Chapter 5
Treatment of Coronary Artery Disease (CAD)

Keywords Treatment · Drug therapy · Invasive therapy · Minimally invasive therapy · Therapeutic guideline · Dual antiplatelet therapy · Coronary artery bypass grafting

The treatment of coronary artery disease (CAD) aims to treat cardiac disease based on its severity and pathological condition. Along with pain, patients may suffer from other symptoms such as severe fatigue, dyspnoea, abdominal pain, nausea and sweating, and to understand cardiac pain one requires knowledge of the interplay between ischemic, metabolic and neurological mechanisms behind the CAD. This chapter will discuss the therapies for stable ischemic heart disease (SIHD) and for acute coronary syndrome (ACS).

For the patient with SIHD, there are five fundamental aspects that need to be followed alone and/or in combination with each other:

1. Identification, treatment and education of the patient
2. Reduction of coronary risk factors
3. Secondary prevention using pharmacologic and/or non-pharmacologic intervention, with attention to adjustments in lifestyle
4. Pharmacologic management of angina
5. Revascularization by catheter-based percutaneous coronary intervention (PCI) or by coronary artery bypass grafting (CABG)

Identification of the cause of SIHD is necessary in order to apply the right therapy. For example, there are several medical conditions which either lead to an increase in myocardial oxygen demand or a reduction in oxygen delivery. Both these conditions contribute to the onset of new angina pectoris as shown in Fig. 5.1 [39].

Reduction of coronary risk factors can also help to manage SIHD effectively. For example, the management of hypertension can reduce CAD events and mortality by up to 16%. Other factors such as cigarette smoking, management of dyslipidaemia, high-density lipoprotein and cholesterol levels, obesity and inflammation have

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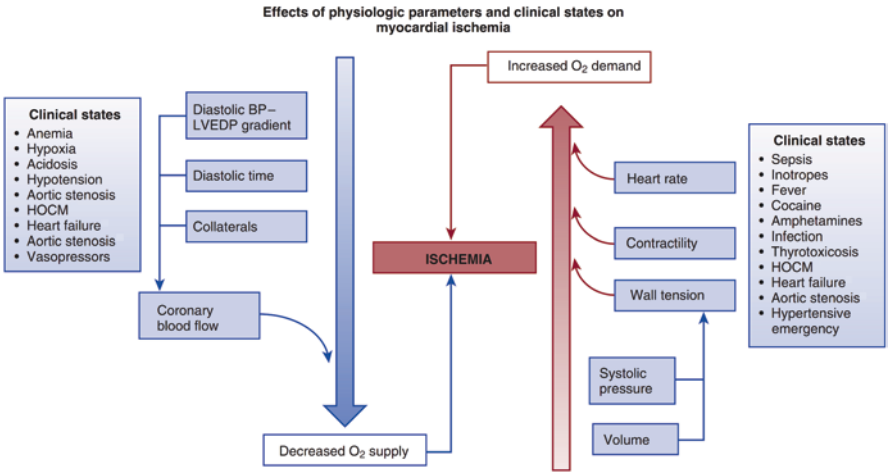

Fig. 5.1 Participants with myocardial ischemia. The hemodynamic consequences of clinical states and their effects on the supply and demand of oxygen and ultimately on ischemia [39]
BP blood pressure, *HOCM* hypertrophic obstructive cardiomyopathy, *LVEDP* left ventricular end-diastolic pressure

also been shown to reduce CAD events and mortality [6, 28]. Antianginal therapy helps to reduce symptoms and helps to prolong the ability to exercise. Therapies such as aspirin, angiotensin-converting enzyme (ACE) inhibitors and lipid-lowering treatments have been shown to reduce mortality and morbidity in patients with SIHD. Other therapies such as long-acting nitrates, beta blockers or calcium channel blockers improve the symptoms and exercise performance, but do not have a beneficial effect on improving the survival of patients. The antianginal drug therapies are listed in Table 5.1 [28].

