An overview of managing patients with coronary heart disease and its pathogenesis: Antiplatelet and/or anticoagulation therapy for uneventful non-cardiac surgery

Abstract

Over the years, due to the high mortality rate among heart patients, the disease has received much attention and has led to many trials and studies on the disease and, of course, at a high cost. This article provides an overview of the pathophysiology, diagnostic methods and, ultimately, new therapies that have been the achievements of scientists over the past decades to date. And because of the large number of myocardial infarction during non-cardiac surgery in the cardiac patients, we review the latest recommendations for reducing the incidence of myocardial infarction and cardiac death during the non-cardiac surgery.

Keywords: coronary artery disease, stable ischemic heart disease, acute coronary syndrome, st. segment elevation myocardial infarction, non st. elevation myocardial infarction, non-cardiac surgery

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Introduction

Coronary artery disease statistics are increasing. On the other hand, the advancement of science in the treatment and utilization of coronary artery bypass grafts and angioplasty, as well as various therapeutic cares, has prolonged life expectancy for heart patients whilst simultaneously increasing the number of non-cardiac operations in heart patients. However, the global number of non-cardiac surgeries is estimated to be around two million cases a year, with cesarean sections accounting for one-third of these cases. How we deal with heart disease patients depends on how well we know the patient's past history. How thoroughly we review all patient records including angiographic, angioplasty stenting films and written records, considering the number and length and type of stents used even knowing the timing of a heart operation and possible peri procedure complications. Ultimately using risk assessment techniques to minimize the potential surgical risks. Considering all mentioned points are too crucial. As to what the medications should be and for how long they are to be taken, including antiplatelet and anticoagulants drugs, the risk of stent thrombosis when discontinued before operation is taken into account, and how much of this risk there is should be considered because the cases of stents or grafts thrombosis are a disaster that causes perioperative myocardial infarction. The major problem with myocardial infarction during non-cardiac surgery is that it is often asymptomatic, and therefore, accompanied by more than fifty percent fatality in this context.

In this article, we broadly review the latest findings on the pathophysiology, diagnosis and different treatment modalities of coronary artery disease. At the end of this article, we discuss introducing different manners to reduce the incidence of myocardial infarction in non-cardiac operations.

Epidemiology

In developed countries, with the improvement of preventive methods and significant advances in the treatment of diseases, in general, we are faced with an increase in the population of older ages. At the same time, the number of atherosclerotic diseases that affect the coronary arteries is increasing in industrial societies with increasing age, although women lag behind men by 10 years [1]. The 2016 Heart Disease and Stroke Statistics update of the American Heart Association (AHA) has reported that 15.5

million American people over the age of twenty suffer from Coronary Heart Disease (CHD), which is estimated to cause an Acute Myocardial Infarction (AMI) every 42 seconds in an American person, causing one third of deaths in people over the age of thirty-five years [2]. In general, the leading cause of death in adults in low-, middle- and high-income countries is CHD [3].

Because in epidemiologic studies clinical symptoms play a major role in screening, these estimates are lower figures than reality. Hence, the results of autopsy studies are more realistic. For instance, in a 1992 study of 2,562 individuals between the ages of 20 and 59 from Minnesota in the US who had undergone autopsies, the prevalence of CHD in men was 32% and in women 16% [4]. In recent decades, and in developed countries, the outbreak of CHD due to atherosclerosis has declined substantially; however, it is growing in developing countries [5]. Of course, the factors affecting the prevalence of atherosclerosis are numerous and, therefore, in different societies we have a different outbreak rate of CHD and death because of it. In a fascinating study over Canadian immigrants, the highest risk of atherosclerosis was in Asian (excluding Chinese immigrants) and European populations, while the lowest risk was for Chinese immigrants [6,7]. In Europe, four million deaths per year are due to Cardiovascular Disease (CVD), including CHD and stroke, causing close to half of all deaths. Even at the level of European countries, there is also a large geographic death rate inequality; higher CVD mortality, as well as premature CVD mortality in the Eastern European countries such as Russian Federation, compared to a country like France in Western Europe [8].

Although numerous studies of an autopsy on soldiers killed in the Vietnam War in 1953 have shown that the onset of illness begins in young adults, differences in the prevalence of atherosclerosis are seen in the reports published over the past sixty years. As a whole, it can be said that in the developed countries, with the exception of the 1990s, there is a downward trend in its prevalence, although this finding is not unanimous in all studies **TABLE 1** [4,9-15].

■ Cost-effectiveness and economic burden of atherosclerosis

From another perspective, the budget impact of Disability-Adjusted Life Years (DALY); measure of years of life lost due to death from a condition, and years lived with disability due to a condition at work, is very important [16]. To clarify the burden on the different aspect, we should consider a few examples; the length of hospital stays of an AMI patient with an average of 10.3 days in Germany and the cost of performing an uneventful coronary PCI in the United States is $21,204. More generally, for healthcare of CVD patients in the United Kingdom at a rate of £6.8 billion, and in the United States the $320 billion contributes annually [17], would make it possible to look at the other problems around the cardiovascular patients. Therefore, cardiovascular prevention programs reduce the burden of DALY, and more effective treatments to decline the death of cardiac patients, have long been considered by government treatment systems. International leaders have called for contributing global cardiovascular preventive projects in developing countries [18] and in 2012, at the World Health Assembly, adopted the global target of 25% reduction in mortality due to non-

TABLE 1. Autopsy proven prevalence of atherosclerotic involvement of coronary arteries in different studies during the past four decades [4,9-15].

Method	Number of cases	Period	Age range	Prevalence of Atherosclerosis in men	Prevalence of Atherosclerosis in women
Olmsted County residents	2,562	1979-1983	16-64	42%	29%
		1990-1994			
			18-59	32%	16%
US military personnel	3,832	2001-2011	18-59	12.10%	N/A
Died from non-cardiac trauma	111	1988-1989	26+/-6	78.30%	N/A
Korean Soldiers Victims	300	1947-1972	18-48	77.30%	N/A
Vietnam Soldiers Victims	105	1971	N/A	45.00%	N/A
IVUS in heart donors for transplantation	262	2001	33.4 ± 13.2	52.00%	51.70%
Serial computed tomography scans for calcium scoring (MESA study)	1062-4837	2000-2012	55-84	52.00%	N/A
Unnatural deaths like suicide	50	2013	30-60	83.72%	57.14%

communicable diseases such as CHD by the year 2025 [19].

Discussion

■ From pathogenesis towards the clinical manifestations of CAD

With the onset of atherosclerosis, the process of coronary artery narrowing begins with the presence of major risk factors (smoking, hyperlipidemia, diabetes mellitus, hypertension, obesity or metabolic syndrome, physical inactivity, and a family history of premature IHD, i.e. onset in a father, brother, or son before age 55 years or a mother, sister, or daughter before age 65 years) precipitate the coronary artery cross-sectional area narrowing. Even in the presence of these risk factors, we continued to see the nonlinear trend of growth in coronary stenosis for several years to decades. However, even in patients with non-obstructive CHD (stenosis ≥ 20% but <70%), it can still have a worse prognosis compare subjects with normal coronaries [20]. Therefore, secondary prevention in this non-obstructive CHD is very important to prevent AMI [21].

■ Patients with Stable Ischemic Heart Disease (SIHD)

Patients with significant coronary obstructive disease, which is anatomically defined as left main coronary stenosis >50.0% and/or coronary stenosis >70.0%, and is physiologically defined as FFR <0.80 (most recent studies used 0.80 rather than 0.75 as cut-off for lesion selection by FFR) [22], are divided into two groups. The first groups are those who are asymptomatic, which is a significant number and commonly found in the screening tests, and the second group of patients who are symptomatic **TABLE 2**. Noteworthy, according to the BART study, thirty percent of these patients with angina pectoris, despite different treatments, can't return to their past jobs [23].

In the United States, more than 17 million people suffer from CHD and more than 10 million Americans have a history of angina pectoris [1,24]. In half of the patients who analog with AMI, recently and in their history, they had unstable angina similar to angina but often more severe **TABLE 3** [25].

For every thirty people with SIHD, one person per year is hospitalized with AMI (angina more severe and often lasting longer than 30 min which is almost always unrelieved by nitroglycerin). Therefore, treatment intervention, medically versus revascularization, following the diagnosis algorithm is promising [26-28]. Considering the pathophysiological events that occur in the heart following ischemia; ischemic cascade, the use of diagnostic methods in CHD can be understood and accepted **FIGURES 1-3**.

Although, each of the diagnostic tests presented in **FIGURE 2 and TABLE4** have different diagnostic sensitivity, specificity, and disadvantage, that, in addition to help diagnoses of CHD, is also helpful for risk stratification. On the other hand, it should be taken into account that the sensitivity of each of the tests in the diagnosis of disease is different in men and women [29-38].

■ Therapeutic strategies for coronary heart disease

The goal of treatment is namely: a) maximize survival, b) preventing complications such

TABLE 2. Typical clinical features of major causes of acute chest discomfort.

Type of chest pain	Clinical characteristics
Typical angina (definite)	1. Substernal chest discomfort (heaviness, pressure, or squeezing), more than 10 seconds and less than 10 min that is retrosternal, often with radiation to, or isolated discomfort in, neck, jaw, shoulders, or arms-frequently on the left. 2. Provoked by exertion or emotional stress and 3. Relieved by rest or nitroglycerine
Atypical angina	Meets 2 of the above characteristics
Non-cardiac chest pain	Meets 1 or none of the typical anginal characteristics

TABLE 3. Typical clinical features of unstable angina [25].

Type of chest pain	Clinical Characteristics
Rest angina	Angina occurring at rest and usually prolonged (20 min), occurring within 1 week of presentation
New-onset angina	Angina of at least Canadian Cardiovascular Society (CCS) Class III severity with onset within 2 months of initial presentation
Crescendo angina	Similar to angina, but often more severe and occurs with low levels of exertion or even at rest, or Post-MI angina

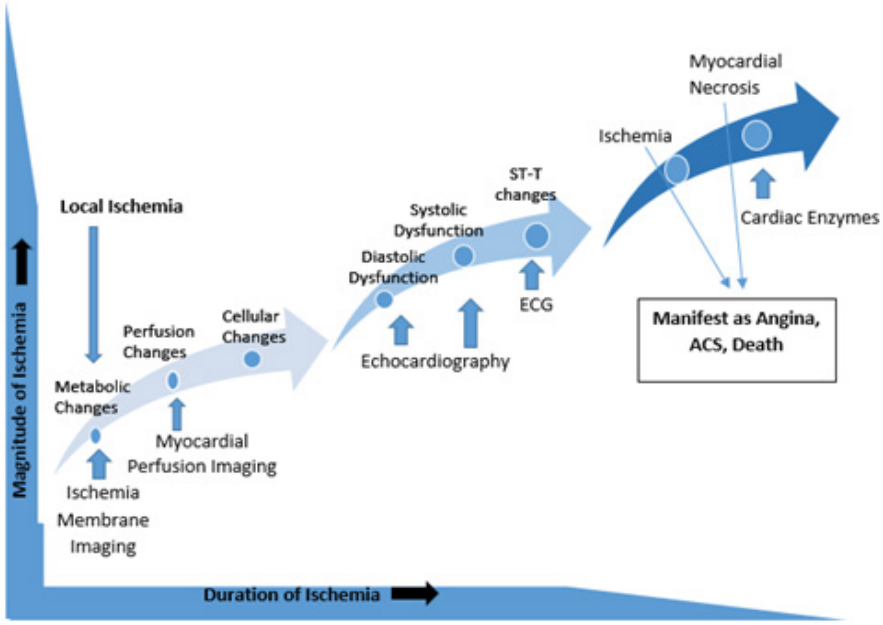


FIGURE 1. Ischemia cascade.

