Coronary Artery Calcium for Risk Assessment in Young Adults

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Abstract

Purpose of Review To review the prognostic significance and clinical utility of coronary artery calcium (CAC) for risk assessment for atherosclerotic cardiovascular disease (ASCVD) in younger adults.

Recent Findings Data from over 3000 young adults (mean age of 40.3 ± 3.6 followed for 12.5 years) in the CARDIA registry found that in an asymptomatic, community representative sample, there was a low prevalence of CAC (~ 10%) but those with CAC had an exponential increase in CAC over time and significantly higher rates of ASCVD events. Alternatively, data from the CAC consortium analyzed 22,346 asymptomatic individuals undergoing CAC for clinical indications (mean age 43.5 ± 4.5 years, followed for 13 ± 4 years) and found a much higher prevalence of CAC at 34% with rates of coronary heart disease mortality that varied significantly according to CAC.

Summary In younger adults, CAC provides clear prognostic value and can be considered in select individuals with uncertainties about their ASCVD risk or the benefit of preventive therapies.

Keywords Coronary artery calcium · Cardiovascular prevention · Young adults

Introduction

In 1990, Agatson et al. employed computed tomography (CT) to detect coronary artery calcium (CAC) as a non-invasive method to approximate the quantity of coronary atherosclerosis [1]. A score was computed for each calcific lesion with a density > 130 Houndsfield units and an area ≥ 1 mm^2. The sum of these scores generated the total CAC score. In the three decades since, accumulating evidence showing significant variation in atherosclerotic cardiovascular disease (ASCVD) events according to baseline CAC, low radiation exposure (< 1 mSv), and rapid, noninvasive nature of CAC scoring has allowed it to become a useful tool in ASCVD risk stratification [2].

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While non-calcified low-attenuation plaque not captured by the CAC score may be the strongest predictor of the risk of future ASCVD events, the CAC score correlates closely with the burden of low-attenuation plaque as well as the total burden of atherosclerosis [3]. There are many large observational studies over the past 30 years supporting added benefit of CAC to traditional risk factors for risk stratification of ASCVD. However, most of these studies have focused on individuals over the age of 50 [4–9]. Atherosclerosis is a lifelong process that usually remains asymptomatic during the early decades of life [10]. Unlike traditional risk factors, the CAC score can categorically identify and quantify subclinical atherosclerosis, offering the potential to identify younger individuals with premature atherosclerosis who could subsequently be targeted for aggressive preventive interventions. In this review, we discuss the current evidence of the prognostic ability and the potential clinical utility of CAC scoring in individuals under the age of 50.

The early data — the prognostic significance of CAC in younger adults

Two studies, published in 2005, first examined the role of CAC in younger, asymptomatic individuals. The Prospective Army Coronary Calcium (PACC) Project conducted

by Taylor et al. at the Walter Reed Medical Center studied 2000 active-duty Army personnel with a mean age of 43 years who underwent coronary calcium CT as a part of an army-mandated physical examination and were followed for 3 years (± 1.4 years). The majority (82%) of the cohort were men. CAC was found in 22.4% of men, with a mean score of 19.5 ± 110.7 and 7.9% of women with a mean score of 3.3 ± 20.0. Nine events occurred in the follow-up period, all of them in men. The presence of any CAC was associated with an increased risk of coronary heart disease (CHD) events (hazard ratio 11.82 (95% CI 2.45–56.93, $p = 0.002$)) after controlling for traditional risk factors. Since the study was underpowered to detect CHD events in women, the analysis was repeated with men only. The association between CAC and CHD events decreased (hazard ratio 4.32 (95% CI = 1.1–16.97, $p = 0.036$)) [11]. While this study had a relatively short follow-up period, low CHD event rates, and was poorly representative of the general population, it did suggest that the presence of CAC in younger, healthy individuals correlated with the risk of subsequent CHD events.

