Editor's key points

- Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of morbidity and mortality worldwide. Risk stratification is undertaken to identify patients at risk of developing ASCVD. Although risk scores remain the foundation of risk assessment, they are imperfect and may underpredict or overpredict a person's risk.
- Biomarkers and imaging tests have the potential to improve risk stratification by bridging the detection gap between traditional risk factors and the multitude of unmeasurable factors that contribute to cardiovascular risk. Biomarkers are best used in patients at intermediate risk of ASCVD and in low-risk patients when traditional risk scores are believed to underestimate risk.
- With Canadian Cardiovascular Society guidelines published in 2021, family physicians should feel empowered to use lipoprotein(a) levels, high-sensitivity C-reactive protein levels, and coronary artery calcium scores in appropriate patients to guide statin therapy. Although not currently guideline directed, there is evidence that high-sensitivity troponin level can also be used to better stratify a patient's cardiovascular risk. It is likely that the use of biomarkers will become more prevalent as research continues into their use in cardiovascular risk stratification.

Approach to risk stratification of atherosclerotic cardiovascular disease

Use of biomarkers and imaging in a Canadian context

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Abstract

Objective To outline the 2021 Canadian Cardiovascular Society (CCS) dyslipidemia guidelines and to present the current approaches to cardiovascular risk stratification, including the incorporation of biomarkers and imaging tests.

Sources of information Current guidelines were reviewed and an Ovid MEDLINE literature search was performed.

Main message Cardiovascular disease (CVD) is the leading cause of global mortality, with ischemic heart disease contributing to nearly half of these deaths. Risk stratification is undertaken to identify patients who would benefit from primary prevention for atherosclerotic CVD (ASCVD), but commonly used methods for risk stratification are imperfect. The CCS guidelines endorse that the presence of risk modifiers (family history of premature ASCVD, high-sensitivity C-reactive protein level ≥2.0 mg/L, lipoprotein[a] level ≥500 mg/L [≥50 mg/dL], or coronary artery calcium >0) supports the use of statin therapy in those at intermediate risk (Framingham risk score 10% to 19.9%) who do not otherwise meet the recommendations for statin use. The CCS guidelines recommend statin therapy in patients at intermediate risk when cholesterol levels are elevated (low-density lipoprotein cholesterol level ≥3.5 mmol/L, non–high-density lipoprotein cholesterol level ≥4.2 mmol/L, or apolipoprotein B level ≥1.05 g/L). In addition, statin therapy should be considered for patients at low risk (Framingham risk score 5% to 9.9%) with elevated cholesterol levels, especially if risk modifiers are present. When cholesterol levels are not elevated, evidence still favours the use of statins in intermediate-risk patients when risk modifiers are present and in men 50 years and older and women 60 years and older with 1 additional risk factor.

Conclusion Biomarkers and imaging tests have the potential to improve ASCVD risk stratification by reclassifying any patient whose risk has been inaccurately estimated by traditional methods. Recently published guidelines by the CCS suggest the use of biomarkers and imaging in certain patient groups.

Cardiovascular disease (CVD) is the leading cause of disease burden in the world, and prevalent cases have nearly doubled since the 1990s.[1] A large proportion of CVD is caused by atherosclerosis.[1,2] Ischemic heart disease encompasses diseases of the heart due to atherosclerotic coronary artery disease (CAD), while atherosclerotic CVD (ASCVD) is a general term for diseases of the cardiovascular system due to cholesterol plaque buildup. Primary prevention of ASCVD involves treating patients who are at risk of developing, or who have already developed, atherosclerotic disease before they experience a cardiovascular event. Risk stratification is undertaken to identify patients who would benefit from primary prevention, but commonly used methods for risk stratification are imperfect. Traditionally, cardiovascular

risk stratification involves a review of the patient's risk factors, characteristic symptoms (if any), a physical examination, a resting electrocardiogram, and bloodwork.[3] The risk of ASCVD can then be estimated using a risk score. The 2021 Canadian Cardiovascular Society (CCS) guidelines[4] recommend the use of the Framingham risk score (FRS),[5] which aims to predict an end point that includes myocardial infarction (MI), angina, coronary death, stroke, claudication, or congestive heart failure.[6] Of note, there are several versions of the FRS that estimate different end points (eg, *hard CAD*, which includes CAD but not angina[5]). A patient may have different FRS estimations depending on which end point is used and may falsely be placed in a lower-risk group if the full complement of outcomes is not considered.

Risk scores are not able to account for risk with complete accuracy, since traditional risk factors (smoking, hypertension, diabetes, dyslipidemia, age, and sex) account for only 65% to 85% of cardiovascular events.[7,8] When abdominal obesity, psychosocial factors, diet, alcohol consumption, and physical activity are also accounted for, 90% to 94% of cardiovascular events can be explained,[9] but these factors are difficult to quantify and are impractical for the purposes of risk scores. Furthermore, cardiovascular risk in women is often underestimated[10,11]: sex-specific differences in the rates of diagnosis and treatment of traditional risk factors, and sex-specific risk factors such as hypertensive disorders of pregnancy,[12,13] are not accounted for by most risk scores. Biomarkers and imaging tests may help close the *detection gap* by accounting for the risk not explained by traditional risk factors.[14]

Case presentation

A 60-year-old woman consults her primary care provider after her brother dies from an MI at the age of 57. She is otherwise healthy, active, and asymptomatic. Her blood pressure is 125/82 mm Hg and physical examination findings are unremarkable. Electrocardiogram findings are normal. Bloodwork results are as follows: total cholesterol level of 4.72 mmol/L, high-density lipoprotein cholesterol (HDL-C) level of 1.57 mmol/L, low-density lipoprotein cholesterol (LDL-C) level of 2.89 mmol/L, non–HDL-C level of 3.15 mmol/L, and triglyceride level of 0.57 mmol/L. She is concerned about her risk of MI and wonders whether she can mitigate this risk.