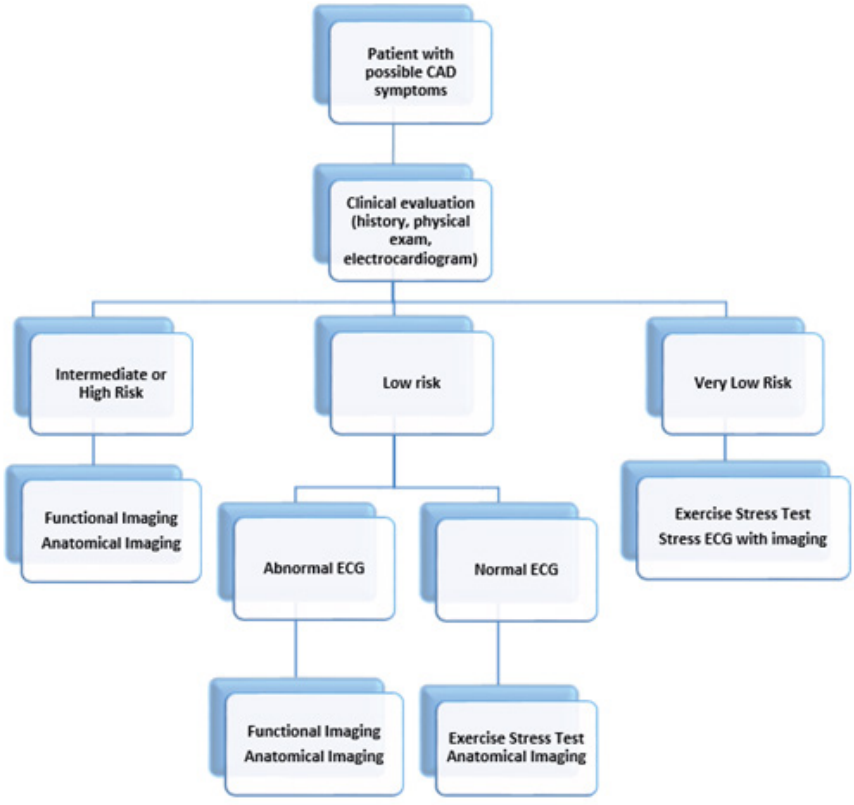


FIGURE 2. Non-invasive test selection algorithm for CHD diagnosis.

as myocardial infarction and heart failure, c) improving the quality of life in the patient's satisfaction, d) eliminating all or almost all ischemic symptoms and, ultimately, e) reducing the cost of treatment, including by reducing the frequency of hospitalizations. Noteworthy, in a study between 1980 and 2000 of over 341, 754 patients between the ages of 25 and 84 years, it was shown that mortality rates have been almost halved due to risk factor modification (primary prevention) and also, near half related to secondary prevention in post MI and post revascularization patients [39].

■ Therapeutic strategies for patients with stable ischemic heart disease

Medical therapy

Based on the result of Coronary Artery

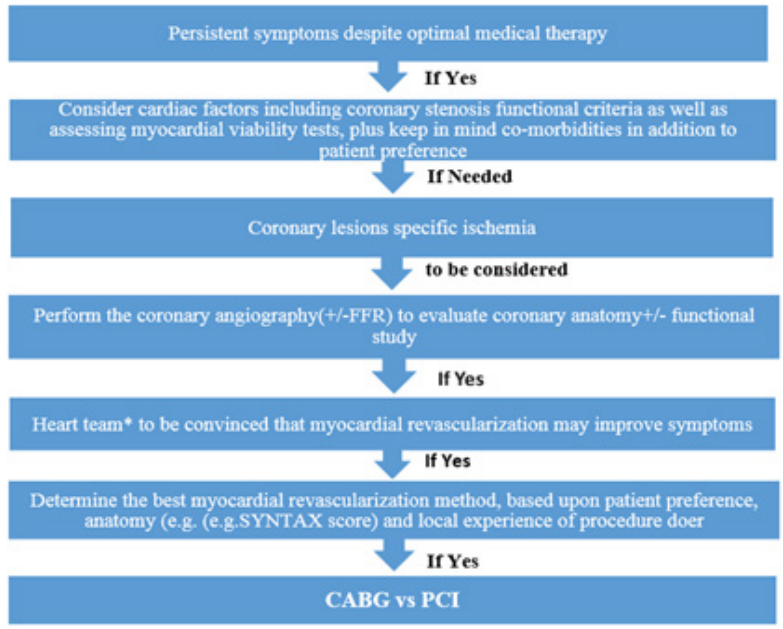


FIGURE 3. Algorithm 1, conduct to choose the PCI vs. CABG as a revascularization method.

TABLE 4. Overview of screening tests [30-38].

Test	Disadvantages	Sensitivities and Specificities	Suitable test for
Electrocardiogram exercise testing	8/100,000 Cardiac complication rate	Sensitivities between 45-50% and specificities of 85-90%*	Exercise ECG is recommended as the initial test for establishing diagnosis of CAD in symptomatic patients with intermediate PTP
Dobutamine Stress Echocardiography	42 VT/VF in 64542 cases;	Sensitivities between 80-85% and specificities of 84-86%*	Patients who are unable to do ETT, have LBBB, or pacemaker
SPECT-MPI (Single Photon Emission Computed Tomography-Myocardial Perfusion Image)	Irradiation, can miss 3 vessel disease because of "balanced ischemia"	Sensitivities between 85-90% and specificities of 70-75%*	Patients who are unable to do ETT or do inconclusive ETT, have LBBB, pacemaker
CCTA (Coronary Computed Tomography Angiography)	Irradiation and contrast toxicity, expensive, unavailable worldwide	Sensitivity of 83.0% and specificity of 81.6%*	Low to intermediate PTP (pretest probability)
Three-dimensional Computed tomography derived fractional flow reserve (CT-FFR) a novel noninvasive method, was approved by FDA in late 2014	Irradiation and contrast toxicity, expensive, unavailable worldwide;	Sensitivity of 90.0% and specificity of 82.0%**	Assessment of correlation between anatomical and functional significance of coronary lesions, overcome to the severe coronary artery calcification which is able to cause blooming artifacts,
			CT-FFR guided strategy resulted in the cancelation of 61.0% of the planned coronary angiogram; saved a 30.0% of medical cost to identify patients
	Currently, clinical trial data with CT-FFR are insufficient to make a recommendation for its use in clinical practice [107].		
Stress Magnetic Resonance Imaging	NSF (nephrogenic systemic fibrosis), costlier than many other noninvasive tests,	More a part of multimodality tests for evaluation of impact on the clinical care of CHD patients	
	Not readily available		
Coronary Angiography	Invasive procedure with 1/1000 mortality rate, irradiation and contrast toxicity,	Anatomical information could be misleading, needs further functional assessment of lesion severity (i.e. fractional flow reserve)	In whom revascularization is expected to improve functional status or quality of life

*sensitivity and specificity comparison to coronary angiography ; **sensitivity and specificity comparison to coronary angiography-FFR

Surgery Study (CASS) registry of medically treated patients, (23,467 patients' enrollment), overall, 12-year survival for patients with zero-, one-, two- and three-vessel disease is 88%, 74%, 59%, and 40%, respectively. Twelve-year survival for patients with at least one diseased vessel and ejection fractions in the ranges of 50% to 100%, 35% to 49% and 0% to 34% is 73%, 54% and 21%, respectively [40]. After using different diagnostic methods and determining the risk, we divide the patients into two groups based on the possibility of annual cardiac mortality rate:

Group one: low risk SIHD patients (mortality rate of <1.0% per year) to intermediate-risk SIHD patients (mortality rate of 1.0% -3.0% per year). For this group, change of lifestyle plus risk factors modification in addition to optimal medical therapy, because the effect of these drugs on symptoms improvement and increase in SIHD patient's longevity has been proven **TABLE 5** [41-47].

Medical therapy starts with aspirin and follows the sequence that follows: sublingual nitroglycerin, beta-blockers (BBs), calcium channel blockers (CCBs) (when BB is contraindicated), long-acting nitrates, lipid-lowering drugs and, finally, ranolazine. Beta-blockers are typically recommended as first-line treatment because of evidence that they reduce the risk of mortality post-MI and in those with hypertension.

Group two: high risk SIHD patients (mortality rate of >3.0% per year). Treatment in this group comprises intensive medical therapy and revascularization, including percutaneous coronary intervention (PCI) versus coronary artery bypass surgery (CABG).

Rationale for myocardial revascularization

In cardiac patients who have not responded to optimal tolerable medical therapy, we consider **TABLE 6** [48] for indication of revascularization and follow algorithm 1 to improve symptoms through myocardial revascularization.

In cardiac patients who have not responded to optimal tolerable medical therapy, we consider **TABLE** 7 to improve symptoms through myocardfiafl revascuflarfizatfion.

■ Percutaneous coronary intervention

As a general principle, the less invasive method of treatment has priority between the two options. Therefore, because PCI is relatively non-invasive compared to CABG, we use the first option for the treatment of a medically unresponsive patient (medically responded patients is a term used for patients that could return to their ordinary life by using drugs with no cardiac symptoms).

TABLE 5. Medical therapy for SIHD; effect on symptoms and/or mortality [41-47].

Drugs	Advantages
Antiplatelets including aspirin/ clopidogrel [68]	33% reduction in nonfatal MI or vascular death.
Statins (Lipid-lowering drugs) [69]	24% reduction in nonfatal MI or coronary death,
Beta blockers	50% reduction in the frequency of angina attacks,
	reduction in mortality in post MI patients only if the drug is started during the first 24 hours post MI and lasts for three years
Calcium Channel Blockers	50% reduction in the frequency of angina attacks
Long acting nitrates	Improve exercise tolerance
Ranolazine (an inward sodium channel inhibitor)	22% reduction in recurrent ischemia
ACE inhibitors (Angiotensin-Converting Enzyme Inhibitors)	In all patients with SIHD who also have hypertension, diabetes mellitus, LVEF 40% or less, or CKD, unless contraindicated; (reduction in cardiovascular death between 22.0%-37%)
Annual Influenza Vaccine	annual influenza vaccinations reduced the risk of mortality by 37% during the winter period

TABLE 6. Indications for revascularization in patients with stable angina or silent ischemia [48].