Beta blockers have anti-ischemic, antiarrhythmic and antihypertensive properties. Beta blockade reduces myocardial O_2 requirements by slowing the heart rate and helping to reduce the exercise-induced blood pressure. Calcium antagonists inhibit calcium ion movement through the slow channels in the cardiac and smooth muscle membranes by noncompetitive blockade of voltage-sensitive L-type calcium channels that lead to a reduction in myocardial O_2 demand and an increase in O_2 supply. Nitrates relax vascular smooth muscle. Nitrates exhibit a vasodilatory effect, which reduces the ventricular preload, leading to reduced myocardial wall tension and O_2 requirements. This makes them a useful drug for heart failure and angina. Other than these conventional drugs some novel antianginal drugs, such as ranolazine, ivabradine, nicorandil, trimetazidine and molsidomine, also have anti-ischemic properties. Ranolazine reduces myocardial ischemia through a reduction in calcium overload in ischemic myocytes by inhibiting the inward movement of sodium. Ivabradine is a heart rate-slowing drug, nicorandil increases nitric oxide concentration that leads directly to coronary vasodilation. Trimetazidine increases myocardial glucose utilization and prevents adenosine triphosphate (ATP) reduction.

Table 5.1 Antianginal drugs based on their effect with side effects and contraindications [28]

Agents	Side effects	Contraindications
Agents with a physiologic effect		
Short- and long-acting nitrates	Headache, flushing, hypotension, syncope and postural hypotension, reflex tachycardia, methaemoglobinaemia	Hypertrophic obstructive cardiomyopathy
Beta blockers	Fatigue, depression, bradycardia, heart block, bronchospasm, peripheral vasoconstriction, postural hypotension, impotence, masked signs of hypoglycemia	Low heart rate or heart conduction disorder, cardiogenic shock, asthma, severe peripheral vascular disease, decompensated heart failure, vasospastic angina; use with caution in patients with COPD (cardioselective beta blockers may be used if the patient receives adequate treatment with inhaled glucocorticoids and long-acting beta agonists)
Calcium channel blockers		
Nondihydropyridine (heart rate–lowering agents)	Bradycardia, heart conduction defect, low EF, constipation, gingival hyperplasia	Cardiogenic shock, severe aortic stenosis, obstructive cardiomyopathy
Dihydropyridine	Headache, ankle swelling, fatigue, flushing, reflex tachycardia	Low heart rate or heart rhythm disorder, sick sinus syndrome, CHF, low blood pressure
Ivabradine	Visual disturbances, headache, dizziness, bradycardia, atrial fibrillation, AV block	Low heart rate or heart rhythm disorder, severe hepatic disease; not to be prescribed with verapamil and diltiazem; caution for use in patients with AF
Nicorandil	Headache, facial flushing, dizziness and weakness, nausea, hypotension; oral, anal or gastrointestinal ulceration	Cardiogenic shock, heart failure, low blood pressure (<100 mm Hg systolic)
Molsidomine	Headache, hypotension	None reported
Agents that affect myocardial metabolism		
Ranolazine	Dizziness, constipation, nausea, QT-interval prolongation	Liver cirrhosis, long QT interval on ECG test
Trimetazidine	Gastric discomfort, nausea, headache, movement disorders	Allergy, Parkinson disease, tremors, movement disorders, severe renal impairment
Perhexiline	Dizziness, nausea, vomiting, lethargy, tremors	Slow hydroxylators of cytochrome P450, abnormal liver function, neuropathy
Allopurinol	Rash, gastric discomfort	Hypersensitivity, renal failure

AF atrial fibrillation, *AV* atrioventricular, *CCB* calcium channel blocker, *CHF* congestive heart failure, *COPD* chronic obstructive pulmonary disease, *ECG* electrocardiography, *EF* ejection fraction

Molsidomine reduces preload, dilates the coronary arteries and increases the donation of nitric oxide. All the medical treatments described above should be used alone or in combination with others based on the patient's need and careful assessment. To achieve this, the physician may use a guideline, such as the National Institute for Health and Care Excellence (NICE) guideline published by the National Clinical Guideline Centre, for the management of stable angina as illustrated in Fig. 5.2 [72].

In the past decade, treatments using living cell-based therapy and gene therapy research are booming due to advanced technologies and increased understanding of the vascular and cellular architecture at the molecular level. There are currently many published research studies using vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) as well as pluripotent stem cells that have proven their safety, angiogenesis and advanced regenerative capacity. At the same time, there is concern that the direct or indirect use of living cells to produce growth factors on the device's surface will limit their long-term therapeutic effect and cause side effects specifically host cell rejection. In order to overcome this limitation, Dr. Ke Cheng and his research group at BioTherapeutics Laboratory at North Carolina State University have demonstrated the use of novel stem cell-like micro and nano particles (CMMP and CMNP) to initiate angiogenesis and the therapeutic regenerative properties of stem cells without using any actual living cells [73–75].