Sources of information

Current guidelines were reviewed and an Ovid MEDLINE literature search was performed.

Main message

Novel biomarkers. Numerous biomarkers are associated with the incidence of cardiovascular events, but the usefulness of a biomarker is better measured by the additional information that is gained over traditional risk stratification. We will review several prominent biomarkers, including high-sensitivity C-reactive protein (hs-CRP) and lipoprotein(a) (Lp[a]), which are *risk modifiers* for ASCVD.[3,4] The CCS guidelines endorse that the presence of risk modifiers (family history of premature ASCVD, hs-CRP level ≥2.0 mg/L, Lp[a] level ≥500 mg/L [≥50 mg/dL], or coronary artery calcium [CAC] >0) supports the use of statin therapy in those at intermediate risk (FRS 10% to 19.9%) who do not otherwise meet the recommendations for statin use.[4]

High-sensitivity troponin (hsTn): The development of hsTn assays, which can detect serum troponin at lower concentrations than older "contemporary" troponin assays, has allowed for accurate measurement of high-sensitivity cardiac troponin I and high-sensitivity cardiac troponin T (hs-cTnT) in seemingly healthy individuals.[15,16] Baseline elevations in hsTn are independently predictive of all-cause mortality,[17-20] cardiovascular mortality,[18-22] and nonfatal MI[18,19,20-22] in ambulatory patients without known ASCVD. In one large study, ambulatory patients with detectable hs-cTnT levels had a 10-year risk of ASCVD of 13.2%.[23] Conversely, patients with hs-cTnT levels below the limit of detection had low rates of ASCVD.[23] Studies have reported improvements in cardiovascular risk stratification with the addition of hsTn to the FRS[20,24-27] and to the European Society of Cardiology SCORE (Systematic COronary Risk Evaluation) risk algorithm.[28] Although more research is needed to investigate whether hsTn provides unique information that is not otherwise captured by an individual's traditional risk factors, it remains useful as a risk marker and patients with detectable or elevated hsTn levels can be considered for earlier and more aggressive preventive interventions.[29]

C-reactive protein: Inflammatory cells play a pathogenic role in the formation of early "fatty streaks," the progression to advanced atherosclerotic lesions, and the development of unstable plaques.[30-33] One of the most ubiquitous markers of inflammation is CRP, an acute-phase reactant that is predominantly made by hepatocytes in response to inflammation, infection, malignancies, or tissue damage.[34,35] Whether CRP is solely a marker for vascular disease or plays a pathogenic role in the development of atherosclerosis is an area of debate.[36,37] Elevated baseline levels of hs-CRP are independently associated with increased all-cause mortality,[38-40] cardiovascular death,[39,40] and cardiovascular events.[34,38,40,41] However, studies examining reclassification after the addition of CRP or hs-CRP to predictive models have shown mixed results.[24,26,38,41-46] The largest analysis to date, which included 166,596 participants, found a very modest improvement in risk stratification with the use of CRP.[45]

Lipoprotein(a): Lipoprotein(a) has substantial atherogenic potential and is an LDL particle with apolipoprotein(a) (apo[a]) covalently bound to the apo B_{100} molecule.[47,48]

Circulating levels of Lp(a) are genetically determined, with little influence of lifestyle factors.[48] There is a linear relationship between future cardiovascular risk and the concentration of Lp(a),[47,49] and Mendelian randomization studies suggest a causative role of Lp(a) in the development of atherosclerosis.[50,51] Research is ongoing to determine whether lowering Lp(a) will lead to reductions in ASCVD outcomes.[52,53] The CCS guidelines consider Lp(a) a risk modifier and recommend Lp(a) testing once in a person's lifetime with earlier and more intensive health behaviour modifications in those with Lp(a) levels 500 mg/L (50 mg/dL) or greater.[4]

Lipid measurements: Conventionally, total cholesterol, LDL-C, and HDL-C are used as biomarkers of dyslipidemia and included in many CVD risk calculators.[5,28,54] However, newer measures to characterize lipid biology exist. Non–HDL-C and apoB have become more prevalent as alternatives to LDL-C measurement.[55-59] Measurements of apo AI[57] and LDL particle number and size[56] are also used. Apolipoprotein AI and apoB are the principal protein components of HDL and non-HDL particles, respectively, and measuring apo AI or apoB is analogous to measuring the lipoprotein particle number.[58-60] Because the number of atherogenic non-HDL particles is more strongly associated with ASCVD risk than is the cholesterol content of the particles,[56] many researchers recommend the use of apoB over LDL-C or non–HDL-C.[61] Canadian guidelines support the use of apoB as an alternative measurement to LDL-C or non–HDL-C.[4]

Low-density lipoprotein particle number, size, and density can also be measured directly by lipoprotein subfractionation techniques,[62] but this is not practical for widespread, routine clinical use. Small dense LDL particles have emerged in population studies as independently associated with CVD risk.[63-66] Small dense LDL particles are highly atherogenic owing to an increased propensity to oxidation, high endothelial permeability, and decreased clearance through hepatic LDL receptors.[67]