Extent of CAD (anatomical and/or functional)		Class of Recommendation	Level of Evidence
For Prognosis	Left main disease with stenosis >50%	I	A
	Proximal LAD stenosis >50%	I	A
	2VD or 3VD with >50% stenosis+LVEF <35.0%	I	A
	Large size of ischemia detected by functional testing i.e. >10.0% or abnormal invasive FFR	I	B
	Single remaining patent coronary artery >50.0% stenosis	I	C
For Symptoms	Hemodynamically significant CAD in the presence of limiting angina or angina equivalent with insufficient response to optimal medical therapy	I	A

Moreover, the main point here is that the purpose of using these two methods is to first determine which group of revascularization procedures (PCI *vs.* CABG) has been able to reduce mortality. On the other hand, are there previous studies sufficiently indicative of the reduction of possible short and long-term potential cardiovascular risks to CHD patients who have been subjected to such invasive procedures?

Anatomical complexity of CAD (SYNTAX score; Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery, summarized in **TABLE 8 and FIGURES 4 and 5**, to grade the anatomical complexity of coronary lesions in patients with left main or three-vessel disease), predicted surgical mortality (EUROSCORE; European System for Cardiac Operative Risk Evaluation, and the STS score; the Society of Thoracic Surgeons score) and the anticipated completeness of revascularization are further important criteria for decision-making to choose PCI versus CABG approach.

The most important goal of PCI is to reduce the pain and cardiac ischemic symptoms, reduce the frequency of repetitive hospitalization and eliminate ischemia. Several Randomized Clinical Trials (RCT) have shown that the PCI procedure does not reduce the number of deaths and myocardial infarction [49,50-59]. Moreover, evaluation of 61 trials of PCI those have done during past three decades shows that despite improvements in PCI technology and pharmacotherapy, PCI has not been demonstrated to reduce the risk of death or MI in patients without recent ACS [60]. In the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation), which had published in 2015 in the New England Journal of Medicine, there were no survival rate differences in the follow-up of 15 years in 2,287 patients who were divided into two groups of drug treatment and PCI [61].

Therefore, the patient should be aware that the general belief that PCI will reduce the chance of heart attacks and cardiac death after PCI is wrong. On the other hand, long-term use of Dual Antiplatelet Therapy (DAPT) after PCI is costly and accompanied with possible complications. The patient's knowledge of the information that has been mentioned would help the patient to cleverly choose his own therapeutic method, a point that is very important, but unfortunately, is usually ignored

TABLE 7. Myocardial Revascularization to improve symptoms in CAD patients unresponsive to optimal medical therapy or who do not have enough compliance to get medical therapy [50].

Clinical Setting	Method	AHA/ACC Class of Recommendation	Level of Evidence
Lack of anatomic/functional criteria for Myocardial Revascularization	CABG or PCI	III	C
One or more significant stenosis feasible for Myocardial Revascularization	CABG or PCI	I	A
Previous CABG with one or more significant stenosis	PCI	IIa	C
	CABG	IIa	B
Complex three vessel disease with or without proximal LAD involvement and a good candidate for CABG	CABG preferred over PCI	IIa	B
Multi-sites ischemia perfused by unfeasible vessels for CABG	Transmyocardial Revascularization as an ancillary procedure to CABG	IIb	B

TABLE 8. SYNTAX Scoring (11 measures of lesion complexity).

Guides for SYNTAX Scoring	
Step 1.	Dominance (LCx or RCA)
Step 2.	Coronary segment
Step 3.	Diameter stenosis
Step 4.	Trifurcation lesion
Step 5.	Bifurcation lesion
Step 6.	Aort-ostial lesion
Step 7.	Severe tortuosity
Step 8.	Lesion length
Step 9.	Calcification
Step10.	Thrombus
Step11.	Diffuse disease/small vessels

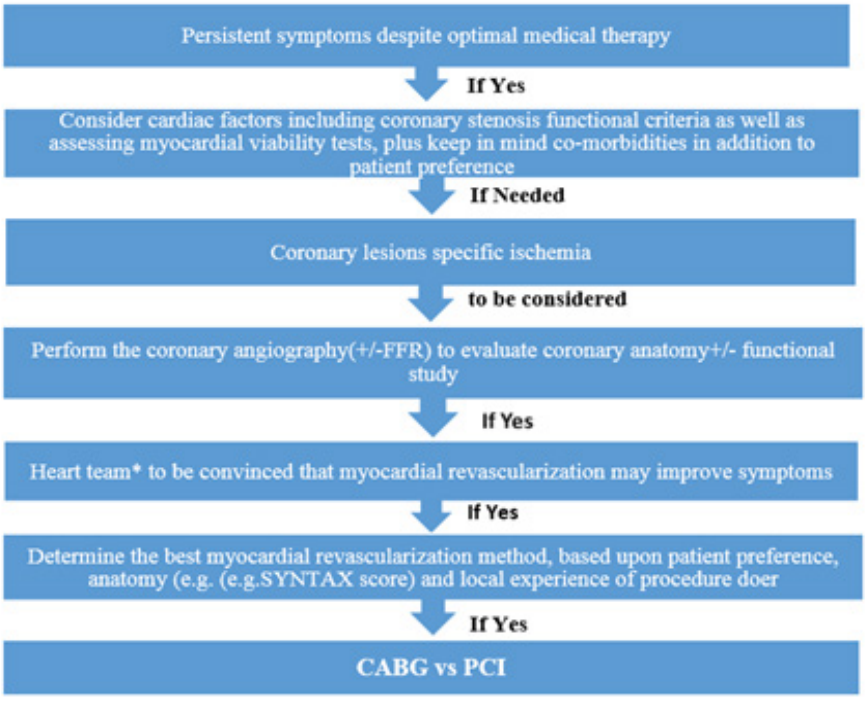


FIGURE 4. Definition of the coronary tree segments.

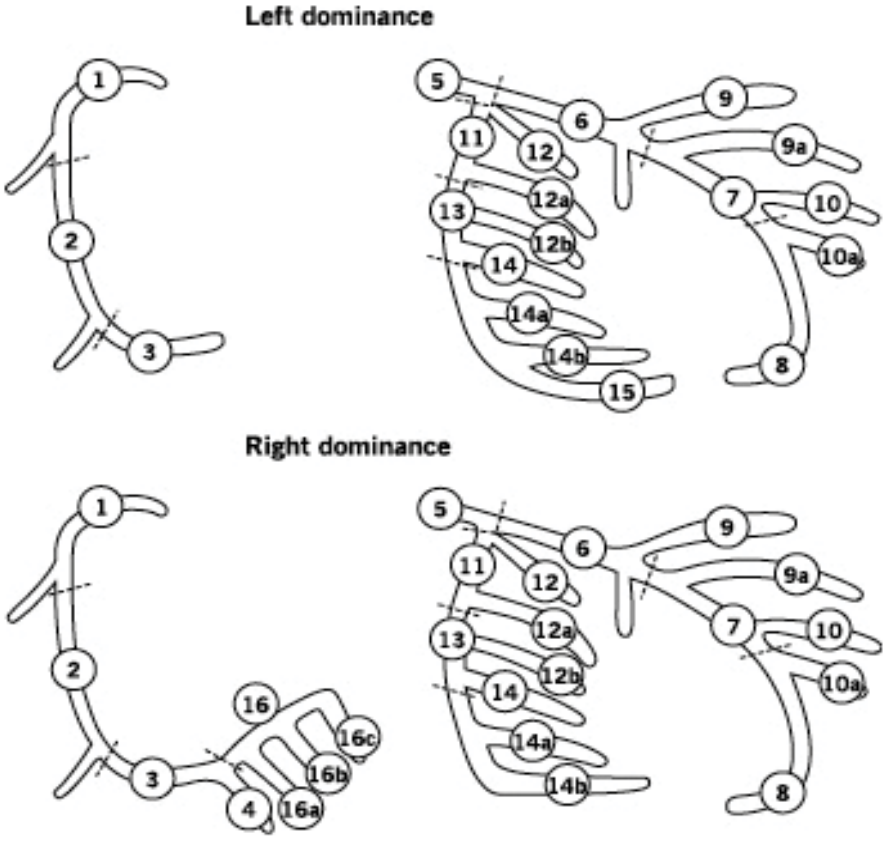


FIGURE 5. Total occlusion length segment.

[24,62,63]. However, newer everolimus drug-eluting stents have better survival rate than older ones [64], especially if the patient is FFR-guided chosen for doing PCI [65].

The SYNTAX Trial randomized 1,800 patients with 3-vessel and/or left main CAD to either PCI with paclitaxel-eluting stents (Taxus) or CABG. A low SYNTAX score was defined as

22; intermediate, 23 to 32 and 33: high. Based on the SYNTAX trial results that were published in 2009 in New England Journal of Medicine, at one year follow up, CABG had lower rates of the Major Cardiac And Cerebrovascular Events (MACCE) compared to PCI for patients with three-vessel or left main CAD. The occurrence of MACCE correlated with the SYNTAX score for DES patients but not for those undergoing CABG. At one-year follow-up, the primary endpoint was similar for CABG and DES in those with a low SYNTAX score. In contrast, MACCE occurred more often after DES implantation than after CABG in those with an intermediate or high SYNTAX score [66]. At 3 years of follow-up, the mortality rate was greater in subjects with 3-vessel CAD treated with PCI than in those treated with CABG (6.2% *vs.* 2.9%).

Because SYNTAX trial was considered to anatomical conditions, further, and in several studies, other parameters that have a clinical aspect such as age, gender, presence of COPD, LVEF status, keratinize clearance and peripheral vascular disease have interfered in the process of investigation in order to determine the selection outcome of the preferred procedure (PCI *vs.* CABG) [67].

Coronary artery bypass graft surgery

Noteworthy, in a study by Pittman MA et al., it has shown that CABG is only associated with a decrease in mortality in a group with left main coronary disease [68]. Although, in the past it was thought that patients with a SIHD and left ventricular systolic dysfunction would have a lower mortality rate with CABG, in the STICH trial (Surgical Treatment for Ischemic Heart Failure), initially and during a five-year period follow up, it was shown that the reduction in CABG patients' deaths differ very little compared to those who received medical therapy alone and did not have CABG (28.0% death due to cardiovascular cause in CABG group compared to 33.0% mortality in group who had been on medical therapy) [69]. However, the extended 10-year follow-up of the STICH trial reported a significant reduction in all-cause mortality rate (59% *vs.* 66% respectively) [70]. Also, in the MASS II study (Medicine, Angioplasty, or Surgery Study II); in the group undergoing CABG, there was a lower incidence of myocardial infarction, frequent revascularization, and cardiac death during the ten-year follow-up period, in comparison to patients who received medical therapy [71].

