Chapter 2
Evidence in Guidelines for Treatment of Coronary Artery Disease

Sida Jia, Yue Liu and Jinqing Yuan

Abstract In this chapter, we focus on evidences in current guidelines for treatment of coronary artery disease (CAD). In Part 1, diet and lifestyle management is discussed, which plays an important role in CAD risk control, including forming healthy dietary pattern, maintaining proper body weight, physical exercise, smoking cessation, and so on. Part 2 elaborated on revascularization strategies and medical treatments in patients presenting with acute coronary syndrome (ACS), including specific AHA and ESC guidelines on ST elevation myocardial infarction (STEMI) and non-ST elevation ACS (NSTE-ACS). Part 3 discussed chronic stable coronary artery disease (SCAD), the treatment objective of which is a combination of both symptomatic and prognostic improvement. Yet many of the recommendations for SCAD are expert-based rather than evidence-based. Initial medical treatment is safe and beneficial for most patients. While cumulating studies have focused on optimizing pharmacological therapy (referring to nitrates, beta-blockers, calcium channel blockers, antiplatelet agents, ACEI/ARB, statins, etc.), education, habitual modification, and social support matters a lot for reducing cardiac morbidity and mortality. Patients with moderate-to-severe symptoms and complex lesions should be considered for revascularization. But practical management of revascularization shall take individual characteristics, preference, and compliance into consideration as well.

Keywords Coronary artery diseases · Treatment guidelines · Diet · Lifestyle management · Acute coronary syndrome · Revascularization strategies · Chronic stable coronary artery disease

Part 1: Diet and lifestyle management of CAD risk factors
Part 2: Evidence in guidelines for treatment of ACS
Part 3: Evidence in guidelines for treatment of chronic stable CAD

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2.1 Part 1: Diet and Lifestyle Management of CAD Risk Factors

Diet and lifestyle management should always be considered necessary for the therapeutic treatment of CAD. Unhealthy diet and lifestyle act as basic CAD risk factors which not only initiate CAD process but also worsen the prognosis of CAD, as supported by various evidences. No matter how effective drugs and revascularization techniques might be, an experienced cardiologist shall never ignore the importance of diet and lifestyle management.

2.1.1 Diet Management of CAD Risk Factors

Diet management is one of the fundamental factors to CAD risk control. According to AHA dietary guidelines, population goals are summarized as (see Table 2.1): forming overall healthy eating pattern, maintaining appropriate body weight, and achieving desirable cholesterol profile and blood pressure levels (Krauss et al. 2000).

As a general principle, the AHA guidelines supports the consumption of a variety of foods from all food categories with special emphasis on fruits and vegetables, including fat-free and low-fat dairy products; cereal and grain products; legumes and nuts; and fish, poultry, and lean meats (Krauss et al. 2000). We did a comprehensive search for new relevant evidences in databases including PubMed, Embase, and so on. In the following part, evidences will be listed per general food categories.

Table 2.1 Summary of dietary guidelines (Krauss et al. 2000)

	Population goals			
	Overall healthy eating pattern	Appropriate body weight	Desirable cholesterol profile	Desirable blood pressure
Major guidelines	Include a variety of fruits, grains, low-fat or nonfat dairy products, fish, legumes, poultry, lean meats	Match energy intake to energy needs, with appropriate changes to achieve weight loss when indicated	Limit foods high in saturated fat and cholesterol; and substitute unsaturated fat from vegetables, fish, legumes, nuts	Limit salt and alcohol; maintain a healthy body weight and a diet with emphasis on vegetables, fruits, and low-fat or non-fat dairy products

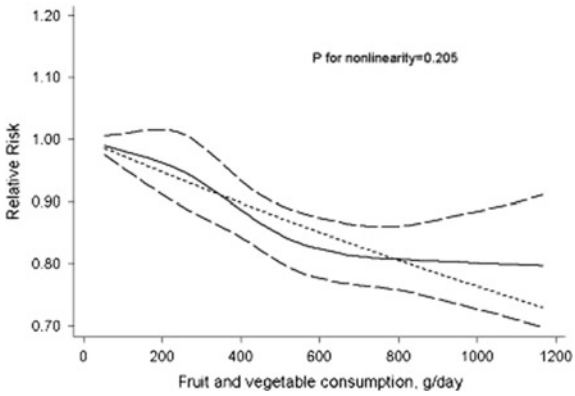

Fig. 2.1 Dose–response relation plots between fruit and vegetable consumption (g/day) and the risk of coronary heart disease (Gan et al. 2015), P for nonlinearity = 0.205