The second early study was conducted by La Monte et al. at the Cooper Clinic in Dallas, Texas, and studied 16,097 individuals without clinical CHD undergoing CAC scoring for CHD risk-stratification [12]. The sample included 64% men, and approximately 20% of individuals were less than 40. They were followed for 3.5 years (± 1.4) for CHD events (non-fatal myocardial infarction, death from coronary disease). After adjusting for sex, individuals aged < 40 with a CAC score of 0 had 0.6 CHD events per 1000 person-years, while those with a CAC score > 0 had 4.8 CHD events per 1000 person-years. Individuals aged 40–65 had 0.03, 0.2, 6.7, and 10.6 CHD events per 1000 person-yearsfor a CAC score of 0, > 0, ≥ 100, and ≥ 1000, respectively. This study reinforced the findings of the PACC Project. Notably, even individuals less than age 40 with elevated CAC were found to be at elevated CHD risk, suggesting that CAC may also have clinical implications in younger individuals with premature atherosclerosis.

Additional data supporting the prognostic significant of CAC in younger adults was seen in a study by Tota-Maharaj et al. in 2012 that followed 8143 healthy individuals younger than 45 referred for CAC, followed for 5.6 years (± 2.6), and examined all-cause mortality [13]. The youngest quintile had individuals with a mean age of 40, 53.6% of which were men. In this quintile, a CAC score of 0, 100–400, and > 400 were associated with markedly different rates of all-cause mortality at 0.7, 6.8, and 27.6 per 1000 person years, respectively. Individuals younger than 45 were more likely to have a family history of CHD than individuals older 75. The strength of this study compared to prior ones was that it was multi-center study and had a

larger percentage of women. However, it did not examine cardiovascular specific outcomes and had a relatively short follow-up period.

A study by Paxaio et al. in 2015 included longer follow-up and specific ASCVD outcomes[14]. They followed 2084 individuals from the Dallas Heart Study, a multi-ethic cohort with a deliberate oversampling of African Americans, for 9 years examining CHD events (non-fatal myocardial infarction, CHD related death, coronary revascularization). The mean age of the cohort was 44.4 years (± 9), 56.2% were women, and 45.4% were African American. After adjusting for traditional risk factors, the presence of any CAC was independently associated with CHD events for the overall cohort (HR 1.9, 95% CI = 1.51–2.38, $p = 0.001$) as well as for individuals ≤ 50 years (HR 1.56, 95% CI = 1.20–2.03, $p = 0.001$). The cohort was then classified by the 10-year Framingham Risk Score (FRS) into three categories: < 6% risk, 6–10% risk, and > 10% risk. The addition of CAC score to their baseline FRS correctly reclassified 21.1% of individuals who had CHD events into a higher risk category and 0.5% of individuals who did not have CHD events into a lower risk category. The C-statistic for the FRS for CHD events was 0.86 (95% CI 0.83–0.91 and improved to 0.89 (95% CI 0.86–0.93, $p = 0.003$) with the addition of the CAC score.

The more recent data — a case for clinical utility

While prior studies were limited by short duration of follow-up, limited outcomes, or biased samples, two recent studies with more generalizable samples, longer duration of follow-up, and clinically relevant outcomes have further solidified the relationship between CAC and ASCVD in younger populations. The first, published in 2017 by Carr et al., utilized the Coronary Artery Risk Development in Young Adults (CARDIA) registry, a community representative sample aimed at defining the determinants of ASCVD in younger adults [15••]. The study followed over 3000 individuals with a mean age of 40.3 (± 3.6) for 12.5 years. Outcomes included CHD events (myocardial infarction, acute coronary syndrome, CHD death, or coronary revascularization), CVD events (CHD events, heart failure, stroke, transient ischemic attack, or peripheral arterial disease), and all-cause mortality. Unlike prior studies, this cohort was not referred for coronary calcium CT for risk-stratification; instead, participants underwent scanning as a routine part of the study protocol. Furthermore, this cohort underwent sequential coronary calcium CT for CAC scores at baseline, 5-year follow-up, and 10-year follow-up. The prevalence of CAC at baseline was 10.2% and increased to 20.1% and 28.4% at 5 years and 10 years, respectively. The geometric mean (IQR) of the CAC scores for individuals with any CAC increased from 21.6 (17.3–26.8) to 59.1 (47.7–73.2) and

