Chapter 13
Stable Ischemic Heart Disease

Daniel Katz and Michael C. Gavin

Abbreviations

ACS	Acute coronary syndrome
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	Blood pressure
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CBC	Complete blood count
CCTA	Coronary computed tomography angiography
CK	Creatinine kinase
CMP	Complete metabolic panel
CMR	Cardiac magnetic resonance imaging
CV	Cardiovascular
ECG	Electrocardiogram
EF	Ejection fraction
GDMT	Guideline directed medical therapy
GI	Gastrointestinal

D. Katz (✉) · M. C. Gavin
Department of Medicine, Division of Cardiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
e-mail: dkatz@bidmc.harvard.edu; mgavin2@bidmc.harvard.edu

A. A. Bhargava et al. (eds.), *Handbook of Outpatient Cardiology*, https://doi.org/10.1007/978-3-030-88953-1_13

HbA1c	Hemoglobin A1c
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA reductase
LDL-C	Low density lipoprotein cholesterol
MI	Myocardial infarction
NEJM	New England Journal of Medicine
NNT	Number needed to treat
PCI	Percutaneous Coronary Intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PDE5	Phosphodiesterase type 5
SARS-Cov-2	Severe acute respiratory syndrome coronavirus 2
SGLT2	Sodium-glucose co-transporter-2
SIHD	Stable ischemic heart disease
SPECT	Single photon Emission Computed Tomography
UA	Unstable angina

Diagnosis and Clinical Assessment

Key Definitions

- Coronary artery disease (CAD): any atheromatous plaque in the coronary arteries, regardless of effect on blood flow.
- Stable ischemic heart disease (SIHD): a clinical syndrome marked by *stable* symptoms. Symptoms are usually angina: pain or pressure brought on reliably by exertion or emotion and relieved by rest or nitroglycerine.
  - CAD is one possible cause of SIHD.
- *Unstable* angina (UA): the symptomatic manifestation of an acute coronary syndrome (ACS).
  - These symptoms (possibly similar to SIHD) are either brought on with less provocation or with no provocation at all, i.e., at rest.

- ACS results from an acute imbalance in myocardial oxygen supply and demand, often from an acute reduction in coronary blood flow.
  - ACS ranges from UA alone to myocardial infarction (MI).
  - ACS requires inpatient management.

- **Clinical Pearl:** Do not confuse a *new* diagnosis of SIHD with ACS!
  - The first presentation of "new" angina does not necessarily mean it is unstable.

History

- Whether seeing a patient with SIHD for the first time or in follow-up, establish details of their symptoms.
  - What symptoms do they typically experience (typical angina, dyspnea, or other atypical symptoms)?
  - What level of stress elicits their symptoms?
  - What do they do when they experience those symptoms (rest, take nitroglycerin, etc.)?
  - Have the symptoms changed or evolved? *Evolution of symptoms should prompt additional workup and management.*
- Assess other vascular beds.
  - Claudication
  - Transient neurologic symptoms
- Watch for *new red flag* symptoms.
  - Previous or new anginal symptoms now occurring at rest
  - Syncope/periodic dizziness/palpitations suggesting arrhythmia
  - New lower extremity edema

Physical Exam

- The physical examination is often normal or nonspecific in patients with SIHD, but it is useful to look for other associated findings that suggest non-coronary atherosclerotic vascular disease [1].
- New or worsening symptoms should prompt more detailed examination:
  - Syncope → auscultation of new murmurs
  - Claudication → peripheral pulses/ankle-brachial index
  - Neurologic symptoms → Neuro exam
  - Lower extremity edema → jugular venous pulsation, point of maximal impulse, auscultation for S3, lung auscultation for rales

Routine Workup in SIHD

- *Labs*
  - Lab work in SIHD focuses on comorbidities: CBC, CMP, lipid panel, HbA1c, BNP, and baseline CK especially upon diagnosis of CAD.
  - If symptoms are progressing, consider repeating lab work.
- *Electrocardiogram*
  - All patients with suspected SIHD should have a resting electrocardiogram (ECG) at initial diagnosis and with new or evolving symptoms [2].
  - ECG is typically normal; pathologic Q waves indicate a prior MI.
  - ECG abnormalities also guide stress test selection (see below and Chap. 7).
- *Rest echocardiography*
  - Not needed routinely
  - Consider if:

Heart failure/valvular disease signs/symptoms
Known prior MI or a pathologic Q-wave on the ECG
Evidence of ventricular arrhythmias, suggesting underlying cardiomyopathy [2]

Advanced Noninvasive Testing: Who and when to Test

- Outpatient noninvasive testing is typically indicated in two groups:
  - Patients with new symptoms suspicious for SIHD.
  - Patients with known SIHD who have new or worsening symptoms.
  - As above, new SIHD and ACS are *distinct clinical syndromes* – new SIHD can be assessed with outpatient testing, whereas ACS requires inpatient management.
- Noninvasive testing can identify patients with CAD and estimate prognosis.
- Most valuable when cause of new chest pain is truly uncertain (i.e., pretest probability 20–80%).
  - When probability of CAD is low (Fig. 13.1 and Table 13.1), additional testing is generally not indicated and risks a false positive [3].

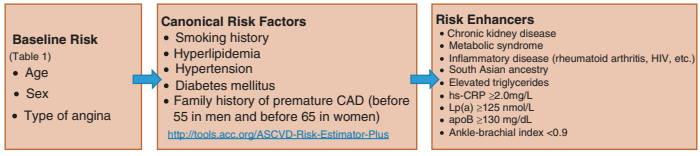

Figure 13.1 Approach to CAD risk assessment. Begin with baseline risk and modify using canonical risk factors, utilizing the risk calculator available online. Further risk stratification can be achieved with risk enhancers

Table 13.1 Pretest likelihood of coronary artery disease with ≥70% obstruction in symptomatic patients according to age and sex[a]

Age, y	Nonangina chest pain, %		Atypical angina, %		Typical angina, %	
	Men	Women	Men	Women	Men	Women
40–49	0 (0.0–8.4)		5 (2.5–7.9)		10 (2.1–26.5)	
50–59	5 (1.7–11.9)	2 (0.2–6.7)	7 (5.1–8.9)	3 (1.9–4.3)	9 (4.3–15.7)	0 (0.0–3.6)
60–69	6 (1.7–15.0)	3 (0.6–7.9)	11 (8.6–14.3)	4 (2.9–6.0)	19 (11.4–29.4)	1 (0.0–5.4)
≥70	5 (0.1–26.0)	8 (1.7–21.9)	13 (7.9–18.9)	6 (3.5–9.3)	40 (21.1–61.3)	8 (2.2–19.2)

[a]Adapted from Ref. [3]

Figure 13.2 Features of an uninterpretable ECG

Uninterpretable ECG for Stress

- Left ventricular hypertrophy with associated repolarization abnormalities
- Left bundle branch block
- Ventricular pacing
- Digitalis effect
- Wolf Parkinson White
- ≥1mm resting ST segment depression

  - Before testing, consider:

    Pretest probability for CAD
    The ability to exercise
    ECG abnormalities (Figs. 13.2 and 13.3) [4]

Types of Testing

- Stress (functional) testing (see Table 13.2).
  - Most common form of noninvasive testing.

