs, for instance embedded in hospital systems or national health registries, might allow for efficient updating of RPMs and improved RPM performance on an individual level (20). Comprehensive technological requirements and privacy issues however make this a challenging approach. RPMs could be used as the gatekeeper to multimodality imaging (i.e., do not test individuals with low or high CVD risk estimated by RPMs), but this has a risk of unjustly withholding further testing in individuals in whom RPMs inaccurately estimate CVD risk.

Improved risk assessment in the general asymptomatic population

Inevitable downside of clinical risk scores is that clinical risk scores only assess risk factors indirectly affecting CVD progression at a single moment in time and are unable to early diagnose CVD (28–30). The CACS is a direct measure of early CVD presence and is strongly associated with incident AMI and SCD (8,31). In contrast to clinical risk scores, CACS reflects lifetime exposure to all atherosclerosis-generating factors. CACS is currently only applied as an arbitrator in asymptomatic individuals with intermediate CVD risk estimated by clinical risk scores (18,19). More generalized use of non-contrast cardiac CT imaging to quantify CACS allows for accurate risk stratification and personalized treatment initiation in a broad asymptomatic population (32). In **Chapter 7**, various selection methods to effectively identify individuals from the general population with a high CACS, who could benefit from early CT and further diagnostic imaging, were investigated. Pre-screening based on an increased Systematic COronary Risk Estimation 2 (SCORE2) risk or increased urine albumin excretion left many asymptomatic individuals from the general population with high CACS unrecognized, whereas pre-screening by presence of at least one traditional CVD risk factor identified nearly

all with a high CACS. On the other hand, selection based on presence of at least one traditional CVD risk factor resulted in many without high CACS receiving 'unnecessary' CACS imaging, potentially increasing harm of such a strategy. Several pre-screening methods evaluated in **Chapter 7** could be executed from home, which could improve accessibility and effectiveness of such approaches. Digital health applications, for instance on smartphones, are increasingly being used by the public to monitor health (33–35). In addition, more and more smartwatches and -phones with advanced blood pressure and heart rate monitoring systems are commercially available (33–35). The development of a home-based pre-screening approach, supported by health monitoring systems on smartwatches and –phones, could be a promising approach to early detect individuals who benefit from further early diagnostic testing, and improve accessibility to preventive care. The ROBINSCA trial, an RCT comparing CACS-based screening against SCORE-based screening and no screening in the general population, will provide proof on the benefit and harms of more generalized use of CT for CACS quantification and provide more insights in the optimal selection of individuals for CT (36). **Chapter 7** provides important evidence on the shifting balance between the amount of required CT-scans and amount of observed individuals with a high CACS for various methods to select individuals from the general population for CACS imaging. The data of this study could be used by future studies performing further cost-utility evaluations to discover the optimal application of CACS imaging in the general population. To enable more generalized use of CT-based CACS in CVD prevention, high throughput of individuals for CACS imaging should be enhanced. Calculating the CACS using the Agatston method is time-consuming (37). Artificial intelligence (AI)-based automatic CACS quantification showed excellent correlation and risk classification compared to semi-automatic CACS quantification by commercially available software (38,39). Importantly, AI-based CACS quantification was less time-demanding than semi-automatic CACS quantification (38). CT for CACS quantification is simple, non-invasive, relatively inexpensive and can be performed without contrast agent. Non-contrast CT imaging combined with AI-based CACS quantification could therefore be executed very fast at low costs and is therefore ideal as a high-throughput first test to accurately estimate CVD risk in the general population.

Optimization of impact evaluation

Reducing potential harm of extra diagnostic and therapeutic interventions in prevention of AMI and SCD is essential to allow widespread implementation. To this end, **Chapter 8** aimed to evaluate the diagnostic performance of quantitative flow ratio (QFR) for OCAD evaluation in patients with a suspicion of OCAD presence. Fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) are generally performed during invasive coronary angiography (ICA) to confirm OCAD diagnosis in individuals with a suspicion of OCAD after non-invasive imaging (11,12,40,41). FFR and iFR can assess hemodynamic significance of coronary artery stenosis by insertion of pressure wires in the coronary arteries during ICA. QFR is able to assess hemodynamic significance of coronary stenosis without using pressure wires and without inducing hyperemia by administering adenosine intracoronary, thereby reducing complication risk of this procedure. QFR showed good diagnostic performance and high sensitivity. QFR

could therefore potentially be used as a gatekeeper to FFR during ICA and could reduce the number of wire-based FFR procedures and associated harms of downstream diagnostic procedures after OCAD evaluation by CMR-MPI in AMI and SCD prevention. However, non-inferiority of QFR-based treatment versus FFR-based treatment remains to be proven by large-scale RCT's.