144.4 (116.9–178.3) for the same time periods, indicating not a linear increase in CAC over time but rather exponential growth. A higher CAC score correlated with a greater risk of future CHD events after adjustment for traditional risk factors. A CAC score of 1–19, 20–99, and ≥ 100 had an adjusted hazard ratio of 2.6 (95% CI = 1.0–5.7, $p = 0.03$), 5.8 (95% CI = 2.6–12.1, $p < 0.001$), and 9.8 (95% CI = 4.5–20.5, $p < 0.001$), respectively, compared to a CAC score of zero. The adjusted hazard ratio for CHD events for any CAC compared to no CAC was 5.0 (95% CI = 2.8–8.7, $p < 0.001$). While a CAC score ≥ 100 was associated with an increase in all-cause mortality 3.7 (95% CI = 1.5–10.0, $p < 0.001$), an association between CAC and non-CHD CVD events was not found.

The second study was published by Miedema et al. in 2019, utilizing data from the CAC Consortium to analyze 22,346 asymptomatic individuals undergoing CAC for clinical indications with a mean age (SD) of 43.5 years (± 4.5) and followed for 12.7 (± 4) years [16••]. Outcomes included CHD mortality, CVD mortality, and all-cause mortality. The prevalence of CAC was higher than the study conducted by Carr et al. at 34.4%, which would be expected as this was a sample with clinical indications for CAC scoring. Hazard ratios were adjusted for age, sex, hyperlipidemia, hypertension, smoking, diabetes, and a family history of CHD. Compared to a CAC score of 0, a CAC score of 1–100 was not associated with a statistically significant increased risk of CHD mortality (HR = 1.7 (95% CI = 0.8–3.9)), CVD mortality (HR = 1.5 (95% CI = 0.9–2.5)), or all-cause mortality (HR = 1.2 (95% CI = 0.9–1.6)). However, a CAC score > 100 was associated with an increased risk for all three outcomes, with an adjusted hazard ratio of 5.6 (95% CI = 2.5–12.7), 3.3 (95% CI = 1.8–6.2), and 2.6 (95% CI = 1.9–3.6) for CHD mortality, CVD mortality, and all-cause mortality, respectively.

Compared to prior studies, these two studies elucidate some important concepts. First, Carr et al. suggested that even evidence of mild atherosclerosis (CAC score 20–99) in relatively young individuals was associated with a significant increase in the risk of CHD events. This is likely in part due to the exponential growth of atherosclerotic plaque over time. While Miedema et al. did not show this association, their cohort had a higher proportion of Caucasian who have a lower risk of CHD events for a given CAC score than Hispanics and African Americans [17]. Second, it suggested that CAC was more specific to CHD events and was less generalizable to non-CHD CVD events or all-cause mortality. Lastly, Carr et al. demonstrated a low prevalence of CAC in a non-referral based cohort in this age group, suggesting that routine screening may not be the ideal use of coronary calcium CT in this population. Conversely, the data from Miedema et al. showed in a population of individuals with clinical indications for CAC scoring there was a relatively high prevalence of CAC with over one-third of individuals having CAC > 0. This suggests that for younger individuals with risk factors for ASCVD, selective use of CAC scoring may be clinically appropriate.

Is there a clinical role for CAC testing in younger adults?

In middle-aged adults, CAC is a well-established tool to aid clinical decision making when there is uncertainty about an individual's ASCVD risk or treatment decisions[18]. Intriguingly, there are data to suggest that CAC can be used to determine an individual's "arterial age," supplanting chronological age for CHD risk stratification. In 2004, Schisterman and Whitcomb utilized prior published data to delineate arterial age categories in 5-year increments that corresponded with the expected CAC score for a chronological age [19]. For example, a 50-year-old man with a CAC score of 100 would have an arterial age of 60–64 years. McClelland et al. built on this concept to assess an arterial age as a function of the CHD risk of a given CAC score [20]. CAC scores of 0, 10, and 100 were equivalent to an arterial age of 39, 56, and 73, respectively. When arterial age was substituted for chronological age into the Framingham risk score, it was more predictive of CHD events (receiver operating characteristic 0.79 versus 0.75). Furthermore, when controlling for the calculated arterial age, the chronological age was no longer found to be a predictive of CHD events. This suggests that an individual's CAC is a better predictor of their CHD risk than their age.

