Chapter 2
Stable Ischemic Heart Disease

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Abbreviations

ACS	Acute Coronary Syndrome
BNP	Brain Natriuretic Peptide
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CCTA	Coronary Computed Tomography Angiography
CMP	Complete Metabolic Profile
ECG	Electrocardiogram
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
PCI	Percutaneous Coronary Intervention
PET	Positron Emission Tomography
SIHD	Stable Ischemic Heart Disease
SPECT	Single Photon Emission Computed Tomography
UA	Unstable Angina

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B. J. Wells et al. (eds.), *Handbook of Inpatient Cardiology*,
https://doi.org/10.1007/978-3-030-47868-1_2

Diagnosis

Differentiating CAD, SIHD, and ACS

- Coronary artery disease (CAD) is the presence of atheromatous plaque in the coronary arteries, which may or may not cause symptoms.
- Stable ischemic heart disease (SIHD) is a syndrome marked by *stable* angina: pain or pressure brought on reliably by exertion or emotion and relieved by rest or nitroglycerin. This may or may not be associated with obstructive CAD.
- In contrast, *unstable* angina (UA) describes angina of increasing severity or frequency beyond baseline, sometimes occuring at rest without an apparent trigger and is the clinical manifestation of an acute coronary syndrome (ACS) (see Chap. 1).
- ACS occurs when there is an abrupt reduction in coronary blood flow or a mismatch in myocardial oxygen supply and demand, and includes a spectrum from UA to myocardial infarction (MI).
- *Do not confuse a new diagnosis of SIHD with ACS*; they are separate clinical syndromes as explained above.
  - Patients may present for the first time with the clinical syndrome of SIHD after many months of symptoms, but they do not have UA.

Cardiovascular Risk in Patients Presenting with Chest Pain (Fig. 2.1)

- Begin with baseline risk using the patient's age, sex, and type of angina (Table 2.1).
- *Add in other canonical risk factors* that increase the likelihood of CAD and can shift the likelihood of a given symptomatic patient having obstructive coronary disease significantly [1].
- The American College of Cardiology provides an online calculator to estimate lifetime and 10-year cardiovas-

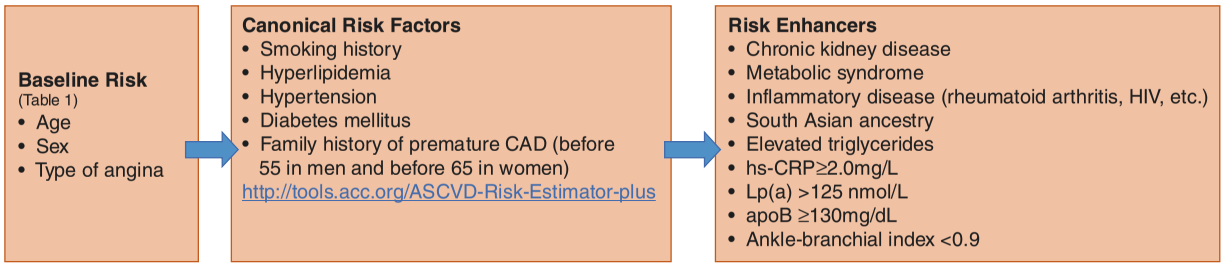

FIGURE 2.1 Approach to CAD risk assessment. Begin with baseline risk and modify using canonical risk factors, utilizing the risk calculator available online. Further risk stratification can be achieved with risk enhancers

Table 2.1 Pretest likelihood of coronary artery disease in symptomatic patients according to age and sex

Age, *y*	Non-anginal Chest Pain, %		Atypical Angina, %		Typical Angina, %	
	Men	Women	Men	Women	Men	Women
30–39	17.7	5.3	28.9	9.6	59.1	27.5
40–49	24.8	8.0	38.4	14.0	68.9	36.7
50–59	33.6	11.7	48.9	20.0	77.3	47.1
60–69	43.7	16.9	59.4	27.7	83.9	57.7
70-79	54.4	23.8	69.2	37.0	88.9	67.7
>80	64.6	32.3	77.5	47.4	92.5	76.3

Adapted with permission from Ref. [4]

cular risk based on risk factors (http://tools.acc.org/ASCVD-Risk-Estimator-Plus).

- Current guidelines acknowledge that certain *risk enhancers* beyond the factors in the calculator exist [2].

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 [3].