The principle guideline for the management of all patients has two main goals: medical management and risk factor reduction. The procedure for revascularization, such as coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) in patients with stable ischemic heart disease, is a topic of debate over the last two decades. On the one hand, PCI and CABG are the most frequently applied treatments for STEMI patients, but for the stable ischemic heart disease patient there are many more factors involved before revascularization can be considered. Such patients, such as those presenting with underlying risk factors, sociodemographic factors like age, and physical capacity, have the ability to adhere to

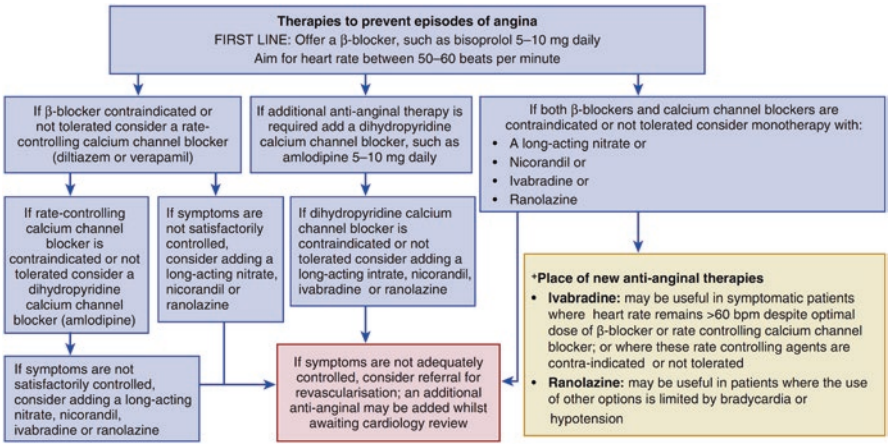

Fig. 5.2 2011 NICE guidelines recommending medical therapy for chronic stable angina [72]

prescribed treatments, lifestyle interventions, overall quality of life, other medical conditions and the patient's preferences. The presence and severity of symptoms, the physiologic conditions of coronary lesions and other anatomical considerations, myocardial ischemia and the presence of LV dysfunction, along with other medical conditions are major deciding factors for the selection of revascularization of patients with stable ischemic heart disease. Such revascularization is normally considered after intensive medical therapy and/or risk factor modification and other conditions that limit the extent of antianginal therapy [28, 76, 77].

For both the NSTEMI and STEMI patient, the goal of treatment is the immediate relief of ischemia and the prevention of MI and death. The patient is treated immediately with antianginal, antiplatelet, fibrinolytic and anticoagulant therapies, and the patient with severe continuing angina or a large MI and other LV functions is managed by CABG or PCI along with continuous medical therapy. Irrespective of the indication for revascularization, PCI should be coupled with optimal medical therapy after the procedure, such as the control of risk factors and other medical therapies as per the published guidelines. Control of hypertension and diabetes, exercise and smoking cessation, lipid management and statin therapy are all important components of optimal medical therapy. CABG has the advantage of a late mortality benefit compared to PCI, but early procedural risks and longer in-hospital recovery periods are the major factors to be considered while selecting PCI or CABG along with other critical factors [78, 79].

Medical therapies involve supplemental oxygen, nitrates, analgesic therapy, beta-adrenergic blockers, calcium channel blockers, the management of cholesterol, inhibitors of the renin-angiotensin-aldosterone system, antiplatelet and anticoagulant therapies alone or in combination. These options are described in the published guidelines and are followed by revascularization if required, as shown in Figs. 5.4 and 5.5 and the 2014 American Heart Association/American College of Cardiology (AHA/ACC) guidelines for the management of patients with NSTEMI (also called NSTE-ACS) and the 2013 guideline for management of patients with STEMI [42, 80]. To prevent such chronic CAD, a wide range of antithrombotic, single and dual antiplatelet therapies are prescribed and the mechanism of actions (MOA) is depicted in Fig. 5.3 [81].