a. **Fruits and vegetables**
Gan et al. (2015) performed a meta-analysis on 23 studies involving 937,665 participants and 18,047 patients with CHD, finding that a nonlinear association exists between CAD risk and consumption of fruits and vegetables separately (see Fig. 2.1 and Table 2.1). They also discovered an interesting fact that such a significant inverse association was found only in Western populations, not in Asian populations, which warrants further research.

Specific recommendations on fruit and vegetable consumption were made in 2000 AHA dietary guidelines, yet there are some contradictory recent evidences regarding the variety of fruits and vegetables intake. It is recommended in 2010 dietary guidelines for Americans to both increase the amount of fruit and vegetable intake and eat a greater variety (McGuire 2010). However, contrary to the 2010 guidelines recommendations, Bhupathiraju et al. (2013) did a large-scale research including a total number of 113,276 patients, finding that absolute quantity, rather than variety, in fruit and vegetable intake is associated with a significantly lower risk of CAD. However, there is an association between higher intakes of various fruit and vegetable subgroups and lower CHD risk (Bhupathiraju et al. 2013). Thus, based on current available evidence, it is still reasonable to focus on increasing overall quantity and variety in fruits and vegetable intake.

b. **Grain products**
It is reported that grain products are beneficial to reducing the risk of CAD. Different kinds of whole grains containing varying nutrient compositions could potentially affect CAD via different mechanisms, such as decreasing serum LDL-cholesterol and blood pressure, improving glucose and insulin responses, and having prebiotic effects (Harris and Kris-Etherton 2010).

A meta-analysis by Tang et al., including 15 cohort studies and 3 case–control studies, suggested that highest whole-grain intake amount compared with the lowest amount was significantly associated with reduced risk for CAD, which proves a protective effect of higher whole-grain intake against CAD (Tang et al. 2015). Furthermore, a meta-analysis by Zong et al. provided strong and robust

evidence that there is an inverse association between whole-grain intake and CVD mortality, which further supports current dietary guidelines for Americans recommending at least three servings per day of whole-grain intake (Zong et al. 2016).

c. **Dairy products**

In terms of dairy products, the AHA guidelines recommended consuming fat-free or low-fat dairy products (Lichtenstein et al. 2006). Evidences concerning dairy product intake have been inconsistent. Dalmeijer et al. (2013) performed a meta-analysis of 17 prospective studies which investigated the relation of total dairy, milk, and low-fat and high-fat dairy with risk of cardiovascular disease or all-cause mortality. The study indicated that milk intake was modestly inversely associated with cardiovascular risk, but found no association between CAD and milk intake.

Another population-based cohort study including 33,625 Dutch men and women found no evidence that dairy products are associated with risk of CAD (Dalmeijer et al. 2013). As for participants without hypertension, the study found high intakes of total and low-fat dairy may be associated with a lower risk of CAD.

To our current knowledge, it might be difficult to draw an optimal amount for dairy intake, but it is fair to recommend dairy products with lower or no fat based on current guidelines on dietary fat intake.

d. **Other issues to be discussed**

i. ***Body Weight Maintenance***

It is established that obesity is a risk factor for CAD, making it important to maintain a healthy body weight. As more countries and regions in the world have been lifted from poverty and famine, excessive energy intake and inadequate physical exercise is turning to be a novel concern for CAD risk control. A pooled analysis of 97 prospective cohorts with 1.8 million participants found that both overweight (BMI $\geq$25 to <30 kg/m^2) and obesity (BMI $\geq$30 kg/m^2) were associated with a significantly increased risk of coronary heart disease compared with normal weight (BMI $\geq$20 to <25 kg/m^2), suggesting that maintenance of optimum bodyweight is needed for the full benefits (Lu and Hajifathalian 2014).

