Integrating coronary atherosclerosis burden and progression with coronary artery disease risk factors to guide therapeutic decision making

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Integrating Coronary Atherosclerosis Burden and Progression with Coronary Artery Disease Risk Factors to Guide Therapeutic Decision Making

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ABSTRACT

IMPORTANCE: Although atherosclerosis represents the primary driver of coronary artery disease, evaluation and treatment approaches have historically relied upon indirect markers of atherosclerosis that include surrogates (cholesterol), signs (angina), and sequelae (ischemia) of atherosclerosis. Direct quantification and characterization of atherosclerosis may encourage a precision heart care paradigm that improves diagnosis, risk stratification, therapeutic decision-making, and longitudinal disease tracking in a personalized fashion.

OBSERVATIONS: The American College of Cardiology Innovations in Prevention Working Group introduce the Atherosclerosis Treatment Algorithms that personalize medical interventions based upon atherosclerosis findings from coronary computed tomography angiography (CTA) and cardiovascular risk factors. Through integration of coronary CTA-based atherosclerosis evaluation, clinical practice guidelines, and contemporary randomized controlled trial evidence, the Atherosclerosis Treatment Algorithms leverage patient-specific atherosclerosis burden and progression as primary targets for therapeutic intervention. After defining stages of atherosclerosis severity by coronary CTA, Atherosclerosis Treatment Algorithms are described for worsening stages of atherosclerosis for patients with lipid disorders, diabetes, hypertension, obesity, and tobacco use. The authors anticipate a rapid pace of research in the field, and conclude by providing perspectives on future needs that may improve efforts to optimize precision prevention of coronary artery disease. Importantly, the Atherosclerosis Treatment Algorithms are not endorsed by the American College of Cardiology, and should not be interpreted as a statement of American College of Cardiology policy.

CONCLUSIONS AND RELEVANCE: We describe a precision heart care approach that emphasizes atherosclerosis as the primary disease target for evaluation and treatment. To our knowledge, this is the first proposal to use coronary atherosclerosis burden and progression to personalize therapy selection and therapy changes, respectively.

DISCLOSURE: The American College of Cardiology Foundation has made an investment in Cleerly, Inc., makers of a software solution that utilizes coronary CT angiography findings to evaluate coronary artery disease.

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KEYWORDS: Atherosclerosis; Coronary disease; Coronary disease burden; Coronary disease progression; Staging

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SCOPE OF THE PROBLEM

Since the identification of atherogenic lipids, elevated blood pressure, diabetes, tobacco use, obesity, and physical inactivity as factors associated with cardiovascular risk in population-based studies, these conditions have served as the cornerstone for treatment targets for coronary artery disease prevention in American College of Cardiology/American Heart Association clinical practice guidelines.[1,2] In daily practice, the contribution of risk factors to atherosclerotic cardiovascular disease risk can be assessed through calculators offered by the American College of Cardiology,[3] and treatment of these conditions has resulted in reductions in major adverse cardiovascular events.[2] Despite these findings, coronary artery disease remains the leading cause of mortality and morbidity in the world, with rates of major adverse cardiovascular events now increasing.[4] Several factors may contribute to the imperfection of a risk factor-based strategy, and include:

- **A Population-Based Approach Misses the Majority of Individuals Who Will Develop Coronary Artery Disease.** While risk factors are associated with coronary artery disease in large populations, they possess significantly less diagnostic and prognostic precision when applied to individual patients. As an example, in the Get with the Guidelines database of 136,905 individuals hospitalized for coronary artery disease, >50% had low-density lipoprotein <100 mg/dL, the level considered ideal at the time of publication.[5] These findings are consistent with the Framingham Heart Study, wherein >80% overlap of cholesterol levels was observed for patients with and without coronary artery disease in a 26-year follow-up.[6]
- **Risk Factor-Guided Approaches Perform Differently in Different Populations.** Atherosclerotic cardiovascular disease risk estimation is known to perform better in certain populations than others. In the Women's Health Initiative of a multiethnic population of 19,995 women, observed risks of atherosclerotic cardiovascular disease events were significantly lower than that estimated by risk calculators.[7] Similar disparities for risk factor scoring are observed for younger patients and those of different races and ethnicities.[8]
- **Risk Factor Presence Does Not Ensure Presence of Coronary Artery Disease, Even in High-Risk Individuals.** While diabetes is widely considered a "coronary artery disease equivalent,"[9] population-based cohorts of diabetic individuals undergoing coronary computed tomography angiography have revealed that one-third have no or minimal coronary artery disease, a finding associated with low rates of major adverse cardiovascular events.[10] Population-based definitions do not ideally classify individuals with diabetes who may actually be at low clinical risk.
- **Risk Factor Control Fails the Majority of Individuals Who Retain High Residual Risk.** Risk factor control does not reliably pinpoint individuals who are successfully treated for risk factors but who retain significant residual risk for major adverse cardiovascular events. As an example, Libby[11] has espoused the concept of the "forgotten majority" to the 62%-75% of individuals with dyslipidemia who are treated with statin therapy but still go on to experience major adverse cardiovascular events.
- **Atherosclerotic Cardiovascular Disease Risk Scoring Does Not Account for Other Well-Known Factors That Predispose an Individual to Major Adverse Cardiovascular Events.** Hundreds of conditions have been identified that predispose an individual to major adverse cardiovascular events, and are unaccounted for in atherosclerotic cardiovascular disease scoring.[4] These include: cardiometabolic disorders such as non-alcoholic steatohepatitis; renal disorders such as chronic kidney disease; pulmonary disorders such as chronic obstructive pulmonary disease and exposure to air pollution; and many others.
- **Atherosclerotic Cardiovascular Disease Risk Scoring Does Not Account for As-Yet Unknown Factors That Predispose an Individual to Major Adverse Cardiovascular Events.** It remains likely that there is an array of contributors to atherosclerotic cardiovascular disease risk that have not yet been identified.[12] Further, beyond risk factor presence, it is likely that its severity, duration, and treatment efficacy contribute to major adverse cardiovascular events risk, and are not accounted for by atherosclerotic cardiovascular disease risk scoring. Precision prevention to reduce atherosclerotic cardiovascular disease risk will ideally integrate the totality of clinical, psychosocial, environmental, and genetic determinants into actionable metrics that can improve personalized evaluation and treatment and can be tracked over time.

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY

Coronary computed tomography angiography (CTA) allows for evaluation of the full spectrum of coronary health and disease. Coronary CTA allows for quantitative measurement of atherosclerotic burden, its secondary anatomic consequences on the coronary lumen (stenosis), and its tertiary late-stage physiologic consequences on flow (ischemia).[13] Coronary CTA demonstrates high performance against 'gold standards' and can be safely performed with low radiation dose.[14]

Large-scale randomized trials applying coronary CTA in individuals with suspected coronary artery disease—such as the Scottish COmputed Tomography of the HEART trial (SCOT-HEART) and the PROspective Multicenter Imaging Study for Evaluation of chest pain (PROMISE)—have demonstrated superior or equivalent clinical outcomes when compared with ischemia-guided approaches.[15-17] These trials have established the necessary evidence to advance coronary CTA to Level IA in guidance documents,

most recently in the 2021 American Heart Association/American College of Cardiology Chest Pain Guidelines.[18,19]

In both SCOT-HEART and PROMISE, the majority who suffered myocardial infarction (MI) possessed only mild stenosis at the time of coronary CTA.[15,16] These findings are consistent with those reported by Saleh and Ambrose[20] for invasive angiography wherein the majority of individuals who will suffer MI have only mild stenosis. Together, these findings suggest a need for definitions of coronary artery disease severity wherein the burden of atherosclerosis may offer independent insights into MI risk.

CORONARY CTA FOR ATHEROSCLEROSIS BURDEN AND TYPE

Coronary CTA performs robustly compared with intravascular ultrasound for atherosclerosis, with sensitivity and specificity of 93% and 92%, respectively.[21] Coronary CTA offers advantages over intravascular ultrasound by enabling whole-heart atherosclerosis quantification rather than limiting evaluation to proximal portions of single arteries. Reporting of plaque burden by coronary CTA is similar to intravascular ultrasound, employing total plaque volume or percent atheroma volume. Atherosclerosis by coronary CTA has been commonly categorized by composition: low-density non-calcified plaque (<30 Hounsfield units [HU]), non-calcified plaque (30-350 HU), and calcified plaque (351+ HU).[22,23]

Coronary CTA atherosclerosis informs prognosis. In the CONFIRM study, presence of atherosclerosis in proximal segments conferred greater predictive value for future major adverse cardiovascular events than stenosis, with both features additive for prognostication of major adverse cardiovascular events.[24] Similarly, by quantitative coronary CTA in the 3V FFR-FRIENDS study, outcomes were worse for non-ischemic vessels exhibiting high-risk atherosclerosis, including increasing total plaque volume and percent atheroma volume.[25,26] These findings demonstrate that atherosclerosis improves identification of risk of major adverse cardiovascular events in a manner independent to risk factor scoring, stenosis, and ischemia.