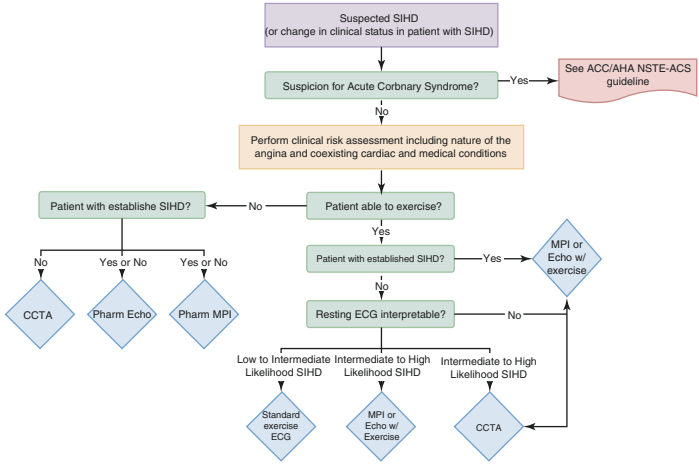

FIGURE 13.3 Choice of noninvasive study for the evaluation of newly suspected SIHD or a change in clinical status in a patient with SIHD. SIHD stable ischemic heart disease, ACC/AHA NSTE-ACS American College of Cardiology/American Heart Association Non-ST segment elevation acute coronary syndrome, MPI myocardial perfusion imaging, Pharm pharmacologic, ECG electrocardiogram, echo echocardiogram, CCTA coronary computed tomography angiogram. (Reproduced with permission from Katz and Gavin. *Ann Intern Med*, 2019 [34])

– Select the stressor.

  Exercise
  Pharmacologic

– Select the modality to assess ischemia.

  ECG
  Echocardiography
  Single-photon emission computed tomography [SPECT]
  And less often, positron emission tomography [PET] or cardiac MRI [CMR]

Table 13.2 Summary of CAD testing options

Test	Preferred stress modalities	Pros	Cons
ECG without imaging	Exercise	Low cost	Lowest sensitivity (61%) Limited by ECG suitability
Stress echo	Exercise, dobutamine	Highly sensitive Also obtain valvular data and filling pressures No radiation	Less interpretable in LBBB or paced hearts Poor image quality can occur in very thin or very obese individuals
SPECT	Exercise, vasodilator (regadenoson, dipyridamole)	Highly sensitive Works well in overweight individuals	Radiation More expensive
PET	Exercise, vasodilator (regadenoson, dipyridamole)	Extremely sensitive Works well in overweight individuals Can provide microvascular dysfunction data	Radiation More expensive Not widely available
MRI	Vasodilator (regadenoson, dipyridamole)	Extremely sensitive Works well in overweight individuals Can provide viability data	Radiation More expensive Not widely available

Table 13.2 (continued)

Test	Preferred stress modalities	Pros	Cons
CCTA	N/A	No exercise required Only noninvasive anatomic test, giving data on coronary anomalies Less radiation than SPECT	Requires iodinated contrast Some radiation Images limited in irregular rhythms or high heart rates

ECG electrocardiogram, *LBBB* left bundle branch block, *echo* echocardiogram, *CCTA* coronary computed tomography angiogram, *SPECT* single-photon emission computed tomography, *PET* positron emission tomography, *MRI* magnetic resonance imaging

- Anatomical testing with coronary computed tomography angiography (CCTA)
  - Increasingly utilized for evaluation of chest pain.
  - The European Society of Cardiology and the National Institute for Health and Care Excellence in the United Kingdom recommend CCTA as the initial test for the evaluation of chest pain in patients without known CAD [5, 6].
  - Key advantages:

    High negative predictive value (avoids unnecessary cardiac catheterization)
    Identifies nonobstructive coronary disease and coronary congenital anomalies
    Does not require exercise

  - Recent key trials:

    PROMISE, NEJM 2015 – *CCTA compared to functional testing as the initial diagnostic test among intermediate-risk patients with symptomatic SIHD: no difference in adverse cardiovascular events* [7].

SCOT-HEART, NEJM 2018 – *CCTA + standard care in SIHD = lowered rates of combined primary endpoint of death from CHD or non-fatal MI* [8].

- Invasive coronary angiography.
  - Not typically indicated for initial evaluation of SIHD.
  - In patients with very high likelihood of disease (i.e., >90%), noninvasive testing provides little additional information, so angiography is used when it will affect therapy.

Test Selection Pearls

- In intermediate-risk patients that can exercise and have an interpretable ECG (Fig. 13.3), exercise with ECG alone carries a Class IA indication [2].
  - Sensitivity of exercise without imaging is limited at 61% (i.e., 39% false-negative rate) and worse for women [2].
  - **Clinical Pearl:** In practice, it is often preferred to add imaging to exercise to improve sensitivity. Use of imaging for this indication carries a Class IIa indication in the guidelines [2].
  - It is essential to add imaging if the ECG is uninterpretable.
- CCTA is an appropriate first-line test for the evaluation of chest pain among patients at intermediate pretest probability regardless of the ability to exercise [9].
- Pharmacologic stress with imaging can be used for patients who [1] cannot exercise or [2] cannot exercise strenuously enough to generate a valid test result.
  - For echocardiography and MRI, dobutamine is used as stressor.
  - For SPECT and PET, vasodilators (regadenoson or dipyridamole).