Despite the theoretical benefits of newer measures of a patient's lipid profile, studies examining their use in risk stratification have been disappointing. The hazard ratios for CAD generated with apoB and apo AI are nearly identical to those generated with non–HDL-C and HDL-C, respectively,[55] and the addition of apoB, apo AI, LDL, or Lp(a) to models that already included total cholesterol and HDL-C has not led to improvement in risk stratification.[60,68]

Imaging tests. Carotid intima-media thickness (C-IMT) and CAC scores are imaging tests commonly used in risk stratification. Abnormal C-IMT or CAC scores are correlated with risks of CAD[69-71] and ASCVD events.[72-75] Both tests have been shown to improve risk stratification[73,75,76] but, when compared head to head, the CAC score performed better than C-IMT.[75,77]

Although C-IMT measurement is popular because of its affordability, availability, and lack of radiation exposure, an absence of standardization and inconsistent definitions of C-IMT have led to varied results in clinical trials.[78-80] In a large meta-analysis, common C-IMT was found to improve risk prediction, but reclassification was small and unlikely to be of clinical importance.[78]

In contrast, although there are several different CAC scoring techniques, all are strongly correlated and have been shown to have excellent interobserver and intraobserver reproducibility.[81] Coronary artery calcium measurements are associated with an average radiation dose of 0.89 mSv, which is approximately equal to 3.6 months of background radiation exposure.[4] The addition of CAC scores improves risk stratification compared with the use of traditional risk factors alone, especially in middle-aged, intermediate-risk populations.[77,82,83] Higher CAC scores are associated with increased risk, with a score of greater than 100 associated with a greater than 2% annual ASCVD risk and a score of greater than 300 associated with a 10-year risk of MI or cardiovascular death of 28%.[4] Conversely, patients with a CAC score of 0 have a low risk of 10-year ASCVD,[23,84] with a CAC of 0 being associated with the greatest downward shift in estimated risk compared with several other risk indicators.[84] However, a CAC score of 0 does not imply a complete lack of risk, as a CAC score measures only late calcified plaque in the coronary arteries and may miss early, noncalcified plaque. Because of this, a patient's age must be considered when ordering a CAC score. Ordering a CAC score for men older than 42.3 years and women older than 57.6 years who do not have other cardiovascular risk factors provides the greatest clinical usefulness.[85] The CCS guidelines considers a CAC score greater than 0 to be a risk modifier and suggests consideration of CAC scoring to detect subclinical atherosclerosis in select individuals.[4]

When to use biomarkers and imaging tests. Biomarkers and imaging tests are most useful in patients at intermediate cardiovascular risk to help guide treatment recommendations. Since all patients, regardless of predicted cardiovascular risk, should be counseled to pursue health behaviour modifications including improved diet, increased exercise, and smoking cessation,[4] the main treatment decision is whether the patient would benefit from statin therapy. A patient with a statin-indicated condition (**Table 1**)[4] or whose FRS is 20% or greater has a strong recommendation to start statin therapy and, in general, no additional information from biomarkers is needed. In contrast, statin therapy is not recommended in most patients at very low (<5%) risk of ASCVD. For a patient with an FRS between 5% and 19.9%, treatment decisions are more nuanced. The CCS guidelines recommend statin therapy in patients at intermediate risk (FRS 10% to 19.9%) when cholesterol levels are elevated (LDL-C level ≥3.5 mmol/L, non–HDL-C level ≥4.2 mmol/L, or apoB level ≥1.05 g/L). In addition, statin therapy should

Table 1. Statin-indicated conditions

CONDITION	DESCRIPTION
Clinical atherosclerosis	Myocardial infarction, acute coronary syndromes, stable angina, documented coronary artery disease by angiography (>10% stenosis), stroke, TIA, documented carotid artery disease, peripheral artery disease, claudication, ankle-brachial index <0.9
Abdominal aortic aneurysm	Abdominal aorta >3.0 cm or previous aneurysm surgery
Diabetes mellitus	In all patients with diabetes ≥40 y or those ≥30 y who have had diabetes for >15 y or any patient with diabetes with microvascular complications
CKD	CKD present for >3 mo with albumin-to-creatinine ratio >3.0 mg/mmol or eGFR <60 mL/min/1.73 m^2
LDL level ≥5.0 mmol/L	Any patients with LDL level ≥5.0 mmol/L (which should raise suspicion for genetic dyslipidemia) in the absence of secondary causes, or any patient with documented familial hypercholesterolemia

CKD—chronic kidney disease, eGFR—estimated glomerular filtration rate, LDL—low-density lipoprotein, TIA—transient ischemic attack.
Adapted with permission from the *Canadian Journal of Cardiology*.[4]

be considered for patients at low risk (FRS 5% to 9.9%) with elevated cholesterol levels (using the same cutoffs), especially if risk modifiers are present. When cholesterol level is not elevated, evidence still favours the use of statins in intermediate-risk patients (FRS 10% to 19.9%) when risk modifiers are present and in men 50 years and older and women 60 years and older with 1 additional risk factor. A summary of these recommendations as they relate to statin therapy is shown in **Figure 1**.[4]

