Vol 1 No. 2 October 2021
Solo Journal of Anesthesi, Pain and Critical Care

E-ISSN : 2797-0035
P- ISSN : 2776-1770

REVIEW ARTICLE

Coronary Heart Disease: Diagnosis and Therapy

Iin Novita Nurhidayati Mahmuda[✉*], Nanda Nurkusumasari[**]
Fakhri Nofaldi[***], Prihatin Puji Astuti[***], Ferika Dian Syafitri[***], Dessy[***]

Article Info :
Submitted :
19-09-2021
Accepted :
29-10-2021
Published :
30-10-2021
https://dx.doi.org/10.20961/soja.v1i2.54984

Authors' affiliation :
[*]Department of Internal Medicine, Faculty of Medicine Universitas Muhammadiyah Surakarta, Indonesia
[**]Department of Cardiology, Faculty of Medicine Universitas Muhammadiyah Surakarta, Indonesia
[***]Medical Students, Faculty of Medicine Universitas Muhammadiyah Surakarta, Indonesia

[✉]Correspondence :
innm209@ums.ac.id

ABSTRACT

Coronary heart disease (CHD), is one of the non-communicable diseases that has a tendency to increase every year and have an impact not only on developed countries, but also in developing countries. According to the World Health Organization (WHO), in 2012 there were 56 million deaths worldwide caused by non-communicable disease and heart disease contributed 46.2% or caused 17.5 million deaths. This review article to give brief explanation about CHD from risk factors, diagnosed criteria, management therapy and prognosis. Risk factors for CHD can be distinguished into major risk factors and minor risk factors. Symptoms of CHD are discomfort in the chest ranging from pain crushed during activity and improved with rest to continuous chest pain. The diagnosis of CHD is established based on anamnesis, physical examination, and laboratory examination. The CHD classification consists of Stable Angina Pectoris (APS) and Acute Coronary Syndrome (ACS). Lifestyle changes accompanied by right medication can reduce complications caused by CHD.

Keywords : Coronary heart disease; chest pain; lifestyle; management; classification

INTRODUCTION

Coronary heart disease is one of the non-communicable diseases that has a tendency to increase every year and have an impact for developing countries. According to the World Health Organization (WHO), in 2012 there were 56 million deaths worldwide caused by non-communicable disease and heart disease contributed 46.2% or caused 17.5 million deaths. Basic Health Research (Riskesdas) 2013 concluded that deaths caused by cardiovascular disease, cancer, chronic obstructive pulmonary disease (COPD) were responsible for 59% of total deaths[1].

Acute Coronary Syndrome (ACS) is a major cardiovascular problem because it causes high hospitalization rates and mortality rates. Many advances have been made through research and therefore guidelines are needed as a summary of existing research[2]. This review article will make young clinician easier to understand diagnosis and updated management of CHD.

The heart is a muscular organ with four chambers located in the chest cavity, under the protection of the rib bone, slightly to the left of the sternum. The chamber of the heart consists of two thin-walled chambers called the atria and two thick-walled chambers called ventricles. The heart is about 300 grams, although its weight and size are affected by age, gender, physical activity, etc. A normal adult heart beats about 60 to 80 times per minute, spouts about 70 ml of blood from both ventricles per beat, and its total output is about 5 L/min.

The heart is located inside the mediastinum cavity of the chest cavity (thoracic), between the two lungs. The membrane that surrounds the heart is called the pericardium, which consists of 2 layers. The parietal epicardium, is the outer layer attached to the breastbone and pulmonary membrane, and the visceral pericardium, the surface layer of the heart itself, which is also called epicardium. Between the two pericardium layers is the pericardial sac that contains pericardial fluid, which serves to reduce friction arising from the movement of the heart when pumping. The heart wall consists of 3 layers, namely the outer layer called the pericardium, the middle layer called the myocardium (which is the muscle layer), and the inner layer called the endocardium.