- To choose between imaging modalities, *consider the resources and technical expertise at your institution* [2].
- Echocardiography has no radiation and provides information on valvular function and filling pressures.

> - **Clinical Pearl:** In patients with left bundle branch block or ventricular pacing, avoid stress echo.
>   - The abnormal electrical activation of the heart impairs evaluation of ischemia in the interventricular septum (LAD territory).

- CCTA, SPECT, or PET imaging are less susceptible to poor image quality related to body habitus.
- When CAD/SIHD is already known, evolving or ongoing symptoms on anti-anginal therapy are ideally assessed by functional testing with imaging to localize and quantify ischemia to inform decisions on revascularization [10].
  - CCTA/non-functional imaging is less valuable in this setting.

SIHD Without Obstructive CAD

- Approximately 30% of patients presenting with angina have no obstructive CAD.
- Angina without obstructive coronary disease is more common among women [11].
- Risk of ischemic events is still increased, and medical therapy is still indicated [12, 13]!
- CCTA is the best test for diagnosing nonobstructive CAD.
- Among patients with angina and nonobstructive CAD, 50–65% are believed to have coronary microvascular dysfunction.
  - Assessment of microvascular function can be done with CMR and PET perfusion [14].

When to Refer to a Cardiologist

- When testing approach is unclear
- Uncertain diagnosis after noninvasive testing, to consider coronary angiography [10]
- Suspected microvascular dysfunction or variant (Prinzmetal's) angina

Treatment

Goals of Treatment

- Prevention of ischemic events (cerebral, coronary, and peripheral) (Fig. 13.4).
- Reducing anginal symptoms.
- These goals are independent!

Behavior Modification

- *Smoking cessation:* Smoking increases cardiovascular disease mortality by 50%.
- *Physical activity:* Current guidelines recommend 150 minutes of at least moderate activity or 75 minutes of vigorous activity per week [15]. Patients with SIHD and those post-MI should participate in a cardiac rehabilitation program [2].
- *Dietary modification:* Emphasize intake of vegetables, fruits, whole grains, legumes, healthy protein sources (low-fat dairy, low-fat poultry, fish/seafood, and nuts), and non-tropical vegetable oils. The intake of sweets, sugar-sweetened beverages, and red meats should be limited [16].
- *Alcohol moderation:* One drink per day, no harm and possible benefit; beyond two drinks per day, no benefit and likely harm [17]. Heavy drinking worsens hypertension and may precipitate ischemia in SIHD and should be avoided [18].