Preliminary Workup of Suspected SIHD

- *Labs*
  - Lab work in SIHD is not a critical element of diagnosis, but is needed to assess comorbidities and risk.
  - CBC, CMP, lipid panel, HbA1c, BNP, and baseline CK should all be considered especially at initial diagnosis of CAD.

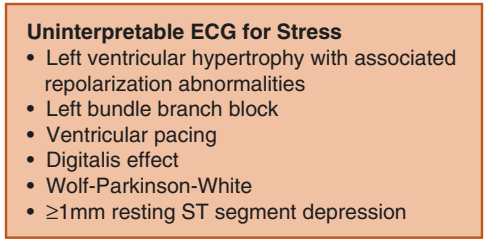

FIGURE 2.2 Features of an uninterpretable ECG

- *Electrocardiogram*
  - All patients with suspected SIHD should have a resting electrocardiogram (ECG) [1].
  - Most patients with SIHD have a normal resting ECG, but pathologic Q waves indicate a prior myocardial infarction (MI).
  - Also, resting ECG abnormalities help determine which stress test to select for patients who need stress testing (Fig. 2.2).
- *Echocardiography*
  - Rest echocardiography is not always needed.
  - Consider rest echocardiography when patients have:
    - Signs or symptoms suggesting heart failure or cardiac valve disease
    - Known prior MI or a pathologic Q-wave on the ECG suggesting prior infarction
    - ECG findings of complex ventricular arrhythmias, which could suggest underlying cardiomyopathy [1].

Specific Testing in Suspected CAD: Who to Test

- The goal of non-invasive testing is to reliably identify patients with CAD and to estimate prognosis.
- The value of testing symptomatic patients is greatest when the cause of chest pain is truly uncertain (i.e., pretest probability between 20% and 80%).

- Among patients with a very low probability of CAD (Fig. 2.1 and Table 2.1), additional testing is generally not indicated and may result in a false positive test.
- Before testing, consider the pretest probability for CAD in symptomatic patients, the ability to exercise, and any abnormalities on the resting ECG (Fig. 2.3) [4].

Specific Testing in Suspected CAD: Stress Testing (See Table 2.2)

- Stress testing, or functional testing, is the most common form of non-invasive testing.
- The clinician must select both the stressor (exercise or pharmacologic) and the modality to assess ischemia (*ECG, Echocardiography, or Single photon Emission Computed Tomography [SPECT]*, and, less often, *Positron Emission Tomography [PET] or cardiac MRI)*.
- If patients have intermediate risk, can exercise, and have an interpretable ECG (Fig. 2.3), exercise ECG without imaging carries a Class IA indication [1].
- Sensitivity of exercise without imaging is limited at 61% (i.e., 39% false negative rate) and worse for women [1].
- *In practice*, it is often preferred to add imaging to improve sensitivity. Use of imaging for this indication carries a Class IIa indication in the guidelines [1]. It is essential to add imaging if the ECG is uninterpretable.
- Adding any imaging modality – echocardiography, SPECT, or PET – can significantly improve sensitivity. See Chap. 31 for more detail.
- Pharmacologic stress with imaging can be used for patients who cannot exercise or cannot exercise strenuously enough to generate a valid test result.
  - Most commonly, dobutamine is the pharmacologic stress agent of choice for echocardiography
  - Vasodilators (regadenoson or dipyridamole) are the preferred agents for SPECT imaging.