The heart system has an important role through the circulatory system which is generally divided into three systems. This circulatory system provide oxygen and nutritional needs for every organ or tissue or cell of the body. This circulatory system namely:

A. Small circulatory system.

Blood is pumped by the right ventricle flowing to the lungs through the pulmonary artery. There is an exchange of gas that is the taking of oxygen and releases carbon dioxide, then blood enters the left atrium through the pulmonary veins. This small circulatory system serves to blood with oxygen. Previously blood which entered the right atrium with low oxygen levels between 60-70% and high carbon dioxide levels between 40-45%. Once circulating through lungs, oxygen levels increase to 96%. The process of cleaning the gas in lung tissue takes place in the alveoli, where oxygen gas is tapped by hemoglobin components

B. Large circulatory system.

Oxygen-rich blood from the left atrium enters the left ventricle through the mitral/ or bicuspidal valve. Thi blood pumped to aorta carrying oxygen and nutrients needed by the body large through blood vessels/ or arteries, go to smaller branches, capillaries and arterioles.

C. Coronary circulatory system.

The coronary circulatory system is different from the small and large circulatory system. The coronary circulatory system specifically supplies blood to the heart muscle, namely through coronary vessels and back through the back vessels which then fuse and empties directly into the right ventricle. Coronary blood vessels fills when the heart is relaxing. Through this coronary circulatory system, the heart gets oxygen, nutrients, and other substances in order to move the heart in accordance with its function[3]. A dysfunction in this circulatory system (e.g. CHD) will cause disruption off oxygen supply to the heart muscle.

Based on the definition from the American Heart Association (AHA), Coronary Heart Disease (CHD) or often called coronary artery disease is a general term for plaque buildup in the heart arteries that can cause a heart attack. Plaque buildup in the coronary arteries is called coronary atherosclerosis[4].

Based on WHO definition, CHD is an acute or chronic incompetence that arises due to a lack of blood supply in the heart muscle (myocardium). Reduced blood supply occurs because there is a blockage in the coronary blood vessels. This blockage is usually caused by an atheroma, which forms as a precipitate or plaque in the inside of the artery wall[5].

World Health Organization (WHO) estimates CHD to be the leading cause of death worldwide with 17 million deaths per year in 2008 and will rise to 23.4 million deaths by 2030, with more than 80% occurring in developing countries. According to Riskesdas data 2013, the prevalence of CHD in Indonesia is 0.5% - 1.5%.

Coronary heart disease also causes major disabilities. This results in a loss of productivity globally. The costs associated with premature death from CHD, low productivity, hospital treatment, and prescription medications are also very high. Losses in one year amounted to 19 trillion pounds for the British region, 196 trillion euros for the European Union economic area, and 327 billion US dollars for the territory of the United States. Interheart, a control case study in 52 countries found that 90% of CHD cases could be attributed to risk factors that could actually be prevented and corrected[5].

CHD risk factors are divided into major and minor risk factors. Major risk factors are geriatric patient, men, hypertension, diabetes mellitus, dyslipidemia (high cholesterol), smoking habit, family history of ischemic heart disease. Minor risk factors are obesity, reduced physical activity or lack of activity, type A personality (hardworking people), and high cholesterol diet[6].

Most CHD is a manifestation of coronary blood vessel atheroma plaque that is torn or ruptured. This is related to changes in the composition of plaque and thinning of the fibrous hood covering the plaque. This event will be followed by the platelet aggregation process and activation of coagulation pathways. Platelet-rich thrombus (white thrombus) is formed. This thrombus will clog the burrows of coronary blood vessels, totally or partially; or become micro emboli that clogs more distal coronary vessels. In addition, there is a release of vasoactive substances that cause vasoconstriction so that it

aggravates coronary blood flow disorders.

Reduced coronary blood flow causes myocardial ischemia. Myocardial infarction happened if myocardium oxygen supply stop for 20 minutes . Myocardial infarction is not always caused by total occlusion of coronary blood vessels.