The AHA dietary guidelines pointed out that intake of energy should match overall energy needs, and that it's necessary to achieve balance between energy expenditure and energy intake (Krauss et al. 2000). Amount of physical activities should be matched with the amount of energy intake for individuals wishing to maintain BMI, while for individuals wishing to decrease BMI, the level of physical activity should exceed energy intake.

ii. ***Limitation of Salt Intake***

Excessive salt intake is an important risk factor for hypertension, which is in turn a risk factor for the development of CAD as well. Particularly in certain regions of industrialized countries, salt intake remains at typically twice the maximum recommended level of 5–6 g/day, halving which

could bring enormous public health benefit in preventing stroke and cardiovascular diseases (Glover et al. 2011). However, despite the rarity, there are contradictory evidences in animal model experiments. Chetboul et al. (2014) carried out a 2-year prospective randomized, blinded, and controlled study on cardiovascular effects of dietary salt intake in aged healthy cats, and found chronic high dietary salt intake was not associated with an increased risk of systemic arterial hypertension and myocardial dysfunction. Despite the contradictory evidence, this kind of evidences are generally rare and of little value of reference. To our current best knowledge, it is safe to stay to guidelines recommendations.

iii. ***Limitation of Alcohol Intake***
It is well known that excessive alcohol consumption leads to increased cardiovascular risk. Excessive consumption of alcohol not only damages coronary artery but also harms various parts of the cardiovascular system, causing cardiomyopathy, arrhythmia, hypertension, and so on. Nevertheless, alcohol limitation should never be taken to the extremes, as it is widely acknowledged that moderate alcohol consumption, and wine consumption in particular, is associated with a significant reduction in cardiovascular morbidity and mortality in epidemiological studies (Worm et al. 2013). The beneficial effect of moderate alcohol consumption is probably due to benevolent interactions between alcohols, beneficial lipid components, and coagulation factors. Therefore, it is vital to maintain a balance optimal for human body. It is suggested in the dietary guidelines that no more than 2 drinks per day (men) and 1 drink per day (women) among those who drink (Krauss et al. 2000).

iv. ***About Supplementary Nutrients***
Several supplementary nutrients are mentioned in the dietary guidelines, including antioxidants, folic acid, vitamin B, soy protein and isoflavones, fiber supplements, ω-3 fatty acid supplements, stenol/sterol ester-containing foods, fat substitutes, and so on. (Krauss et al. 2000). It is unrealistic to list all up-to-date evidences about these nutrients here, but most of these supplementary nutrients are generally considered to have protective effect against CAD. Given current knowledge, further research on these nutrients is warranted.

e. **Author's Comments on Dietary Guidelines**
This part unfolds mainly according to AHA Dietary Guidelines Recommendations, providing additional recent evidences for readers to refer to. Maintenance of healthy diet and lifestyle is absolutely essential for CAD risk reduction.

It's worth mentioning that in an era of big data and precision medicine, dietary recommendations is getting more and more personalized with the accumulation of new evidences. Advances in genomic, proteomic, and other "-omics" studies are gradually enabling precise dietary intervention targeting each individual's unique genomic trait. There is no doubt that more genomic-scale researches are widely needed for CAD dietary database to be established. It is predictable that in

the near future, with advancing technologies bringing down related cost, precise dietary intervention will be economically affordable to most population, making CAD risk control cost-effective for general population.

2.1.2 Lifestyle Management

Early clinical trials and meta-analyses have provided substantive and convincing evidence on the preventive strengths of lifestyle adjustment. Even though some tips have been amended so far, conclusion from a recent meta-analysis of 48 RCTs (1999–2009) accorded with formal results. Lifestyle modification programs were associated with reduced all-cause mortality (summary OR 1.34, 95% CI 1.10–1.64), cardiac mortality (summary OR 1.48, 95% CI 1.17–1.88), and cardiac readmission and non-fatal reinfarction (summary OR 1.35, 95% CI 1.17–1.55) (Janssen et al. 2012).

Analysis from a large RCT (the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS) 5 trials) revealed that patients who change their behavior (quit smoking, modify diet, and exercise) after ACS were at lower repeat CV events in 6 months. The benefits from each behavior modification are additive as the highest risk of a repeat CV event belonged to those who change none of them (OR, 3.77; 95% CI, 2.40–5.91; $p < 0.0001$) (Chow et al. 2010).

What should be emphasized is that changing the habits never too easy to achieve and even sustain for a lifetime. Support and guidance from physicians and other external factors, comprehensive, continuing, and individualized, is deemed to be of great importance.