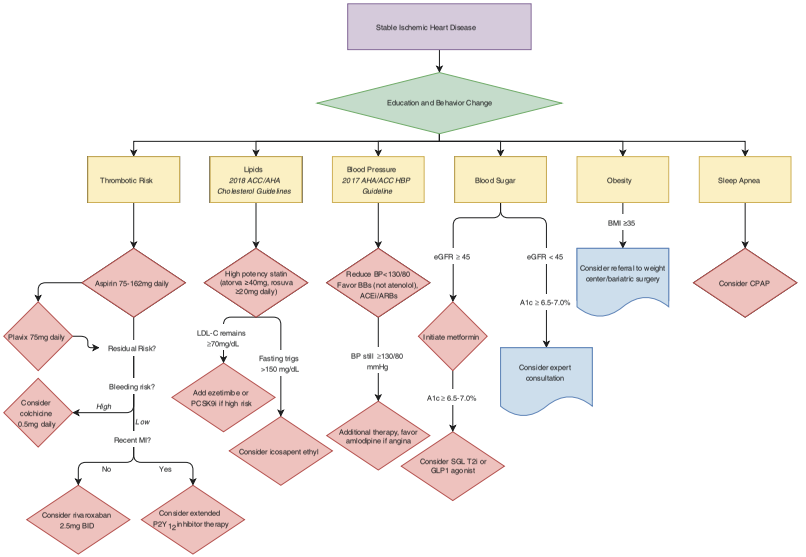

FIGURE 13.4 Guideline-directed medical therapy for patients with stable ischemic heart disease. A1c hemoglobin A1c, ACC American College of Cardiology, ACEi angiotensin-converting enzyme inhibitor, AHA American Heart Association, ARB angiotensin receptor blocker, BBs beta-blockers, BID twice daily, BMI body mass index, CPAP continuous positive airway pressure, eGFR estimated glomerular filtration rate, GLP1 glucagon-like peptide 1, HBP high blood pressure, LDL-C low-density lipoprotein cholesterol, MI myocardial infarction, SGLT2i sodium-glucose cotransporter 2 inhibitor. (Reproduced with permission from Katz and Gavin. *Ann Intern Med*, 2019 [34])

- *Psychological well-being:* Interventions to reduce psychological stress may improve clinical outcomes in patients with SIHD [19].

Pharmacologic Therapy for Specific Risk Factors/ Comorbidities

Lipids

- HMG-COA reductase inhibitors (*statins*) are the mainstay of lipid management.
- In SIHD patients: < 75 years, high potency statin (atorvastatin 80 mg or rosuvastatin 20–40 mg) is recommended; >75 years reasonable to reduce potency.
- Target LDL-C < 70 mg/dL with addition of *ezetimibe and PCKS9 inhibitors in sequence* in patients at high risk [16]. High risk = multiple previous CV events or CV event + multiple risk factors.
- *Niacin is no longer recommended* for the lowering of LDL-C [16].
- *Fish oil*: Over-the-counter formulations have not shown consistent benefit [20], but *icosapent ethyl* reduced cardiovascular events 25% on top of high-dose statins and aspirin in patients with SIHD and elevated triglycerides (REDUCE-IT, NEJM 2019) [21].

Hypertension

- Guidelines: goal BP of <130/80 mmHg in SIHD [22].
  - Recent trial: SPRINT, NEJM 2015 – in SIHD patients over 50, targeting lower BP (121 vs 136 mmHg) decreased CV events by 31%, NNT = 44 [23].
- Agent of choice depends on comorbidities and other targets (i.e., angina, congestive heart failure, chronic kidney disease, or diabetes).

Diabetes

- Start with metformin when possible [24, 25].
- For SIHD patients with HbA1c still >6.5–7%, consider SGLT2 inhibitors (e.g., *empagliflozin, canagliflozin, dapagliflozin*) and/or GLP-1 receptor agonists (e.g., *liraglutide, semaglutide*). Both have been shown to reduce CV events [24].

Obesity

- Lifestyle change is critical.
- If BMI >35, consider weight loss surgery.
  - In patients with type 2 diabetes, Roux-en-Y gastric bypass has been shown to reduce CV events [26].

Pharmacologic Therapy to Prevent MI or Death in SIHD Independent of Risk Factors

Antiplatelet Therapy

- If any atherosclerotic cardiovascular disease (CAD, SIHD, peripheral arterial disease, etc.), treat with medium-dose *aspirin*, usually 81 mg [15].
- When aspirin is contraindicated (e.g., allergy), patients can be treated with *clopidogrel* 75 mg daily.

Anticoagulation

- Anticoagulation reduces ischemic events but raises bleeding events! Consider risk/benefit with a cardiologist.
  - Recent trial: COMPASS, NEJM 2017 – *Rivaroxaban* at a very reduced dose of 2.5 mg twice daily reduced cardiovascular mortality in SIHD at the expense of increased bleeding [27].

Anti-inflammatory Therapy

- *Colchicine* 0.5 mg daily was shown in the LoDoCo2 trial (NEJM 2020) to reduce cardiovascular events in patients with chronic coronary disease [28].

Other Therapies

- Patients with SIHD should receive an annual influenza vaccine [2, 29].
- Patients with SIHD are at increased risk for complications from SARS-CoV-2 and vaccination is recommended [30].

Medications that Treat Angina

- β-Blockers,
  - Initial therapy for prolonged relief of symptoms. Typically start here!