The activation of platelets occurs when the first blood agents adhere to ruptured or eroded surfaces of the plaque, aggregate at the site and then ultimately start the coagulation cascade. Drugs like aspirin, as shown in Fig. 5.3, block the cyclooxygenase-1 enzyme which promotes the synthesis of thromboxane A_2 receptor expressed in platelets and other inflammatory cells, and this is the first line of treatment for suspected ACS patient. $P2Y_{12}$ inhibitors such as thienopyridines (ticlopidine, clopidogrel and prasugrel), ticagrelor (cyclopentyl-triazolo-pyrimidine CPTP inhibitor) and cangrelor (ADP inhibitor) prevent platelet aggregation by inhibiting the release of the platelet adenosine diphosphate (ADP) receptor $P2Y_{12}$. Dual antiplatelet therapy involving a combination of aspirin and $P2Y_{12}$ receptor blocker such as clopidogrel has become the standard procedure of care for patients undergoing revascularization. GP IIb/IIIa antagonists, such as Abciximab, Eptifibatide, Tirofiban, interfere with platelet cross-linking and platelet-derived thrombus formation [81–84].

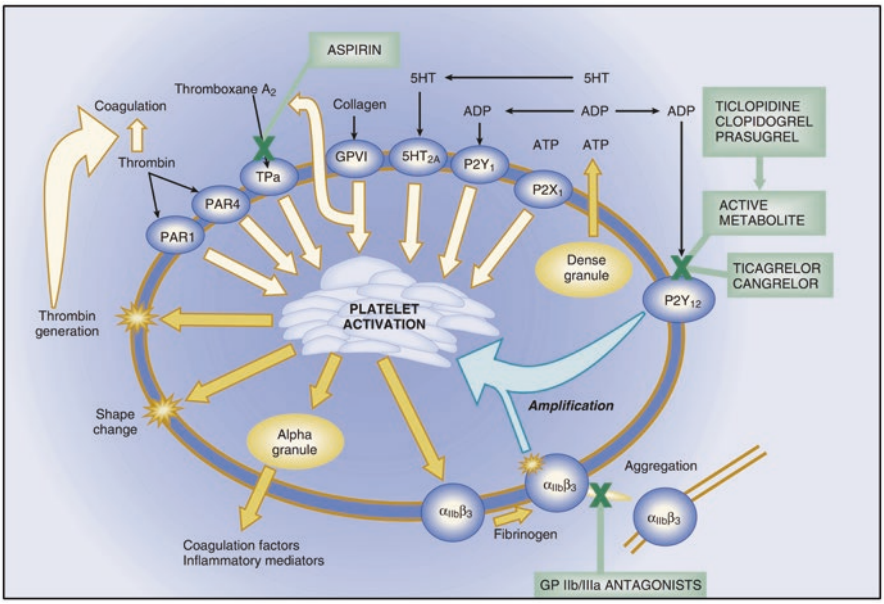

Fig. 5.3 Platelet activation and aggregation inhibitors [81] *ADP* adenosine diphosphate, *ATP* adenosine triphosphate, *GP* glycoprotein, *HT* hydroxytryptamine, *PAR* protease activated receptor; *TP* thromboxane A_2 receptor

As described in Figs. 5.4 and 5.5, the timeline to undergo revascularization for the patient with ACS is important. Early PCI helps the coronary system to restore blood circulation and limits any permanent damage to the heart muscle or, in other words, irreversible myocardial injury. As shown in Fig. 5.5, and as per the guideline, once admitted to a PCI-capable hospital, the first medical contact (FMC) to PCI time should be less than 90 min for STEMI patients, and if admitted to a non-PCI-capable hospital and fibrinolytic agents have not been administered, the FMC to PCI time should be less than 120 min.

Such a revascularization technique is the therapy of choice for ST-elevated myocardial infarction (STEMI) patients. Approximately 95% of patients are treated with PCI to get their blood flow restored by opening a blocked artery, compared with

Fig. 5.4 (continued) See corresponding full-sentence recommendations and their explanatory footnotes in 2014 AHA/ACC guideline for the management of patients with non-ST-elevated acute coronary syndrome (NSTE ACS). †In patients who have been treated with fondaparinux (as upfront therapy) who are undergoing percutaneous coronary intervention (PCI), an additional anticoagulant with anti-IIa activity should be administered at the time of PCI because of the risk of catheter thrombosis. *ASA* indicates aspirin, *CABG* coronary artery bypass graft, *cath* catheter, *COR* class of recommendation, *DAPT* dual antiplatelet therapy, *GPI* glycoprotein IIb/IIIa inhibitor, *LOE* level of evidence, *NSTE-ACS* non-ST-elevated acute coronary syndrome, *PCI* percutaneous coronary intervention, *pts*. patients, *UFH* unfractionated heparin