1. Exercise

The effectiveness of regular physical activity to reduce all-cause and CVD mortality has a sound basis. For patients following either STEMI or NSE-ACS, exercise training plays a major role in cardiac rehabilitation. Despite insufficient data from RCTs in the population of stable coronary artery disease, it is well accepted that physical activity contributes to meliorate ischemic symptoms and progression.

Several pathophysiological mechanisms are considered to explain its protective impact: (i) improvement of endothelial function; (ii) reduced progression of atherosclerosis; (iii) reduced thrombotic risk; and (iv) improved formation of collaterals (Members et al. 2012). Furthermore, it has positive effects on many other risk factors, including hypertension, dyslipidemia, obesity, diabetes mellitus, and major depression.

Guidelines encourage CAD patients to acquire 30–60 min of moderate-intensity aerobic activity, such as brisk walking, at least 5 days and preferably 7 days per week (I, B), in line with recommendation in healthy population.

2. Cigarette cessation

Smoking is a strongly and independently evoking factor of CAD. From the last century, several observational studies have established clear conclusion about the increased risk of CV events in smokers. Moreover, passive smoking also has adverse influence on the development and progression of CVD.

Thus, quitting smoking is definitely a desirable and powerful preventive measure for patients with CAD, for example, result from the CASS Registry revealed higher rate of six-year mortality among continuing smokers than among those who quit smoking during the year before enrollment and abstained throughout the study (relative risk, 1.7; 95% CI 1.4–2.0). Furthermore, no difference was found in assorted ages (Hermanson 1988). A meta-analysis of 20 studies further confirmed that quitting smoking was associated with a substantial reduction in risk of all-cause mortality among patients with CHD (crude relative risk, 0.64; 95% CI 0.58–0.71). This risk reduction appears to be consistent regardless of any other characteristics like age, sex, index cardiac event, and so on (Critchley and Capewell 2003).

Admittedly, cessation is a troubling task for a large number of smokers. Various strategies and policies have been formed. Notwithstanding, evidence-based treatment for smoking cessation was underused. Physicians should provide a specific plan for smokers after thorough discussion with them.

The safety and effectiveness of adjuvant pharmacotherapy including nicotine replacement, antidepressant drug bupropion, and varenicline is called for question. No significant adverse functions on cardiovascular system have been reported, though, the application must be rational with other strategies' company.

2.1.2.1 Nicotine Replacement Therapy (NRT)

An RCT assessed the safety and efficacy of 10-week aid of transdermal nicotine in patients with cardiovascular disease and found that: (1) The primary endpoints were comparable in the nicotine group as that in the placebo group (5.4 vs 7.9%; 95% CI 1.6–6.5%; $P = 0.23$). (2) Transdermal nicotine significantly lowered the cessation rate after 14 weeks ($p < 0.001$) but this vantage eroded after 24 weeks. Some other small RCTs also confirmed that NRT is safe for quitters with CAD (stable angina, after myocardial infarction) regardless of its possible cardiovascular toxicity (Joseph et al. 1996). In addition, it is of importance to ensure that dosing does not exceed the manufacturer's recommendation and to warn patients to stop using NRT if they relapse to smoking (Mcrobbie and Hajek 2001).

2.1.2.2 Bupropion

Bupropion, approved initially as an antidepressant medicine, showed its strengths in abstinence from cigarette. In a small RCT, at the end of treatment (8–12 weeks), bupropion was associated with a significant increase in point prevalence abstinence

(relative risk 1.21; 95% CI 1.02–1.45) but not continuous abstinence (RR, 1.19; 95% CI 0.97–1.45). However, these effects didn't last for 12 months (Grandi et al. 2013).

2.1.2.3 Varenicline

Varenicline is the latest drug approved by FDA for smoking cessation. An RCT has been conducted in smokers with SCAD. After 12-week use, varenicline showed higher continuous abstinence rate (CAR) than placebo during weeks 9 through 12 (47.0 vs 13.9%; OR 6.11; 95% CI 4.18–8.93) and weeks 9 through 52 (19.2 vs 7.2%; OR, 3.14; 95% CI 1.93–5.11), and no significant difference in cardiovascular outcomes (Rigotti et al. 2010).

