Coronary artery calcium scoring in individuals at risk for coronary artery disease

Vonder, Marleen; van der Aalst, Carlijn M.; de Koning, Harry J.

Published in:
British journal of radiology

DOI:
10.1259/bjr.20190880

Publication date:
2020

BJR

https://doi.org/10.1259/bjr.20190880

Received:
16 October 2019

Accepted:
27 January 2020

Cite this article as:
Vonder M, van der Aalst CM, de Koning HJ. Coronary artery calcium scoring in individuals at risk for coronary artery disease: current status and future perspectives. *Br J Radiol* 2020; **93**: 20190880.

IMAGING PATIENTS WITH STABLE CHEST PAIN SPECIAL FEATURE: REVIEW ARTICLE

Coronary artery calcium scoring in individuals at risk for coronary artery disease: current status and future perspectives

[1]MARLEEN VONDER, PhD, [2]CARLIJN M VAN DER AALST, PhD and [2]HARRY J DE KONING, MD, PhD

[1]Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[2]Department of Public Health, Erasmus MC – University Medical Center Rotterdam, Rotterdam, The Netherlands

Address correspondence to: Dr Marleen Vonder
E-mail: *m.vonder@umcg.nl*

ABSTRACT

The aim of this review is to provide clinicians with an overview of the role of coronary artery calcium (CAC) scoring across the spectrum ranging from asymptomatic individuals to chronic chest pain patients. We will briefly introduce the technical background of CAC scoring, summarize the major guidelines per type of patient at risk and discuss latest research with respect to CAC. Finally, the reader should be able to determine when CAC scoring is indicated or may be of added value.

INTRODUCTION

Worldwide over 30% of people are suffering from cardiovascular disease, with annual mortality rate over 17 million.[1] Ways to reduce this burden is by early detection of subclinical disease and adequate use of diagnostic testing and corresponding treatment. Recently, the World Health Organization updated the cardiovascular risk charts used for 10 year risk prediction models for fatal and non-fatal cardiovascular disease.[2] This should allow to identify more accurately the individuals at increased risk for cardiovascular disease based on traditional risk factors. Traditional risk factors (like age, gender, blood pressure, cholesterol levels, smoking status) are used in many of the current preventive risk assessment methods like the American Cardiovascular Risk Calculator or the European Heart SCORE.[3,4] In the last decades, the use of coronary artery calcium (CAC) score has been investigated thoroughly to determine the overall plaque burden in subclinical and symptomatic individuals. Nevertheless, CAC scoring has not a clear and established role in the prevention, diagnosis and work-up of coronary artery disease (CAD) patients so far.

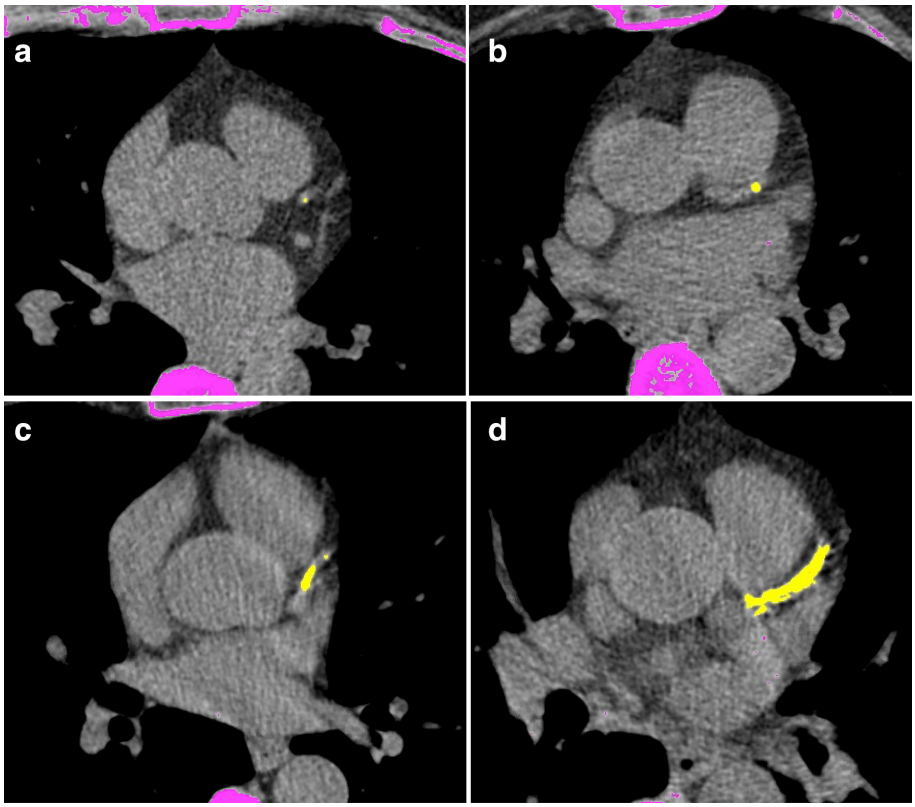
The aim of this review is to provide clinicians with an overview of the current role of CAC scoring across the spectrum of asymptomatic individuals to chronic chest pain patients. We will briefly introduce the technical background of CAC scoring, summarize the major guidelines per type of individual at risk for CAD and discuss latest research with respect to CAC. Finally, the reader should be able to determine when CAC scoring is indicated or may be of added value.