Given the lower prevalence of CAC in younger individuals, more selective use of coronary calcium CT should be considered. Younger individuals with evidence of familial hypercholesterolemia or multiple traditional CHD risk factors have a significantly elevated lifetime risk and likely warrant aggressive treatment regardless of their CAC score. However, even in those with familial hypercholesterolemia, recent data demonstrate low CHD event rates in those with a CAC score of zero. In a systematic analysis of nine cohorts consisting of 1176 of asymptomatic individuals with a mean age of 47 years and heterozygous familial hypercholesterolemia found that 45% of individuals did not have any CAC, despite an elevated low-density lipoprotein [21]. A pooled analysis of two of these cohorts, the French Registry of Familial Hypercholesterolemia and the Spanish Familial Hypercholesterolemia Cohort Study, examined the incidence of CHD, stroke, transient ischemic attack, peripheral arterial disease, cardiovascular death, and sudden death in 1624 individuals with a mean age of 48.5 years. Of the 630 individuals with a CAC of 0, only 3 had an event over the 2.7 (0.4–5.0)-year follow-up period [22].

Additionally, younger individuals without any traditional risk factors are unlikely to have CAC and routine screening with CAC will likely not be cost-effective in this age group. A study by Okwuosa et al. attempted to define which individuals would benefit from coronary calcium CT [23]. They utilized the CARDIA registry to assess CAC in 2832 individuals, aged 33–45 and found 9.9% of this cohort had a CAC score > 0 and 1.8% had a CAC score > 100. Thus, the number needed to screen (NNS) was 10 for any CAC and over 50 for a CAC > 100. The authors then stratified the cohort according to baseline FRS. A FRS > 10% reduced the NNS to 2.2 for any CAC and 5.8 for a CAC > 100. The study concluded that younger adults with an FRS between 10 and 20% were most likely to benefit from CAC scoring for future CHD risk-stratification. Concordantly, the 2019 ACC/AHA Guidelines recommend that adults at intermediate 10-year ASCVD risk ($\geq 7.5\%$ to < 20%) or selected adults at borderline 10-year ASCVD risk (5% to < 7.5%) can consider undergoing CAC scoring to help guide the initiation of preventative interventions [18].

A retrospective study conducted by Mitchell et al. at the Walter Reed Medical Center highlights the importance of identifying and intervening on younger adults with premature atherosclerosis [24]. The study analyzed 13,644 individuals without prior ASCVD who underwent coronary calcium CT were followed for 9.4 years for incident myocardial infarction, stroke, and cardiovascular death. The mean age was 50 years, and 71% were men. Individuals without CAC at baseline were not found to benefit from statin treatment. However, individuals with any amount of CAC at baseline who were started on a statin within 5 years had a lower incidence of the primary outcome (HR = 0.76 (95% CI 0.60–0.95, $p = 0.015$) than individuals with CAC who were not started on a statin. The most significant benefit was found in individuals with a CAC score of 100–400 (HR = 0.32 (95% CI 0.21–0.48, $p < 0.0001$). While prospective studies are needed to confirm these results, the findings demonstrate the potential impact of CAC in clinical decision making and long-term risk reduction.

Given the overall data, it is reasonable to consider CAC testing in men and women in their 40's if there is uncertainty about their ASCVD risk or uncertainty about treatment decisions. In more select situations, it also seems reasonable to proceed with CAC testing in men in their 30's. For women in their 30's and men and women in their 20's, CAC testing should consider only in rare situations. As with middle-aged adults, the decision to proceed with CAC testing should occur in the context of shared decision making as part of the clinician patient risk discussion.