A large cohort study evaluated the safety of varenicline and bupropion and they didn't differ in either the primary or secondary endpoint of cardiovascular events when applied to the elderly (Graham et al. 2014).

2.1.3 Weight Control

Obesity has a predisposition to the development and progression of atherosclerosis and coronary heart disease (CHD). As BMI increases, patients are more likely to have hypertension, diabetes, hyperlipidemia, and sleep dyspnea, which are labeled as CAD risk factors as well. What makes this problem vague is that some retrospective researches and meta-analyses have suggested an "obesity paradox". It denotes a trend of lower mortality as weight increases, among patients with CAD, HF, hypertension, or undergoing PCI (Lavie et al. 2009). Further evaluation attributed this puzzling phenomenon to more aggressive management in obese people (Diercks et al. 2006). But it requires further investigations to fully explain this finding.

With regard to the outcome of weight loss, several studies found a trend of better prognosis (revealed by serum biochemical parameters) or noted reduction in CV events and mortality. Thus it is encouraged to lose weight in overweight and obese CHD patients with administration of dietary and physical strategies, despite the obesity paradox.

All these findings, from another angle, call for attention to those underweight patients with CAD.

Alcohol consumption

The relationship between alcohol consumption and CVD is complicated. It is widely accepted that light-to-moderate drinking is associated with the lowest rate of CV events and death, while multiple risks exceedingly outweigh potential benefits in people who have alcohol abuse. Thus, total abstinence isn't preferable and reasonable for patients with CAD. Consensus are well established in different guidelines on the appropriate intake of 1 drink (4 oz of wine, 12 oz of beer, or 1 oz of spirits) for women and 1 or 2 drinks for men (Fihn et al. 2012).

2.2 Part 2: Evidence in Guidelines for Treatment of ACS

Acute coronary syndrome (ACS), according to the definition, consists of three cardiac conditions: ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA). The combination of NSTEMI and UA is non-ST elevation acute coronary syndrome (NSTE-ACS). Contrary to stable coronary artery disease, ACS is an urgent and sometimes a fatal condition that requires immediate medical treatment. Complete management of ACS involves multiple aspects, including pre-hospital care, in-hospital care in different settings, post-hospitalization care, and so on. Limited by the length of this part, we will mainly elaborate on in-hospital care in PCI-available hospitals.

The American Heart Association/American College of Cardiology (AHA/ACC) and European Society of Cardiology have published various guidelines based on clinical evidences. In this part, we will summarize parts of the recommendations from these guidelines and try to update with new evidences.

2.2.1 Guidelines on Treatment of STEMI

AHA/ACC guidelines elaborated on recommendations as whether or not to initiate PCI in different STEMI situations (American College of Emergency 2013) (see Table 2.1), while ESC guidelines provided more details on procedural aspects of primary PCI (Task Force Members Steg et al. 2012) (see Table 2.2).

PCI in elderly STEMI patients

However, there is little mention of PCI in elderly STEMI in the guidelines, as very few studies show the clinical outcomes of PCI in elderly STEMI patients (≥75 years old). Peiyuan et al. (2016) reported in CAMI registry research, which involved 3082 elderly patients, that rates of death were 7.7, 15.0, and 19.9%, respectively, with primary PCI, fibrinolysis, and no reperfusion ($P < 0.001$). The study came to a conclusion that early reperfusion, especially primary PCI, was safe and effective with absolute reduction of mortality compared with no reperfusion.

Stent size selection

It is mentioned in the ESC guidelines that operators performing primary PCIs in

Table 2.2 Concluded result of meta-analysis by Gan et al. (2015)

Items consumed	Amount consumed (g/day)	Percentage of CAD risk reduced (%)
Fruit and vegetable	477	12
Fruit	300	16
Vegetable	400	18

STEMI should be aware of the importance of selecting an appropriate stent size. There is little evidence regarding stent sizes in STEMI patients so far. Nagumo et al. (2016) found that an oversized-stenting approach in patients with STEMI was associated with a higher incidence of ST re-elevation and a lower total ST resolution in a small-scale study including 102 consecutive STEMI patients who underwent primary PCI. Future evidences are needed to establish a detailed recommendation for stent size.