On the other hand, in comparison between CABG and PCI with Drug-Eluting Stent (DES) in a meta-analysis of 24, 268 patients with multi-vessel CAD, it was found that there is no difference between the rate of myocardial infarction and mortality between both groups, but the frequency of repeat revascularization was four times higher after DES implantation [72].

The note that should be addressed is patients with left ventricular systolic dysfunction that can be due to hibernation or stunning, and performing myocardial revascularization would help to improve the function of the left ventricle, as long as the process of checking the muscle's vitality is determined and approved by performing tests such as dobutamine stress echocardiography, late gadolinium enhancement cardiac magnetic resonance or PET scan (Class IIb recommendation with level of evidence B) [73-76]. However, the meta-analysis from published series examining late survival with revascularization versus medical therapy after myocardial viability testing in patients with severe Coronary Artery Disease (CAD) and Left Ventricular (LV) dysfunction demonstrates a strong association between myocardial viability on noninvasive testing and improved survival after revascularization in patients with chronic CAD and LV dysfunction. Absence of viability was associated with no significant difference in outcomes, irrespective of treatment strategy [74].

It should also be pointed out that if coronary stenosis adjusted myocardial ischemia/viability approved by the tests have described, it is not necessary to carry out FFR guided decision making for doing myocardial revascularization in patients with stenosis of intermediate stenosis [48].

What is important in choosing the method of PCI versus CABG selection is the prediction of residual SYNTAX score, which we get at the end of the procedure, i.e. when more than the number 8 for residual score, would be with negative consequences and poor prognosis (associated with significant increases in the 5-year risk of death and of the composite of death, MI, and stroke) [77]. The aim of choosing each type revascularization is to reduce the risk of death and MI by reducing residual stress-induced ischemia from >10% of the myocardium to ≤ 5% [78]. Also, calculation of in hospital 30 days' mortality for patients who are candidates for CABG by using STS (Society of Thoracic Surgeons) scoring is another important thing

that should be considered (ESC Guideline class I level of evidence B) [76].

It is easy to make decisions for the heart team in a summary that is summarized in **TABLE 9**.

For diabetic patients with advanced CAD, based on the FREEDOM trial results (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease), CABG was superior to PCI, i.e. significantly reduced rates of death and myocardial infarction, with a higher rate of stroke of 5 years' duration with a minimum of 3 years of follow-up [79].

On the other hand, if we incorporate results of SYNTAX score and FREEDOM Trial, CABG should be offered as the first-line therapy in patients which mentioned in **TABLE 10** for myocardial revascularization.

■ Therapeutic strategies for patients with acute coronary syndrome/ Non-ST elevation myocardial infarction (ACS)/ NSTE)

In surveys of patients referred to the hospital with chest pain, it has been shown that 50% of them are non-cardiac pain, 35% are ACS and ultimately 15% are other cardiac conditions. The acute coronary syndrome is commonly associated with three clinical manifestations: ST-elevation myocardial infarction (STEMI, 10%), non-ST elevation myocardial infarction (NSTEMI, 15%), or unstable angina (10%) [80].

The main initiating mechanism in ACS is a rupture of the coronary atherosclerotic plaque with superimposed thrombus formation. Vascular endothelial response to inflammatory and mitogenic substances that were released from activated platelets in addition to coronary spasm may cause ACS **FIGURE 6**.

In case of suspicion of unstable angina, if the patient has no ongoing ischemic symptoms, normal ECGs in addition to normal results of two/three serial (hs) cTn tests, the patient is not required to stay in hospital and could perform a non-invasive stress test in outpatient follow up, preferably with imaging because of superiority to exercise ECG testing.

For patients with a high degree of clinical suspicion of NSTEMI, coronary angiography and for patients with low to intermediate likelihood, CCTA should be considered [80].

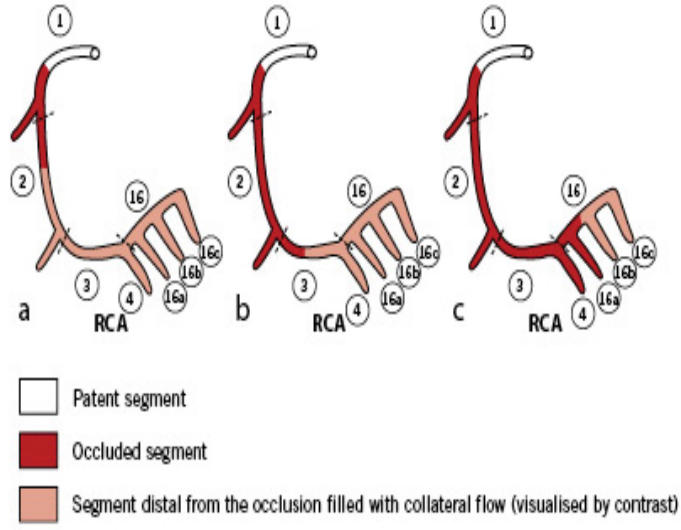
If the hospital test results were positive, the ECG changes were in favor of ischemia/ infarction and/or regional wall motion abnormality was noted on echocardiography, even with negative biomarkers and normal ECGs, the patient should remain in the hospital. During the hospital course, the patient needs heart monitoring, continuing anti-ischemic therapy including oxygen therapy if saturation

TABLE 9. Simplified criteria for PCI versus CABG selection in patients with left main and/or multi-vessel disease.

PCI would be first choice	CABG would be the first choice
Anatomical criteria	**Anatomical criteria**
Multi-vessel disease with SYNTAX score=0-22	Multi-vessel disease with SYNTAX score ≥ 23
Possibility of incomplete revascularization with CABG is high	Possibility of incomplete revascularization with PCI is high
Chest wall or spine deformity	Severely calcified coronaries that possibility of stent under-expansion would be high
Chet radiotherapy in past with sequelae	
Porcelain aorta	
Clinical criteria	**Clinical criteria**
Presence of severe co-morbidity	Diabetes
Advanced age	LVEF <35.0%
Restricted post op rehabilitation would be predicted	DAPT would be contraindicated
	Recurrent in-stent restenosis

TABLE 10. Incorporation of SYNTAX score and FREEDOM trial.

CABG should be offered as the first line for myocardial revascularization:	
1	3VD and SYNTAX score >32
2	3VD with proximal LAD involvement and SYNTAX score >22
3	3VD in a diabetic patient
4	2VD in a diabetic patient with proximal LAD involvement and SYNTAX
	score >22
5	Unprotected left main (ULM) disease with SYNTAX score >32



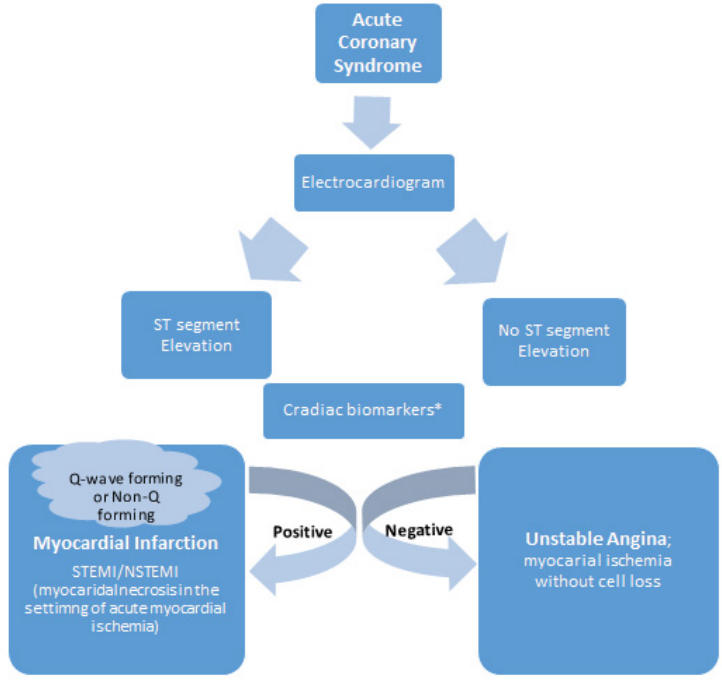


FIGURE 6. Classification of acute coronary syndromes based on ECG and cardiac isoenzymes. *Cardiac biomarker; preferably high-sensitivity cardiac troponin; (hs)cTn, couple blood samples taking at admission and three hours later (+/- another sample six hours later) [111].

is less than 90%. Also drug therapy namely intravenous nitrate, Dual Antiplatelet Therapy (DAPT) comprising plain aspirin and a P2Y12 inhibitor (prasugrel or ticagrelor preferred over clopidogrel) in combination with anticoagulants; LMWH (fondaparinux is recommended as having the most favorable efficacy-safety profile regardless of the management strategy) [81,82] or UFH, early administration of beta-blocker (BB), and calcium channel blocker instead of BB if coronary spasm is most likely cause should be continued and considering immediate diagnostic coronary angiography [80].

From a certain point of view, the main advantages of PCI compared to CABG in the setting of NSTE-ACS are faster revascularization of the culprit lesion, a lower risk of stroke and the absence of deleterious effects of cardiopulmonary bypass on the ischemic myocardium. However, from another view, CABG may more frequently offer complete revascularization in advanced multivessel CAD.

Overall, in patients considered at very high or high risks of ischemic events, especially in biomarker positive cases, invasive therapeutic strategy including stenting of the culprit lesion in addition to antiplatelet and GPIIb / IIIa inhibitor would lower mortality rate and

ischemic recurrences. Although this strategy is accompanied with higher peri-procedural complication, it would cause a shorter duration of hospital stay rather than medical therapy (as it has been shown in at least seven RCTs) [83] **FIGURE 7**.

While in patients with SIHD, the functional assessment of coronary stenosis severity by using FFR is considered, so far, the value of FFR-guided PCI in NSTEMI has not been properly addressed (because maximal hyperemia in NSTEMI patients would not be achieved) [84].

A Danish nationwide cohort study has shown that from 2001 to 2009, the proportion of NSTEMI patients undergoing coronary angiography and PCI markedly increased, causing only 10% of NSTEMI patients undergoing coronary angiography scheduled for CABG and expecting higher mortality/morbidity (like bleeding) in comparison with elective CABGs [85]. Notably, aspirin as well as a P2Y12 inhibitor is recommended and should be maintained over 12 months for post NSTEMI patients undergone CABG as well (class I indication, level of evidence A) [86,87].

Although NSTEMI patients who are not amenable for revascularization (due to severe/diffuse CAD) are sparse, intensification of anti-ischemic therapy would be the best therapeutic modality, albeit, with the prediction of poorer response and higher mortality.

Decisions to perform staged PCI or planned CABG for non-culprit lesions in the presence of the multivessel disease may be determined at a later date. Recommendations for PCI and CABG in stabilized NSTE-ACS are similar to those for stable CAD.