Cost Effectiveness of CAC in Younger Adults

While a non-contrast CT itself is relatively inexpensive (CAC scores typically cost ~ $100–$400) [25], it is worth examining its cost-effectiveness as clinical tool. A recent analysis by Ventakaraman et al. examined the cost-effectiveness of CAC in individuals with a family history of CHD, utilizing the CAC Score: Use to Guide management of Hereditary Coronary Artery Disease registry. This analysis compared initiating statin therapy in individuals with a CAC score > 0 and Pooled Cohort Equations (PCE) 10-year ASCVD risk > 2% versus all individuals with a PCE 10-year ASCVD risk > 7.5%, as recommended by the 2019 AHA/ACC primary prevention guidelines [18]. Utilizing CAC, 45% of the cohort would be eligible for statin therapy while 27% would be eligible for statin therapy based on the AHA/ACC primary prevention guideline strategy. Relevant variables in the model included the cost of the CT, investigation of incidental findings on CT, the increase in life-time cancer risk from the radiation exposure, the cost of statin therapy, the costs of treating acute and chronic CVD events, and the disutility of statin therapy. Over a period of 15 years, the CAC-based strategy added 0.0097 quality adjusted life years (QALY) per patient, but also increased annual costs by $145 per patient. The NNS to prevent one CVD event was high, at 152. For individuals aged 50–60, the cost of the CAC strategy was $23,663/QALY. For individuals less than 50, the cost of a routine screening approach grew dramatically to $358,656/QALY due the lower prevalence of CAC in this age group [26]. These findings highlight the importance of selective use of CAC testing in younger adults as opposed to a broader screening approach.

Conclusion

In younger adults, CAC provides clear prognostic value, with significant variation in CHD and ASCVD outcomes according to the presence and quantity of calcified coronary atherosclerosis. Given the low prevalence of CAC in younger adults, CAC testing should be selective and offered in the context of shared decision making as part of the clinician-patient risk discussion. In individuals with uncertainty about clinical decisions, such as starting statin therapy, the absence of CAC may provide enough reassurance for a short-term delay in treatment, while the presence of calcified atherosclerosis can provide justification the initiation of preventive therapies.

Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

References

Papers of particular interest, published recently, have been highlighted as:
● Of importance
●● Of major importance

1. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990;15(4):827–32. https://doi.org/10.1016/0735-1097(90)90282-T.

2. Messenger B, Li D, Nasir K, Carr JJ, Blankstein R, Budoff MJ. Coronary calcium scans and radiation exposure in the multiethnic study of atherosclerosis. Int J Cardiovasc Imaging. 2016;32(3):525–9. https://doi.org/10.1007/s10554-015-0799-3.

3. Williams M. C., Kwiecinski J., Doris M., McElhinney P., D'Souza M. S., Cadet S., Adamson P. D., Moss A. J., Alam S., Hunter A., Shah A. S. V., Mills N. L., Pawade T., Wang C., Weir McCall J., Bonnici-Mallia M., Murrills C., Roditi G., van Beek E. J. R., … Dey D. (2020). Low-attenuation noncalcified plaque on coronary computed tomography angiography predicts myocardial infarction: results from the multicenter SCOT-HEART Trial (Scottish Computed Tomography of the HEART). *Circulation*, *141*(18), 1452–1462. https://doi.org/10.1161/CIRCULATIONAHA.119.044720

4. Kavousi M, Elias-Smale S, Rutten J. H. W, Leening M. J. G., Vliegenthart R., Verwoert G. C., Krestin G. P., & Oudkerk M. *Evaluation of newer risk markers for coronary heart disease risk classification*. (2012) 12

5. Detrano R., Bild, D. E., Liu, K., Bluemke, D. A., & Watson, K. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl j Med,* (2008) 10

6. Hoffmann U., Massaro J. M., D'Agostino R. B., Kathiresan S., Fox C. S., & O'Donnell C. J. Cardiovascular event prediction and risk reclassification by coronary, aortic, and valvular calcification in the Framingham heart study. *Journal of the American Heart Association*, (2016) *5*(2). https://doi.org/10.1161/JAHA.115.003144

7. Shah RV, Spahillari A, Mwasongwe S, Carr JJ, Terry JG, Mentz RJ, Addison D, Hoffmann U, Reis J, Freedman JE, Lima JAC, Correa A, Murthy VL. Subclinical atherosclerosis, statin eligibility, and outcomes in African American individuals: The Jackson Heart Study. JAMA Cardiology. 2017;2(6):644. https://doi.org/10.1001/jamacardio.2017.0944.