Aspiration Thrombectomy

Aspiration thrombectomy is an interventional procedure in which the thrombus inside a vessel is removed by suction through interventional catheterization techniques. It is a rapid and an effective way of removing thrombi in thromboembolic occlusions of the limb arteries below the inguinal ligament (Oguzkurt et al. 2010). The AHA guidelines stated that manual aspiration thrombectomy is reasonable for patients undergoing primary PCI (IIa, B). The ESC guidelines also stated routine thrombus aspiration should be considered (IIa, B). Nevertheless, strong recent evidences suggest against aspiration thrombectomy. A meta-analysis of 17 trials with 20,960 patients found aspiration thrombectomy before primary PCI is not associated with any benefit on clinical endpoints and might increase the risk of stroke (Elgendy et al. 2015). Jolly et al. (2016) found in a 1-year follow-up of the largest randomized trial of thrombus aspiration that routine thrombus aspiration during PCI for STEMI did not reduce long-term clinical outcomes and might be associated with an increase in stroke. Based on recent evidences, routine aspiration thrombectomy should not be recommended as treatment strategy for STEMI patients.

Antiplatelet and antithrombin therapies

In terms of adjunctive antithrombotic therapy to support reperfusion with primary PCI, both AHA and ESC guidelines made detailed recommendations on types and doses of each medication.

It is suggested in the AHA guidelines that it may be reasonable to administer intracoronary abciximab to patients with STEMI undergoing primary PCI (IIb, B). A randomized evaluation of intralesion versus intracoronary abciximab in 128 patients with STEMI showed that intralesion (IL) versus intracoronary (IC) abciximab did not reduce post-procedure intrastent atherothrombotic burden in patients with STEMI undergoing PCI (Prati et al. 2015). But IL abciximab improved indices of angiographic and myocardial reperfusion compared to IC abciximab (Prati et al. 2015). Large-scale trials are needed to make better comparison between different administration routes of abciximab.

In terms of anticoagulants, the ESC guidelines recommended enoxaparin over unfractionated heparin (UFH) and a GPIIb/IIIa blocker. A prospective registry involving a total of 1720 patients found no significant differences in the rates of in-hospital MACE or major bleeding after pre-hospital initiation of UFH, enoxaparin, or bivalirudin in patients treated by primary PCI for STEMI (Auffret et al. 2016).

Since the publication of the ESC and AHA guidelines on STEMI, there are a number of new antiplatelet and anticoagulant agents approved for clinical use. Cangrelor is a potent, rapid-acting, reversible intravenous platelet inhibitor that was tested for PCI (Steg et al. 2013). In a pooled analysis of three large randomized trials that included 24,910 patients, cangrelor was found to have significantly reduced PCI periprocedural thrombotic complications, although at the expense of increased bleeding (Lu et al. 2014). A recent evidence from a small-scale trial of 32 patients showed cangrelor in combination with ticagrelor resulted in consistent and strong P2Y12 inhibition during and after infusion, which also demonstrated cangrelor may bridge the gap until oral P2Y12 inhibiters achieve effect in real-world STEMI patients undergoing primary PCI (Mohammad et al. 2016).

Sarpogrelate, a specific 5HT2-receptor antagonist, is another novel antiplatelet agent which blocks serotonin-induced platelet aggregation. Yet usage of sarpogrelate in STEMI is rarely reported. Noh et al. (2016) carried out a retrospective cohort study, including a total of 93,876 patients undergoing PCI, and found that sarpogrelate-containing triple antiplatelet therapy demonstrated comparable rates of MACCE prevention compared to the conventional dual antiplatelet therapy (DAPT) after PCI, without significantly increasing bleeding risk during the two-year follow-up period. Further large-scale studies are needed for the evaluation of sarpogrelate.

2.2.2 Guidelines on Treatment of NSTE-ACS

In contrast to AHA and ESC guidelines on STEMI, both AHA and ESC guidelines on NSTE-ACS made more detailed recommendations on early management and pharmacological treatment of NSTE-ACS patients with less emphasis on invasive PCI recommendations. ACC/AHA guidelines on NSTE-ACS provided an algorithm for management of patients with definite or likely NSTE-ACS (see Fig. 2.2) (Amsterdam et al. 2014). As for whether to initiate invasive strategy or the timing of initiating invasive strategy, ESC guidelines gave a clear recommendation using a flowchart based on risk criteria grading (see Table 2.3 and Fig. 2.3) (Roffi et al. 2016).