Subtotal obstruction accompanied by dynamic vasoconstriction can lead to ischemia and necrosis of heart muscle tissue (myocardial). The result of ischemia, in addition to necrosis, is a disorder of myocardial contractility due to the process of hibernating and stunning (after ischemia is gone), dysrhythmia and ventricular remodeling (changes in the shape, size and function of the ventricles). Some ACS patients do not experience plaque tear as described above. They experience ACS due to dynamic obstruction due to local spasm of the epicardial coronary arteries (Prinzmetal angina). Narrowing of the coronary arteries, without spasm or thrombus, can result from plaque progression or restenosis after Percutaneous Coronary Intervention (PCI). Some extrinsic factors, such as fever, anemia, tyotoxicosis, hypotension, tachycardia, can be the trigger for ACS in patients who already have atherosclerotic plaques[2].

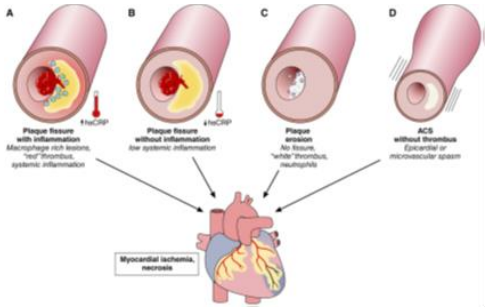


Figure 1. Patophysiology of Acute Coronary Syndrome

Based on anamnesis, physical examination, electrocardiogram (ECG), and heart disease examination, coronary heart disease consists of :

a. APS : Stable Angina Pectoris which is further divided into : CCS Class I when regular activity does not cause angina, such as walking or climbing stairs. Angina appears by straining or fast and prolonged activity while working or exercising ; CCS Class II when Slight restrictions on regular activities. Angina appears when walking fast or climbing stairs, walking or climbing stairs after eating or in cold weather, angina in emotional stress, or just a few hours after waking up. Walk more than two

blocks or climb more than one ladder at normal speed and conditions ; CCS Class II when clear restrictions on regular physical activity. Angina appears when walking a block or two, going up one floor at normal conditions and speeds and ; CCS Class IV when inability to perform physical activity without discomfort, angina can arise while resting.

b. Myocardial infarction with ST segment elevation (STEMI: ST segment elevation myocardial infarction).
c. Myocardial infarction with non-elevation segment ST (NSTEACS) consisting of NSTEMI and UAP (NSTEMI:non ST segment elevation myocardial infarction)/UAP (Unstable Angina Pectoris)[7].

DISCUSSION

APS / Stable Angina Pectoris presented with chest pain ; substernal during activity, location near the sternum, can spread to the left arm, back, jaw, and heartburn, duration is usually <10 minutes.

Myocardial infarction with STEMI presented with chest pain ; substernal, duration > 20 minutes, accompanied by cold sweats. can spread to the left arm, back, jaw, and heartburn.

Myocardial infarction with NSTEMI/UAP presented with typical persistent angina for more than 20 minutes experienced by most patients (80%), angina de novo class III classification of The Canadian Cardiovascular Society (20%) of patients, destabilising stable angina (progressive or crescendo angina): becomes more frequent, longer, or becomes increasingly severe at least class III CCS classification, postinfarc-myocardial angina: angina that occurs within 2 weeks after myocardial infarction[7].

Diagnosis

APS / Stable Angina Pectoris :

Anamnesis: The patient feels uncomfortable in the chest (near the sternum), but can be felt also in other places near the epigastric to the lower jaw or lower teeth, between the shoulders or in the arms to the wrists and fingers. The duration of the discomfort is short, no more than 10 minutes, symptoms are generally aggravated by an increase in the intensity of activities, and quickly disappears within minutes if these factors are stopped or eliminated.

Physical examination: There are no signs of physical examination typical of angina pectoris.