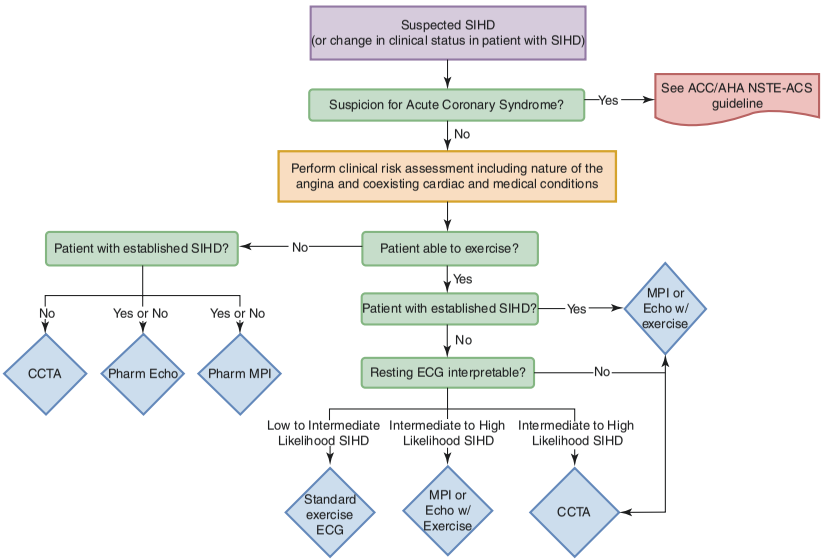

FIGURE 2.3 Choice of non-invasive study for the evaluation of newly suspected SIHD or a change in clinical status in a patient with SIHD. SIHD stable ischemic heart disease; ACC/AHA NSTE-ACS American College of Cardiology/ American Heart Association Non-ST segment elevation Acute Coronary Syndrome; MPI myocardial perfusion imaging; Pharm pharmacologic; ECG electrocardiogram; Echo echocardiogram; CCTA Coronary Computed Tomography Angiogram. (Reproduced with permission from Katz and Gavin [29])

Table 2.2 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, adenosine)	Highly sensitive Works well in overweight individuals	Radiation More expensive
PET	Vasodilator (regadenoson, dipyridamole, adenosine)	Extremely sensitive Works well in overweight individuals Can provide microvascular dysfunction data	Radiation More expensive Not widely available
MRI	Dobutamine, Vasodilator (regadenoson, dipyridamole, adenosine)	Extremely sensitive Works well in overweight individuals Can provide viability data	Requires breath-holds for quality More expensive Not widely available

Table 2.2 (continued)

Test	Preferred Stress Modalities	Pros	Cons
CCTA	N/A	No exercise required Only non-invasive 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

- The sensitivity of SPECT and stress echo for CAD are similar enough that choice of test depends in part on *the resources and technical expertise at a given institution* [1]. These additional factors should also be considered:
  - 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, stress echo is not recommended because the abnormal electrical activation of the heart impairs the interpretation of ischemia in the interventricular septum (LAD territory).

  - SPECT and PET imaging are less susceptible to poor image quality related to body habitus.

Specific Testing in Suspected CAD: Anatomical Testing

- An alternative to functional testing is non-invasive anatomical testing in the form of coronary computed tomography angiography (CCTA).
- Anatomical testing is best in those with contraindication to stress testing or who cannot exercise.
- It also has the advantage of identifying non-obstructive coronary disease and coronary congenital anomalies.
- *CCTA showed no difference in adverse cardiovascular events compared to functional testing when used as the initial diagnostic test among intermediate risk patients with symptomatic SIHD* (PROMISE, NEJM 2015) [5].
- *When added to standard care in SIHD, CCTA lowered rates of combined primary endpoint of death from CHD or non-fatal MI* (SCOT-HEART, NEJM 2018) [6].

Specific Testing in Suspected CAD: Invasive Coronary Angiography

- Often the best initial test in ACS, less useful in SIHD
- In patients with a high likelihood of disease (i.e., >90%) based on symptoms and clinical risk factors (especially when already on anti-anginal medication), non-invasive testing provides little additional information, so invasive testing is required if it will affect therapy.

Specific Testing in Already Known CAD

- For patients who carry a confirmed diagnosis of CAD and are having symptoms on anti-anginal therapy, functional testing with imaging is used to localize and quantify the extent of ischemic myocardium to inform decisions on revascularization [7].
- CCTA is less valuable in this setting.

SIHD Without Obstructive CAD

- Up to 30% of patients presenting with angina have no obstructive CAD.
- Among these patients, 50–65% are believed to have coronary microvascular dysfunction.
- Angina without obstructive coronary disease is more common among women [8].
- MRI and PET protocols have the ability to detect microvascular dysfunction non-invasively [9].
- There is an increased risk of ischemic events in both microvascular disease and non-obstructive epicardial coronary atherosclerosis [10, 11]. Medical therapy is still indicated!

When to Refer to a Cardiologist

- Patients in whom noninvasive testing is contraindicated.
- Patients with a high likelihood of CAD, or uncertain diagnosis after noninvasive testing in whom coronary angiography should be considered [7].
- Patients with suspected microvascular dysfunction or variant (Prinzmetal's) angina.

Guideline-Directed Medical Treatment (GDMT)

Goals of Treatment

- Prevention of ischemic events (cerebral, coronary, and peripheral) (Fig. 2.4).
- Reducing the burden of anginal symptoms.
- Patients with CAD still benefit substantially from treatments that reduce cardiovascular events even if symptoms are minimal or none.