CORONARY ARTERY CALCIUM SCORING

Coronary calcifications can be relatively easy determined with non-contrast CT and analyzed with several (semi) quantitative methods. For a dedicated CAC scan, the acquisition should be performed at 120 kVp with ECG-gating and use of tube current modulation that results in noise-levels <23 Hounsfield unit to preserve adequate image quality but a radiation dose as low as possible.[5,6] Images should be reconstructed with filtered-back projection, a fixed field of view and a slice-thickness of 3.0 mm. Images can be analyzed with dedicated software to quantify the amount of CAC by means of the Agatston score method, or by semi-quantifying the amount of CAC by visual assessment, see Figure 1. In March 2018 The Society of Cardiovascular Computed Tomography (SCCT) released a Coronary Artery Calcium Data and Reporting System document on how to report and interpret these quantitative and visual measures of CAC for clinicians.[7]

In general, state-of-the-art CT systems allow for scanning with lowest dose reduction and highest temporal resolution

Figure 1. Example of asymptomatic individuals with a) very mild (visible calcification 1 AU / total CAC was 5 AU), (b) mild (29 AU/ 61 AU), intermediate (169 AU / 230 AU) and severe (1000 AU / 2230 AU) calcifications based on non-contrast cardiac CT. AU, Agatston Unit; CAC, coronary artery calcium.



by covering the heart in a single heart beat and thus limiting cardiac motion artifacts. In the last decade, numerous attempts for dose reduction in CAC scanning with various techniques have been made, with current effective doses ranging from 0.9 to 4.8 mGy to potentially reduced doses of 0.1–3.0 mGy.[8] Yet, the impact of the reduced-dose protocols on CAC quantification should be carefully determined before these protocols can be implemented in clinical practice. The Agatston score method and its risk stratification categories [0, 1–99, 100–399, ≥ 400 Agatston Unit (AU)] were originally used and extensively validated based on electron beam CT acquisitions.[9–11] For electron beam CT studies, acquisition and reconstruction settings were highly standardized, whereas for more recent multidetector CT or dual-source CT studies, information about parameter settings was often poorly documented or parameter settings varied significantly between systems and hospitals. Ultimately, these variations could impact the final management in individuals at risk for CAD.

INDIVIDUALS AT RISK

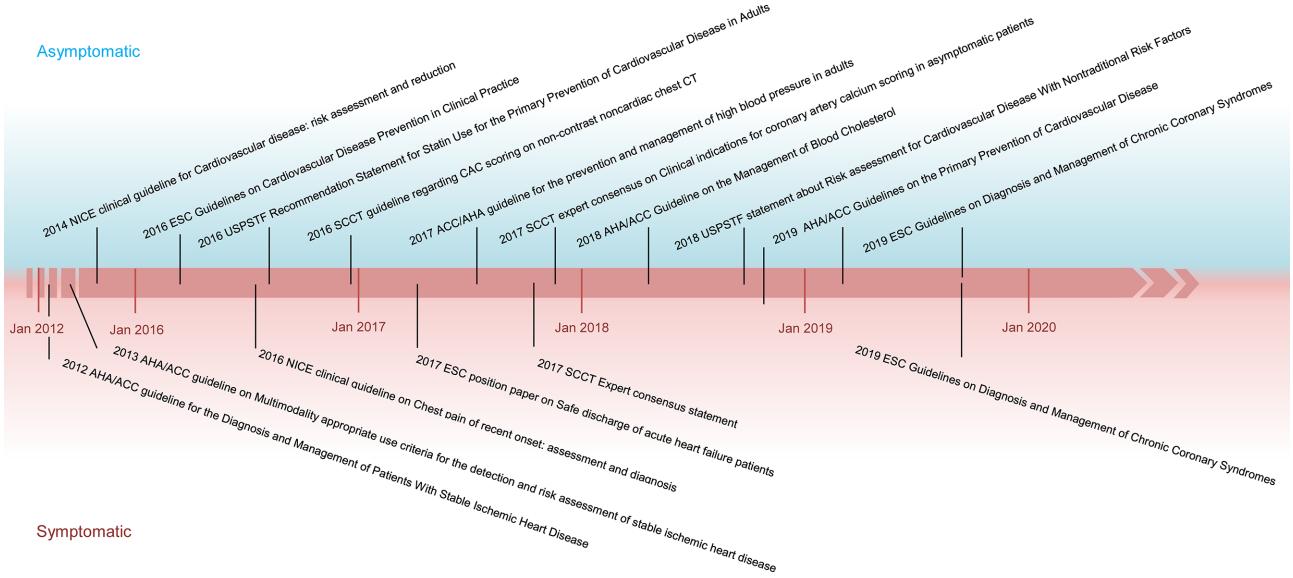
In general, every individual is at risk of developing CAD during their lifetime. Depending on the group or population's characteristics (traditional risk factors and/or (a)typical angina complaints, diagnosed with CVD) the likelihood of having (sub)clinical CAD, the pre-test probability (PTP), can differ significantly between individuals or patients. The majority of recommendations of current CVD guidelines depend on a correct estimation of this PTP in which CAC scoring can play an important role. We therefore choose to distinguish two major groups: asymptomatic individuals and symptomatic patients, see Figure 2. Nevertheless, smaller more specific subgroups can be distinguished as well. In the following paragraphs, the current guidelines are reviewed for each group.