Follow-up examination: electrocardiography (ECG), laboratory blood examination for risk factors of cardiovascular atherosclerosis disease such as glycated hemoglobin (HbA1c), lipid profile and resting echocardiography. Patients with echocardiography results showing an ejection fraction of less than 50% with typical angina, deserve to be recommended invasive angiography with possible revascularization[1].

Myocardial Infarction with STEMI

Anamnesis: Substernal chest pain, duration > 20 minutes, accompanied by cold sweats and can spread to the left arm, back, jaw, heartburn. There are more than one risk factors: diabetes, cholesterol, high blood pressure, heredity.

Physical Examination: Generally within normal limits unless accompanied by complications and/or comorbidities.

Follow-up examination: Meets the ECG anamnesis criteria: The elevation of the ST> segment is 1 mm at least two adjacent leads, and there is evolution in the ECG 1 hour later. Other examinations are biomarkers of heart damage namely creatinine kinase (CK)MB and cardiac specific troponin (cTn)T[3].

Myocardial Infarction with NSTEMI/UAP

Anamnesis: Complaints in the form of angina arise at rest time, or due to minimal activity. Chest pain can be accompanied by shortness of breath, nausea, vomitus sometimes accompanied by cold sweats.

Physical examination: Generally within normal limits unless accompanied by complications and/or comorbids.

Follow-up examination: ECG: elevation the ST-segment by 1 mm at least two nearby leads, and there is evolution in the ECG 1 hour later. The diagnosis of NSTEMI is upheld if cardiac enzymes increases slightly beyond the upper limit of normal. Transthorasic echocardiography examination at rest can provide an overview of the function of the left ventricle in general and is useful for determining the differential diagnosis. Hypokinesia or segmental akinesia of the left ventricular wall can be seen during ischemia and become normal when ischemia disappears[7].

Management

APS/Stable Angina Pectoris

Pharmacology therapy : Aspilet1x80-160mg, Simvastatin1x20-40 mg or Atorvastatin 1x20-40 mg or Rosuvastatin1x10-20 mg, Beta blocker: Bisoprolol 1x5-10 mg or Carvedilol 2x25 mg or Metoprolol 2x50 mg, Ivabradine 2x5 mg, if the patient is intolerant with beta blockers, Isosorbid dinitrat 3x 5-20 mg or Isosorbid mononitrat 2x 20 mg