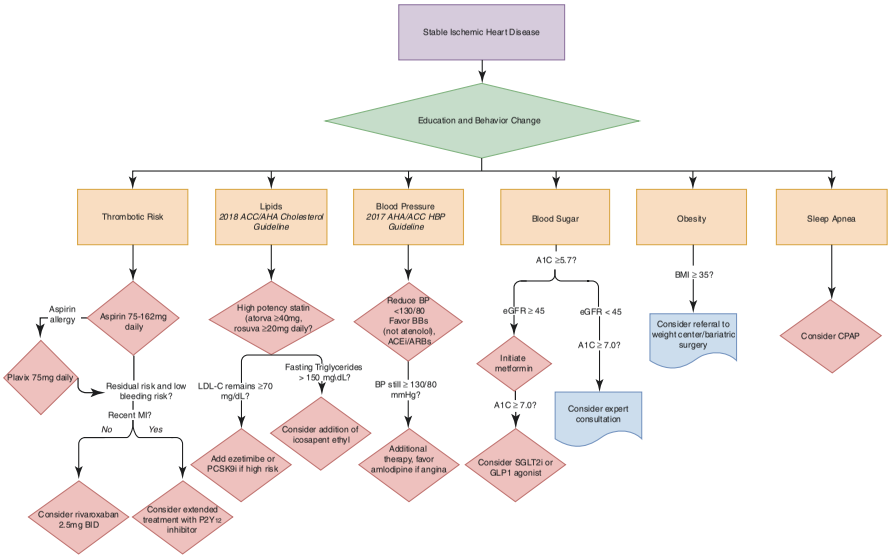

FIGURE 2.4 Guideline-directed medical therapy for patients with stable ischemic heart disease. A1c hemoglobin A1c; ACC American College of Cardiology; ACEi Angiotensin converting enzyme inhibitor; AHA American Heart Association; ARB angiotensin receptor blocker; BBs beta blockers; BID twice daily; BMI 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 [29])

Behavior Modification

- *Smoking cessation:* Smoking increases cardiovascular disease mortality by 50%.
- *Physical activity:* Current guidelines recommend 150 minutes of at least moderate activity per week [22]. Patients with SIHD and those post-MI should participate in a cardiac rehabilitation program [1].
- *Dietary modification:* Emphasize intake of vegetables, fruits, whole grains, legumes, healthy protein sources (low-fat dairy products, low-fat poultry (without the skin), fish/seafood, and nuts), and non-tropical vegetable oils. The intake of sweets, sugar-sweetened beverages, and red meats should be limited [2].
- *Alcohol Moderation:* No harm and possible cardiovascular benefit for one drink per day with no benefit and likely harm beyond two drinks per day [12]. Bouts of heavy drinking worsen hypertension and precipitate ischemia in SIHD, and should be avoided [13].
- *Psychological well-being:* Interventions to reduce psychological stress may improve clinical outcomes in patients with SIHD [14].

Pharmacologic Therapy for Specific Risk Factors

Lipids

- HMG-COA reductase inhibitors (*statins*) should be used for lipid management, unless contraindicated or adverse events occur.
- In SIHD patients under 75, high-potency statin (atorvastatin 80 mg or rosuvastatin 20–40 mg) is recommended.
- A moderate potency statin can be considered for patients over 75.
- As an update in the 2018 guidelines, adding *ezetimibe and PCKS9 inhibitors in sequence* to reach a low-density lipoprotein cholesterol (LDL-C) goal of <70 mg/dL should be considered for patients at high risk

  - This group includes patients with a history of multiple previous events, or those with one event and multiple risk factors
- *Niacin is no longer recommended* for the lowering of LDL-C [2].
- Low doses of over-the-counter fish oil have not shown consistent benefits, and are not presently recommended [15].
- *However,* icosapent ethyl*, a highly purified and stable EPA ethyl ester, reduced cardiovascular events 25% on top of high-dose statins and aspirin in patients with SIHD and elevated triglycerides (LDL-C between 41 and 100 mg/dL and fasting triglycerides 135–499 mg/dL)* (REDUCE-IT, NEJM 2019) [16].