Coronary CTA also allows for quantification of advanced coronary artery disease features, including low-density non-calcified plaque and positive remodeling. Together, low-density non-calcified plaque and positive remodeling in a single lesion has been termed "high-risk plaque." In the Incident COroNary syndromes Identified by Computed tomography (ICONIC) study of 25,251 patients, low-density non-calcified plaque volume was the strongest discriminator of future MI.[27] SCOT-HEART also found low-density non-calcified plaque to be the strongest predictor of MI.[28,29] Similarly, in PROMISE, high-risk plaque was associated with major adverse cardiovascular events independent of conventional markers such as stenosis, with predictive value of high-risk plaque generalizable to individuals without severe stenosis.[30] Mechanistically, high-risk plaques may offer inflammatory and anatomic insights into plaque biology. High-risk plaques by coronary CTA are associated with features considered prototypic of the "vulnerable plaque," such as thin fibrous caps, macrophage infiltration, and necrotic intraplaque cores.[32]

On the opposite end of the spectrum from dark low-density non-calcified plaques are bright calcified plaques. Calcified plaques include 1K plaques (with HU >1000), which were found in ICONIC to be associated with a lower risk of future acute coronary syndrome. Indeed, a continuum of risk of acute coronary syndrome from high to low is observed for plaques with compositions between low-density non-calcified plaque (dark) and 1K plaques (bright) (Figure 1[31]).

CORONARY CTA FOR ATHEROSCLEROSIS PROGRESSION

Atherosclerosis is a dynamic process that progresses, with plaque composition also demonstrating changes over time. Motoyama et al[34] showed that plaque progression in individuals was the strongest predictor of future major adverse cardiovascular events over stenosis and risk factors. Coronary CTA may be used for direct assessment of coronary artery disease changes over time to personalize determination of the efficacy of medical therapy.[35,36]

In the Progression of AtheRosclerotic plAque DetermIned by computed tomoGraphic angiography iMaging (PARADIGM) study, statins were associated with 21% reduction in annualized percent atheroma volume progression and 35% reduction in high-risk plaque at a 3.4-year follow-up serial coronary CTA.[35] While statins were associated with slower progression, the overall reduction was modest, as statins slowed non-calcified plaque formation while accelerating calcified plaque formation. Independent of statin use, rate of plaque progression was independently associated with major adverse cardiovascular events, indicating that atherosclerosis changes over time may be an essential tool to identify individuals who are not responding optimally to medical therapy.[36] Results similar to PARADIGM have been observed for icosapent ethyl, PCSK9 inhibitors, colchicine, Dietary Approaches to Stop Hypertension diet, and physical activity, wherein these therapies transformed plaque composition from non-calcified plaque to calcified plaque, findings associated with improvement in outcomes[37-41] (Table 1).

RATIONALE AND AIM OF THE ATHEROSCLEROSIS TREATMENT ALGORITHMS

The Atherosclerosis Treatment Algorithms were developed as an evidence-based disease-focused approach to more accurately personalized coronary artery disease risk assessment and treatment efficacy. Whole-heart atherosclerosis phenotyping allows for a non-invasive approach for personalized, quantitative disease tracking, and integrates into a single metric an individual's exposure to all coronary artery

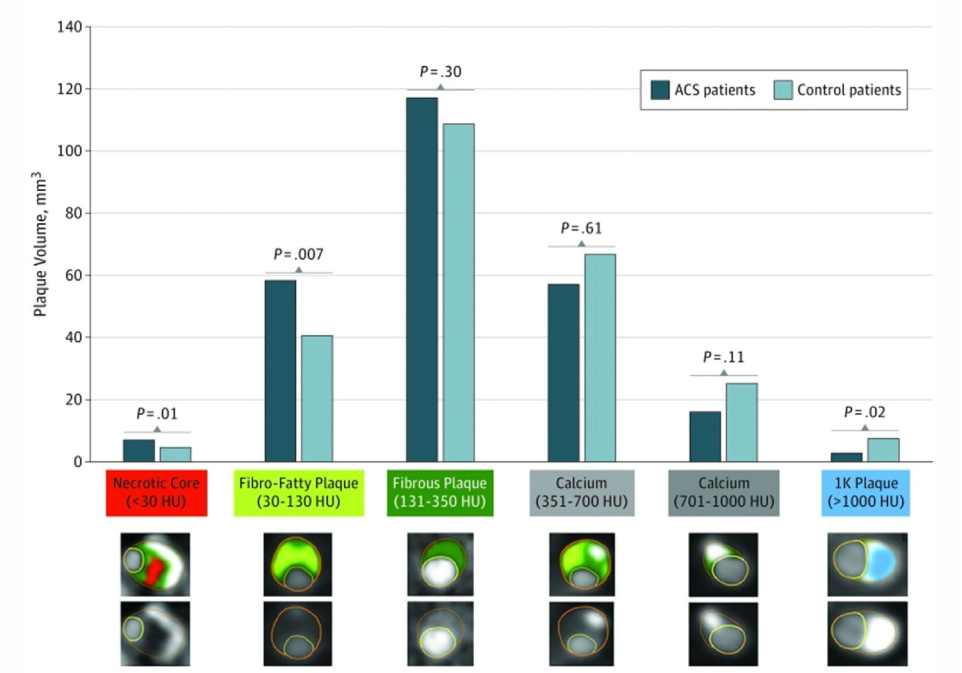

Figure 1 Plaque composition assessment demonstrates lower-density non-calcified plaques to be associated with higher risk of future acute coronary syndrome, and higher-density calcified plaques to be associated with lower risk of future acute coronary syndrome. Adapted from: van Rosendael AR, Narula J, Lin FY, et al. Association of high-density calcified 1K plaque with risk of acute coronary syndrome; *JAMA Cardiol*. 2020;5:282-290.[35]

disease risk factors—whether known or unknown—over the course of their lifetime.[36]

The Atherosclerosis Treatment Algorithms emulate the most successful prevention paradigms, such as those for cancer.[43-45] Advanced non-invasive imaging—including mammography, colonoscopy, and lung CT—for direct visualization of disease has proven effective in reducing cancer mortality.[43-45] These pathways share 5 steps:

1. Advanced imaging for disease visualization;
2. Staging by presence (tumor), extent (lymph nodes), and severity (metastasis);
3. Classification of type of cancer;
4. Personalization of treatment to an individual's actual disease characteristics, and;
5. Repeat advanced imaging to assess therapeutic response.

Importantly, the Atherosclerosis Treatment Algorithms are *not* intended to serve as a replacement to practice guidelines or consensus statements, nor are they expected to be divorced from risk factor scoring.

DEFINING SEVERITY OF CORONARY ATHEROSCLEROSIS BY CORONARY CTA

To quantify atherosclerosis burden, we used total plaque volume and percent atheroma volume, defined as (plaque volume/vessel volume) × 100%, as these approaches are least influenced by a patient's body size and surface area.[47] To stage atherosclerosis, we contemplated several definitions, including 1) population-based ranges of age, sex, and ethnicity; 2) plaque volumes for stable individuals who experience future acute coronary syndrome; and 3) plaque volumes according to stenosis severity by QCA. We chose the latter, given the widespread familiarity of these cut points in clinical care for angiographically non-obstructive and obstructive 1-vessel, 2-vessel, or 3-vessel/left main >50% diameter stenosis. Given significant overlap of atheroma volume in patients with non-obstructive and 1-vessel angiographic coronary artery disease, we combined these groups in a single stage.[33] The coronary atherosclerosis stages were derived from a multinational trial wherein patients underwent coronary CTA and quantitative coronary angiography[33] (Table 2, Figure 2).

Atherosclerosis stages were categorized as:[33,77]

- Stage 0 = 0 mm^3 (0% percent atheroma volume);
- Stage 1 = >0-250 mm^3 (>0-5.0% percent atheroma volume);
- Stage 2 = >250-750 mm^3 (>5%-15% percent atheroma volume);
- Stage 3 = >750 mm^3 (>15% percent atheroma volume).