8. Erbel R, Möhlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, Dragano N, Grönemeyer D, Seibel R, Kälsch H, Bröcker-Preuss M, Mann K, Siegrist J, Jöckel K-H. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis. J Am Coll Cardiol. 2010;56(17):1397–406. https://doi.org/10.1016/j.jacc.2010.06.030.

9. Vliegenthart R, Oudkerk M, Hofman A, Oei H-HS, van Dijck W, van Rooij FJA, Witteman JCM. Coronary calcification improves cardiovascular risk prediction in the elderly. Circulation. 2005;112(4):572–7. https://doi.org/10.1161/CIRCULATIONAHA.104.488916.

10. Tuzcu EM, Kapadia SR, Tutar E, Ziada KM, Hobbs RE, McCarthy PM, Young JB, Nissen SE. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: evidence from intravascular ultrasound. Circulation. 2001;103(22):2705–10. https://doi.org/10.1161/01.CIR.103.22.2705.

11. Taylor AJ, Bindeman J, Feuerstein I, Cao F, Brazaitis M, O'Malley PG. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors. J Am Coll Cardiol. 2005;46(5):807–14. https://doi.org/10.1016/j.jacc.2005.05.049.

12. LaMonte MJ, FitzGerald SJ, Church TS, Barlow CE, Radford NB, Levine BD, Pippin JJ, Gibbons LW, Blair SN, Nichaman MZ. Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. Am J Epidemiol. 2005;162(5):421–9. https://doi.org/10.1093/aje/kwi228.

13. Tota-Maharaj R, Blaha MJ, McEvoy JW, Blumenthal RS, Muse ED, Budoff MJ, Shaw LJ, Berman DS, Rana JS, Rumberger J, Callister T, Rivera J, Agatston A, Nasir K. Coronary artery calcium for the prediction of mortality in young adults 75 years old. Eur Heart J. 2012;33(23):2955–62. https://doi.org/10.1093/eurheartj/ehs230.

14. Paixao ARM, Ayers CR, El Sabbagh A, Sanghavi M, Berry JD, Rohatgi A, Kumbhani DJ, McGuire DK, Das SR, de Lemos JA, Khera A. Coronary artery calcium improves risk classification in younger populations. JACC: Cardiovascular Imaging. 2015;8(11):1285–93. https://doi.org/10.1016/j.jcmg.2015.06.015.

15.●● Carr J. J., Jr, D. R. J. Terry J. G., Shay C. M., Sidney S., Liu K., Schreiner P. J., Lewis C. E., Shikany J. M., Reis J. P., & Jr, D. C. G. (2017). *Association of coronary artery calcium in adults aged 32 to 46 years with incident coronary heart disease and death*. 9. https://doi.org/10.1001/jamacardio.2016.5493. (**This study prospectively assessed a community sample of individuals, rather than those referred for cardiovascular risk stratification. It demonstrated that coronary artery calcium increases exponentially once present and correlates with long term cardiovascular outcomes.**)

16.●● Miedema MD, Dardari ZA, Nasir K, Blankstein R, Knickelbine T, Oberembt S, Shaw L, Rumberger J, Michos ED, Rozanski A, Berman DS, Budoff MJ, Blaha MJ. Association of coronary artery calcium with long-term, cause-specific mortality among young adults. JAMA Netw Open. 2019;2(7): e197440. https://doi.org/10.1001/jamanetworkopen.2019.7440. (**This is the largest study to date that demonstrates an associated between coronary artery calcium and long-term cardiovascular specific outcomes.**)