Hypertension

- Current guidelines recommend a goal BP of <130/80 mmHg in SIHD [17].
- *In patients over 50 with SIHD, achieving a systolic blood pressure of 121 mmHg* versus *136 mmHg with antihypertensives decreased major adverse cardiovascular events (MACE) by 31% with a number needed to treat (NNT) of 44* (SPRINT, NEJM 2015) [18].
- Agent of choice depends on other comorbidities (e.g., angina, congestive heart failure, chronic kidney disease, or diabetes)

Diabetes

- Certain SGLT2 inhibitors (*empagliflozin and canagliflozin*) have been shown to reduce cardiovascular events [19].
- Certain GLP-1 receptor agonists (*liraglutide and semaglutide*) have also been shown to reduce ischemic events in patient with SIHD [19].
- It is recommended to add these agents to metformin in SIHD patients not at their glycemic target [19, 20].

Obesity

- Beyond lifestyle change, if BMI > 35, weight loss surgery should be discussed in all patients with SIHD, especially in patients with type 2 diabetes for whom Roux-en-Y gastric bypass has been shown to reduce cardiovascular events [21].

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

Antiplatelet Therapy

- All patients with CAD should be treated with low-dose *aspirin*, usually 81 mg.
- When aspirin is contraindicated, patients can be treated with *clopidogrel* 75 mg daily.

Anticoagulation

- *Rivaroxaban* at a very reduced dose of 2.5 mg twice daily likewise demonstrated a reduction in cardiovascular mortality among patients with SIHD at the expense of increased bleeding (COMPASS, NEJM 2017) [22] and may be useful in patients with favorable bleeding profiles.

Other Therapies

- Patients with SIHD should receive an annual influenza vaccine [1, 23].

Medications that Treat Angina

- Short acting nitrates in the form of *sublingual nitroglycerin or nitroglycerin spray* should be used for immediate relief of angina.

  - Patients can administer one dose every 5 minutes for up to three doses.
  - Warn patients about the interaction between nitrates and PDE5 inhibitors leading to hypotension.
- *β-blockers* should be prescribed as initial therapy for prolonged relief of symptoms.

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 [1].

  - In patients with reduced EF, carvedilol, metoprolol succinate, and bisoprolol should be favored per guidelines [24].
- *Calcium channel blockers* or long-acting nitrates (*isosorbide or nitropaste*) can be prescribed when β-blockers are contraindicated (e.g., severe bronchospastic lung disease) or produce unacceptable side effects.
  - Non-dihydropyridine calcium channel blockers (*diltiazem and verapamil*) should be avoided in patients with reduced ejection fraction given their negative inotropic effects; dihydropyridine calcium channel blockers such as *amlodipine* are preferred.
- 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) [1].
  - Among patients with a low burden of angina, a sham-controlled trial of up front revascularization plus aggressive medical management did not demonstrate additional angina reduction. (ORBITA, Lancet 2018) Anginal frequency should therefore be taken into consideration when making revascularization decisions.
  - In a large randomized control trial of patients with SIHD and moderate-severe ischemia on stress test, routine invasive therapy did not reduce major adverse cardiac events vs medical therapy alone, but improved angina burden and quality of life if they had angina at baseline (ISCHEMIA, NEJM 2020).
- It is not clear if routine revascularization in combination with GDMT reduces rates of death or ischemic events.
- Based on observational data, many treat symptomatic patients with proximal left anterior descending artery disease or multivessel disease with an initial strategy of revascularization plus GDMT given the large area of ischemia [25, 26]. The guidelines generally support CABG over PCI for the intention of improving survival in these cases [1, 27, 28].

Key Learning Points

- The most useful preliminary predictors of clinically significant CAD are age, sex, type of chest pain, and comorbid conditions including tobacco use, hyperlipidemia, hypertension, family history of premature CAD, and diabetes mellitus.
- Nearly all patients should have a non-invasive functional (exercise or pharmacologic stress test with ECG, echo, or nuclear imaging) or anatomic (CCTA) assessment for CAD. The type of non-invasive test is determined using pre-test probability of CAD, resting ECG, and the ability to exercise.
- The clinician should consider moving directly to coronary angiography in a limited subset of patients.

- The goals of treatment are to minimize adverse cardiovascular outcomes and death and reduce symptoms. These goals can involve independent pharmacotherapy.
- All patients should have guideline-directed medical therapy to reduce the risk for mortality and relieve symptoms.
- Consider revascularization in conjunction with a specialist for patients at high risk for mortality, especially those with persistent symptoms despite GDMT.

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