Potential use of QFR as a gatekeeper to FFR is an example of a strategy to reduce potential harm and the costs of early subclinical OCAD evaluation. Strategies to replace CMR-MPI by other potentially less costly but equally accurate diagnostic tests could also reduce the costs, both monetary and nonmonetary. Coronary CT angiography (CCTA) could be performed simultaneously with non-contrast CT for CACS quantification to evaluate subclinical OCAD presence (42). However, CCTA is unable to accurately determine hemodynamic significance of coronary stenosis and has inferior diagnostic performance for OCAD evaluation compared to CMR-MPI (43). In addition, CCTA involves relatively high radiation burden (2.5-5 mSV) (44), which is less desirable in a preventive setting. CT-FFR is a promising tool to perform hemodynamic assessment by CCTA, but clinical implementation has been limited so far, partly caused by even higher radiation burden compared to conventional CCTA (45). Single-photon emission computed tomography (SPECT) has lower sensitivity and positron emission tomography (PET) is less widely available compared to CMR-MPI (43).

Effectiveness of preventive measures is currently often assessed by hard outcomes based on physicians ideas of patient demands and not personal health preferences of the individual. Individuals or patients may value importance of health outcomes differently from physicians (46). Optimal assessment of quality of life is essential to reliably measure the impact of preventive interventions and to avoid falsely rejecting potent preventive interventions caused by not accurately measuring what patients or individuals truly find important. Putting the patient central in health outcome assessment and taking into account personal preferences in health aspects could improve health outcome assessment. Besides impact on prevention of AMI and SCD and impact on clinical outcome, health economic impact is an important aspect of new prevention strategies. An improved cost-utility ratio for multimodality imaging when compared to no multimodality imaging (i.e., the natural course of coronary atherosclerosis) is highly important to allow potential implementation of such a strategy in prevention practice in the future. The cost-utility ratio is the ratio of incremental monetary costs and incremental quality-adjusted life years (QALYs). Incremental costs of the multimodality imaging strategy include costs for additional diagnostic procedures and additional therapeutic interventions, minus costs saved by a reduction in expensive treatments and urgent hospitalizations caused by AMI and SCD and by a reduction in productivity losses. Incremental QALYs include the QALYs gained by prevention of AMI and SCD minus the QALYs lost by living with early knowledge of critical disease presence. As described in **Chapter 2**, cost-utility analyses are part of the EARLY-SYNERGY trial and will be conducted on completion of the gathering of long-term follow-up data. In **Chapter 9**, the development of a novel patient-centered preference-based patient reported outcome measure (PROM), specifically designed for CVD patients, is described. This novel PROM was specifically designed to tackle issues of current PROMs (i.e.,

generic rather than disease-specific, neglecting personal preferences for aspects of health, development without patient input) and could therefore improve quality of life assessment. Future RCT's aiming to perform quality of life assessments could already use this patient-centered preference-based PROM alongside other conventional PROMs to raise the odds of adequately measuring the impact of interventions. Validation of this novel tool against existing PROMs, such as the 36-Item Short Form Health Survey (SF-36), should be performed to provide definite proof that this novel PROM improves outcome assessment.

Conclusions and future perspectives

Despite uptake of CVD prevention in clinical practice, CVD burden for society is expected to increase over the next decades. Improvement of the current risk-based approach is essential to more effectively prevent AMI and its sequelae causing reduced quality of life and high healthcare costs in the general asymptomatic population. More generalized use of CT-based CACS instead of clinical risk scoring could allow for early evaluation of the presence of CVD, potentially leading to better risk stratification and personalized preventive drug therapy initiation. RCT's evaluating the benefits and harms of more generalized use of CACS imaging or CACS screening in the general asymptomatic population are warranted. The ROBINSCA trial will provide first evidence on this topic (36). Further diagnostic work-up to early detect advanced CVD and more powerfully treat very-high-risk individuals is promising to further improve AMI and SCD prevention. The first results of the EARLY-SYNERGY trial prove that early detection of subclinical OCAD by a multimodality imaging approach combining CT-based CACS imaging and CMR-MPI is feasible. Whether early powerful treatment of early detected critical disease improves clinical outcome of asymptomatic individuals remains to be confirmed by the second stage of the EARLY-SYNERGY trial and other future RCT's. The long-term follow-up data of the EARLY-SYNERGY trial will provide first evidence on the benefit of early OCAD evaluation, but additional large-scale RCT's and population-screening trials investigating the benefit, harms and cost-effectiveness of early OCAD evaluation are warranted to provide further support for implementation in clinical practice or even in a population-based screening setting. To reduce costs in order to improve the cost-utility ratio of early OCAD evaluation, further optimization of a multimodality imaging strategy might be required. Conventional cardiac circulating biomarkers and circulating biomarkers reflecting cardiovascular risk factors are unable to accurately detect subclinical OCAD and are therefore unlikely to improve the multimodality imaging strategy. Other strategies to optimize referral of asymptomatic individuals for further imaging, for instance based on sex-specific CACS cutoffs, might aid in improving the cost-utility ratio and reducing harm of early OCAD evaluation. QFR to replace FFR in the further clinical work-up of asymptomatic individuals is a promising tool to reduce harms of downstream subclinical OCAD evaluation. RCT's comparing clinical outcome after QFR- versus FFR-based treatment in both symptomatic and asymptomatic individuals are warranted to establish standard use of QFR in clinical practice. Accurate quality of life assessment is essential to perform adequate evaluation of the impact of new interventions, such as multimodality imaging in prevention of AMI and SCD. The novel CVD-specific patient-

centered preference-based PROM developed here could improve quality of life assessment, but should be compared head-to-head against existing PROMs to provide definitive proof.

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