Noteworthy, approximately 25% of NSTEMI patients have myocardial infarction in the absence of obstructive coronary artery disease (MINOCA), management of these patients are medically like patients with SIHD, surely excluding oral nitrates [88]. CMR is indicated within 2 weeks after the onset of symptoms to increase the diagnostic accuracy of the test for identifying the etiological cause of MINOCA [89].

■ Therapeutic strategies for patients with ST segment elevation MI (STEMI)

Definition of acute myocardial infarction is based on the evidence of clinical ischemia in addition to biomarker stigmata in favor of myocardial necrosis; the best biomarker test in high sensitivity cardiac troponin with at least one value above the 99th percentile upper reference limit [90]. The majority of STEMI patients classified as type 1 MI (coronary thrombus related) and a minority of them as type 2 (MINOCA). Because the immediate reperfusion therapy should be considered in patients with STEMI, therefore, carefully and

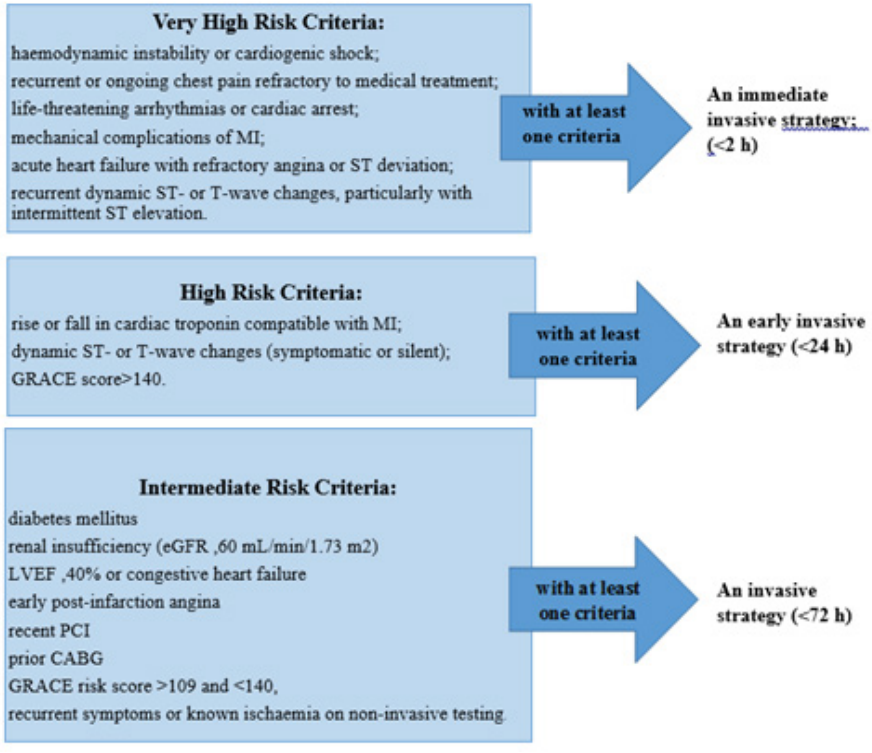


FIGURE 7. Suggested policy for choosing appropriate time of invasive strategy in NSTE-ACS patients; Based on 2015 ECG guidelines.

obsessively, ECG should be assessed for ST-segment elevation to diagnose promptly. To define STEMI, it needs to be in at least two contiguous leads with ST-segment elevation in leads V2-V3, 2.5 mm in men <40 years, 2 mm in men 40 years, or 1.5 mm in women and/or in the other leads 1 mm [90]. Leads V3R and V4R for right ventricular MI and leads V7-V9 ST elevation during the first 6 hours could be helpful.

■ Pre-hospital care

In the context of a possible diagnosis of myocardial infarction, prevention of delay for further steps is very crucial. "Count every minute" is a short but important message that has a long history regarding treatment of STEMI patient to minimize pre and in-hospital delays.

One of the most important points is to delay between the onset of pain and contact with the Emergency Medical Service (EMS). Of course, it is very important to raise public awareness regarding the symptoms of myocardial infarction so they can quickly inform the EMS.

The initial visit of the EMS staff to the first ECG should preferably take less than ten minutes. Also, the EMS staff should be highly skilled for ECG interpretation to allow for rapid diagnosis of STEMI, have fully trained in advanced life support and be able to undertake defibrillation if needed. To shorten time to treatment, fibrinolysis should be administered in the pre-hospital setting if possible [91].

■ In-hospital care

Quickly transferring the STEMI patient to hospitals with an established PPCI programmer available 24/7 and bypassing the emergency department to bring the patient directly to the well-equipped catheterization lab, surely minimizes the pre-hospital delay and have impressive positive impact on prognosis. Optimal acceptable delay (pre and in-hospital) for interrogation regarding STEMI patients is summarized in algorithm 3 **FIGURE 8**.

■ Some important points that should be considered in STEMI patients classified with class I indications

1. Transradial access is superior to trans femoral access by an experienced operator [92]
2. Stenting is recommended (over balloon angioplasty) for primary PCI [93]
3. Stenting with new-generation DES (such as everolimus or biolimus-eluting stents) is recommended over BMS for primary PCI [94,95]

■ Some important points that should be considered in STEMI patients classified with class IIa indications

1. Routine revascularization of non-IRA lesions should be considered in STEMI patients with the multivessel disease before hospital discharge [96,97]
2. Non-IRA PCI during the index procedure should be considered in patients with cardiogenic shock

■ Some important points that should be considered in STEMI patients classified with class III indications

1. Routine use of thrombus aspiration is not recommended [98,99]
2. Routine use of deferred stenting is not recommended [100,101]

■ Some important points that are noteworthy to know

1. In terms of the same time delay to choose a method, primary PCI strategy is superior to fibrinolysis in reducing mortality, re-infarction, or stroke, However, when primary PCI is not an immediate option, fibrinolysis should be initiated promptly [102-105]
2. Based on DANAMI 3-DEFER trial and in 1, 215 STEMI patients that deferred stenting to reduce microvascular obstruction (MVO) and preserve microcirculatory function (48 h after the index procedure) no positive impact on the primary clinical outcome was shown [106]
3. Although elderly patients are at particularly higher risks, there is no upper age limit with respect to reperfusion, especially with primary PCI; based on TRIANA trial results [107]
4. In various published studies, the beneficial effect of the intra-aortic balloon counterpulsation during primary PCI for anterior wall STEMI without cardiogenic shock had not shown on infarct size reducing [108] and even no improvement in outcomes in AMI patients with cardiogenic shock [109]

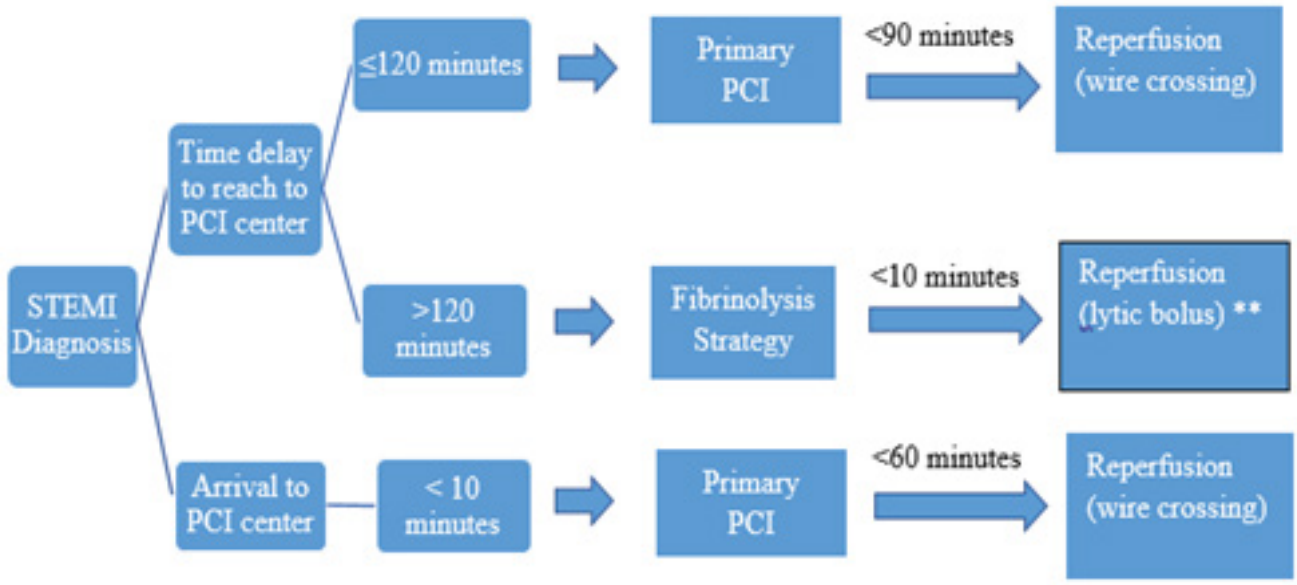


FIGURE 8. Algorithm 3-Optimal acceptable delay for interrogation regarding STEMI patients. *Definition of Primary PCI (PPCI) strategy is emergent coronary angiography and PCI of infracted related atery (IRA) if needed. **Patients with fibrinolysis should be transferred to a PCI centre immediately after administration of the lytic bolus for performing rescue PCI strategy (indicated in the case of failed fibrinolysis, i.e. ST-segment resolution <50% within 60-90 min of fibrinolytic administration, in the presence of haemodynamic or electrical instability, worsening ischemia, or persistent chest pain, maximum expected delay <one hour) or pharmacoinvasive strategy (coronary angiography and PCI of IRA if needed between 2 and 24 hours after successful fibrinolysis).