Case resolution

This 60-year-old woman has a low FRS of 5.3%. Although her calculated 10-year risk of ASCVD places her in the low-risk category, the death of her brother from MI at a young age is concerning. Although his MI at age 57 did not technically occur prematurely (defined as before age 55 in men and 65 in women),[86] he almost certainly had atherosclerosis before age 55 that went undiagnosed. Owing to these concerns and to better stratify her risk, several biomarker measurements were ordered. Her Lp(a) level was elevated at 830 mg/L (83 mg/dL) and her hs-cTnT level was elevated at 5.8×10^{-3} µg/L (5.8 pg/mL). In one study, women with a hs-cTnT value above 3×10^{-3} µg/L (3 pg/mL) had a 10.7% 10-year risk of ASCVD.[23] In addition to being a risk modifier in the CCS guidelines, an Lp(a) level of 830 mg/L (83 mg/dL) is associated with an odds ratio of approximately 2 for MI.[50,51] By incorporating biomarkers into risk stratification, both physician and patient have more information regarding 10-year and lifetime risk. In addition to health behaviour modifications, statin therapy should strongly be considered given these findings. Coronary artery calcium scoring could also be considered to guide treatment recommendations, but in this case it was not performed as both the patient and the care team were satisfied that there was sufficient evidence to initiate statin therapy.

Conclusion

Atherosclerotic CVD is a leading cause of morbidity and mortality worldwide, and risk stratification is undertaken to identify patients at risk of developing ASCVD. Although risk scores remain the foundation of risk assessment, they are imperfect and may underpredict or overpredict a person's risk. Biomarkers and imaging tests have the potential to improve risk stratification by bridging the detection gap between traditional risk factors and the multitude of unmeasurable factors that contribute to cardiovascular risk. Biomarkers are best used in patients at intermediate risk of ASCVD and in low-risk patients when traditional risk scores are believed to underestimate risk. With the recent CCS guidelines, family physicians should feel empowered to use Lp(a), hs-CRP, and CAC scores in appropriate patients to guide statin therapy. Although not currently guideline directed, there is evidence that hsTn can also be used to better stratify a patient's CVD risk. It is likely that the use of biomarkers will become more prevalent as research continues into their use in CVD risk stratification.

Dr Daniel Esau recently completed a fellowship in ambulatory and preventive cardiology in the Division of Cardiology at St Michael's Hospital in Toronto, Ont, and is now working in Victoria, BC. **Dr Beth L. Abramson** is the Paul Albrechtsen Professor in Cardiac Prevention and Women's Health in the Division of Cardiology at St Michael's Hospital and Associate Professor of Medicine at the University of Toronto.

Contributors
Both authors contributed to the literature review and interpretation, and to preparing the manuscript for submission.

Competing interests
None declared

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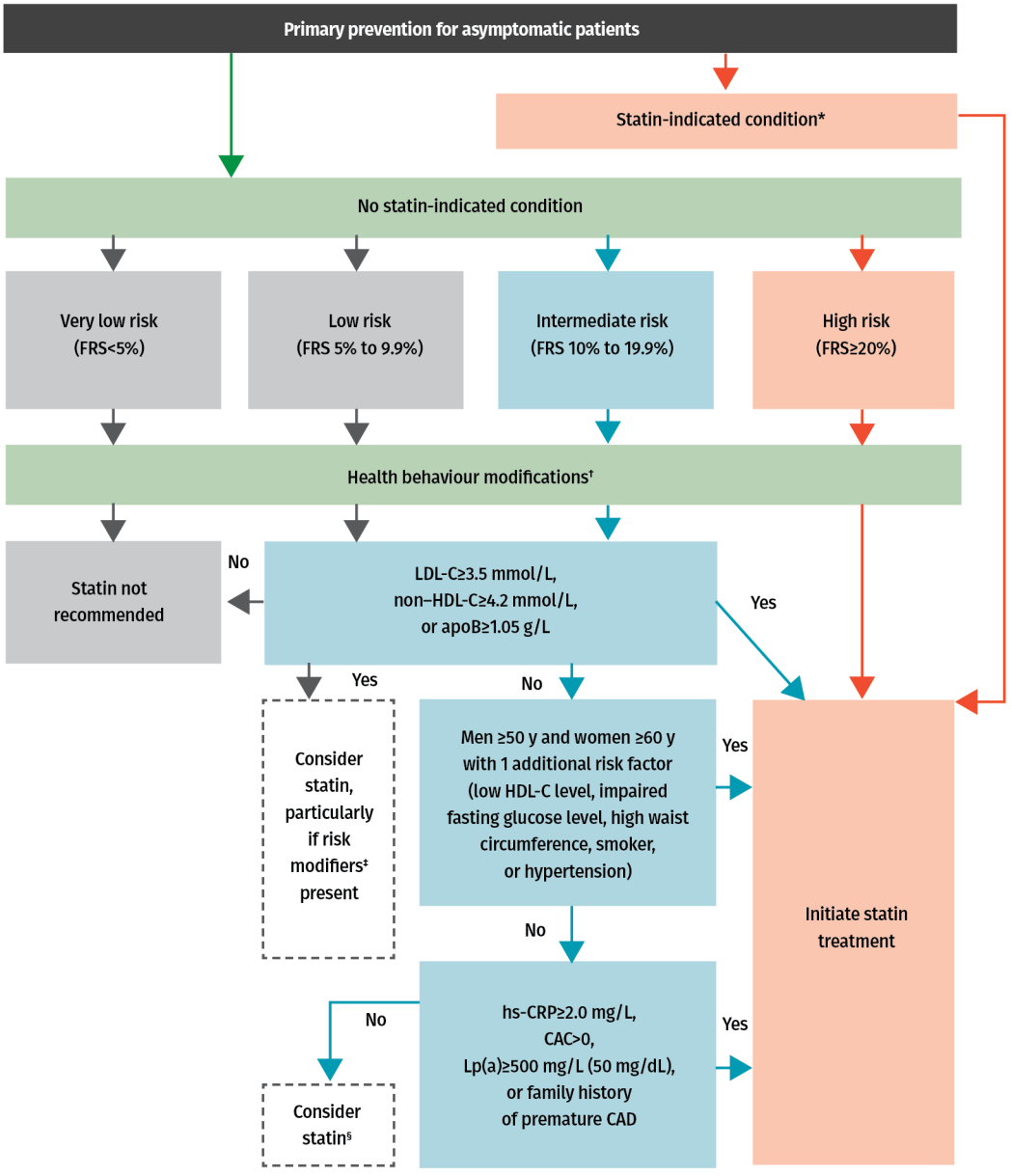
References