17. Orimoloye O. A., Budoff M. J., Dardari Z. A., Mirbolouk M., Uddin, S. M. I., Berman D. S., Rozanski A., Shaw L. J., Rumberger J. A., Nasir K., Miedema M. D., Blumenthal R. S., & Blaha M. J. Race/ethnicity and the prognostic implications of coronary artery calcium for all-cause and cardiovascular disease mortality: the coronary artery calcium consortium. *Journal of the American Heart Association*, (2018) *7*(20). https://doi.org/10.1161/JAHA.118.010471

18. Arnett D. K., Blumenthal R. S., Albert M. A., Buroker A. B., Goldberger Z. D., Hahn E. J., Himmelfarb C. D., Khera A., Lloyd-Jones D., McEvoy J. W., Michos E. D., Miedema M. D., Muñoz D., Smith S. C., Virani S. S., Williams K. A., Yeboah J., & Ziaeian B. 2019 ACC/AHA Guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*, (2019) *140*(11). https://doi.org/10.1161/CIR.0000000000000678

19. Schisterman EF, Whitcomb BW. Coronary age as a risk factor in the modified Framingham risk score. BMC Med Imaging. 2004;4(1):1. https://doi.org/10.1186/1471-2342-4-1.

20. McClelland RL, Nasir K, Budoff M, Blumenthal RS, Kronmal RA. Arterial age as a function of coronary artery calcium (from the Multi-Ethnic Study of Atherosclerosis [MESA]). Am J Cardiol. 2009;103(1):59–63. https://doi.org/10.1016/j.amjcard.2008.08.031.

21. Mszar R, Grandhi GR, Valero-Elizondo J, Virani SS, Blankstein R, Blaha M, Mata P, Miname MH, Al Rasadi K, Krumholz HM, Santos RD, Nasir K. Absence of coronary artery calcification in middle-aged familial hypercholesterolemia patients without atherosclerotic cardiovascular disease. JACC: Cardiovascular Imaging. 2020;13(4):1090–2. https://doi.org/10.1016/j.jcmg.2019.11.001.

22. Gallo A., Pérez de Isla L., Charrière S., Vimont A., Alonso R., Muñiz-Grijalvo O., Díaz-Díaz J. L., Zambón D., Moulin P., Bruckert E., Mata P., Béliard S., Angoulvant D., Beliard S., Boccara F., Bruckert E., Cariou B., Carreau V., Carrie A., … Zambón D. (2021). The added value of coronary calcium score in predicting cardiovascular events in familial hypercholesterolemia. *JACC: Cardiovascular Imaging*, S1936878X21005015. https://doi.org/10.1016/j.jcmg.2021.06.011

23. Okwuosa TM, Greenland P, Ning H, Liu K, Lloyd-Jones DM. Yield of screening for coronary artery calcium in early middle-age adults based on the 10-year Framingham risk score. JACC Cardiovascular Imaging. 2012;5(9):923–30. https://doi.org/10.1016/j.jcmg.2012.01.022.

24. Mitchell JD, Fergestrom N, Gage BF, Paisley R, Moon P, Novak E, Cheezum M, Shaw LJ, Villines TC. Impact of statins on cardiovascular outcomes following coronary artery calcium scoring. J Am Coll Cardiol. 2018;72(25):3233–42. https://doi.org/10.1016/j.jacc.2018.09.051.

25. Coronary calcium test could help clarify heart disease risk and control cholesterol. https://www.heart.org/en/news/2018/11/13/coronary-calcium-test-could-help-clarify-heart-disease-risk-and-control-cholesterol

26. Venkataraman P, Kawakami H, Huynh Q, Mitchell G, Nicholls SJ, Stanton T, Tonkin A, Watts GF, Marwick TH. Cost-effectiveness of coronary artery calcium scoring in people with a family history of coronary disease. JACC: Cardiovascular Imaging. 2021;14(6):1206–17. https://doi.org/10.1016/j.jcmg.2020.11.008.