5. In the absence of ST-segment elevation, a primary PCI strategy is indicated in patients with suspected ongoing ischaemic symptoms suggestive of MI and at least one of the following criteria present:

- hemodynamic instability or cardiogenic shock
- recurrent or ongoing chest pain refractory to medical treatment
- life-threatening arrhythmias or cardiac arrest
- mechanical complications of MI
- acute heart failure
- Recurrent dynamic ST-segment or wave changes, particularly with intermittent ST-segment elevation

1. In the situation with time delay >12 hrs, a primary PCI strategy is still indicated in the presence of ongoing symptoms suggestive of ischemia, hemodynamic instability, or life-threatening arrhythmias [110]

2. Coronary angiography is justified within 24 hrs. if STEMI patient becomes ischemic symptoms-free, in addition, to complete restoration of elevated ST-segment to baseline or after nitroglycerine administration

3. Patients with ST-elevation on post-resuscitation ECG should undergo a primary PCI strategy (class I indication, Level of evidence B)

4. Elevated levels of cTn measurements in patients with heart failure, either HFpEF or HFrEF, may be seen, therefore, always raising the level of the cTn test does not mean an AMI, and its interpretation should be accompanied by other clinical signs with ECG ischemic evidence, and even after some more workups such as angiography, to make sure that myocardial infarction happened

5. Takotsubo syndrome (TTS): can mimic MI and is found in 1%-2% of patients presenting with suspected STEMI, however, this syndrome is a myocardial injury and not categorized as MI

- TTS is secondary to the high catecholamine surges that are known to trigger cTn release from cardiomyocytes and causing modest elevation of cTn, nevertheless, the clinical manifestations and ECG abnormalities are out of proportion to the degree of elevation

of cTn values. However, coronary angiography (in most cases is normal) and ventriculography are often needed to secure the diagnosis

- Although the inpatient mortality is similar to STEMI (4%-5%) due to cardiogenic shock, ventricular rupture, or malignant arrhythmias, meanwhile, almost always the long term outcome is excellent, because the systolic function usually returns to normal during hours to weeks. The distinction between MI and TTS can be challenging, particularly when concurrent CAD is present. CMR is very helpful in this context, especially in the absence of recovery of regional wall motion abnormalities, LGE-CMR is recommended to exclude MI with spontaneous recanalization. Two additional features that are helpful in distinguishing TTS from acute MI are QTc prolongation >500 ms during the acute phase and the recovery of LV function over 2-4 weeks [111-113]

1. MINOCA: The prevalence of MINOCA is estimated to be 6%-8% among patients diagnosed with MI and more common in women than men, as well as in patients presenting with NSTEMI compared with those presenting with STEMI. Atherosclerotic plaque disruption and coronary thrombosis may be a cause of MINOCA, i.e. type 1 MI. However, coronary spasm and spontaneous coronary dissection may be involved as well, i.e. type 2 MI, along with other possible causes [114]

2. Contrary to chronic heart failure, natriuretic peptides are of limited value for the diagnosis of acute heart failure following MI due to the lack of definite cut-off values for diagnosis in these patients [115]

3. It should be emphasized that despite greater use of reperfusion therapy, primary percutaneous coronary intervention (PPCI), modern antithrombotic therapy, and secondary prevention, the hospital and one-year mortality among the STEMI patients are still substantial and had been reported as 12.0% and 10.0% respectively [116,117]

■ Atypical electrocardiographic presentations in patients with ongoing myocardial ischemia symptoms

In the clinical context with ongoing chest pain, not uncommonly, ECGs are inconclusive. For example, patients with LBBB, RBBB, pacemaker or graft vein occlusion.

LBBB pattern or Pacemaker rhythm

For diagnosis of MI in the presence of LBBB, different algorithms have been offered in various reports but no one has enough certainty so far. Although in this context, concordant ST elevation in leads with positive QRS might be very helpful for STEMI diagnosis, overall it is logical to consider these with clinical evidence of ongoing ischemia and LBBB to be the same as STEMI patients [118]. We do have the same dilemma regarding pacemaker dependent patients [119].

RBBB pattern

In the other side, because the diagnosis of trans mural ischemia as well as STEMI in the presence of RBBB is usually difficult, therefore, for these patients, the primary PCI policy like for the other STEMI patients should be considered [120].

Vein grafts left circumflex artery acute occlusion

In daily practice, cardiologists are not uncommon facing to cases of acute coronary occlusion with no ST elevation, such as graft vein or left circumflex artery occlusion, so fibrinolytic therapy is denied. Thus, it is reasonable to do primary PCI strategy in any suspicious patient suffering from ongoing myocardial ischemia [121,122].

Left main coronary obstruction

In patients who presented with chest pain and one millimeter or more ST depression in ≥ 8 surface leads (inferolateral ST depression), in addition to ST-segment elevation in aVR and/or V1, suggests multivessel ischemia or left main coronary artery obstruction, particularly if the patient presents with haemodynamic compromise and, therefore, needs primary PCI strategy [123].

Old age, CKD and DM patients

Owing to the ageing of the population, a higher proportion of elderly patients is expected

to present with STEMI. The prevalence of diabetes mellitus and/or kidney dysfunction in patients with myocardial infarction is higher than in the general population, and both are associated with a higher incidence of infarction related complications as well as mortality. Although several antithrombotic agents should either be withheld or their doses reduced in CKD patients, selection of antithrombotics and reperfusion therapy is the same as in patients without diabetes. The blood glucose level goal in STEMI patients would be <200 mg/Dl. In the other side of view, hypoglycemia is very harmful in this context.

Post MI cardiac arrest

In patients following out of hospital cardiac arrest and ST-segment elevation on the ECG, primary PCI is the strategy of choice. Given the high prevalence of coronary occlusions and the potential difficulties in interpreting the ECG in patients after cardiac arrest, urgent angiography (within 2 hrs.) should be considered in survivors of cardiac arrest, including unresponsive survivors, when there is a high index of suspicion of ongoing infarction (such as the presence of chest pain before arrest, a history of established CAD, and abnormal or uncertain ECG results). Given the high prevalence of coronary occlusions and the potential difficulties in interpreting the ECG in patients after cardiac arrest, urgent angiography (within 2hrs) should be considered in survivors of cardiac arrest, including unresponsive survivors, when there is a high index of suspicion of ongoing infarction (such as the presence of chest pain before arrest, a history of established CAD, and abnormal or uncertain ECG results).

Also, it should be reemphasized that in cases without ST-segment elevation on post-resuscitation ECG but with a high suspicion of ongoing myocardial ischemia, urgent angiography should be done within 2 hrs. after a quick evaluation to exclude non-coronary causes. In all cases, the decision to perform urgent coronary angiography should take into account factors associated with poor neurological outcome.

Targeted temperature management is indicated early after resuscitation of cardiac arrest patients who remain unresponsive (class I indication, Level of evidence B). Targeted temperature management refers to active methods (i.e. cooling catheters, cooling blankets, and application of ice applied around the body) to achieve and maintain a constant specific body temperature between 32°C and 36°C in a person for a specific duration of time (most commonly used 24 h) [124]. Keep in mind, that cooling like opioids have a negative impact on gastrointestinal clopidogrel absorption.

■ Periprocedural and post-procedural antithrombotic therapy in patients undergoing primary percutaneous coronary intervention

Patients undergoing primary PCI should receive DAPT, a combination of aspirin and a P2Y12 inhibitor, and a parenteral anticoagulant.

Antiplatelets

Aspirin: Aspirin (non-enteric-coated formulation) should preferably be 150-300 mg. The superiority of single dose of 250 or 500 mg acetylsalicylic acid intravenously compare to oral chewable 300 mg aspirin has been shown, based on a recent published RCT [125].

P2Y12 inhibitors

1. Prasugrel: [60 mg loading dose and 10 mg maintenance dose once daily (p.o.)]
2. Ticagrelor: (180 mg p.o. loading dose and 90 mg maintenance dose twice daily)
3. Both of the above drugs have a more rapid onset of action, greater potency, and are superior to clopidogrel in clinical outcomes, however, neither should be used in patients with a previous haemorrhagic stroke, in patients on oral anticoagulants, or in patients with moderate-to-severe liver disease [126,127].
4. Clopidogrel: when neither of the above drugs is available (or if they are contraindicated), clopidogrel should be given instead (600 mg p.o. loading dose and 150mg maintenance dose daily) [128],

- Notably, opioids, as well as hypothermia which are used for unconscious patients, have a negative impact on clopidogrel absorption
- Early treatment with high-dose clopidogrel was superior to in-catheterization laboratory treatment in observational studies and one small randomized trial [129-131]

5. Cangrelor: is an i.v. Adenosine Triphosphate (ATP) analog that binds

reversibly and with high affinity to the platelet P2Y12 receptor and has a short plasma half-life (10 min). It may be considered in patients not pre-treated with oral P2Y12 receptor inhibitors at the time of PCI or in those who are considered unable to absorb oral agents [88,132].

GP IIb/IIIa inhibitors

Abciximab, eptifibatide (integrin), tirofiban: All are not recommended for routine use in the setting of primary PCI. In few circumstances and for special cases like post-procedure thrombus burden stent or when no-reflow phenomenon happened, these drugs might be used. Nonetheless, intracoronary administration of GP IIb/IIIa inhibitors is not superior to its use [133].

Anticoagulants

1. Ultra Fractionated Heparin (UFH), initial i.e. bolus 70-100 U/kg: While there is a long-term experience with UHF in PPCI, there is no published placebo-controlled trial in this context so far
2. Enoxaparin, i.e. bolus of enoxaparin 0.5 mg/kg. In a meta-analysis of 23 PCI trials (30 966 patients, 33% primary PCI), an i.e. bolus of enoxaparin 0.5 mg/kg was associated with a significant reduction in death compared to UHF; this effect was particularly significant in the primary PCI context and was associated with a reduction in major bleeding (class II an indication with level of evidence A) [134]
3. Bivalirudin i.e. bolus 0.75 mg/kg followed by infusion of 1.75 mg/kg/hour for up to 4 hours after the procedure: A meta-analysis of five RCT trials showed no mortality advantage with bivalirudin and a reduction in the risk of major bleeding, but at the cost of an increased risk of acute stent thrombosis [135], however, for patients with heparin-induced thrombocytopenia, bivalirudin is recommended as the anticoagulant agent during primary PCI
4. Fondaparinux is not recommended for primary PCI, based on the result of the OASIS 6 trial; Organization for the Assessment of Strategies for Ischemic Syndromes 6 (class III indication) [136]

In the presence of separate indication for full-dose anticoagulation, such as left ventricular clot, post-procedural anticoagulation therapy would be indicated; otherwise, it should be stopped to minimize peri-procedural bleeding risk.

However, approximately 6%-8% of patients undergoing PCI have an indication for long-term Oral Anticoagulation Therapy (OAC) with Vitamin K Antagonist (VKA) or Novel Oral Anticoagulants (NOACs) due to various conditions. In this context, for most post PPCI patients, triple therapy in the form of aspirin, clopidogrel and oral anticoagulation, (albeit with a target international normalized ratio in the lower part of the recommended target range for VKA and the lowest effective tested dose for NOAC), should be considered for 6 months. Then, oral anticoagulation plus aspirin or clopidogrel should be considered for an additional 6 months, the latter is superior to the former. After 1 year, it is indicated to maintain only oral anticoagulation.

Fibrinolytic therapy

Fibrinolytic therapy prevents 30 deaths per 1000 patients treated within 6 h after symptom onset [137].

For patients who had been on oral anticoagulation since before, fibrinolysis is a relative contraindication. DAPT should be added to OAC to prepare the STEMI patients for PPCI. GP IIb/IIIa inhibitors, prasugrel, and ticagrelor should be avoided.