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J Am Coll Cardiol* 2020;76(25):2982-3021. Erratum in: *J Am Coll Cardiol* 2021;77(15):1958-9.
2. Severino P, D'Amato A, Pucci M, Infusino F, Adamo F, Birtolo LI, et al. Ischemic heart disease pathophysicology paradigms overview: from plaque activation to microvascular dysfunction. *Int J Mol Sci* 2020;21(21):8118.
3. Mancini GBJ, Gosselin G, Chow B, Kostuk W, Stone J, Yvorchuk KJ, et al. Canadian Cardiovascular Society guidelines for the diagnosis and management of stable ischemic heart disease. *Can J Cardiol* 2014;30(8);837-49. Epub 2014 May 28.
4. Pearson GJ, Thanassoulis G, Anderson TJ, Barry AR, Couture P, Dayan N, et al. 2021 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in adults. *Can J Cardiol* 2021;37(8):1129-50. Epub 2021 Mar 26.
5. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97(18):1837-47.
6. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117(6):743-53. Epub 2008 Jan 22.

Figure 1. Summary of statin therapy recommendations



apoB—apolipoprotein B, CAC—coronary artery calcium, CAD—coronary artery disease, FRS—Framingham risk score, HDL-C—high-density lipoprotein cholesterol, hs-CRP—high-sensitivity C-reactive protein, LDL-C—low-density lipoprotein cholesterol, Lp(a)—lipoprotein(a).

*See Table 1 for a list of statin-indicated conditions.

†Health behaviour modifications include diet, exercise, and smoking cessation.

‡Risk modifiers include a family history of premature atherosclerotic CVD, hs-CRP≥2.0 mg/L, Lp(a)≥500 mg/L (50 mg/dL), or CAC>0.

§No specific guidelines given for patients in this risk group; in general, statin therapy is considered based on patient preferences and priorities.