Asymptomatic individuals

According to the **2018 AHA/ACC** *Guideline on the Management of Blood Cholesterol* the CAC score can be of added value if a decision about statin therapy is uncertain.[12] This is reasonable in adults of 40–75 years of age at a 10 year ASCVD risk of ≥7.5% to <20% estimated by Pooled Cohort Equations and LDL-C levels ≥ 70–189 mg dl^{-1}, or selected borderline-risk adults (5% to <7.5% 10 year ASCVD risk). However, CAC scan is not recommended in individuals that have any additional high-risk conditions like diabetes, family history of premature coronary heart disease (CHD), or persistent smoking, since CAC score should not be used to reclassify these individuals to lower risk categories.

In the case of a zero CAC score, an individual can be reclassified to a lower risk category and the statin therapy can be withheld or post-poned with reassessment after 5–10 year. Whereas for a positive CAC score, it is advised to initiate statin therapy especially for patients ≥55 years of age, and for all ages in case of CAC score of ≥100 or in ≥75th percentile. For patients of 76–80 years, a CAC score *may be* reasonable to reclassify patients to a lower risk category and withheld statins in case of a zero score.

Figure 2. Overview of guidelines and statements regarding the role of CAC scoring in individuals at risk. ACC/AHA: American College of Cardiology/American Heart Association, ESC: European Society of Cardiology, NICE: National institute for Health and Care Excellence SCCT: Society of Cardiovascular Computed Tomography, USPSTF: US Preventive Services Task Force.



Nevertheless, the guideline strongly recommends to first have a clinician-patient risk discussion considering pro and cons of statin therapy before considering additional CAC scanning. Of note, the guideline discourages CAC measurement in patients already treated with statins. Likewise, for adults of 40–75 with a high 10 year risk (>20%) CAC measurement is not recommended.

The new **2019 guideline of the AHA/ACC** regarding the *Primary Prevention of Cardiovascular Disease* in adults reports identical recommendations.[3,13] The Pooled Cohort Equations, used for the risk calculation, have shown to overestimate the 10 year ASCVD risk, and therefore it is reasonable to use additional risk-enhancing factors, like the CAC score, to guide decisions about preventive interventions. Of note, the guideline explicitly states "CAC measurement is not intended as a *screening* test for all but rather may be used as a decision aid in select adults." In addition to help guide shared decision-making about statin, this guideline also mentions the potential of CAC score in the guidance of decision-making of aspirin. CAC is not mentioned in relation to treatment of hypertension. The **2017 ACC/AHA** *guideline for the prevention and management of high blood pressure in adults* states that there is inadequate information about the role of CAC score in improving the management or treatment of hypertension, which prevents the use of CAC in the treatment of hypertension.[14]

The **European Society of Cardiology (ESC)** reported in their **2016 guidelines** on *Cardiovascular Disease Prevention in Clinical Practice*, that CT CAC score can be regarded as a risk modifier that is likely to have reclassification potential.[4] The ESC recommends to systematically determine the CVD risk with the SCORE method in individuals at increased risk, *i.e.* with family history of premature CVD, familial hyperlipidemia, major CV risk factors (such as smoking, high BP, DM or raised lipid levels) or comorbidities increasing CV risk. Besides, the risk may be assessed in men of >40y and in female of >50y. Subsequently, the CAC scoring may be considered as a risk modifier and thus may be used additionally in CV risk assessment in subjects with calculated SCORE risks around 5% or 10% thresholds. Unlike the 2018 AHA/ACC guideline, the 2016 ESC guideline does not provide cut-off values for CVD risk based on CAC score, nor does it state how the (SCORE) risk can be reclassified. Hence, the management of individuals stratified for CVD risk by the SCORE method and additional CAC remains uncertain.

The **2019 ESC** guidelines for *the Diagnosis and Management of Chronic Coronary Syndromes* states that CAC score may be considered as a risk modifier in the CVD risk assessment, since it has a net reclassification improvement of 66% over traditional risk factors.[15] Although the risk prediction can be improved, no data have demonstrated that applying an optimized management leads to improved prognosis. Therefore, the guideline does not give recommendations based on CAC score for asymptomatic subjects. Besides, the guideline explicitly states that the routine use of other imaging tests for CAD, like coronary CT angiography (cCTA) or functional imaging for ischemia, are not recommended in asymptomatic low-risk non-diabetic individuals.

Contrary to the 2019/2018 AHA/ACC and 2018 ESC guidelines, the **2018 US Preventive Services Task Force (USPSTF)** statement about *Risk assessment for Cardiovascular Disease With Nontraditional Risk Factors* states that CAC score results only in small improvements in discrimination and risk reclassification.[16] The USPSTF concludes that there is inadequate evidence that management based on the CAC score, in addition to current risk factors, leads to reduced incidence of CVD morbidity and mortality. In accordance with this guideline, the **2016 USPSTF** *Recommendation Statement for Statin Use for the Primary Prevention of Cardiovascular Disease in Adults* does not mention the use of CAC to alter statin use.[17]

The National Institute for Health and Care Excellence (**NICE**) recommends in their clinical *Cardiovascular disease: risk assessment and reduction* guideline of **2014** to use the QRISK2 tool to assess CVD risk in individuals 40–85 years. Again, this guideline does not mention the use of CAC score in the risk assessment.[18] However, if the QRISK2 tool is used for medication treatment decision, the physician should take other factors into account that are not included in the risk tool when the decision is near the threshold for treatment. The CAC score might be considered as one of these factors.