Multivessel PCI

It is recommended in the AHA guidelines that a strategy of multivessel PCI, in contrast to culprit lesion-only PCI, may be reasonable in patients undergoing coronary revascularization as part of the treatment for NSTE-ACS (IIb, B). It is still unclear whether multivessel PCI is beneficial to NSTE-ACS patients with multivessel lesions. Jang et al. (2015) performed a meta-analysis of eight observational studies with 8,425 patients, finding no significant differences in all-cause mortality and myocardial infarction. However, it is found that multivessel PCI was associated with a significantly lower rate of repeat revascularization (OR 0.75, 95% CI 0.56–1.00). It is concluded that multivessel PCI reduced repeat revascularization without significant benefits in terms of mortality or myocardial infarction at the long-term follow-up in patients with NSTE-ACS and multivessel coronary disease. Since there

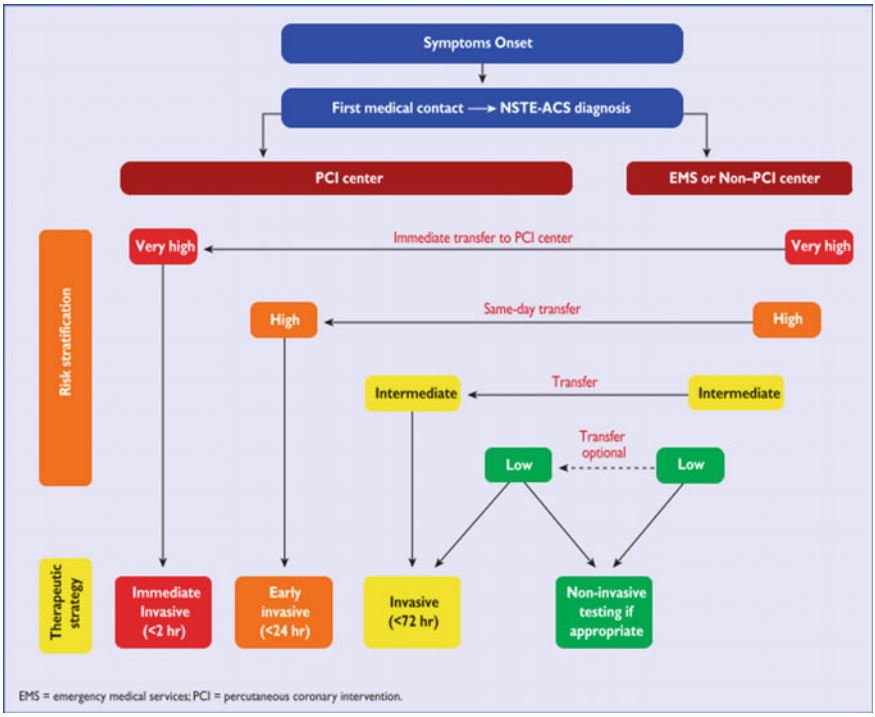

Fig. 2.2 Selection of non-ST-elevation acute coronary syndrome (NSTE-ACS) treatment strategy and timing according to initial risk stratification

Table 2.3 Primary PCI in STEMI (American College of Emergency et al. 2013)

	Class of Recommendation	Level of Evidence
Ischemic symptoms <12 h	I	A
Ischemic symptoms <12 h and contraindications to fibrinolytic therapy irrespective of time delay from FMC (First Medical Contact)	I	B
Cardiogenic shock or acute severe heart failure (HF) irrespective of time delay from myocardial infarction (MI)	I	B
Evidence of ongoing ischemia 12–24 h after symptom onset	IIa	B
PCI of a non-infarct artery at the time of primary PCI in patients without hemodynamic compromise	III: Harm	B