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7. Hozawa A, Folsom AR, Sharrett AR, Chambless LE. Absolute and attributable risks of cardiovascular disease incidence in relation to optimal and borderline risk factors. Comparison of African American with White subjects—Atherosclerosis Risk in Communities Study. *Arch Intern Med* 2007;167(6):573-9.
8. Khot UN, Khot MB, Bajzer CT, Sapp SK, Ohman EM, Brener SJ, et al. Prevalence of conventional risk factors in patients with coronary heart disease. *JAMA* 2003;290(7):898-904.
9. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364(9438):937-52.
10. Michos ED, Nasir K, Braunstein JB, Rumberger JA, Budoff MJ, Post WS, et al. Framingham risk equation underestimates subclinical atherosclerosis risk in asymptomatic women. *Atherosclerosis* 2006;184(1):201-6.
11. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA* 2007;297(6):611-9. Erratum in: *JAMA* 2007;297(13):1433.
12. Garcia M, Mulvagh SL, Bairey Merz CN, Buring JE, Manson JE. Cardiovascular disease in women: clinical perspectives. *Circ Res* 2016;118(8):1273-93.
13. Abramson BL, Melvin RG. Cardiovascular risk in women: focus on hypertension. *Can J Cardiol* 2014;30(5):553-9. Epub 2014 Feb 26.
14. Ge Y, Wang TJ. Identifying novel biomarkers for cardiovascular disease risk prediction. *J Intern Med* 2012;272(5):430-9. Epub 2012 Oct 15.
15. Apple FS, Ler R, Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. *Clin Chem* 2012;58(11):1574-81. Epub 2012 Sep 14.
16. Wu AHB, Christenson RH, Greene DN, Jaffe AS, Kavsak PA, Ordonez-Llanos J, et al. Clinical laboratory practice recommendations for the use of cardiac troponin in acute coronary syndrome: expert opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine. *Clin Chem* 2018;64(4):645-55. Epub 2018 Jan 17.
17. Carda R, Aceña Á, Pello A, Cristóbal C, Tarín N, Huelmos A, et al. The prognostic value of high-sensitive troponin I in stable coronary artery disease depends on age and other clinical variables. *Cardiology* 2015;132(1):1-8. Epub 2015 May 14.
18. Daniels LB, Laughlin GA, Clopton P, Maisel AS, Barrett-Connor E. Minimally elevated cardiac troponin T and elevated N-terminal pro-B-type natriuretic peptide predict mortality in older adults: results from the Rancho Bernardo Study. *J Am Coll Cardiol* 2008;52(6):450-9.
19. Everett BM, Brooks MM, Vlachos HEA, Chaitman BR, Frye RL, Bhatt DL, et al. Troponin and cardiac events in stable ischemic heart disease and diabetes. *N Engl J Med* 2015;373(7):610-20.
20. Blankenberg S, Salomaa V, Makarova N, Ojeda F, Wild P, Lackner KJ, et al. Troponin I and cardiovascular risk prediction in the general population: the BiomarCaRE consortium. *Eur Heart J* 2016;37(30):2428-37. Epub 2016 May 12.
21. Omland T, Pfeffer MA, Solomon SD, De Lemos JA, Røsjø H, Šaltytė Benth J, et al. Prognostic value of cardiac troponin I measured with a highly sensitive assay in patients with stable coronary artery disease. *J Am Coll Cardiol* 2013;61(12):1240-9. Epub 2013 Feb 13. Erratum in: *J Am Coll Cardiol* 2014;63(2):195-200.
22. Willeit P, Welsh P, Evans JDW, Tschiderer L, Boachie C, Jukema JW, et al. High-sensitivity cardiac troponin concentration and risk of first-ever cardiovascular outcomes in 154,052 participants. *J Am Coll Cardiol* 2017;70(5):558-68.
23. Sandoval Y, Bielinski SJ, Daniels LB, Blaha MJ, Michos ED, DeFilippis AP, et al. Atherosclerotic cardiovascular disease risk stratification based on measurements of troponin and coronary artery calcium. *J Am Coll Cardiol* 2020;76(4):357-70.
24. Sigurdardottir FD, Lyngbakken MN, Holmen OL, Dalen H, Hveem K, Røsjø H, et al. Relative prognostic value of cardiac troponin I and C-reactive protein in the general population (from the Nord-Trøndelag Health [HUNT] study). *Am J Cardiol* 2018;121(8):949-55. Epub 2018 Feb 2.
25. Lan NSR, Bell DA, McCaul KA, Vasikaran SD, Yeap BB, Norman PE, et al. High-sensitivity cardiac troponin I improves cardiovascular risk prediction in older men: HIMS (the Health in Men Study). *J Am Heart Assoc* 2019;8(5):e011818.
26. Saeed A, Nambi V, Sun W, Virani SS, Taffet GE, Deswal A, et al. Short-term global cardiovascular disease risk prediction in older adults. *J Am Coll Cardiol* 2018;71(22):2527-36. Epub 2018 Mar 10.
27. Iribarren C, Chandra M, Rana JS, Hlatky MA, Fortmann SP, Quertermous T, et al. High-sensitivity cardiac troponin I and incident coronary heart disease among asymptomatic older adults. *Heart* 2016;102(15):1177-82. Epub 2016 Mar 30.
28. Conroy R, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;24(11):987-1003.
29. Muscente F, De Caterina R. New insights from the MESA study: increased high-sensitivity troponins as a cardiovascular risk factor. *Eur Heart J Suppl* 2021;23(Suppl E):E68-72.
30. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med* 1999;340(2):115-26.
31. Raggi P, Genest J, Giles JT, Rayner KJ, Dwivedi G, Beanlands RS, et al. Role of inflammation in the pathogenesis of atherosclerosis and therapeutic interventions. *Atherosclerosis* 2018;276:98-108. Epub 2018 Jul 25.
32. Stary HC, Chandler AB, Glagov S, Guyton JR, Insull W Jr, Rosenfeld ME, et al. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation* 1994;89(5):2462-78.
33. Libby P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol* 2012;32(9):2045-51.
34. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest* 2003;111(12):1805-12. Erratum in: *J Clin Invest* 2003;112(2):299.