The **2017** expert consensus of the **SCCT** recommends that it is appropriate to determine the CAC score in asymptomatic individuals under almost similar conditions as the AHA/ACC 2019 and 2018 guidelines in the process of shared decision-making.[3,12,13,19] Contrary to the AHA/ACC guidelines, the 2017 SCCT expert opinion states that CAC could be determined selectively in <5% ASCVD risk group for example in individuals with a family history of premature CAD. Moreover, it reports that it may be appropriate to consider repeated CAC score after 5 years and 3–5 years for individuals with baseline CAC score of respectively 0 and >0.

Concluding, individuals at intermediate risk according to traditional risk factors may be reclassified by the CAC score and help in the shared decision-making about statin use, although some guidelines oppose this, see Table 1. Besides, management based on CAC score alone is not recommended by any of the guidelines.

Symptomatic individuals

Relatively few societies and their guidelines report on the role of CAC score in symptomatic individuals who have not been diagnosed with CHD before or in patients with long-standing diagnosis of chronic coronary syndrome.

In the past 7 years, the **AHA/ACC** has published multiple guidelines on the diagnosis and management of ischemic heart disease.[13,20–22] CAC is not mentioned in any of the recent guidelines, except for the **2013** guideline on *Multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease*.[21] In this guideline, the CAC score is deemed as rarely appropriate in the diagnosis of ischemic heart disease, even regardless of the PTP. This is in contrast with the **2012** guideline for the *Diagnosis and Management of Patients With Stable Ischemic Heart Disease*, which states that CAC score may be considered for patients with a low to intermediate PTP of obstructive ischemic heart disease considered.[22] However, at that time, there was limited evidence about the negative predictive value of CAC in symptomatic individuals.

Similar to the 2013 AHA/ACC guidelines, the **2019 ESC** *Guideline for the diagnosis and management of chronic coronary syndromes* discourages CAC detection to identify individuals with obstructive CAD.[15] However, if the CAC score is already known, this knowledge should be used in determining the PTP. On the other hand, the same guideline warns that a zero CAC score cannot exclude obstructive CAD (although prevalence is <5%, annual MI risk <1%) and the presence of any CAC is a weak predictor of obstructive CAD, especially in young and acute patients. Similarly, the **2017 ESC** position paper on *Safe discharge of acute heart failure patients* does not report on the use of CAC score.[23] Nevertheless, a CAC scan could be used to determine whether cCTA is useful. cCTA is not recommended with CAC score >400 since the prevalence of obstructive CAD in symptomatic patients with this score is high.[15] However, this is less of a problem in patients with low heart rates (<65 bmp) and when modern CT systems are used. In the case of severe calcifications and a CTA is performed, physicians could refrain from stenosis quantification in areas of extensive calcifications and call the test "unclear."[24] Finally, a CAC score could be used as one of the factors among others (exercise ECG, traditional risk factors of CVD, left ventricular dysfunction and/or resting ECG changes) to determine the clinical likelihood of CAD. This clinical likelihood is then used to select the appropriate diagnostic imaging test.

One of the often-used diagnostic imaging tests is cCTA. The **2017 Expert consensus statement of the SCCT** reports that it may be appropriate to include CAC scanning in cCTA protocols in symptomatic patients without established CAD undergoing CTA.[19] One of the advantages of CAC scan is that it provides a quantitative risk assessment and disease progression could be determined. Apart from the CAD evaluation, a CAC scan prior to cCTA could also have some practical and dose-saving advantages. A CAC scan with high amount of CAC may impact the decision whether or not to proceed with the cCTA. Besides, based on the CAC scan, the z-axis ranges of the cCTA can be optimized, reducing the radiation dose of the cCTA scan. In the end, the benefits of CAC scan should be balanced against the radiation dose of the scan.

In big contrast to the AHA/ACC, ESC and SCCT guidelines, the **2016 NICE** clinical guideline on *Chest pain of recent onset: assessment and diagnosis* discarded the calculation of PTP in the diagnostic work-up of suspected obstructive CAD.[25] The clinical guideline recommends to perform cCTA in all individuals with angina or with non-angina but with abnormal ECG. The predecessor **2010 NICE** guideline did recommend CAC score as a gatekeeper before cCTA in symptomatic individuals with low PTP, but this is currently no longer recommended.[26] One of the important arguments for not performing a CAC scan before the cCTA is the added radiation dose and the debated negative predictive value of zero-score for obstructive CAD. Moreover, the NICE argued that even in the case of high amount of CAC, with current modern CT scanners the cCTA contains valuable information with high accuracy.[27]

Concluding, the NICE very clearly eliminated the use of the CAC score in symptomatic patients whereas the guidelines of AHA/ACA, ESC and SCCT are less stringent, see Table 2.