Intervention : PCI or CABG

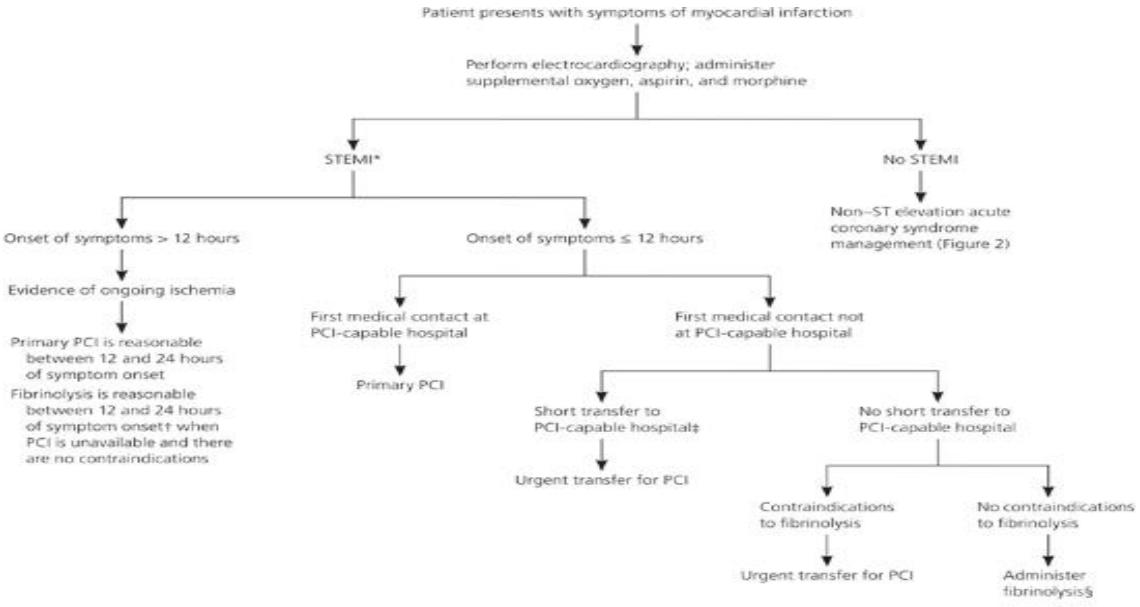
Myocardial Infarction with STEMI

Acute phase in ER : Total bed rest, Oxygen 2-4 liters/minute if oxygen saturation is < 94%, and setting-up IVFD immediately. Medication : Aspilet 160 mg chewable, Clopidogrel (for <75 years of age and does not routinely take clopidogrel) give 300 mg if the patient gets fibrinolytic therapy or Clopidogrel 600 mg or Ticagrelor 180 mg if the patient gets primary PCI, Atorvastatin 40 mg, sublingual nitrate 5 mg, repeated 3 times if there are still complaints, and continued with nitrate IV when persistent complaints arrived, Morfin 2-4 mg IV if there is chest pain, continues heart monitoring.

If the onset < 12 hours : Fibrinolytic (in ER) or Primary PCI (at Cathlab) when the facilities and human resources at cathlab are ready to perform within 2 hours.

Intensive Care phase at CVCU (2x24 hours)

Medication : Simvastatin 1x20 or Atorvastatin 1x20 mg or 1x40 mg if LDL levels are above target, Aspilet 1 x 80 mg, Clopidogrel 1 x 75 mg or Ticagrelor 2 x 90 mg, Bisoprolol 1x1.25 mg if kidney function is good, Carvedilol 2x3,125 mg if kidney function decreases, the dose can be uptitred (it is given if there is no contraindication), Ramipril 1 x 2,5 mg if there is an anterior infarction or LV function decreases EF <50% (it is given if there is no contraindication). If intolerant with ACE-I group can be given class ARB drugs: Candesartan 1 x 16 mg, Valsartan 2x80 mg, Laxatives 2 x 1 tablespoon, Diazepam 2 x 5 mg. If no primary PCI is given, heparinization can be given: UF heparin bolus 60 Units / kgBW maximum 4000 Units, followed by a dose of 12 Units / kgBB maximum 1000 Units / hour or Enoxaparin 2 x 60 mg (previously bolus 30 mg iv) or,



*—Electrocardiography shows new ST elevation at the J point in at least two contiguous leads of ≥ 2 mm (0.2 mV) in men or ≥ 1.5 mm (0.15 mV) in women in leads V_2-V_3 and/or of ≥ 1 mm (0.1 mV) in other contiguous chest leads or the limb leads, or new left bundle branch block, or true posterior myocardial infarction.
†—Fibrinolytic therapy should be administered if there is a large area of myocardium at risk or hemodynamic instability.
‡—Interhospital transfer is recommended if PCI can be performed within 120 minutes of first medical contact.
§—When fibrinolytic therapy is indicated or chosen as the primary reperfusion strategy, it should be administered within 30 minutes of first medical contact.

Figure 2. Reperfusion therapy in patients with STEMI [9].

fondaparinux 1 x 2,5 mg, continues heart monitoring.

Patient shoud be fasting for 6 hours, follow by heart diet 1800 kcal/24 hours. Total liquid should be 1800 cc/24 hours. Laboratory lipid profiles (total cholesterol, HDL, LDL, triglycerides) and uric acid taken as soon as possible.