Increases in atherosclerosis >1.0% percent atheroma volume/year are associated with worsened prognosis, and

Table 1 Effects of Medical Therapy and Lifestyle Interventions on Plaque Progression and Composition

Intervention	Study Design	Follow-Up Serial CCTA	CCTA Atherosclerosis	Results
Statins	• Multicenter observational cohort	• ≥2 y	• Annualized plaque volume △ • Annualized plaque volume △ by composition	• Statins associated with lower rate of plaque progression • Statins associated with higher rate of calcified plaque formation, lower rate of non-calcified plaque formation
Icosapent ethyl	• RCT	• 18 mo	• LD-NCP volume	• Icosapent ethyl reduced LD-NCP volume compared with placebo
Evolocumab	• Single center, retrospective	• 6 mo	• Stability and size of plaques at 6 months	• Evolocumab increased CT density of plaques • Evolocumab decreased % stenosis
Colchicine	• Single center, prospective	• 12.6 mo	• LD-NCP volume	• Colchicine reduced LD-NCP
DASH diet + physical activity	• RCT	• 15.4 mo	• △ in percent atheroma volume and plaque composition	• Diet + activity slowed the progression of atherosclerosis • Diet + activity reduced non-calcified plaque

CCTA = coronary computed tomography angiography; CT = computed tomography; DASH = Dietary Approaches to Stop Hypertension; LD-NCP = Low-density non-calcified plaque; RCT = randomized controlled trial.

higher baseline atherosclerosis is the strongest driver of coronary artery disease progression.[36] In the Effect of Icosapent Ethyl on Progression of Coronary Atherosclerosis in Patients with Elevated Triglycerides on Statin Therapy (EVAPORATE) and PARADIGM trials, significant atherosclerosis changes were noted within 9 months and 2 years, respectively.[35,37,38,48] In both, atherosclerosis changes were directly related to major adverse cardiovascular events.[49,50] It follows that an earlier follow-up coronary CTA to determine therapeutic success may be more valuable for those with higher baseline coronary artery disease burden. Our proposal is that serial coronary CTA may be beneficial for patients with Stage 0, 1, 2, and 3 atherosclerosis at 4, 3, 2, and 1 years, respectively. In the event of significant atherosclerosis progression, therapeutic decision-making can then be informed by changes in an individual's actual disease process.

TREATING ATHEROSCLEROSIS BURDEN AND PROGRESSION

Less than 5 years ago, the "toolbox" of primary prevention for coronary artery disease was limited, with statins, ezetimibe, aspirin, and antihypertensive agents largely the only agents available. Today, there are myriad of Food and Drug Administration-approved therapies (with several others anticipated shortly) that have a beneficial impact on risk factors or reducing major adverse cardiovascular events (Supplementary Table[47-60,62]). These novel medications target coronary artery disease as a chronic inflammatory atherothrombotic disease process, and include:[51,52]

- **Lipid-lowering agents:** (1) PCSK9 inhibitors, (2) Icosapent ethyl, (3) Bempedoic acid, (4) Inclisiran[49,53-56]
- **Antithrombotic agents:** (5) Rivaroxaban[57]
- **Anti-inflammatory agents:** (6) Colchicine[58]

Table 2 Stages of Coronary Atherosclerosis by Total Plaque Volume and Percent Atheroma Volume

Stage of Atherosclerosis	Angiographic Stenosis Severity	Total Plaque Volume (mm^3)	Percent Atheroma Volume (%)
None	No stenosis	0	0%
Stage 1	1%-49% stenosis 1-vessel CAD >50% stenosis	>0 to 250	>0%-5.0%
Stage 2	2-vessel CAD >50% stenosis	>250 to 750	>5%-15.0%
Stage 3	3-vessel CAD >50% stenosis	>750	>15.0%

CAD = coronary artery disease.

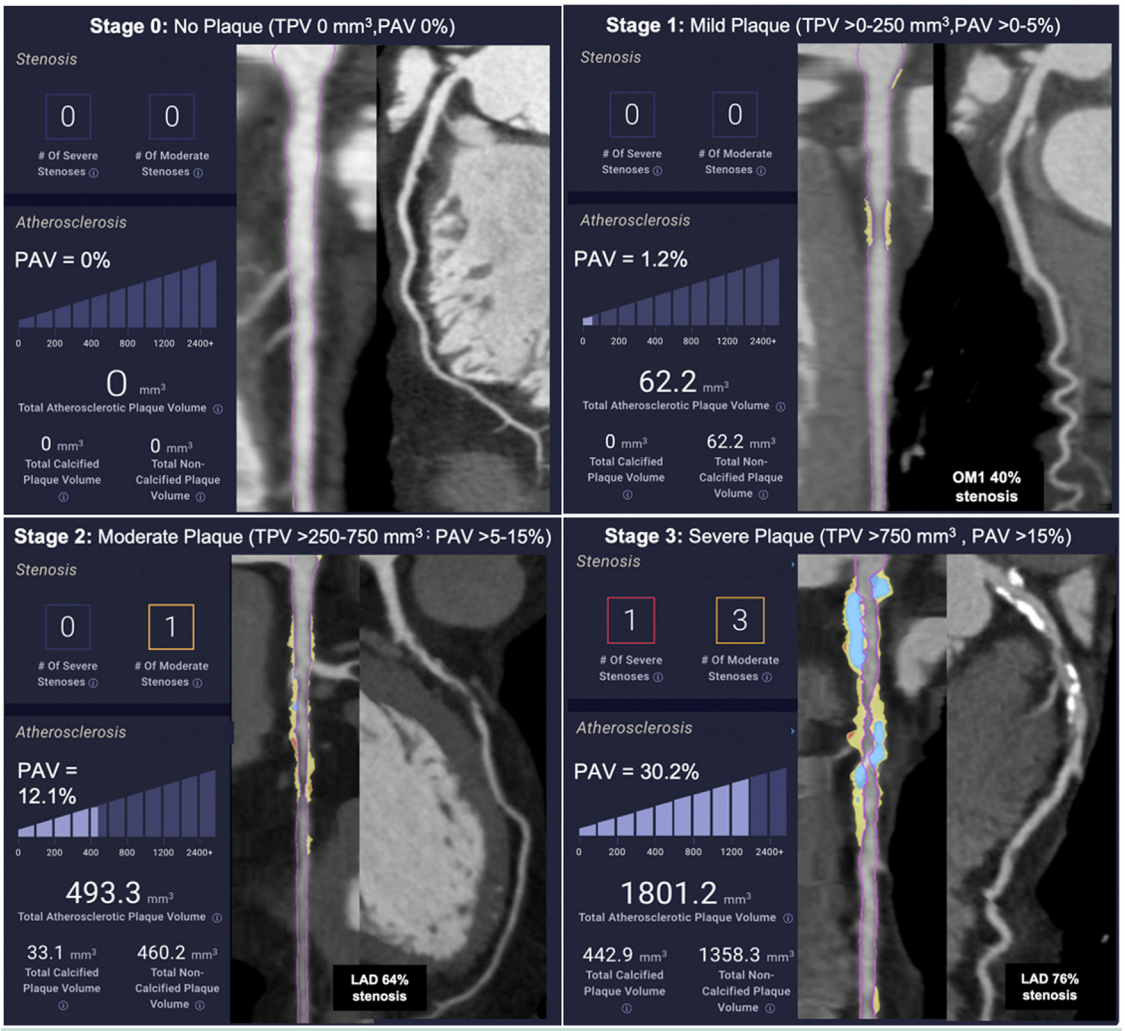

Figure 2 Examples of patients with Stage 0, Stage 1, Stage 2 and Stage 3 atherosclerosis. Staging of coronary atherosclerosis should say total Cleerly Labs and Cleerly Coronary (Cleerly Inc., Denver, Colo). PAV = percent atheroma volume; TPV = total plaque volume. Adapted from *J Cardiovasc Comput Tomogr.* 2022 16(5):415−422.

- **Novel anti-atherosclerotic diabetic agents:** (7) Glucagon-like peptide (GLP)-1 receptor agonists, and (8) Sodium-glucose transport protein 2 (SGLT2) inhibitors[59-68]

The "toolbox" now enables >10 classes of medications to treat atherosclerosis, with newer agents—such as those targeting Lp(a) and GLP-1/glucose-dependent insulinotropic polypeptide (GIP) agonists—expected shortly. Notably, the Atherosclerosis Treatment Algorithms emphasize therapies with the most robust outcomes data at the time of writing. This does not preclude other medications as having utility and, as evidence develops, the Atherosclerosis Treatment Algorithms will be adjusted accordingly.