■ All of the below statements are regarding fibrinolytic therapy and classified as class I indication (ESC Guideline 2017)

1. When fibrinolysis is the reperfusion strategy, it is recommended to initiate this treatment as soon as possible after STEMI diagnosis, preferably in the pre-hospital setting [138,139]
2. A fibrin-specific agent (tenecteplase, alteplase or reteplase) is recommended and is superior to streptokinase [140]

- Alteplase (tPA): 15 mg i.e. bolus, 0.75 mg/kg i.e. over 30 min, then 0.5 mg/kg i.e. over 60 min
- Reteplase (rPA): 10 units+10 units i.e. bolus given 30 min apart
- Tenecteplase (TNK-tPA): 30 mg for <60 kg, 35 mg for <70 kg, 40 mg for <80 kg, 45 mg for <90 kg, and 50 mg for ≥ 90 kg

3. Streptokinase: 1.5 million units over 30-60 min i.e
4. Clopidogrel is indicated in addition to aspirin [140]
5. Anticoagulation is recommended in patients treated with a fibrin-specific agent until revascularization (if performed) or for the duration of hospital stay up to 8 days with

- enoxaparin i.e. followed by s.c. preferred over UFH [141]
- regarding streptokinase, the scenario is different
- Significantly fewer reinfarctions were seen with bivalirudin given for 48 h compared with UFH [142]

6. Transfer to a PCI-capable center following fibrinolysis is indicated in all patients immediately after fibrinolysis (pharmacoinvasive strategy) [143] and, of course, a shorter time from symptom onset to angiography (<4hours) would be appreciated, however, a time window of 2-24 h after successful lysis is recommended [144]
7. When fibrinolysis has failed, rescue PCI is indicated immediately; in this setting, fibrinolysis re-administration has not been shown to be beneficial and should be discouraged [145]
8. Emergency angiography and PCI if indicated is recommended in patients with heart failure/shock [146]
9. Prolonged, or traumatic but successful, resuscitation increases bleeding risk and is a relative contraindication to fibrinolysis; otherwise, short successful resuscitation would not be contraindicated

■ CABG as a therapeutic modality in the setting of STEMI should be considered in the below situations

1. For patients with a patent IRA but with unsuitable anatomy for PCI, emergent CABG is needed
2. For patients with a patent IRA and a large myocardial with cardiogenic shock [147]
3. For patients with a patent IRA and a large myocardial area at jeopardy
4. For patients with MI-related mechanical complications who require coronary revascularization
5. In patients with failed PCI or coronary occlusion not amenable to PCI, emergent CABG in this setting is uncertain
6. In stabilized post-MI patients, optimal timing for no emergent CABG is uncertain
7. No difference is present between STEMI and NSTEMI patients who underwent PPCI and on DAPT; if the patient is hemodynamically unstable with recurrent ischemic episodes, emergent CABG is needed, despite the presence of antiplatelet effects due to DAPT usage
8. DAPT usage up to one-year post CABG has class I indication

■ Post-hospital care

Lifestyle interventions

1. Quit smoking (36% reduction of mortality in quitters)
2. Optimal blood pressure control; systolic blood pressure (SBP) target of <140 mmHg
3. Diet advice (a diet similar to the Mediterranean diet)
4. Weight control
5. Exercise-based cardiac rehabilitation; all AMI patients should participate in an exercise-based cardiac, rehabilitation program with expected 22% reduction in cardiac mortality rate [148]

Drug therapy (all the below drugs are classified as class I indication in STEMI patients)

1. Beta-blockers in past, had recommended in all MI patients to reduce long term mortality, however, it should be considered in STEMI patients only as discussed in detail in the heart failure guidelines (in patients with LVEF ≤ 40%, in the absence of contraindications such as acute heart failure, hemodynamic instability, or higher degree AV block) [149]
2. Statins with intensive therapy method are recommended in all patients with AMI, irrespective of cholesterol concentration at presentation, with the treatment goal of an LDL-C concentration of <70 mg/dL
3. Ezetimibe is an alternative for statins in

patients who are statin intolerants and as co-adjuvant in patients who not responded properly to intensive statin alone

4. Nitrates are not recommended as routine use in STEMI, based on the non-beneficial results in a randomized controlled trial against placebo [89], however, following the acute phase, nitrates remain valuable agents to control residual angina symptoms
5. Calcium channel blockers are only indicated in STEMI patients with contraindications to beta-blockers, albeit in patients without heart failure or impaired LV function
6. Angiotensin Converting Enzyme (ACE) inhibitors is recommended in all STEMI patients with LVEF ≤ 40%, hypertension, or diabetes
7. Angiotensin Ii Receptor Blockers (ARBs) are recommended in STEMI patients who need ACE inhibitors but can't tolerate it
8. Mineralocorticoid Receptor Antagonist (MRA) therapy is recommended in patients with LVEF ≤ 40% and heart failure after STEMI
9. Aspirin (75-100 mg) is recommended indefinitely in all patients with STEMI that have shown in a meta-analysis of RCTs [150]
10. P2Y12 inhibitor in addition to aspirin (DAPT) is not only recommended in patients with STEMI who are undergoing primary PCI (for up to 12 months), but also in patients treated with fibrinolysis without subsequent PCI [151]; Clopidogrel is the P2Y12 inhibitor of choice as co-adjuvant and after fibrinolysis, because of results of two major studies, there are no

TABLE 11. Clinical classification of myocardial infarction (from fourth universal definition of myocardial infarction, 2018).

Type of Myocardial Infarction	Definition Criteria
	Type 1 MI: The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:
	• Symptoms of myocardial ischemia;
	• New ischemic ECG changes;
Criteria for acute myocardial infarction (types 1, 2 and 3 MI)	• Development of pathological Q waves;
	• Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology;
	• Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs), Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for type 1 MI
	Type 2 MI: Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for type 2 MI.
	Type 3 MI: Cardiac death in patients with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes before cTn values become available or abnormal meets criteria for type 3 MI.
	Type 4a,4b,4c and 5 MI: Percutaneous Coronary Intervention (PCI) related MI is termed type 4a MI. Coronary Artery Bypass Grafting (CABG) related MI is termed type 5 MI. Coronary procedure-related MI ≤ 48 hours after the index procedure is arbitrarily defined by an elevation of cTn values > 5 times for type 4a MI and > 10 times for type 5 MI of the 99th percentile URL in patients with normal baseline values. Patients with elevated pre-procedural cTn values, in whom the pre-procedural cTn level are stable (≤ 20% variation) or falling, must meet the criteria for a >5 or >10-fold increase and manifest a change from the baseline value of >20%. In addition, with at least one of the following:
	• New ischemic ECG changes (this criterion is related to type 4a MI only);
Criteria for coronary procedure-related myocardial infarction	• Development of new pathological Q waves
(types 4 and 5 MI)	• Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischemic etiology;
	• Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization. Isolated development of new pathological Q waves meets the type 4a MI or type 5 MI criteria with either revascularization procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG.
	Other types of 4 MI include type 4b MI stent thrombosis and type 4c MI restenosis that both meet type 1 MI criteria. Post-mortem demonstration of a procedure-related thrombus meets the type 4a MI criteria or type 4b MI criteria if associated with a stent.

formal recommendations for the use of clopidogrel or prasugrel beyond 1 year [152,153]

Oral anticoagulation in STEMI patients with stent implantation who need to receive it, then, triple therapy should be considered for 1-6 months.

Device therapy

ICD therapy is recommended to reduce sudden cardiac death in patients with symptomatic heart failure (New York Heart Association class II-III) and ≤ 35%, despite optimal medical therapy for >3 months and at least 6 weeks after MI, who are expected to survive for at least 1 year with good functional status.

Lately, in 2018, a universal definition of myocardial infarction with updated concepts has categorized to five below types **TABLE 11**.

■ Focused Update of the different guidelines for the use of antiplatelet therapy

The important point that is quoted in the 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation, which contains unanswered questions, should be insisted: "What is the best acute and maintenance antithrombotic regimen in patients who have an indication for oral anticoagulants? What is the best timing for the loading dose of oral P2Y12 inhibitors and what are the best strategies for i.e. antithrombotic therapies? What is the role of potent P2Y12 inhibitors in patients undergoing fibrinolysis? What is the real role of aspirin in this new era of potent antiplatelet agents and low dose anticoagulation? What is the best duration of maintenance therapy with P2Y12 inhibitors as single or multiple antithrombotic regimens?"

Although, maintenance therapy in the majority of patients is based on one-year DAPT in the form of aspirin plus prasugrel/ticagrelor, however, another unresolved issue that should be added to above-mentioned questions is the duration of using dual antiplatelet drugs in post PCI and/ or CABG, which is still debated. In selected patients with low bleeding risk and very high ischemic risk, extended DAPT (>12 months) could be considered [115]. Therefore, additional data is necessary to establish the optimal duration of dual antiplatelet therapy following stent implantation

Of course, another dilemma is the decision about the best time of discontinuing DAPT and/or anticoagulation in post PCI and/ or CABG patients who scheduled for non-cardiac operations.

Among the available and updated guidelines to conduct the use of DAPT, from our point of view, "2018 Update of the Canadian Cardiovascular Society Antiplatelet Guidelines" is more practical and feasible and. of course complete and reliable, so in this article, we recommend using it. Also, the recommendation provided in this guideline for heart patients on DAPT and/or OAC who need non-cardiac surgery is more applicable to the authors of this overview article **TABLES 12-14 and FIGURES 9 and 10**.

■ 2018 update of the canadian cardiovascular society/canadian association of interventional cardiology antiplatelet guidelines [154]

■ Management of patients with implanted coronary stents and/or CABG who on dual antiplatelet therapy and need to undergo non-cardiac surgery

Based on 2016 ACC/AHA Guideline Focused

TABLE 12. Recommendations for duration of DAPT in patients with ACS (STEMI or NSTEACS) who undergo PCI.

Recommendations:
In patients with ACS (STEMI or NSTEMI) who receive PCI:
• We recommend DAPT with ASA 81 mg daily with either ticagrelor 90 mg BID or prasugrel 10 mg once daily over clopidogrel 75 mg once daily for 1 year (Strong Recommendation; High-Quality Evidence)
• We recommend that, in patients who tolerate 1 year of DAPT without a major bleeding event and who are not at high risk of bleeding, DAPT should be extended beyond 1 year (Strong Recommendation; High-Quality Evidence for up to 3 years of treatment)
• After 1 year, we recommend a DAPT regimen of ASA 81 mg daily plus either ticagrelor 60 mg BID or clopidogrel 75 mg once daily (Strong Recommendation; High-Quality Evidence) or prasugrel 10 mg once daily (Weak Recommendation; Moderate-Quality Evidence)
Values and preferences. These recommendations place greater emphasis on reduction of major CV events and stent thrombosis vs an increase in bleeding complications

TABLE 13. Recommendations for duration of DAPT in patients who undergo elective PCI.
Recommendations:
In patients undergoing PCI for a non-ACS indication (e.g., stable ischemic heart disease):
• We recommend 6 months (and up to 1 year) of DAPT with ASA and clopidogrel (Strong Recommendation; Moderate-Quality Evidence)
• We suggest that in patients who have additional high risk clinical or angiographic features for thrombotic CV events and who are at low risk of bleeding, it is reasonable to extend the duration of DAPT to >1 year (Weak Recommendation; Moderate-Quality Evidence for up to 3 years of treatment)
• We suggest that in patients who are at high risk of bleeding, the duration of DAPT be shortened to a minimum of 1 month (if a bare-metal stent (BMS) is used) or 3 months (if a DES is used) (Weak Recommendation; Low-Quality Evidence)
Values and preferences These recommendations place greater emphasis on reduction of major CV thrombotic events and stent thrombosis v.s. an increase in bleeding complications. These recommendations presume that patients who experience a clinically significant bleed or at high risk of bleeding would be reassessed for the appropriateness of continuation of DAPT at 1 year.