> – **Clinical Pearl:** All beta-blockers reduce symptoms, though in patients with peripheral arterial disease, drugs with additional alpha blockade, such as *carvedilol or labetalol*, may prevent vasoconstriction mediated by unopposed alpha agonism [2].

  - In patients with reduced EF, carvedilol, metoprolol succinate, and bisoprolol should be favored per guidelines [31].
  - Contraindicated in severe bronchospastic lung disease.
- *Calcium channel blockers*
  - *Amlodipine*: the preferred option, a dihydropyridine calcium channel blocker
  - *Diltiazem and verapamil*: non-dihydropyridine calcium channel blockers

    Useful if beta-blockers produce side effects
    Should be avoided in patients with reduced ejection fraction given their negative inotropic effects

- *Nitrates*
  - *Short-acting nitrates*: in the form of *sublingual nitroglycerin or nitroglycerin spray* are ideal for immediate relief of angina.

    Patients can administer one dose every 5 minutes for up to three doses.
  - *Long-acting nitrates*:

    Three times daily isosorbide dinitrate
    Once (sometimes twice) daily isosorbide mononitrate
    Nitropaste
  - Warn patients about the interaction between nitrates and PDE5 inhibitors leading to hypotension.
- *Ranolazine* is an anti-anginal that appears to reduce angina through its effect on the late sodium current.
  - It prolongs QTc and therefore should be used with caution if a patient is on other QT-prolonging medications.
  - Side effects are primarily GI upset.
  - Usually a fourth-line agent.

Revascularization in SIHD

- Revascularization (either by PCI or CABG) is indicated in patients with ischemic symptoms that are *progressive or refractory to maximal medical management* (*Class 1A recommendation*) [2].
- In the ISCHEMIA trial (NEJM 2020), *revascularization did not reduce ischemic cardiovascular events or death* in SIHD patients with moderate or severe ischemia. However revascularization did improve symptoms.
- Based on observational data, treatment of symptomatic patients with proximal left anterior descending artery disease or multivessel disease with an initial strategy of

revascularization plus GDMT may be considered [32, 33]. Discuss with a cardiologist.

Key Learning Points

- In patients presenting with new symptoms: differentiate new SIHD and ACS, and consider baseline risk based on demographics and comorbidities.
- Consider noninvasive functional (exercise or pharmacologic stress test with ECG, echo, or nuclear imaging) or anatomic (CCTA) assessment for CAD in patients with new SIHD evaluation. CCTA is increasingly being recommended as a first-line test.
- The goals of treatment are to minimize adverse cardiovascular outcomes and death and reduce symptoms. These goals are often achieved with different pharmacotherapy. Therapy should be guideline based.
- Consider angiography/revascularization in conjunction with a cardiologist, particularly for patients with severe proximal disease when there are persistent symptoms despite GDMT.

Adapted with permission from Ref. [3]

References

1. Pryor DB, Shaw L, Harrell FE, Lee KL, Hlatky MA, Mark DB, et al. Estimating the likelihood of severe coronary artery disease. Am J Med. 1991;90(5):553–62.
2. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. J Am Coll Cardiol. 2012;60(24):e44–164.

3. Foldyna B, Udelson JE, Karády J, Banerji D, Lu MT, Mayrhofer T, et al. Pretest probability for patients with suspected obstructive coronary artery disease: re-evaluating Diamond-Forrester for the contemporary era and clinical implications: insights from the PROMISE trial. Eur Heart J Cardiovasc Imaging. 2019;20(5):574–81.
4. Genders TSS, Steyerberg EW, Alkadhi H, Leschka S, Desbiolles L, Nieman K, et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. Eur Heart J. 2011;32(11):1316–30.
5. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41(3):407–77.
6. Moss AJ, Williams MC, Newby DE, Nicol ED. The updated NICE guidelines: cardiac CT as the first-line test for coronary artery disease. Curr Cardiovasc Imaging Rep [Internet]. 2017 [cited 2021 Jan 30];10(5). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5368205/.
7. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med. 2015;372(14):1291–300.
8. Investigators SCOT-HEART, Newby DE, Adamson PD, Berry C, Boon NA, Dweck MR, et al. Coronary CT angiography and 5-year risk of myocardial infarction. N Engl J Med. 2018;379(10):924–33.
9. Ferraro R, Latina JM, Alfaddagh A, Michos ED, Blaha MJ, Jones SR, et al. Evaluation and management of patients with stable angina: beyond the ischemia paradigm: JACC state-of-the-art review. J Am Coll Cardiol. 2020;76(19):2252–66.
10. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2014;64(18):1929–49.