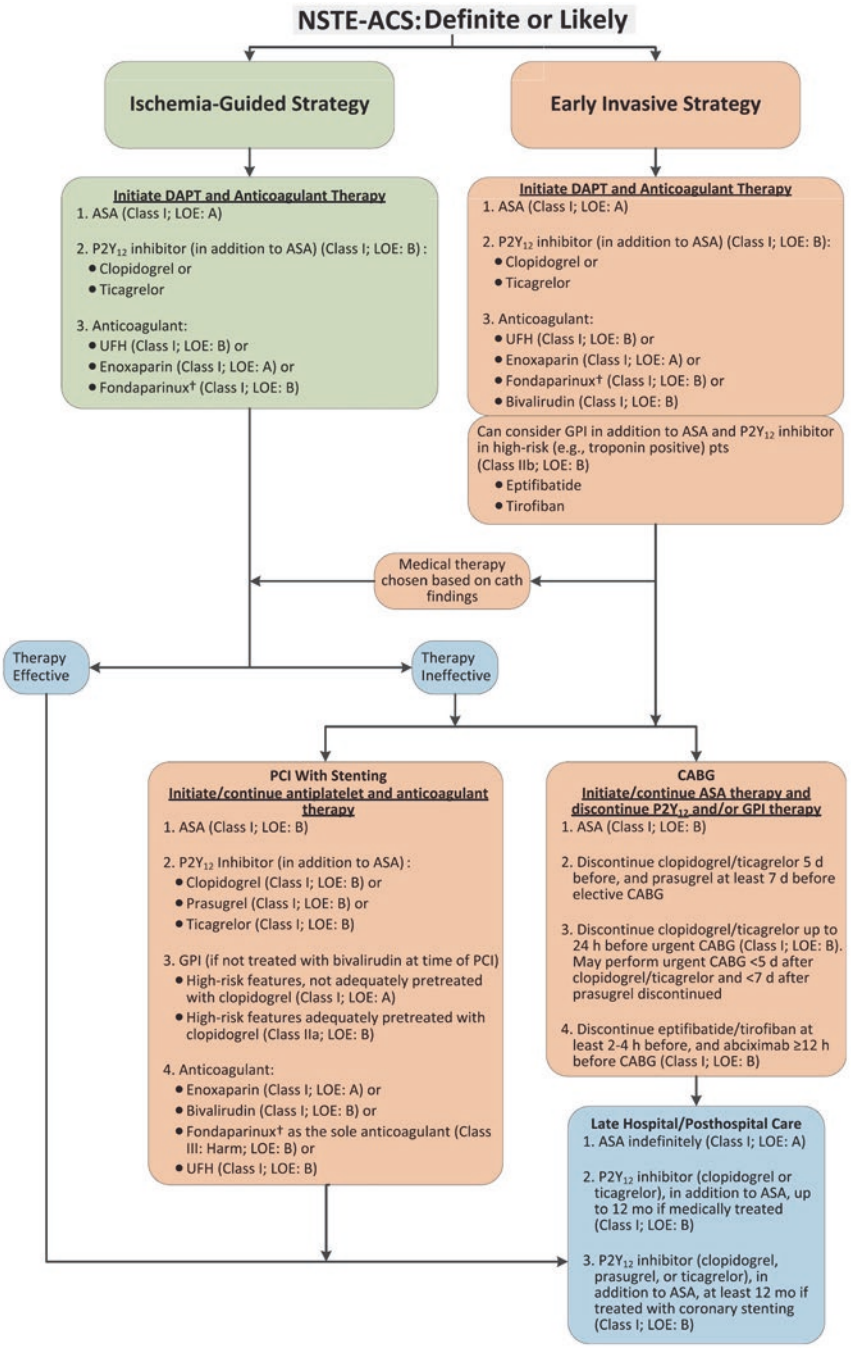

Fig. 5.4 Algorithm for management of patients with definite or likely non-ST-elevated acute coronary syndrome (NSTE-ACS) [42]