Every patient risk stratification prognostics counted according to the patient's priority scale (choose one): 6 minutes walk test, Treadmill test, Echocardiography Stress test, Stress test perfusion scanning or MRI.

Rehabilitation and secondary prevention could be started after the patient gone through critical time safety.

Myocardial Infarction with NSTEMI/ UAP

Acute phase in ER : Total bed rest, Oxygen 2-4 L/minute, and setting-up IVFD immediately. Medication : Aspilet 160 mg chewable, Clopidogrel (for the age of <75 years and does not routinely consume clopidogrel) give 300 mg or Ticagrelor 180 mg, Sublingual nitrate 5mg, can be repeated up to 3 times if there are still complaints, continued Nitrate IV if persistent complaints,

Morfin 2-4 mg iv if there is still chest pain, continues heart monitoring.

Every patients should be stratification of risks in ER to determine invasive strategies. Patients at very high risk should be PCI in 2 hours taking into account the availability of power and cathlab facilities. The risk criteria are very high when there is one of the following criteria: recurrent angina, cardiogenic shock, malignant arrhythmia (VT, VF, TAVB), and unstable haemodynamic.

Patients with increased heart enzymes but without the above very high risk criteria, are treated for 5 days and PCI may be performed during or after discharge from the hospital taking into account clinical conditions and availability of cathlab personnel and facilities.

Patients without changes in ECG and enzyme increase, ischemic stress test: Treadmill test, Echocardiography Stress test, Stress perfusion scanning test or MRI. If the schemic tress test is negative, patient can be discharged.

Intensive care phase at CVCU (2x24 hours)

Medication: Simvastatin 1x20-40 mg or Atorvastatin 1x20-40 mg or rosuvastatin 1x20 mg if LDL levels are above target, Aspilet 1x80-160 mg, Clopidogrel 1x75 mg or Ticagrelor 2x90 mg, Bisoprolol 1x5-10 mg if kidney function is good or Carvedilol 2x12.5 mg if kidney function decreases, the dose can be uptitred (given if there is no contraindication), Ramipril1 x 10 mg or Lisinopril 1x 10, Captopril 3x25 mg or if LV function decreases EF <50% (given if there is no contraindication). If intolerant with ACE-I group can be given class ARB drugs: Candesartan 1 x 16, Valsartan 2x80 mg, Laxative 2x tablespoon, Diazepam 2x5 mg. Heparinization with UF heparin bolus 60 Units / kgBW maximum 4000 Units, followed by a dose of 12 units / kgBW maximum 1000 Units / hour or Enoxaparin 2x60 mg SC (previously 30mg iv in the ER) or Fondaparinux 1x2.5 mg SC, continues heart monitoring

Patients should be fasting for 6 hours, follow by heart diet I 25-35 kcal/KgBW/ 24 hours. Total liquid 25-35 cc/KgBW/24 hours. Examination of lipid profiles (total cholesterol, HDL, LDL, triglycerides) and uric acid should be taken as soon as possible.

Risk Stratification for prognostic according to the patient's priority scale

(choose one): Treadmill test, Echocardiography Stress test, Stress perfusion scanning test or MRI. Rehabilitation and Secondary prevention could be started after the patient gone through critical time safety[7]

exercise, limit alcohol consumption (moderate), stop smoking, control blood pressure and blood sugar levels, maintain and maintain an ideal body weight and a low cholesterol diet.