ATHEROSCLEROSIS TREATMENT ALGORITHMS

The Atherosclerosis Treatment Algorithms (Table 3, Supplementary Figures 1−4, available online) emphasize lifestyle interventions, including a plant-forward diet, and regular physical activity, as recommended in guidelines.[2] In extreme cases, use of metabolic surgery may be considered for the treatment of obesity-related atherosclerotic cardiovascular disease.[69]

Several important issues should be considered when applying the Atherosclerosis Treatment Algorithms into daily clinical practice:

- Atherosclerosis Treatment Algorithms emphasize patient-based, rather than lesion-based, measures of atherosclerosis burden and progression. We advocate the concept of assessing the "vulnerable patient" over that of the "vulnerable plaque." In part, this may be due to the dynamism of atherosclerosis and morphologic changes over time that contribute to the likelihood of any given plaque to become culprit in future acute coronary syndrome.[70,71] The authors' current thinking is that morphologic quantitative assessment of plaques alone is inadequate to precisely pinpoint lesions at risk of becoming culprit, and that significant contributors to major adverse cardiovascular events risk beyond atherosclerosis itself—

Table 3 Simplified Approach to Medical Therapy Based Upon Stage of Atherosclerosis

Stage	Treatment	Serial CCTA
Stage 0	• GDMT/Shared decision for de-escalation of therapy	4 years
Stage 1	• Statin: (rosuvastatin 10-20 mg QD/ atorvastatin 20-40 mg QD) • Ezetimibe 10 mg QD	3 years
Stage 2	• High-intensity statin (rosuvastatin 40 mg QD/atorvastatin 80 mg QD) • Ezetimibe 10 mg QD • Aspirin 81-100 mg QD • Rivaroxaban 2.5 mg BID *If diabetic, GLP-1 receptor agonist*	2 years
Stage 3	• High-intensity statin (rosuvastatin 40 mg QD/atorvastatin 80 mg QD) • Ezetimibe 10 mg QD • ASA 81-100 mg QD* • Rivaroxaban 2.5 mg BID* • Other lipid-lowering medications: PCSK-9 inhibitors, icosapent ethyl, inclisiran, bempedoic acid • Colchicine 0.6 mg QD • Cardiac rehabilitation or other supervised exercise program (if covered) *If diabetic: GLP-1 receptor agonist and SGLT2 inhibitor*	1 year

ASA = acetylsalicylic acid; BID = twice a day; CCTA = coronary CT angiography; GDMT = guideline-directed medical therapy; GLP-1 = glucagon-like peptide 1; QD = once a day; SGLT2 = sodium-glucose transport protein 2.

Comprehensive atherosclerosis treatment algorithms for patients with lipid disorders, diabetes, hypertension, obesity, and tobacco use can be seen in Supplementary Figures 1–4 (available online).

*For patients at bleeding risk, use of rivaroxaban and aspirin is suggested only after shared decision making to ensure patient literacy of elevated bleeding risk.

such as inflammation and thrombosis—will improve predictive precision.

- Atherosclerosis Treatment Algorithms highlight total atherosclerosis burden rather than focusing on a specific plaque composition. The preponderance of prognostic data has emphasized overall atherosclerotic burden for risk stratification.[27-29,31,42] As future studies are performed examining the differential prognostic utility of atherosclerotic plaques by compositional phenotype, the Atherosclerosis Treatment Algorithms may be updated accordingly to account for not only atherosclerosis stage, but also classification of phenotypic disease type.
- Atherosclerosis Treatment Algorithms do not incorporate advanced atherosclerosis markers of risk by coronary CTA (eg, high-risk plaques). Several high-risk features have been observed by coronary CTA to be predictive of future major adverse cardiovascular events, including low-density non-calcified plaque, positive remodeling, and others.[32] We elected not to include these Atherosclerosis Treatment Algorithms for reasons of simplicity, and to offer a single integrated metric (percent atheroma volume) that represents a patient's total atherosclerotic burden.[47]
- Atherosclerosis Treatment Algorithms propose longitudinal coronary CTA-based evaluation commensurate to the burden of disease. Given that baseline plaque burden is the strongest predictor of plaque progression, we reasoned that those with higher atherosclerotic burden should undergo re-evaluation after therapeutic initiation at a shorter inter-scan interval than individuals with lesser amounts of disease. A 4-3-2-1-year inter-scan interval for repeat coronary CTA was considered reasonable for patients with Stage 0, 1, 2, and 3 atherosclerosis, respectively.

FUTURE OUTLOOK

As additional evidence is developed, we expect the Atherosclerosis Treatment Algorithms to evolve to include other features; for example:

- **Atherosclerotic Plaque Composition.** Given the continuum of prognosis that has been observed across the continuum of Hounsfield unit gray scale (ie, lower-density = greater risk, higher density = lower risk), incorporating continuous measures of plaque compositions may improve understanding of patient- and plaque-level risk.[31]
- **Additional Atherosclerosis Features.** In addition to measures of high-risk plaque—such as low-density non-calcified plaque and positive remodeling—several other atherosclerosis and vascular morphology features have been demonstrated to impart prognostic importance.[32] These include plaque location, diffuseness, geometry, vessel and lumen volume; and may accentuate evaluation of those undergoing coronary CTA .

As prior treatment trials have emphasized surrogate markers of coronary artery disease in lieu of coronary artery disease itself, our proposed approach to targeting atherosclerosis as the primary disease target is intuitive but unproven. Validation of the Atherosclerosis Treatment Algorithms will require randomized trials and observational cohort studies, which are ongoing. Given the multitude of available treatments for coronary artery disease, it is likely that real-world strategy trials that enable comparison of an approach to atherosclerosis treatment will be most informative.

ECONOMIC IMPLICATIONS OF A PERSONALIZED APPROACH TO CORONARY ARTERY DISEASE DIAGNOSIS

The Atherosclerosis Treatment Algorithms incorporate an array of novel, highly effective medications, some of which are costly.

There are ~40 million in the United States alone who may qualify for these therapies based upon risk factors.[64,72-75] However, in both symptomatic and population-based cohorts, the majority of individuals with coronary artery disease risk

factors do not, in fact, possess significant coronary artery disease.[10,46] In this regard, a precision diagnostics approach to serve as a judicious referral management tool that espouses the "right treatment for the right patient at the right time" based upon quantitative disease burden may allow for a more rationale and individualized approach to guide therapy. This approach may reduce the economic burden for the physician and Pharmacy Benefit Manager. At present, more than $80,000 per physician per annum is spent on prior authorizations.[76] A personalized approach with objective measures of disease may be effective at curbing prior authorization costs while ensuring that the patients receive the most appropriate medications. These cost savings should be balanced by the cost of coronary CTA, which may in some instances be performed serially. At present, the approximate Medicare reimbursement for coronary CTA is ~$180 USD.

CONCLUSION

The authors describe a precision heart care approach that emphasizes atherosclerosis as the primary disease target for evaluation and treatment. By integrating visualized coronary atherosclerosis with risk factors to personalize therapy, Atherosclerosis Treatment Algorithms are, to our knowledge, the first to propose using coronary atherosclerosis burden and progression to personalize therapy selection and therapy changes, respectively.