Specific subgroups at risk

In addition to the broad group of asymptomatic and symptomatic individuals at risk previously described, CAC score could be of added value in several specific subgroups. It has been suggested that CAC may also reclassify lower risk female (7.5%

Table 1. CAC scoring in asymptomatic individuals

Year	Author	Society	Guideline	Specified group	Assessment of CAC score
2019	Knuuti et al.[15]	ESC	Guidelines for the diagnosis and management of chronic coronary syndromes	Asymptomatic adults	May be reasonable
2019	Arnett et al.[13]	AHA/ACC	Guideline on the primary prevention of cardiovascular disease	Adults at intermediate risk (≥7.5% to <20% 10 year ASCVD risk) or selected adults at borderline risk (5% to <7.5% 10 year ASCVD risk)	Is reasonable
2018	Grundy et al.[12]	AHA/ACC	Guideline on the management of blood cholesterol	Asymptomatic adults, 40–75 y without diabetes and with LDL-C levels ≥ 70–189 mg dl^{-1} (≥1.8-4.9 mmol l^{-1}), at a 10 year ASCVD risk of ≥7.5–19.9%, or selected borderline-risk adults	Is reasonable
2018	Curry et al.[16]	USPSTF	Recommendation statement: Risk assessment for cardiovascular disease with nontraditional risk factors	Asymptomatic adults without history of CVD	Is not recommended
2017	Whelton et al.[14]	ACC/AHA	Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults	Asymptomatic adults	Is not recommended
2017	Hecht et al.[19]	SCCT	Clinical indications for CAC; Expert consensus statement	Asymptomatic individuals without clinical ASCVD who are 40–75 years of age in the 5–20% 10 year ASCVD risk group and selectively in the <5% ASCVD group	Is reasonable
2016	Piepoli et al.[4]	ESC	European guidelines on cardiovascular disease prevention in clinical practice	Asymptomatic individuals at increased CV risk with calculated SCORE risks around 5% or 10% thresholds	May be reasonable

ACC/AHA, American College of Cardiology/American Heart Association; CAC, Coronary artery calcium; CVD, Cardiovascular disease; ESC, European Society of Cardiology; SCCT, Society of Cardiovascular Computed Tomography; STR, Society of Thoracic Radiology; USPSTF, US Preventive Services Task Force.

Table 2. CAC scoring in symptomatic individuals

Year	Author	Society	Guideline	Specified group	Assessment of CAC score
2019	Knuuti et al.[15]	ESC	Guidelines for the diagnosis and management of chronic coronary syndromes	Symptomatic patients with suspected CAD	Is not recommended
2017	Hecht et al.[19]	SCCT	Clinical indications for coronary artery calcium scoring in (a)symptomatic patients	Symptomatic patients without established CAD undergoing CTA	May be reasonable
2016	NICE[25]	NICE	Clinical guideline [CG95]: Chest pain of recent onset: assessment and diagnosis	Symptomatic patients (with chest pain)	Is not recommended
2013	Wolk et al.[21]	AHA	Multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease	Symptomatic patients	Rarely appropriate
2012	Fihn et al.[22]	AHA	Guideline for the diagnosis and management of patients with stable ischemic heart disease	Patients with stable ischemic heart disease	May be reasonable

ACC/AHA, American College of Cardiology/American Heart Association; CAC, Coronary artery calcium; CAD, Coronary artery disease; ESC, European Society of Cardiology; NICE, National Institute of Health and Care Excellence; SCCT, Society of Cardiovascular Computed Tomography.

10 year risk), younger adults (<45 years of age) and older adults (≥75 years of age).[3,12,13,19,28]

For instance, CAC scanning may also be considered in females with breast arterial calcifications (BAC) on their mammogram[19,28] or in younger and elder individuals since the disadvantages of CAC scanning are reducing with the development of (ultra)low-dose CAC CT screening and decreasing costs.[8,12] Still, more data are needed to support the added value of CAC score in these subgroups.

Besides the intentional CAC scan in the above described groups, CAC should also be evaluated on chest CT examinations according to the 2016 SCCT guideline regarding *CAC scoring on non-contrast noncardiac chest CT*.[29] This guideline states that CAC should at least be estimated (mild, moderate severe) or ordinally or quantitatively assessed.

ONGOING STUDIES AND RECENT RESEARCH OUTCOMES

Based on evidence of the past years, the AHA/ACC and ESC guidelines recommend that CAC score may be of added value as risk modifier in the CVD risk assessment in asymptomatic individuals at intermediate risk. Like the USPSTF, all guidelines do recognize the lack of evidence that management based on the CAC score leads to reduction in CVD. Moreover, according to today's guidelines, CAC should not be used as a screening tool.

The currently ongoing ROBINSCA trial is a first and only population-based randomized controlled screening trial for cardiovascular diseases (n = 43,447), which contains CAC scoring in one of the intervention arms.[30] The trial goes beyond the current guidelines: it does not only include individuals at intermediate risk that were identified opportunistically, but is a population-based screening trial. This trial will provide evidence whether population-based screening based on high CVD risk (determined by CAC scoring) followed by preventive treatment is (cost-) effective in reducing CHD-related morbidity and mortality compared to screening with traditional risk factors or no screening. Up to now, over 25,000 asymptomatic participants have been screened with the SCORE method or CAC scoring (1:1) and risk stratification was performed.[31] Based on the CAC scoring, significantly less males and females were classified at intermediate and high-risk compared to the SCORE model. Therefore, less preventive treatment was indicated in the CAC scoring screening arm (in case CAC score ≥100 and ≥400 AU) with a relative reduction of >28% compared to the SCORE screening arm. Moreover, ROBINSCA participants with increased CAC score consulted their general practitioner more often compared to participants with increased risk based on SCORE, for lifestyle advice and/or initiation of preventive treatment.[32] This is in line with AHA/ACC and SCCT guidelines that highlighted the fact that CAC scan increases the adherence to preventive treatment and healthy lifestyle based on large systematic reviews and meta-analysis.[12,19] The final results of the ROBINSCA trial are expected in 2023.