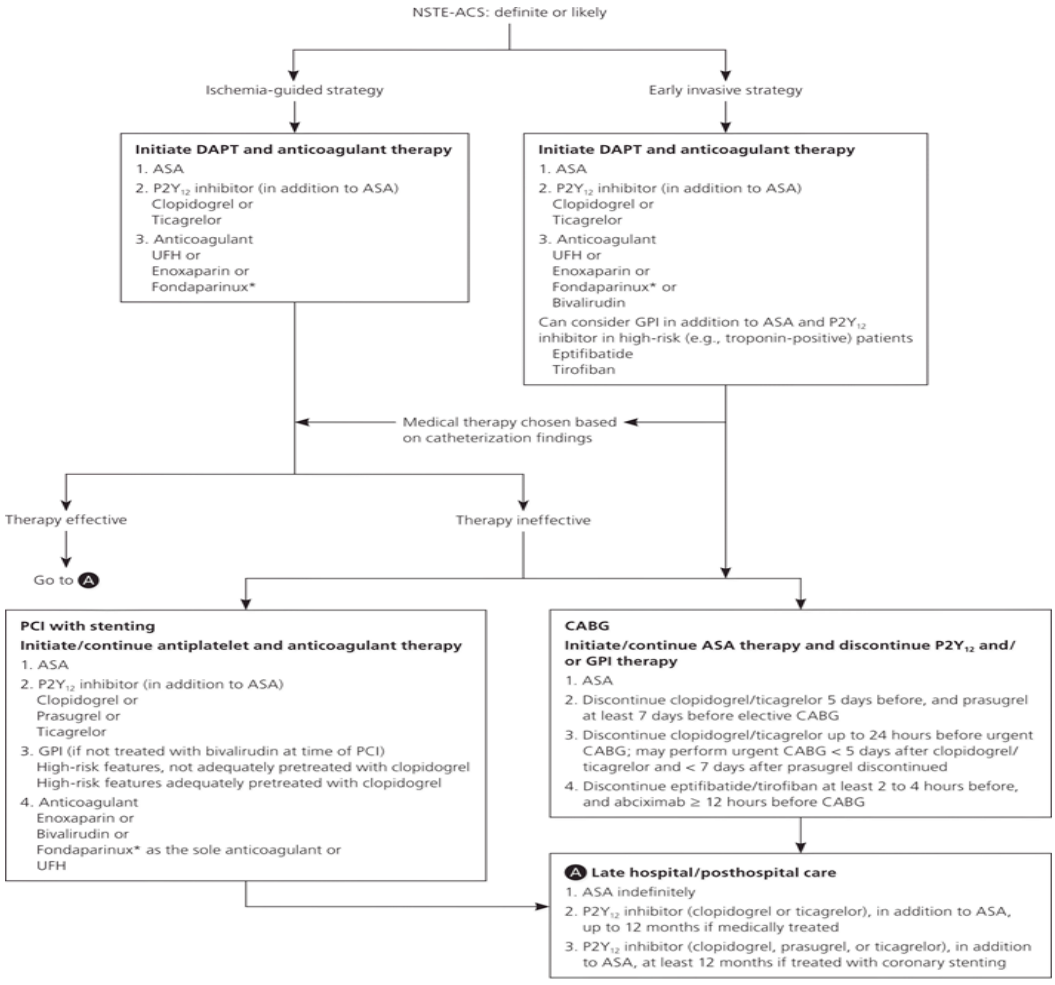


Figure 3. Reperfusion therapy in patients with NSTEM[9]

Education

Lifestyle changes are the spearhead of CHD prevention efforts. What needs to be done are : regular

Consumption of antioxidants: green tea flavonoids, olive oil and red wine. Diet low in trans and saturated

fats. Consume omega 3 fatty acids, fruits, fresh vegetables, and nuts.

Keep the waist circumference optimal and BMI at least <27 kg / m2 or optimal <25 kg / m2. Exercise regularly for 4 to 7 days. Keep the waist circumference optimal and BMI at least <27 kg / m2 or optimal <25 kg / m2.

The most important way to prevent CHD is to promote healthy lifestyle (physical activity, reduces body weight, nutition and especially not smoking. Others factor also important psychosocial, optimum treatment for comorbid, anti thrombotic therapy and specific intervention[8].

Patients at very high risk could be initiated with statin therapy and low dose aspirin as long as no contraindication[10,11].

Blood pressure target < 140/85 is wellcome for all. Glucose lowering agent should be effective and consider metformin as first choice for type 2 diabetes[12].