References

1. Andersson C, Nayor M, Tsao CW, Levy D, Vasan RS. Framingham Heart Study: JACC Focus Seminar, 1/8. *J Am Coll Cardiol* 2021;77(21):2680–92.
2. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019;74(10):1376–414.
3. American College of Cardiology. ASCVD Risk Estimator Plus. Available at: https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/. Accessed October 27, 2022.
4. Virani SS, Alonso A, Aparicio HJ, et al. Heart Disease and Stroke Statistics—2021 Update: a report from the American Heart Association. *Circulation* 2021;143(8):e254–743.
5. Sachdeva A, CP Cannon, Deedwania PC, et al. Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalizations in Get With The Guidelines. *Am Heart J* 2009;157(1) [111-117 e2.
6. Castelli WP. Lipids, risk factors and ischaemic heart disease. *Atherosclerosis* 1996;124(suppl):S1–9.
7. Mora S, Wenger NK, Cook NR, et al. Evaluation of the pooled cohort risk equations for cardiovascular risk prediction in a multiethnic cohort from the Women's Health Initiative. *JAMA Intern Med* 2018;178(9):1231–40.
8. Akosah KO, Schaper A, Cogbill C, Schoenfeld P. Preventing myocardial infarction in the young adult in the first place: how do the National Cholesterol Education Panel III guidelines perform? *J Am Coll Cardiol* 2003;41(9):1475–9.
9. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339(4):229–34.
10. Muhlestein JB, Lappe DL, Lima JA, et al. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. *JAMA* 2014;312(21):2234–43.
11. Libby P. The forgotten majority: unfinished business in cardiovascular risk reduction. *J Am Coll Cardiol* 2005;46(7):1225–8.
12. Vakili D, Radenkovic D, Chawla S, Bhatt DL. Panomics: new databases for advancing cardiology. *Front Cardiovasc Med* 2021;8:587768.
13. Marwick TH, Cho I, O Hartaigh B, Min JK. Finding the gatekeeper to the cardiac catheterization laboratory: coronary CT angiography or stress testing? *J Am Coll Cardiol* 2015;65(25):2747–56.
14. Schicchi N, Fogante M, Palumbo P, et al. The sub-millisievert era in CTCA: the technical basis of the new radiation dose approach. *Radiol Med* 2020;125(11):1024–39.
15. SCOT-HEART Investigators, Newby DE, Adamson PD, et al. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med* 2018;379(10):924–33.
16. Douglas PS, Hoffmann U. Anatomical versus functional testing for coronary artery disease. *N Engl J Med* 2015;373(1):91.
17. Blankstein R, Bittencourt MS, Bhatt DL. Coronary CTA in the evaluation of stable chest pain: clear benefits, but not for all. *J Am Coll Cardiol* 2017;69(14):1771–3.
18. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;41(3):407–77.
19. National Institute for Health and Care Excellence (NICE). NICE Guidance for Stable Chest Pain Patients (CG95 & MTG32) to Appropriately Diagnose Patients with Suspected Coronary Artery Disease. Available at: https://www.nice.org.uk/sharedlearning/nice-guidance-for-stable-chest-pain-patients-cg95-mtg32-to-appropriately-diagnose-patients-with-suspected-coronary-artery. Accessed October 27, 2022.
20. Saleh M, Ambrose JA. Understanding myocardial infarction. *F1000Res*. 2018;7:F1000 Faculty Rev-1378. Ecollection 2018. doi:10.12688/f1000research.15096.1.
21. Fischer C, Hulten E, Belur P, Smith R, Voros S, Villines TC. Coronary computed tomographyangiography versus intravascular ultrasound for estimation of coronary stenosis and atherosclerotic plaque burden: a meta-analysis. *J Cardiovasc Comput Tomogr* 2013;7(4):256–66.
22. de Graaf MA, Broersen A, Kitslaar PH, et al. Automatic quantification and characterization of coronary atherosclerosis with computed tomography coronary angiography: cross-correlation with intravascular ultrasound virtual histology. *Int J Cardiovasc Imaging* 2013;29(5):1177–90.
23. van Velzen JE, Schuijf JD, de Graaf FR, et al. Plaque type and composition as evaluated non-invasively by MSCT angiography and invasively by VH IVUS in relation to the degree of stenosis. *Heart* 2009;95(24):1990–6.
24. Hadamitzky M, Achenbach S, Al-Mallah M, et al. Optimized prognostic score for coronary computed tomographic angiography: results from the CONFIRM registry (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry). *J Am Coll Cardiol* 2013;62(5):468–76.
25. Min JK, Budoff MJ, Bax JJ. The multidimensionality of coronary artery disease: combining, conflating, and changing. *JACC Asia* 2021;1(1):49–52.
26. Yang S, Lee JM, Hoshino M, et al. Prognostic implications of comprehensive whole vessel plaque quantification using coronary computed tomography angiography. *JACC Asia* 2021;1(1):37–48.
27. Chang HJ, Lin FY, Lee SE, et al. Coronary atherosclerotic precursors of acute coronary syndromes. *J Am Coll Cardiol* 2018;71(22):2511–22.
28. Ferencik M, Mayrhofer T, Bittner DO, et al. Use of high-risk coronary atherosclerotic plaque detection for risk stratification of patients with stable chest pain: a secondary analysis of the PROMISE randomized clinical trial. *JAMA Cardiol* 2018;3(2):144–52.
29. Williams MC, Kwiecinski J, Doris M, et al. 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* 2020;141(18):1452–62.

30. Taron J, Foldyna B, Mayrhofer T, et al. Risk stratification with the use of coronary computed tomographic angiography in patients with nonobstructive coronary artery disease. *JACC Cardiovasc Imaging* 2021;14(11):2186–95.
31. van Rosendael AR, Narula J, Lin FY, et al. Association of high-density calcified 1K plaque with risk of acute coronary syndrome. *JAMA Cardiol* 2020;5(3):282–90.
32. Abdelrahman KM, Chen MY, Dey AK, et al. Coronary computed tomography angiography from clinical uses to emerging technologies: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;76(10):1226–43.
33. Stuijfzand WJ, van Rosendael AR, Lin FY, et al. Stress myocardial perfusion imaging vs coronary computed tomographic angiography for diagnosis of invasive vessel-specific coronary physiology: predictive modeling results from the computed tomographic evaluation of atherosclerotic determinants of myocardial ischemia (CREDENCE) trial. *JAMA Cardiol* 2020;5(12):1338–48.
34. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. *J Am Coll Cardiol* 2015;66(4):337–46.
35. Lee SE, Chang HJ, Sung JM, et al. Effects of statins on coronary atherosclerotic plaques: the PARADIGM study. *JACC Cardiovasc Imaging* 2018;11(10):1475–84.
36. van Rosendael AR, Lin FY, van den Hoogen IJ, et al. Progression of whole-heart atherosclerosis by coronary CT and major adverse cardiovascular events. *J Cardiovasc Comput Tomogr* 2021;15(4):322–30.
37. Budoff MJ, Bhatt DL, Kinninger A, et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. *Eur Heart J* 2020;41(40):3925–32.
38. Budoff MJ, Muhlestein JB, Bhatt DL, et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: a prospective, placebo-controlled randomized trial (EVAPORATE): interim results. *Cardiovasc Res* 2021;117(4):1070–7.
39. Hirai K, Imamura S, Hirai A, Ookawara S, Morishita Y. Effect of evolocumab on vulnerable coronary plaques: a serial coronary computed tomography angiography study. *J Clin Med* 2020;9(10):3338.
40. Henzel J, Kepka C, Kruk M, et al. High-risk coronary plaque regression after intensive lifestyle intervention in nonobstructive coronary disease: a randomized study. *JACC Cardiovasc Imaging* 2021;14(6):1192–202.
41. Vaidya K, Arnott C, Martinez GJ, et al. Colchicine therapy and plaque stabilization in patients with acute coronary syndrome: a CT coronary angiography study. *JACC Cardiovasc Imaging* 2018;11(2 Pt 2):305–16.
42. 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.
43. Lauby-Secretan B, Loomis D, Straif K. Breast-cancer screening −viewpoint of the IARC Working Group. *N Engl J Med* 2015;373(15):1479.
44. Lauby-Secretan B, Vilahur N, Bianchini F, Guha N, Straif K, International Agency for Research on Cancer Handbook Working Group. The IARC perspective on colorectal cancer screening. *N Engl J Med* 2018;378(18):1734–40.
45. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365(5):395–409.
46. Min JK, Dunning A, Lin FY, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol* 2011;58(8):849–60.
47. van Rosendael AR, Lin FY, Ma X, et al. Percent atheroma volume: optimal variable to report whole-heart atherosclerotic plaque burden with coronary CTA, the PARADIGM study. *J Cardiovasc Comput Tomogr* 2020;14(5):400–6.
48. Budoff M, Lakshmanan S, Bhatt DL. The EVAPORATE trial provides important mechanistic data on plaque characteristics that have relevance to the REDUCE-IT results and clinical use of icosapent ethyl. *Eur Heart J* 2021;42(31):3025–6.
49. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med* 2019;380(1):11–22.
50. Watanabe T, Ando K, Daidoji H, et al. A randomized controlled trial of eicosapentaenoic acid in patients with coronary heart disease on statins. *J Cardiol* 2017;70(6):537–44.
51. Shapiro MD, Bhatt DL. "Cholesterol-Years" for ASCVD risk prediction and treatment. *J Am Coll Cardiol* 2020;76(13):1517–20.
52. Lawler PR, Bhatt DL, Godoy LC, et al. Targeting cardiovascular inflammation: next steps in clinical translation. *Eur Heart J* 2021;42(1):113–31.
53. Sabatine MS, Giugliano RP, Pedersen TR. Evolocumab in patients with cardiovascular disease. *N Engl J Med* 2017;377(8):787–8.
54. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;379(22):2097–107.
55. Ray KK, Bays HE, Catapano AL, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. *N Engl J Med* 2019;380(11):1022–32.
56. Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med* 2020;382(16):1507–19.
57. Eikelboom JW, Connolly SJ, Yusuf S. Rivaroxaban in stable cardiovascular disease. *N Engl J Med* 2018;378(4):397–8.
58. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020;383(19):1838–47.
59. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375(19):1834–44.
60. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375(4):311–22.
61. Holman RR, Bethel MA, Hernandez AF. Once-weekly exenatide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017;377(25):2502.
62. Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017;377(13):1228–39.
63. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019;394(10193):121–30.
64. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373(22):2117–28.
65. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;380(4):347–57.
66. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377(7):644–57.
67. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021;384(2):117–28.
68. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015;373(23):2247–57.
69. Pareek M, Schauer PR, Kaplan LM, Leiter LA, Rubino F, Bhatt DL. Metabolic surgery: weight loss, diabetes, and beyond. *J Am Coll Cardiol* 2018;71(6):670–87.
70. Ahmadi A, Argulian E, Leipsic J, Newby DE, Narula J. From subclinical atherosclerosis to plaque progression and acute coronary events: JACC state-of-the-art review. *J Am Coll Cardiol* 2019;74(12):1608–17.