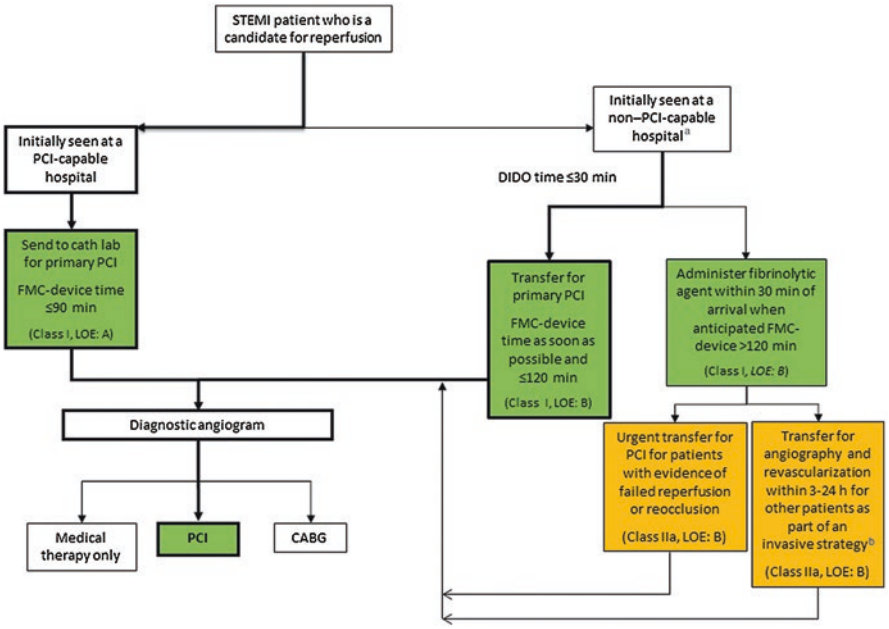

Fig. 5.5 Reperfusion therapy for patients with STEMI [80] [a]The bold arrows and boxes are the preferred strategies. Performance of PCI is dictated by an anatomically appropriate stenosis. Patients with cardiogenic shock or severe heart failure initially seen at a non-PCI-capable hospital should be transferred for cardiac catheterization and revascularization as soon as possible, irrespective of the delay since the onset of MI (Class I, LOE: B). [b]Angiography and revascularization should not be performed within the first 2–3 h after administration of fibrinolytic therapy. *CABG* coronary artery bypass graft, *DIDO* door-in-door-out, *FMC* first medical contact, *LOE* level of evidence, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *STEMI* ST-elevated myocardial infarction. Please refer to the 2013 ACCF/AHA guideline for patients with STEMI for LOE and classification details

only 54% of patients who are treated by medical therapy. The evolution in angioplasty techniques is described later in the next chapter together with a detailed discussion about PCI techniques and new updated research studies.

As described earlier in this chapter, there are certain risk-benefit ratios involved in recommending the therapies regarding revascularization, whether it be PCI or CABG. For example, Table 5.2 lists the appropriate use criteria for PCI and CABG in patients with multivessel coronary artery disease, whether it is A – Appropriate, I – Inappropriate or U – Uncertain to apply the particular revascularization procedure using the SYNTAX score. The SYNTAX score, by combining anatomical and clinical prognostic variables, creates accurate mortality predictions to guide the choice between PCI and CABG for patients with multivessel coronary disease [85].

Table 5.2 Appropriate use criteria for common indications in patients with multivessel coronary disease [85]

Multivessel coronary disease	CABG	PCI
Two-vessel CAD with proximal LAD stenosis	A	A
Three-vessel CAD with low CAD burden (i.e. 3 focal stenosis, low SYNTAX score)	A	A
Three-vessel CAD with intermediate to high CAD burden (i.e. multiple diffuse lesions, presence of CTO or high SYNTAX score)	A	U
Isolated left main stenosis	A	U
Left main stenosis and additional CAD with low CAD burden (i.e. one to two vessel additional involvement, low SYNTAX score)	A	U
Left main stenosis and additional CAD with intermediate to high CAD burden (i.e. three vessel involvement, presence of CTO or high SYNTAX score)	A	I

A appropriate, *I* inappropriate, *U* uncertain, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *CTO* chronic total occlusion, *LAD* left anterior descending artery, *PCI* percutaneous coronary intervention, *SYNTAX* synergy between PCI with TAXUS and cardiac surgery