35. Krintus M, Kozinski M, Kubica J, Sypniewska G. Critical appraisal of inflammatory markers in cardiovascular risk stratification. *Crit Rev Clin Lab Sci* 2014;51(5):263-79. Epub 2014 Jun 11.
36. Schunkert H, Samani NJ. Elevated C-reactive protein in atherosclerosis—chicken or egg? *N Engl J Med* 2008;359(18):1953-5.
37. Stancel N, Chen CC, Ke LY, Chu CS, Lu J, Sawamura T, et al. Interplay between CRP, atherogenic LDL, and LOX-1 and its potential role in the pathogenesis of atherosclerosis. *Clin Chem* 2016;62(2):320-7. Epub 2015 Nov 25.
38. Leistner DM, Klotsche J, Pieper L, Palm S, Stalla GK, Lehnert H, et al. Prognostic value of NT-pro-BNP and hs-CRP for risk stratification in primary care: results from the population-based DETECT study. *Clin Res Cardiol* 2013;102(4):259-68. Epub 2013 Jan 4.
39. Li Y, Zhong X, Cheng G, Zhao C, Zhang L, Hong Y, et al. Hs-CRP and all-cause, cardiovascular, and cancer mortality risk: a meta-analysis. *Atherosclerosis* 2017;259:75-82. Epub 2017 Feb 9.
40. Emerging Risk Factors Collaboration; Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* 2010;375(9709):132-40. Epub 2009 Dec 22.
41. Dong Y, Wang X, Zhang L, Chen Z, Zheng C, Wang J, et al. High-sensitivity C reactive protein and risk of cardiovascular disease in China-CVD study. *J Epidemiol Community Health* 2019;73(2):188-92. Epub 2018 Dec 7.
42. Lahoud R, Chongthammakun V, Wu Y, Hawwa N, Brennan DM, Cho L. Comparing SF-36® scores versus biomarkers to predict mortality in primary cardiac prevention patients. *Eur J Intern Med* 2017;46:47-55. Epub 2017 Jul 29.
43. Frary CE, Blicher MK, Olesen TB, Stidsen JV, Greve SV, Vishram-Nielsen JKK, et al. Circulating biomarkers for long-term cardiovascular risk stratification in apparently healthy individuals from the MONICA 10 cohort. *Eur J Prev Cardiol* 2020;27(6):570-8. Epub 2019 Nov 12.
44. Chong Y, Ren Q, Li Y, Li C, Feng F, Zhou Y. Biomarkers for prediction of cardiovascular events in community-dwelling adults aged 40 or older. *Int Heart J* 2020;61(1):109-14. Epub 2019 Dec 26.
45. Emerging Risk Factors Collaboration; Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, White IR, et al. C-reactive protein, fibrinogen, and cardiovascular disease prediction. *N Engl J Med* 2012;367(14):1310-20.
46. Kavousi M, Elias-Smale S, Rutten JHW, Leening MJG, Vliegenthart R, Verwoert GC, et al. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. *Ann Intern Med* 2012;156(6):438-44.
47. Shah NP, Pajidipati NJ, McGarrah RW, Navar AM, Vemulapalli S, Blazing MA, et al. Lipoprotein (a): an update on a marker of residual risk and associated clinical manifestations. *Am J Cardiol* 2020;126:94-102. Epub 2020 Apr 7.
48. Tsimikas S, Hall JL. Lipoprotein(a) as a potential causal genetic risk factor of cardiovascular disease: a rationale for increased efforts to understand its pathophysiology and develop targeted therapies. *J Am Coll Cardiol* 2012;60(8):716-21.
49. Patel AP, Wang M, Pirruccello JP, Ellinor PT, Ng K, Kathiresan S, et al. Lp(a) (Lipoprotein[a]) concentrations and incident atherosclerotic cardiovascular disease: new insights from a large national biobank. *Arterioscler Thromb Vasc Biol* 2021;41(1):465-74. Epub 2020 Oct 29.
50. Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med* 2009;361(26):2518-28.
51. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA* 2009;301(22):2331-9.
52. Parish S, Hopewell JC, Hill MR, Marcovina S, Valdes-Marquez E, Haynes R, et al. Impact of apolipoprotein(a) isoform size on lipoprotein(a) lowering in the HPS2-THRIVE study. *Circ Genom Precis Med* 2018;11(2):e001696.
53. O'Donoghue ML, Fazio S, Giugliano RP, Stroes ESG, Kanevsky E, Gouni-Berthold I, et al. Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk. *Circulation* 2019;139(12):1483-92.
54. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ* 2017;357:j2099.
55. Emerging Risk Factors Collaboration; Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;302(18):1993-2000.
56. Langlois MR, Nordestgaard BG, Langsted A, Chapman MJ, Aakre KM, Baum H, et al. Quantifying atherogenic lipoproteins for lipid-lowering strategies: consensus-based recommendations from EAS and EFLM. *Clin Chem Lab Med* 2020;58(4):496-517.
57. Thompson A, Danesh J. Associations between apolipoprotein B, apolipoprotein AI, the apolipoprotein B/AI ratio and coronary heart disease: a literature-based meta-analysis of prospective studies. *J Intern Med* 2006;259(5):481-92.
58. Contois JH, McConnell JP, Sethi AA, Csako G, Devaraj S, Hoefner DM, et al. Apolipoprotein B and cardiovascular disease risk: position statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices. *Clin Chem* 2009;55(3):407-19. Epub 2009 Jan 23.
59. Glavinovic T, Sniderman AD. Apolipoprotein B: the Rosetta Stone of lipidology. *Curr Opin Endocrinol Diabetes Obes* 2021;28(2):90-6.
60. Welsh C, Celis-Morales CA, Brown R, Mackay DF, Lewsey J, Mark PB, et al. Comparison of conventional lipoprotein tests and apolipoproteins in the prediction of cardiovascular disease. *Circulation* 2019;140(7):542-52. Epub 2019 Jun 20.
61. Sniderman AD, Navar AM, Thanassoulis G. Apolipoprotein B vs low-density lipoprotein cholesterol and non–high-density lipoprotein cholesterol as the primary measure of apolipoprotein B lipoprotein-related risk: the debate is over. *JAMA Cardiol* 2022;7(3):257-8.