71. Mori H, Torii S, Kutyna M, Sakamoto A, Finn AV, Virmani R. Coronary artery calcification and its progression: what does it really mean? *JACC Cardiovasc Imaging* 2018;11(1):127–42.
72. Ko DT, Khan AM, Kotrri G, et al. Eligibility, clinical outcomes, and budget impact of PCSK9 inhibitor adoption: the CANHEART PCSK9 study. *J Am Heart Assoc* 2018;7(21):e010007.
73. Salami JA, Warraich H, Valero-Elizondo J, et al. National trends in statin use and ein the US adult population from 2002 to 2013: insights from the Medical Expenditure Panel Survey. *JAMA Cardiol* 2017;2 (1):56–65.
74. Akyea RK, Kai J, Qureshi N, Iyen B, Weng SF. LDL cholesterol response to statins and future risk of cardiovascular disease. *Heart* 2019;105(16):1290–1.
75. Caparrotta TM, Blackbourn LAK, McGurnaghan SJ, et al. Prescribing paradigm shift? Applying the 2019 European Society of Cardiology-led guidelines on diabetes, prediabetes, and cardiovascular disease to assess eligibility for sodium-glucose cotransporter 2 inhibitors or glucagon-like peptide 1 receptor agonists as first-line monotherapy (or add-on to metformin monotherapy) in type 2 diabetes in Scotland. *Diabetes Care* 2020;43(9):2034–41.
76. Casalino LP, Nicholson S, Gans DN, et al. What does it cost physician practices to interact with health insurance plans? *Health Aff (Millwood)* 2009;28(4):w533–43.
77. Min JK, Chang HJ, Andreini D, et al. Coronary CTA plaque volume severity stages according to invasive coronary angiography and FFR. *J Cardiovasc Comput Tomogr*. 2022;16(5):415−422.

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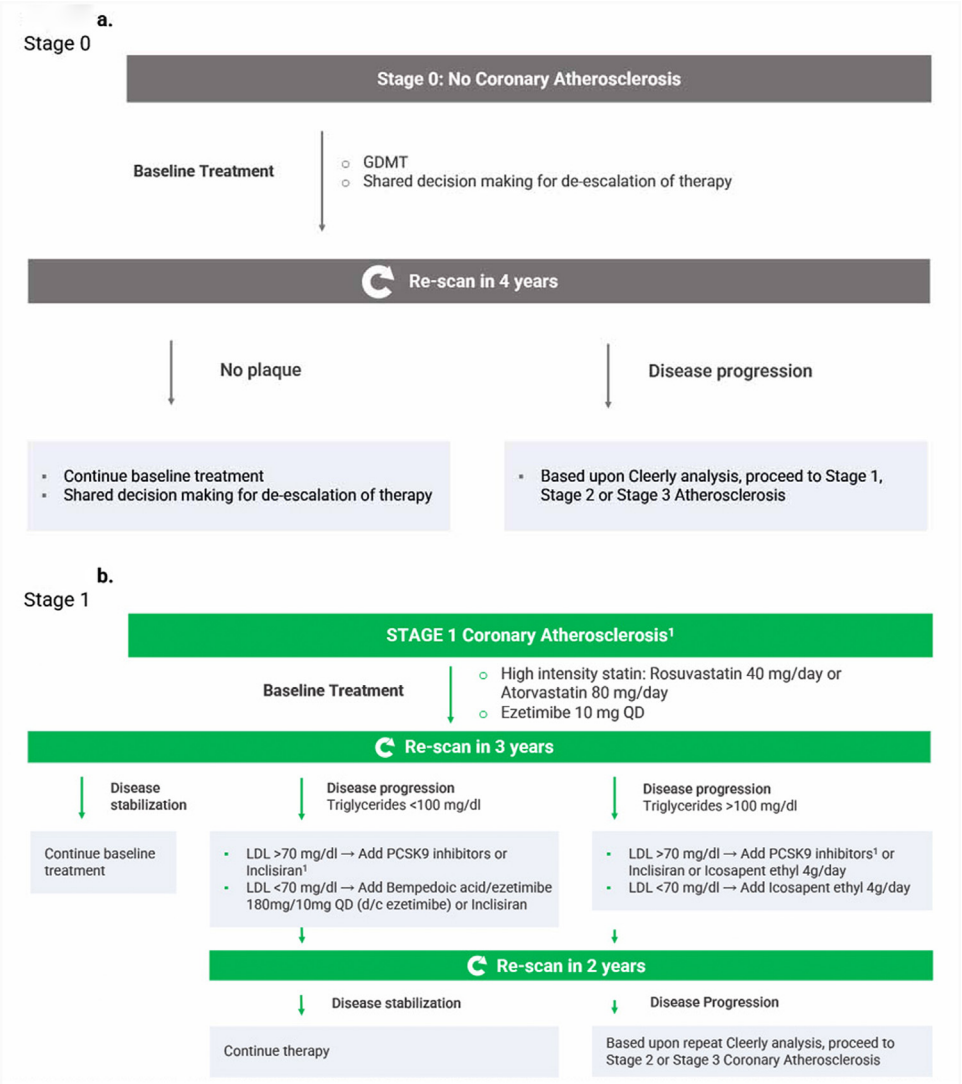
Supplementary Table Clinical Evidence for Medications on Coronary Artery Disease Risk Factor Control and Major Adverse Cardiac Events

Medication	Eligibility Criteria	Study Size	Duration	Primary Endpoint	Results	Relative Risk Reduction	Ref
Lipid-lowering medications							
Bempedoic acid	ASCVD (clinically significant CHD by imaging), heterozygous FH or both; LDL ≥70 mg/dL	2230	52 wk	LDL lowering	16.5% lower LDL	N/A	45
Evolocumab	40-85 y, clinical ASCVD; ≥70 mg/dL LDL or non-HDL 100 mg/dL; on ≥20 mg atorvastatin	27,564	2.2 y	CV death, MI, stroke, UA, TVR	9.8% vs 11.3%, HR 0.85	15%	46
Alirocumab	>40, h/o ACS 1-2 mo prior to randomization, LDL ≥70 mg/dL, non-HDL ≥100 mg/dL, or apolipoprotein B ≥80 mg, on statin	18,924	2.8 y	CHD death, MI, stroke, UA	9.5% vs 11.1%	15%	47
Isocapent ethyl	>45 y w/ established CVD or >50 y w/ DM + 1 RF, TG≥135 mg/dl and LDL 41-100 mg/dl	8179	4.9 y	CV death, MI, stroke, revasc, UA	17.2% vs 22.0%	25%	48
Inclisiran	Adults w/ h/o ASCVD (CHD, CVD, or PAD) or ASCVD-risk equivalent (T2DM, familial hypercholesterolemia) and 10-y FRS risk w/ target LDL <100 mg/dL; LDL ≥70 mg/dL or ≥100 mg/dL for ASCVD-risk equivalent	3178	510 d	% change LDL at 510 d; and time-adjusted % change LDL 90-540 d	∼50% lower LDL and time-adjusted LDL	N/A	50
Antithrombotic medications							
Rivaroxaban	>65 w/ CAD or <65 w/ atherosclerosis in ≥2 vascular beds or ≥2 RFs	27,395	1.9 y	CV death, stroke, MI	17.2% vs 22.0%	25%	51
Anti-inflammatory medications							
Colchicine	Age >35 and ≤82 y; proven CAD by CCTA or CACS >400 or h/o CABG >10 y prior, or angiographic evidence of graft failure or PCI after CABG	5522	28.6 mo	CV death, MI, ischemic stroke or ischemia-driven revascularization	6.8% vs 9.6%	31%	52