Currently, two trials are investigating the impact of CAC scoring in reducing CVD events in specific asymptomatic subgroups.[33,34] The DANCAVAS trial is a population-based CVD screening study in males (n = 45,000) aged 65–74 y.[35] The participants were randomized to a CVD screening examination (n = 10.471) using low-dose non-contrast CT, ankle and brachial BP measurements, and blood tests or no screening (1:2).[33] Contrary to the ROBINSCA trial that used absolute Agatston categorization, in the DANCAVAS trial CAC score above the age- and sex-standardized median was regarded as abnormal. Besides the CAC score, also presence of aortic/iliac aneurysm, peripheral arterial disease, and hypertension were evaluated. In total, 49.5% of the males had an abnormal score

and were offered an additional consultation that included healthy lifestyle advice and initiation of aspirin and/or statins. The first follow-up outcomes on all cause death (primary outcome), and costs after 3, 5 and 10 years (secondary outcome) are expected in 2021.

In the CAUGHT-CAD trial asymptomatic individuals ($n \geq 734$) of 40–70 y. at intermediate risk with a family history of CHD will be randomized to CAC scan or standard risk scoring and CAC scan but blinded for the scan outcome.[34] Thereafter, participants will be treated according to risk based on CAC scan in the first arm, and according to the standard risk in the second study arm. Treatment includes lifestyle advice in both arms and initiation of statin therapy in case of positive CAC scan for the first arm. In addition, cCTA will be performed to analyze plaque volume in participants with CAC score of 1–400. After 36 months, the effectiveness will be evaluated based on absolute change in plaque volume at cCTA. The authors argue that the extent of plaque has been strongly linked to (hard CVD) outcome and can therefore be used as a primary outcome measure.[34] Finally, this trial aims to provide evidence to inform the guidelines about the use of CAC score in individuals with a positive family history of premature CHD. The first outcome results may be expected in 2022.

Contrary to guidelines for asymptomatic individuals, the majority of guidelines do not recommend the use of CAC score in symptomatic patients to exclude obstructive CHD. Somewhat in line with these guidelines, the SCOT-HEART trial recently published in 2019 their results regarding the role of adverse plaque characteristics (positive remodeling/low density), obstructive disease (stenosis >70%) and calcium score in outpatients ($n = 1769$) with suspected angina pectoris due to CHD.[36] Both adverse plaque and obstructive disease by themselves were major predictors of risk of CHD or non-fatal myocardial infarction, with highest risk for patients with a combination of both. Nevertheless, after a period of 5 years, the reported risk was similar for patients with only obstructive disease and patients with non-obstructive disease with or without adverse plaque. Interestingly, the only major prognostic risk predictor after 5 years was the overall plaque burden expressed with the CAC score, highlighting that overall on the longer term the presence and amount of coronary plaque is of significance and not the luminal stenosis.[36] Nonetheless, the authors of the SCOT-HEART trial warn that on the individual short-term the CAC score alone is not sufficient to guide management, because it cannot inform on any acute pathophysiological status of a plaque. However, for the long-term, stable patients with a high plaque burden as measured by CAC score, may benefit from more intensive medical treatment. Correspondingly, a recent study of van Rosendeal et al showed that a new comprehensive CTA score provides better discrimination and reclassification of events, in 2134 patients suspected of CAC, compared with the CAD-RADS score that is based on stenosis severity only.[37] The new CTA score does not contain the CAC score, but does rely on estimates of amount of plaque and whether or not plaque is calcified.

In 2017 and 2016, the results of the prognostic value of CAC score in combination with cCTA were compared to functional testing in several studies. The PROMISE study included a large cohort of symptomatic low- to intermediate-risk patients ($n = 8901$) that either underwent CAC scoring as part of cardiac CT or functional testing.[38] As reported by the **2019 ESC** Guideline for the diagnosis and management of chronic coronary syndromes, this study showed that a zero CAC score has a very low annual CVD event risk. The authors suggest this knowledge may be used to avoid further cardiac testing in symptomatic stable patients. Correspondingly, Mittal et al also showed that a zero score could rule out obstructive CHD and could be used as a "gatekeeper" for further testing based on study with 2730 stable chest pain patients.[39] The CRESCENT study included 350 outpatients with stable chest pain that were prospectively randomized between cardiac CT and functional testing (2:1).[40] The authors concluded that the cardiac CT protocol including a CAC scan is effective and can be safely used instead of functional testing. Moreover, by including a CAC scan the diagnostic expense and radiation dose could be reduced. Nevertheless, the current guidelines do not recommend CAC scoring in stable chest pain patients because of former studies that reported substantial proportion of patients with obstructive disease while having a zero CAC score. However, the more recent studies include stable chest pain patients, and it is debated that former studies that are referred to in the guidelines include studies that also include more acutely chest pain patients with higher PTP. Therefore, careful evaluation of clinical presentation of typical *vs* atypical and acute *vs* chronic chest pain remains important in future studies and critical appraisal of these studies in the development of new guidelines is crucial.

CONCLUSION

The coronary calcium score is relatively easy to acquire, but is worldwide only recommended in individuals at intermediate risk according to traditional risk factors and may be of help in the shared decision-making about statin use in asymptomatic individuals. Nevertheless, management based on CAC score alone is not yet recommended by any of the guidelines. Currently, ongoing population-based studies will have to provide the evidence for the (cost) effectiveness of CVD management based on CAC scoring.