11. Gulati M, Shaw LJ, Bairey Merz CN. Myocardial ischemia in women: lessons from the NHLBI WISE study. Clin Cardiol. 2012;35(3):141–8.
12. Hoffmann U, Ferencik M, Udelson JE, Picard MH, Truong QA, Patel MR, et al. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE trial (prospective multicenter imaging study for evaluation of chest pain). Circulation. 2017;135(24):2320–32.
13. Chow BJW, Small G, Yam Y, Chen L, McPherson R, Achenbach S, et al. Prognostic and therapeutic implications of statin and aspirin therapy in individuals with nonobstructive coronary artery disease: results from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter registry) registry. Arterioscler Thromb Vasc Biol. 2015;35(4):981–9.
14. Marinescu MA, Löffler AI, Ouellette M, Smith L, Kramer CM, Bourque JM. Coronary microvascular dysfunction, microvascular angina, and treatment strategies. JACC Cardiovasc Imaging. 2015;8(2):210–20.
15. 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. Circulation. 2019;13:E157–98.
16. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. J Am Coll Cardiol. 2018;2018:25709.
17. McClelland RL, Bild DE, Burke GL, Mukamal KJ, Lima JA, Kronmal RA. Alcohol and coronary artery calcium prevalence, incidence and progression: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr. 2008;88(6):1593–601.
18. Rossinen J, Partanen J, Koskinen P, Toivonen L, Kupari M, Nieminen MS. Acute heavy alcohol intake increases silent myocardial ischaemia in patients with stable angina pectoris. Heart Br Card Soc. 1996;75(6):563–7.
19. Dimsdale JE. Psychological stress and cardiovascular disease. J Am Coll Cardiol. 2008;51(13):1237–46.
20. Abdelhamid AS, Brown TJ, Brainard JS, Biswas P, Thorpe GC, Moore HJ, et al. Omega-3 fatty acids for the primary and second-

ary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2018;7:CD003177.
21. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med. 2019;380(1):11–22.
22. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. J Am Coll Cardiol. 2018;71(19):e127–248.
23. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373(22):2103–16.
24. Association, American Medical. Cardiovascular benefits of SGLT2 inhibitors and GLP-1 receptor agonists in type 2 diabetes. JAMA J Am Med Assoc. 2019;321(17):1720–1.
25. American Diabetes Association. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2019. Diabetes Care. 2019;42(Suppl 1):S90–102.
26. Fisher DP, Johnson E, Haneuse S, Arterburn D, Coleman KJ, O'Connor PJ, et al. Association between bariatric surgery and macrovascular disease outcomes in patients with type 2 diabetes and severe obesity. JAMA. 2018;320(15):1570–82.
27. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med. 2017;377(14):1319–30.
28. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, et al. Colchicine in patients with chronic coronary disease. N Engl J Med. 2020;383(19):1838–47.
29. de Diego C, Vila-Córcoles A, Ochoa O, Rodriguez-Blanco T, Salsench E, Hospital I, et al. Effects of annual influenza vaccination on winter mortality in elderly people with chronic heart disease. Eur Heart J. 2009;30(2):209–16.
30. CDC. COVID-19 and Your Health [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2021 Jan 30]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.
31. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, et al. 2017 ACC/AHA/HFSA Focused Update of the

2013 ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart failure society of America. J Am Coll Cardiol. 2017;70(6):776–803.
32. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation. 2003;107(23):2900–7.
33. Windecker S, Stortecky S, Stefanini GG, da Costa BR, Rutjes AW, et al. Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis. BMJ. 2014;348(8):g3859.
34. Katz D, Gavin MC. Stable ischemic heart disease. Ann Intern Med. 2019;171(3):ITC17.