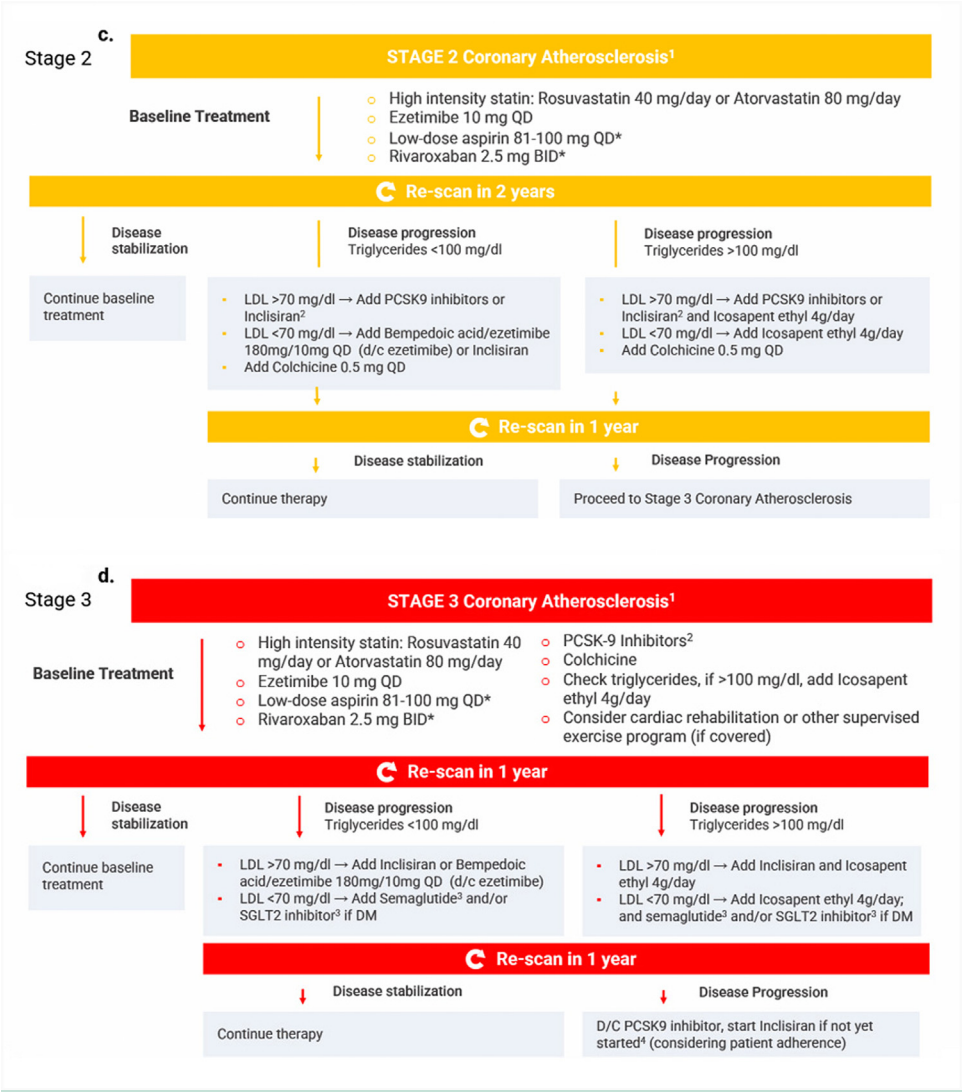
Supplementary Table (*Continued*)

Medication	Eligibility Criteria	Study Size	Duration	Primary Endpoint	Results	Relative Risk Reduction	Ref
SGLT2 inhibitors							
Empagliflozin	Type 2 diabetes w/ BMI <40 and eGFR >30 w/ CVD (≥2 vessels w/ 50% stenosis or 1 vessel 50% stenosis and ischemia)	7020	3.1 y	CV death, MI, stroke	10.5% vs 12.1%	14%	58
Dapagliflozin	>40 y/o, type 2 diabetes; HgbA1C >6.5%; CrCl >60; multiple risk factors for ASCVD	17,160	4.2 y	CV death, MI, stroke, heart failure	8.8% vs 9.4%	None	59
Canagliflozin	Type 2 diabetes + ASCVD (>30 y) or ≥2 risk factors (>50 y), eGFR >30	10,142	2.4 y	CV death, MI, stroke	26.9 vs 31.5 participants / 1000 pt-years	14%	60
GLP-1 receptor agonists							
Semaglutide	T2DM + HgbA1C >7%; >50 w/ ASCVD or >60 w/ 1 CV RF	2735	2 y	CV death, MI, stroke	6.6% vs 8.9%	26%	53
Exenatide	Type 2 diabetes w/ h/o ASCVD events (70%) or not (30%)	14,752	3.2 y	CV death, MI, stroke	11.4% vs 12.2%	None	54,55
Liraglutide	Type 2 diabetes, HgbA1C >7.0%; >50 years w/ ASCVD; >60 years w/ >1 CV RF	9340	3.8 y	CV death, MI, stroke	13.0% vs 14.9%	13%	56
Dulaglutide	Type 2 diabetes; >50 w/ prior CV event or CV risk factors	9901	5.4 y	CV death, MI, stroke	12.0%vs 13.4%	12%	57
Lixisenatide	Type 2 diabetes w/ prior MI or UA hospitalization	6068	25 mo	CV death, MI, stroke, UA	13.4% vs 13.2%	N/A	62

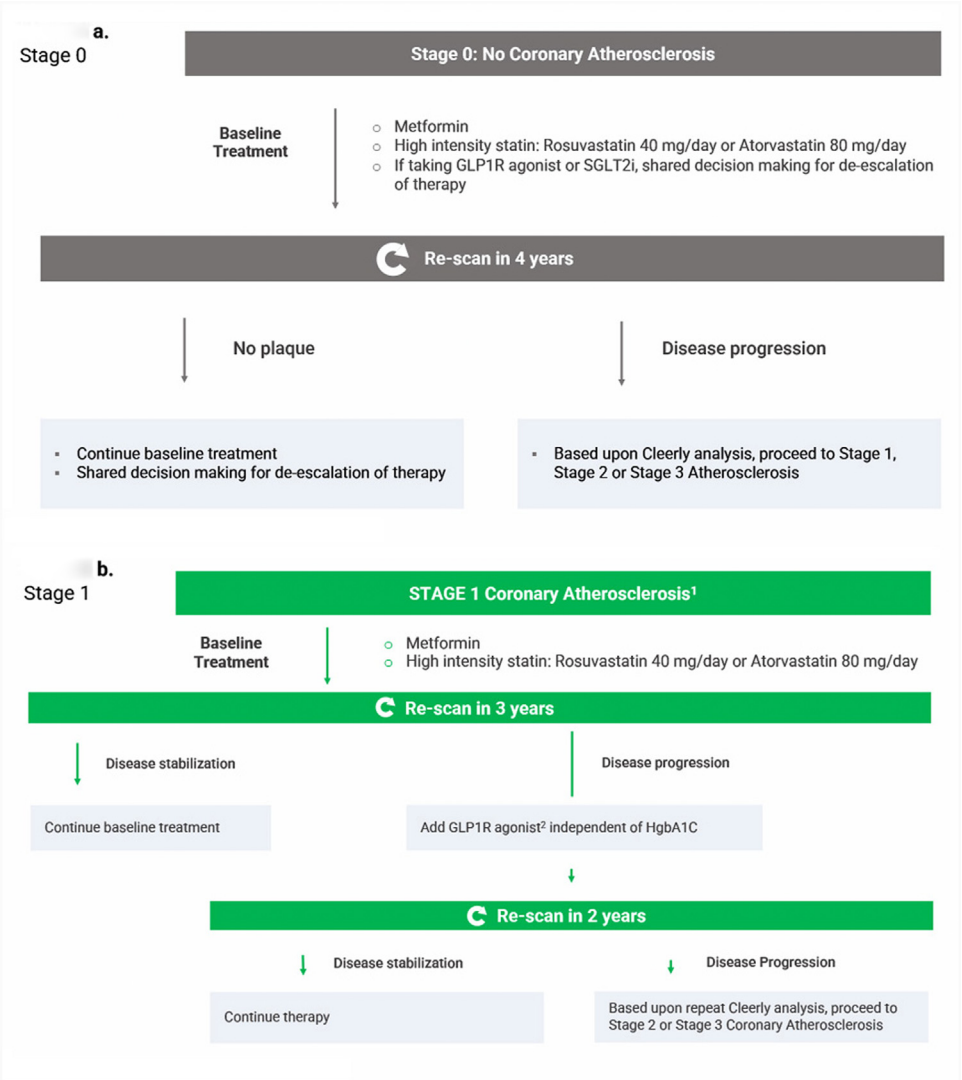
ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CABG = coronary artery bypass surgery; CACS = coronary artery calcium score; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CHD = coronary heart disease; CrCl = creatinine clearance; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = effective glomerular filtration rate; FH = familial hypercholesterolemia; FRS = Framingham Risk Score; GLP-1 = glucagon-like peptide 1; HDL = high-density lipoprotein; HgbA1C = glycosylated hemoglobin; HR = hazard ratio; LDL = low-density lipoprotein; MI = myocardial infarction; N/A = not applicable; PCI = percutaneous coronary intervention; RF = risk factor; SGLT2 = sodium-glucose transport protein 2; T2DM = type 2 diabetes mellitus; TG = triglyceride; TVR = target vessel revascularization; UA = unstable angina.