TABLE 14. Recommendations for patients on DAPT who candidate for surgery.
Recommendations:
• In patients undergoing PCI who are treated with a BMS and who require elective noncardiac surgery, we recommend delaying surgery for at least 1 month after PCI (Strong Recommendation; Moderate-Quality Evidence)
• In patients undergoing PCI who are treated with a DES and who require elective noncardiac surgery, we recommend delaying surgery for at least 3 months after PCI (Strong Recommendation; Moderate-Quality Evidence). If there is a need for semi-urgent noncardiac surgery, we suggest delaying surgery for at least 1 month after PCI (Weak Recommendation; Low-Quality Evidence)
• In patients undergoing PCI who are treated with either a BMS or DES and who require elective noncardiac surgery, we suggest continuing ASA perioperatively whenever possible (Weak Recommendation; Low-Quality Evidence)
• In patients undergoing PCI who are treated with a BMS or DES and who require elective noncardiac surgery, we suggest withholding clopidogrel and ticagrelor for 5-7 days preoperatively, and prasugrel for 7-10 days preoperatively (Weak Recommendation; Low-Quality Evidence)
• In patients undergoing PCI who are treated with a BMS or DES and who have undergone noncardiac surgery, we suggest restarting maintenance-dose DAPT after surgery, as soon as it is deemed safe by the surgeon (Weak Recommendation; Very Low-Quality Evidence)
• We recommend continuation of ASA in all patients with ACS who require CABG surgery (Strong Recommendation; Moderate-Quality Evidence)
• To minimize the risk of bleeding, for patients with an ACS who are receiving ticagrelor and need semi-urgent CABG, we suggest a minimum interruption of ticagrelor for 48-72 hours before CABG (Weak Recommendation; Low-Quality Evidence) and recommend an ideal interruption period of 5 days before elective CABG (Strong Recommendation; Moderate-Quality Evidence)
• To minimize the risk of bleeding, for patients with an ACS who are receiving clopidogrel and need semi-urgent CABG, we suggest a minimum interruption of clopidogrel for 48-72 hours before CABG (Weak Recommendation; Low-Quality Evidence) and recommend an ideal interruption period of 5 days before elective CABG (Strong Recommendation; Moderate-Quality Evidence)
• To minimize the risk of bleeding, for patients with an ACS who are receiving prasugrel and need semi-urgent CABG, we suggest a minimum interruption of prasugrel for 5 days before CABG (Weak Recommendation; Very Low-Quality Evidence) and recommend an ideal interruption period of 7 days before elective CABG (Strong Recommendation; Moderate-Quality Evidence)
In patients with a previous valve replacement who undergo PCI for an ACS or non-ACS indication:
• For patients with a mechanical valve replacement, we suggest an initial regimen of ASA 81 mg daily plus clopidogrel 75 mg daily plus a VKA (triple therapy). ASA may be discontinued as early as the day after PCI or it can be continued up to 6 months of treatment, depending on the risk of recurrent thrombotic events vs major bleeding (Weak Recommendation; Very Low-Quality Evidence)
• For patients with a mechanical valve replacement, we recommend against the use of a NOAC regardless of whether it is in combination with antiplatelet therapy or used alone (Strong Recommendation; Moderate-Quality Evidence)

Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease, regarding patients with an indication for oral anticoagulation in addition to DAPT, the below recommendation has introduced **TABLE 15** [155]:

CHA2DS2-VASc indicates congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65-74 years, sex category; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly; INR, international normalized ratio; and PPIs, proton pump inhibitors.

Based on a 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS, regarding patients with an indication for oral anticoagulation in addition to DAPT, the below recommendation were introduced **TABLE 16**.

Some important below key messages have notified by 2017 ESC focused update on DAPT that need to be considered:

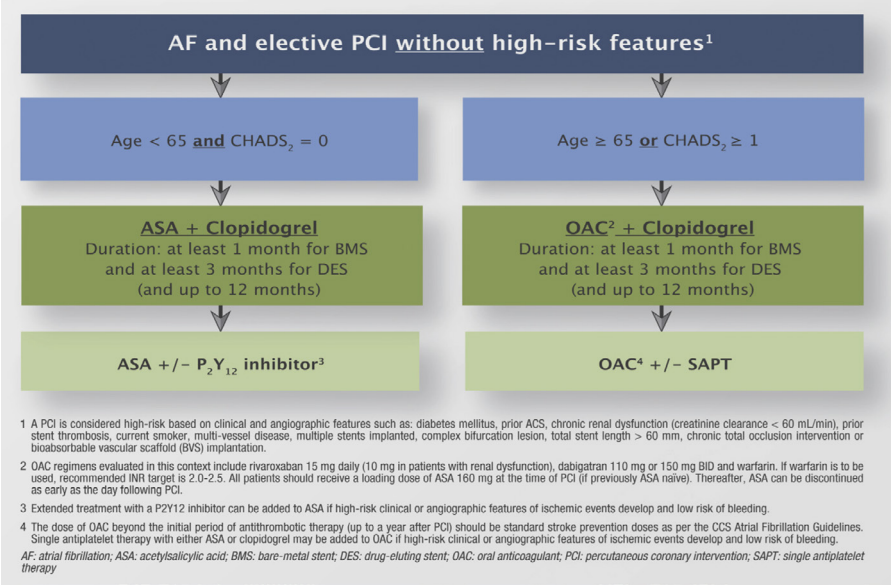


FIGURE 9. Recommendations for patients with AF without high-risk features who undergo elective PCI.

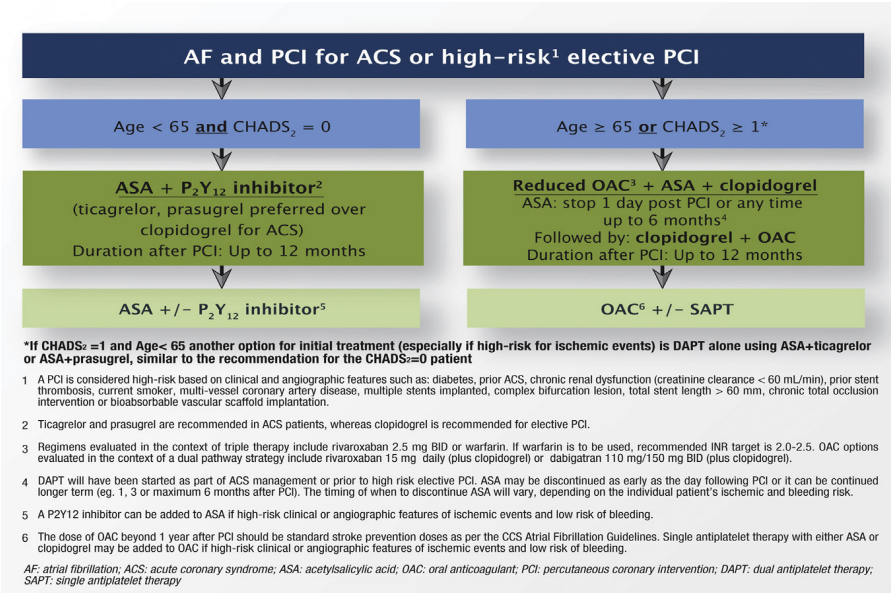


FIGURE 10. Recommendations for patients with AF who undergo PCI for ACS or high-risk elective PCI.

TABLE 15. Summary and synthesis of guideline, expert consensus documents, and comprehensive review article recommendations on the management of patients treated with triple therapy.

Recommendations:
Assess ischemic and bleeding risks using validated risk predictors (e.g., CHA2DS2-VASc, HAS-BLED)
Keep triple therapy duration as short as possible; dual therapy only (oral anticoagulant and clopidogrel) may be considered in select patients
Consider a target INR of 2.0-2.5 when warfarin is used
Clopidogrel is the P2Y12 inhibitor of choice
Use low-dose (#100 mg daily) aspirin
PPIs should be used in patients with a history of gastrointestinal bleeding and are reasonable to use in patients with increased risk of gastrointestinal bleeding

1. Similar type and duration of DAPT are recommended in male and female patients
2. Similar type and duration of DAPT are recommended in patients with and without diabetes mellitus
3. Patients with prior stent thrombosis, especially in the absence of correctable causes, should receive prolonged DAPT
4. A prolonged DAPT regimen may also be considered in patients with Lower-Extremities Artery Disease (LEAD) or who have undergone complex PCI

TABLE 16. Patients with indication for oral anticoagulation.
Recommendations:
• Compared with OAC therapy alone, the addition of DAPT to OAC therapy results in at least a two-to three-fold increase in bleeding complications
• Therefore, these patients should be considered at high risk of bleeding and the indication for OAC should be reassessed and treatment continued only if a compelling indication exists
• The duration of triple therapy should be limited up to a maximum of 6 months or omitted after hospital discharge, taking into account the ischemic (e.g. complexity of treated CAD, amount of disease left untreated, technical considerations regarding stent implantation techniques, and results) as well as the bleeding risk. The use of ticagrelor or prasugrel in this setting is not recommended

A published article in JAMA in 2012 has shown the result of prospective, randomized double-blind, placebo-controlled, multicenter trial in 210 patients who were awaiting surgery and who discontinued DAPT was used to the beneficial effect of intravenous cangrelor as a bridge to fill this time without a DAPT, but further studies on suggesting this strategy in this context are needed for sure.

Conclusion

It should be kept in mind that the enormous budget, coupled with the great effort of researchers over the past decades, has made the diagnosis and treatment of heart disease the conditions we are in today. On the other hand, for long years, coronary stenting had performed without the use of advanced vascular imaging techniques and causing early and delayed stent failure and thrombosis. Also, nowadays, routine use of vascular imaging to verify the optimal results besides the coronary stenting still performing in a small fraction of patients and limited in some professional centers even in developed countries. Therefore, the possibility of stent failure including thrombosis is a reality in the following years post-procedure such as very late stent thrombosis (even after ten years), especially when we face patients who are candidates for operation and consultants have to discontinue antiplatelet/anticoagulants for any reason. Therefore, we face the risk of myocardial infarction with proven high mortality rate in the pre-operative period, which still requires a great deal of effort so that patients who have avoided the potential risks of myocardial infarction and ischemia due to strenuous efforts before are not easily exposed to an eventful procedure.

Conflict of Interest

The author declares no conflict of interest.

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