62. Krauss RM, Burke DJ. Identification of multiple subclasses of plasma low density lipoproteins in normal humans. *J Lipid Res* 1982;23(1):97-104.
63. Arai H, Kokubo Y, Watanabe M, Sawamura T, Ito Y, Minagawa A, et al. Small dense low-density lipoproteins cholesterol can predict incident cardiovascular disease in an urban Japanese cohort: the Suita study. *J Atheroscler Thromb* 2013;20(2):195-203. Epub 2012 Oct 17.
64. Hoogeveen RC, Gaubatz JW, Sun W, Dodge RC, Crosby JR, Jiang J, et al. Small dense low-density lipoprotein-cholesterol concentrations predict risk for coronary heart disease: the Atherosclerosis Risk In Communities (ARIC) study. *Arterioscler Thromb Vasc Biol* 2014;34(5):1069-77. Epub 2014 Feb 20.
65. Tsai MY, Steffen BT, Guan W, McClelland RL, Warnick R, McConnell J, et al. New automated assay of small dense low-density lipoprotein cholesterol identifies risk of coronary heart disease: the Multi-ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol* 2014;34(1):196-201. Epub 2013 Nov 14.
66. Higashioka M, Sakata S, Honda T, Hata J, Yoshida D, Hirakawa Y, et al. Small dense low-density lipoprotein cholesterol and the risk of coronary heart disease in a Japanese community. *J Atheroscler Thromb* 2020;27(7):669-82. Epub 2019 Nov 11.
67. Ivanova EA, Myasoedova VA, Melnichenko AA, Grechko AV, Orekhov AN. Small dense low-density lipoprotein as biomarker for atherosclerotic diseases. *Oxid Med Cell Longev* 2017;2017:1273042. Epub 2017 May 7.
68. Emerging Risk Factors Collaboration; Di Angelantonio E, Gao P, Pennells L, Kaptoge S, Caslake M, et al. Lipid-related markers and cardiovascular disease prediction. *JAMA* 2012;307(23):2499-506.
69. Rosen BD, Fernandes V, McClelland RL, Carr JJ, Detrano R, Bluemke DA, et al. Relationship between baseline coronary calcium score and demonstration of coronary artery stenoses during follow-up: MESA (Multi-Ethnic Study of Atherosclerosis). *JACC Cardiovasc Imaging* 2009;2(10):1175-83.
70. Kablak-Ziembicka A, Tracz W, Przewlocki T, Pieniazek P, Sokolowski A, Konieczynska M. Association of increased carotid intima-media thickness with the extent of coronary artery disease. *Heart* 2004;90(11):1286-90.
71. Granér M, Varpula M, Kahri J, Salonen RM, Nyyssönen K, Nieminen MS, et al. Association of carotid intima-media thickness with angiographic severity and extent of coronary artery disease. *Am J Cardiol* 2006;97(5):624-9. Epub 2006 Jan 6.
72. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008;358(13):1336-45.
73. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. *J Am Coll Cardiol* 2005;46(1):158-65.
74. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med* 1999;340(1):14-22.
75. Geisel MH, Bauer M, Hennig F, Hoffmann B, Lehmann N, Möhlenkamp S, et al. Comparison of coronary artery calcification, carotid intima-media thickness and ankle-brachial index for predicting 10-year incident cardiovascular events in the general population. *Eur Heart J* 2017;38(23):1815-22.
76. Nambi V, Chambless L, He M, Folsom AR, Mosley T, Boerwinkle E, et al. Common carotid artery intima-media thickness is as good as carotid intima-media thickness of all carotid artery segments in improving prediction of coronary heart disease risk in the Atherosclerosis Risk in Communities (ARIC) study. *Eur Heart J* 2012;33(2):183-90. Epub 2011 Jun 11.
77. Peters SAE, den Ruijter HM, Bots ML, Moons KGM. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. *Heart* 2012;98(3):177-84. Epub 2011 Nov 17.
78. Den Ruijter HM, Peters SAE, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA* 2012;308(8):796-803. Erratum in: *JAMA* 2013;310(16):1739.
79. Zaid M, Fujiyoshi A, Hisamatsu T, Kadota A, Kadowaki S, Satoh A, et al. A comparison of segment-specific and composite measures of carotid intima-media thickness and their relationships with coronary calcium. *J Atheroscler Thromb* 2022;29(2):282-95. Epub 2021 Feb 5.
80. Ravani A, Werba JP, Frigerio B, Sansaro D, Amato M, Tremoli E, et al. Assessment and relevance of carotid intima-media thickness (C-IMT) in primary and secondary cardiovascular prevention. *Curr Pharm Des* 2015;21(9):1164-71.
81. Alluri K, Joshi PH, Henry TS, Blumenthal RS, Nasir K, Blaha MJ. Scoring of coronary artery calcium scans: history, assumptions, current limitations, and future directions. *Atherosclerosis* 2015;239(1):109-17. Epub 2015 Jan 2.
82. McClelland RL, Jorgensen NW, Budoff M, Blaha MJ, Post WS, Kronmal RA, et al. 10-Year coronary heart disease risk prediction using coronary artery calcium and traditional risk factors: derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) with validation in the HNR (Heinz Nixdorf Recall) study and the DHS (Dallas Heart Study). *J Am Coll Cardiol* 2015;66(15):1643-53.
83. Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE. Coronary calcium score and cardiovascular risk. *J Am Coll Cardiol* 2018;72(4):434-47.
84. Blaha MJ, Cainzos-Achirica M, Greenland P, McEvoy JW, Blankstein R, Budoff MJ, et al. Role of coronary artery calcium score of zero and other negative risk markers for cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2016;133(9):849-58. Epub 2016 Jan 22.
85. Dzaye O, Razavi AC, Dardari ZA, Shaw LJ, Berman DS, Budoff MJ, et al. Modeling the recommended age for initiating coronary artery calcium testing among at-risk young adults. *J Am Coll Cardiol* 2021;78(16):1573-83.
86. 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: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;140(11):e596-646. Epub 2019 Mar 17. Errata in: *Circulation* 2019;140(11):e649-50, *Circulation* 2020;141(4):e60, *Circulation* 2020;141(16):e774.

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