Prognosis

The prognosis of coronary heart disease will largely depend on the amount of coronary plaque, the severity of the obstruction, left ventricular function and the presence of complex arrhythmias. Worse prognosis if people with coronary heart disease have experienced clinical symptoms in the form of myocard infarction until there is sudden death due to ventricular arrhythmias. Sufferers are said to be at high risk if there has been damage to the base of the left coronary artery[4].

SUMMARY

Basically what is meant by primary prevention is an attempt to avoid cardiovascular events in asymptomatic patients. Therefore the basic concept is integrated assessment of risk factors, identification, and intervention of obesity, and diabetes at an early age and the administration of pharmacological therapy after adulthood. There are several ways to classify patients at risk.

The most commonly used is the Framingham score, which is to group patients based on calculations of the magnitude of the risk of heart disease, as well as as a guide in screening, handling and evaluating patients.

In line with the magnitude of the calculation of the risks obtained, begins the anticipation of handling it. In a small risk group, intervention / handling of risk factors. In the risk group moderate or

severe handling should be better. As much as possible risk factors should be corrected. LDL level is lowered in such a way as to prevent the possibility of atherosclerosis. In addition, drugs are also used regularly and lifestyle changes in the form of regular exercise[3].

CONFLICT OF INTEREST

The authors whose name are listed immediately below certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or material discussed in this manuscript.

REFERENCE

1. Alkatiri, Amir Aziz; Wicaksono, Sony Hilal; Pakpahan, Henry; Dwiputra, Bambang, 2019. Panduan Tatalaksana Angina Pektoris Stabil. Edisi Pertama ed. Jakarta Centra Communication.
2. Irmalita, Juzar, Andriyanto, 2015. Pedoman Tatalaksana Sindrom Koroner Akut. Edisi Ketiga ed. Jakarta Centra Communication.
3. Setiati, S, Alwi I, Sudoyo AW, Stiyohadi B. 2014. Buku Ajar Ilmu Penyakit Dalam. VI ed. Jakarta Pusat: Interna Publishing.
4. Amsterdam, E. A, Wenger N. K, Brindis R. G., 2014. AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes. Circulation.
5. WHO, 2017. Cardiovascular Disease (CVDs).
6. Rampengan, S. H., 2014. Buku Praktis Kardiologi. Edisi Pertama ed. Jakarta: Badan Penerbit FKUI.
7. Firdaus Isman, Rahajoe Anna Ulfah, Yahya Fauzi. A, Lukito Antonia Anna, Kuncoro Ario Soeryo, Lilyasari Oktavia. et al., 2016. Panduan Praktik Klinis (PPK) dan Clinical Pathway (CP) Penyakit Jantung dan Pembuluh darah. Edisi Pertama ed. Jakarta: Centra Communication.
8. Visseren Frank L. J, Mach Francois, Smulders Yvo. M, Carballo David, Koskinas Konstantinos. C, Back Maria. et al., 2021. ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and

12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). European Heart Journal, Volume 42, Issue 34, 7 September 2021, Pages 3227–3337

9. Switaj, T. L., Christensen, S. R. & Brewer, D. M., 2017. American Family Physician.
10. Mach Francois, Baigent Colin, Catapano Alberico. L, Koskinas Konstantinos. C, Casula Manuela, Badimon Lina., et al. 2019 ESC/EAS Guidelines for the Management of Dyslipidemias: Lipid Modification to Reduce Cardiovascular Risk: The Task Force for the Management of Dyslipidemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J, Aug 31.
11. Rajan, T., Mortesen, M., 2019 ESC Guidelines on diabetes, prediabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2020;41:255-323
12. Williams Bryan, Mancia Giuseppe, Spiering Wilko, Rosei Enrico Agabiti, Azizi Michael, Burnier Michel, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). Eur Heart J, Volume 39, Issue 33, 01 September 2018, Pages 3021–3104