The majority of guidelines do not recommend the use of CAC score in symptomatic patients to exclude obstructive CHD. The NICE very clearly eliminated the use of the CAC score in symptomatic patients whereas the guidelines of AHA/ACA, ESC and SCCT are less stringent. Current studies show that CAC score may be of added value in stable chest pain patients by either ruling out CHD in case of zero score, or by accurately stratifying patients at increased risk who may require more intensive treatment.

REFERENCES

1. Cardiovascular Disease Factsheet [Internet]. World Health Organization.. Available from: https://www.who.int/health-topics/cardiovascular-diseases [cited 2019 Sep 23].
2. Kaptoge S, Pennells L, De Bacquer D, Cooney MT, Kavousi M, Stevens G, et al. World Health organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. *Lancet Glob Health* 2019; **7**: e1332–45. doi: https://doi.org/10.1016/S2214-109X(19)30318-3
3. Bittner VA. The New 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease [Internet. *Circulation* 2019; **040625**.
4. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2016; **37**: 2315–81. doi: https://doi.org/10.1093/eurheartj/ehw106
5. McCollough CH, Ulzheimer S, Halliburton SS, Shanneik K, White RD, Kalender WA. Coronary artery calcium: a multi-institutional, multimanufacturer international standard for quantification at cardiac CT. *Radiology* 2007; **243**: 527–38. doi: https://doi.org/10.1148/radiol.2432050808
6. Heuvelmans MA, Vonder M, Rook M, Groen HJM, De Bock GH, Xie X, et al. Screening for early lung cancer, chronic obstructive pulmonary disease, and cardiovascular disease (the Big-3) using low-dose chest computed tomography: current evidence and technical considerations. *J Thorac Imaging* 2019; **34**: 160–9. doi: https://doi.org/10.1097/RTI.0000000000000379
7. Hecht HS, Blaha MJ, Kazerooni EA, Cury RC, Budoff M, Leipsic J, et al. CAC-DRS: coronary artery calcium data and reporting system. An expert consensus document of the Society of cardiovascular computed tomography (SCCT. *J Cardiovasc Comput Tomogr* 2018; **12**: 185–91. doi: https://doi.org/10.1016/j.jcct.2018.03.008
8. Vonder M, van der Werf NR, Leiner T, Greuter MJW, Fleischmann D, Vliegenthart R, et al. The impact of dose reduction on the quantification of coronary artery calcifications and risk categorization: a systematic review. *J Cardiovasc Comput Tomogr* 2018; **12**: 352–63. doi: https://doi.org/10.1016/j.jcct.2018.06.001
9. Vliegenthart R, Oudkerk M, Hofman A, Oei H-HS, van Dijck W, van Rooij FJA, et al. Coronary calcification improves cardiovascular risk prediction in the elderly. *Circulation* 2005; **112**: 572–7. doi: https://doi.org/10.1161/CIRCULATIONAHA.104.488916
10. Carr JJ, Nelson JC, Wong ND, McNitt-Gray M, Arad Y, Jacobs DR, et al. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of multi-ethnic study of atherosclerosis (MESA) and coronary artery risk development in young adults (cardia) study. *Radiology* 2005; **234**: 35–43. doi: https://doi.org/10.1148/radiol.2341040439
11. Schmermund A, Lehmann N, Bielak LF, Yu P, Sheedy PF, Cassidy-Bushrow AE, et al. Comparison of subclinical coronary atherosclerosis and risk factors in unselected populations in Germany and US-America. *Atherosclerosis* 2007; **195**: e207–16. doi: https://doi.org/10.1016/j.atherosclerosis.2007.04.009
12. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. *J Am Coll Cardiol* 2019; **73**: e285–350. doi: https://doi.org/10.1016/j.jacc.2018.11.003
13. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: Executive summary. *J Am Coll Cardiol* 2019; **74**: 1376–414. doi: https://doi.org/10.1016/j.jacc.2019.03.009
14. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American heart association Task force on clinical practice guidelines. *Hypertension* 2018; **71**: E13–115. doi: https://doi.org/10.1161/HYP.0000000000000065
15. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. Esc guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2019; **31**: 1–71.
16. Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW, et al. Risk assessment for cardiovascular disease with nontraditional risk factors. *JAMA* 2018; **320**: 272.
17. Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, García FAR, et al. Statin use for the primary prevention of cardiovascular disease in adults. *JAMA* 2016; **316**: 1997.
18. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification [Internet]. Vol. 1, NICE Guideline. 2014. Available from: https://www.nice.org.uk/guidance/cg181.
19. Hecht H, Blaha MJ, Berman DS, Nasir K, Budoff M, Leipsic J, et al. Clinical indications for coronary artery calcium scoring in asymptomatic patients: expert consensus statement from the Society of cardiovascular computed tomography. *J Cardiovasc Comput Tomogr* 2017; **11**: 157–68. doi: https://doi.org/10.1016/j.jcct.2017.02.010
20. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the Guideline for the diagnosis and management of patients with stable ischemic heart disease. *Circulation* 2014; **130**: 1749–67. doi: https://doi.org/10.1161/CIR.0000000000000095
21. Wolk MJ, Bailey SR, Doherty JU, Douglas PS, Hendel RC, Kramer CM, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease. *J Card Fail* 2014; **20**: 65–90. doi: https://doi.org/10.1016/j.cardfail.2013.12.002
22. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol* 2012; **60**: e44–164. doi: https://doi.org/10.1016/j.jacc.2012.07.013
23. Ò M, Peacock FW, McMurray JJ, Bueno H, Christ M, Maisel AS, et al. European Society of cardiology – acute cardiovascular care association position paper on safe discharge of acute heart failure patients from the emergency department. *Eur Hear J Acute Cardiovasc Care [Internet]* 2017; **6**: 311–20.
24. Claeys MJ. Esc guidelines on the management of stable coronary artery disease. *Eur Heart J* 2013; ; **34**: 2949–3003.
25. NICE. Chest pain of recent onset: assessment and diagnosis - Clinical guideline CG95 [Internet]. 2016. Available from: www.nice.org.uk/guidance/cg95.
26. Kelion AD, Nicol ED. The rationale for the Primacy of coronary CT angiography in the National Institute for health and care excellence (NICE) guideline (CG95) for the investigation of chest pain of recent onset. *J Cardiovasc Comput Tomogr* 2018; **12**:

516–22. doi: https://doi.org/10.1016/j.jcct.2018.09.001
27. Roobottom C. Radical changes to the investigation of stable chest pain following the 2016 NICE update. *Br J Radiol* 2017; **17**: 20170694.
28. Truong QA, Rinehart S, Abbara S, Achenbach S, Berman DS, Bullock-Palmer R, et al. Coronary computed tomographic imaging in women: an expert consensus statement from the Society of cardiovascular computed tomography. *J Cardiovasc Comput Tomogr* 2018; **12**: 451–66. doi: https://doi.org/10.1016/j.jcct.2018.10.019
29. Hecht HS. Coronary artery calcium analysis and reporting on noncontrast chest CT scans: a paradigm shift in prevention. *Curr Cardiovasc Imaging Rep* 2016; **9**: 11. doi: https://doi.org/10.1007/s12410-016-9372-2
30. Der ACMV, Vonder M, Gratama J, Adriaansen HJ, Kuijpers D, Denissen S, et al. Risk or benefit in screening for cardiovascular disease (ROBINSCA): the rationale and study design of a population-based Randomized-Controlled screening trial for cardiovascular disease. *J Clin Trials* 2019; **9**: 1–8.
31. van der Aalst CM, Denissen SJA, Vonder M, Gratama JW, Adriaansen HJ, Dijkstra J, et al. Screening for cardiovascular disease risk using traditional risk factor assessment or coronary artery calcium scoring: the ROBINSCA trial. **2019**.
32. Denissen SJ, van der Aalst CM, Vonder M, Oudkerk M, de Koning HJ. Impact of a cardiovascular disease risk screening result on preventive behaviour in asymptomatic participants of the ROBINSCA trial. *Eur J Prev Cardiol* 2019; **204748731984339**.
33. Lindholt JS, Rasmussen LM, Søgaard R, Lambrechtsen J, Steffensen FH, Frost L, et al. Baseline findings of the population-based, randomized, multifaceted Danish cardiovascular screening trial (DANCAVAS) of men aged 65–74 years. *BJS* 2019; **106**: 862–71. doi: https://doi.org/10.1002/bjs.11135
34. Marwick TH, Whitmore K, Nicholls SJ, Stanton T, Mitchell G, Tonkin A, et al. Rationale and design of a trial to personalize risk assessment in familial coronary artery disease. *Am Heart J* 2018; **199**: 22–30. doi: https://doi.org/10.1016/j.ahj.2017.09.011
35. Diederichsen ACP, Rasmussen LM, Søgaard R, Lambrechtsen J, Steffensen FH, Frost L, et al. The Danish cardiovascular screening trial (DANCAVAS): study protocol for a randomized controlled trial. *Trials* 2015; **16**: 554. doi: https://doi.org/10.1186/s13063-015-1082-6
36. Williams MC, Moss AJ, Dweck M, Adamson PD, Alam S, Hunter A, et al. Coronary Artery Plaque Characteristics Associated With Adverse Outcomes in the SCOT-HEART Study. *J Am Coll Cardiol* 2019; **73**: 291–301. doi: https://doi.org/10.1016/j.jacc.2018.10.066
37. van Rosendael AR, Shaw LJ, Xie JX, Dimitriu-Leen AC, Smit JM, Scholte AJ, et al. Superior risk stratification with coronary computed tomography angiography using a comprehensive atherosclerotic risk score. *JACC Cardiovasc Imaging* 2019; **12**: 1987–97. doi: https://doi.org/10.1016/j.jcmg.2018.10.024
38. Budoff MJ, Mayrhofer T, Ferencik M, Bittner D, Lee KL, Lu MT, et al. Prognostic value of coronary artery calcium in the promise study (prospective multicenter imaging study for evaluation of chest pain. *Circulation* 2017; **136**: 1993–2005. doi: https://doi.org/10.1161/CIRCULATIONAHA.117.030578
39. Mittal TK, Pottle A, Nicol E, Barbir M, Ariff B, Mirsadraee S, et al. Prevalence of obstructive coronary artery disease and prognosis in patients with stable symptoms and a zero-coronary calcium score. *Eur Heart J Cardiovasc Imaging* 2017; **18**: 922–9. doi: https://doi.org/10.1093/ehjci/jex037
40. Lubbers M, Dedic A, Coenen A, Galema T, Akkerhuis J, Bruning T, et al. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized crescent trial. *Eur Heart J* 2016; **37**: 1232–43. doi: https://doi.org/10.1093/eurheartj/ehv700