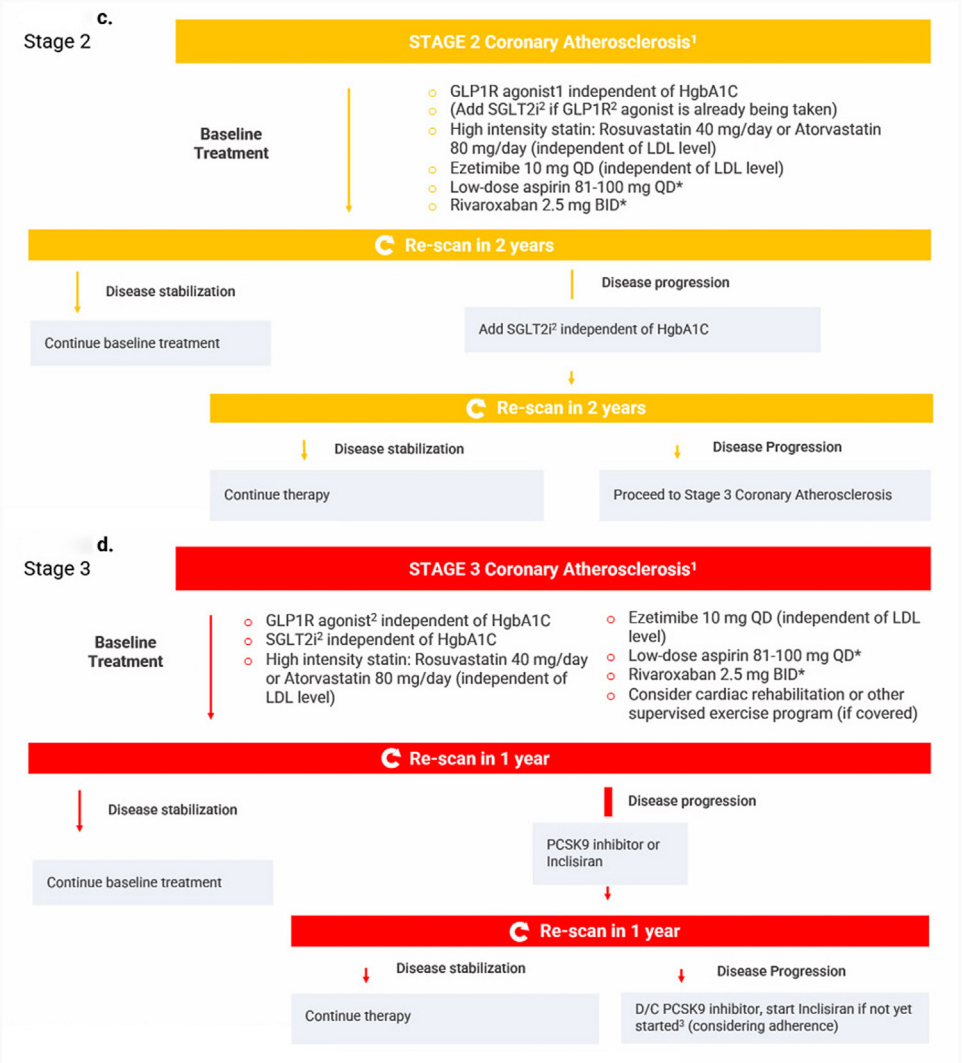
Supplementary Figure 1 "Treat Disease" algorithms for patients with dyslipidemia. **(B)** [1]PCSK9 inhibitors include: alirocumab (starting 75 mg/2 weeks or 300 mg/4 weeks, maintenance 150 mg/2 weeks or 300 mg/4 weeks); evolocumab (140 mg/mL SQ 2 weeks or 420 mg SQ month); Inclisiran administered at 284 mg at baseline, 3 months and then every 6 months. **(C)** [1]For all patients with PAV >10.0%, suggest check Lp(a) >50 mg/dL or >125 nmol/L, consider PCSK9 inhibitors as first-line lipid-lowering agent. [2]PCSK9 inhibitors include: alirocumab (starting 75 mg/2 weeks or 300 mg/4 weeks, maintenance 150 mg/2 weeks or 300 mg/4 weeks); evolocumab (140 mg/2 weeks or 420 mg/month). *For patients at bleeding risk, use of rivaroxaban and aspirin is suggested only after shared decision-making to ensure patient literacy of elevated bleeding risk. **(D)** [1]For all patients with PAV >10.0%, suggest check Lp(a) >50 mg/dL or >125 nmol/L, consider PCSK9 inhibitors as first-line lipid-lowering agent. [2]PCSK9 inhibitors include: alirocumab (starting 75 mg/2 weeks or 300 mg/4 weeks, maintenance 150 mg/2 weeks or 300 mg/4 weeks); evolocumab (140 mg/2 weeks or 420 mg/month). [3]See dosing table. [4]Pending Food and Drug Administration approval, availability, and safety profile. *For patients at bleeding risk, use of rivaroxaban and aspirin is suggested only after shared decision-making to ensure patient literacy of elevated bleeding risk. LDL = low-density lipoprotein; PAV = percent atheroma volume; QD = once a day; SQ = subcutaneous.



Supplementary Figure 1. Continued

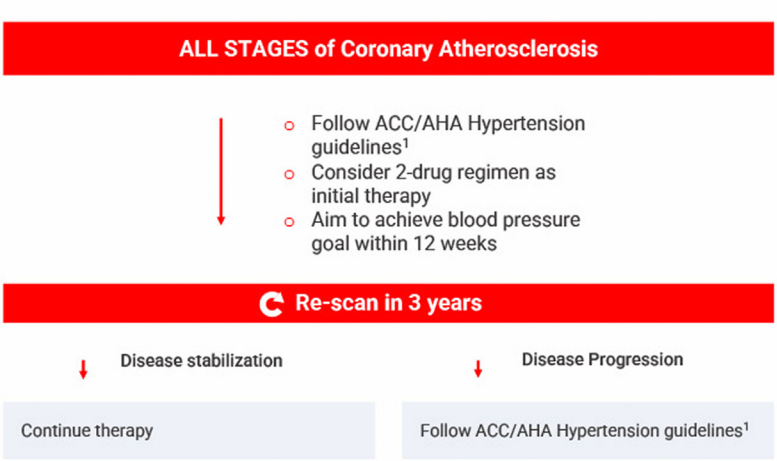


Supplementary Figure 2 "Treat Disease" algorithms for patients with diabetes. **(A)** If patient LDL >70 mg/dL, please refer to Lipid algorithm; standard lipid guidelines apply. **(B)** [1]If patient LDL >70 mg/dL, please refer to Lipid algorithm; standard lipid guidelines apply. [2]See dosing table. **(C)** [1]If patient LDL >70 mg/dL, please refer to Lipid algorithm; standard lipid guidelines apply. [2]See dosing table. *For patients at bleeding risk, use of rivaroxaban and aspirin is suggested only after shared decision-making to ensure patient literacy of elevated bleeding risk. **(D)** [1]If patient LDL >70 mg/dL, please refer to Lipid algorithm; standard lipid guidelines apply. [2]See dosing table. [3]Pending Food and Drug Administration approval, availability, and safety profile. *For patients at bleeding risk, use of rivaroxaban and aspirin is suggested only after shared decision-making to ensure patient literacy of elevated bleeding risk. GLP = glucagon-like peptide; HgbA1c = glycosylated hemoglobin; LDL = low-density lipoprotein; SGLT2 = sodium-glucose transport protein 2.



Supplementary Figure 2. Continued

Supplementary Figure 3 "Treat Disease" algorithms for patients with obesity or tobacco use. [1]WildingJP, Batterham RL, Calanna S et al. *N Engl J Med* 2021; 384-989-1002. [2]Poirier P, Comier MA, Mazzone T et al. *Circulation* 2011.



Supplementary Figure 4 "Treat Disease" algorithms for patients with hypertension. ACC = American College of Cardiology; AHA = American Heart Association. [1]Welton PK, Carey RM, Aronow WS et al. *Hypertension* 2018; 71:e13-115.