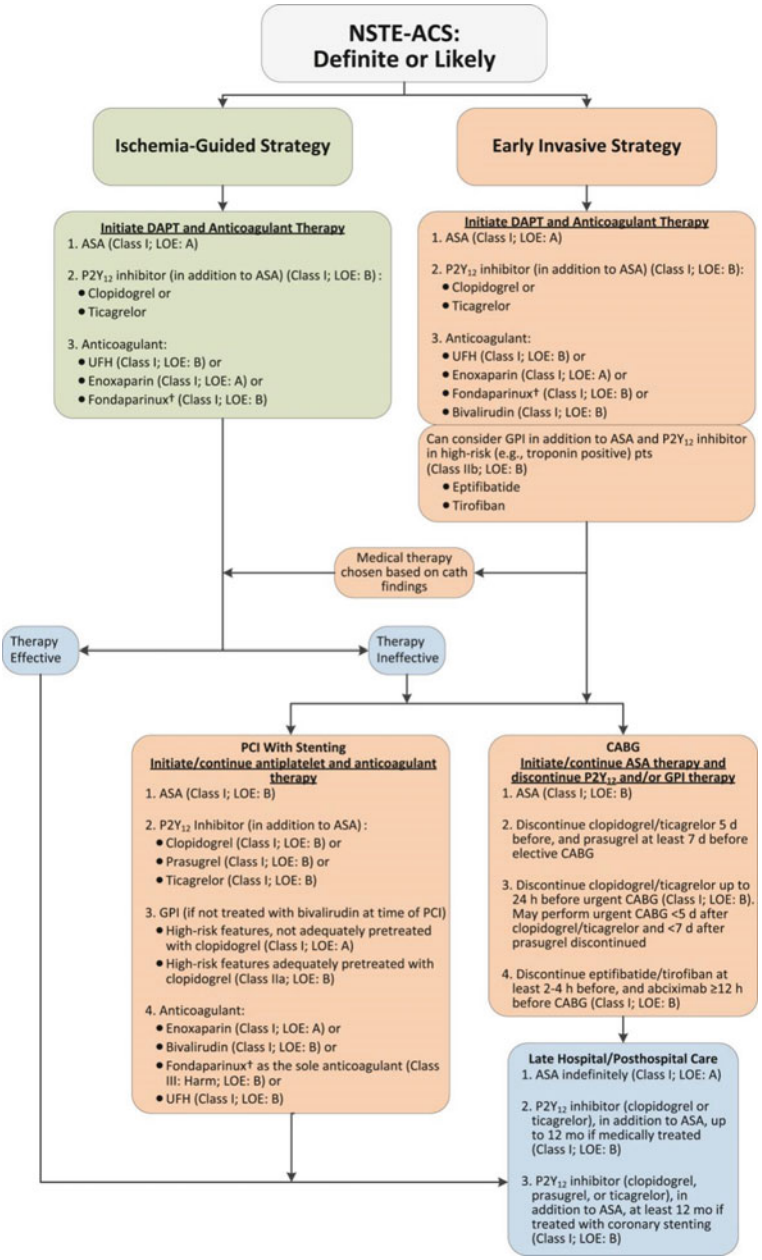

Fig. 2.3 Algorithm for management of patients with definite or likely NSTE-ACS (Worm et al. 2013) (In patients who have been treated with fondaparinux (as upfront therapy) who are undergoing PCI, an additional anticoagulant with anti-IIa activity should be administered at the time of PCI because of the risk of catheter thrombosis. ASA indicates aspirin; CABG, coronary artery bypass graft; cath, catheter; COR, Class of Recommendation; DAPT, dual antiplatelet therapy; GPI, glycoprotein IIb/IIIa inhibitor; LOE, Level of Evidence; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; pts, patients; and UFH, unfractionated heparin)

Table 2.4 Primary PCI: indications and procedural aspects (Task Force Members Steg et al. 2012)

Recommendations	Class[a]	Level[b]
Indications for primary PCI		
Primary PCI is the recommended reperfusion therapy over fibrinolysis if performed by an experienced team within 120 min of FMC	I	A
Primary PCI is indicated for patients with severe acute heart failure or cardiogenic shock, unless the expected PCI related delay is excessive and the patient presents early after symptom onset.	I	B
Procedural aspects of primary PCI		
Stenting is recommended (over balloon angioplasty alone) for primary PCI	I	A
Primary PCI should be limited to the culprit vessel with the exception of cardiogenic shock and persistent ischemia after PCI of the supposed culprit lesion	IIa	B
If performed by an experienced radial operator, radial access should be preferred over femoral access	IIa	B
If the patient has no contraindications to prolonged DAPT (indication for oral anticoagulation, or estimated high long-term bleeding risk) and is likely to be compliant, DES should be preferred over BMS	IIa	A
Routine thrombus aspiration should be considered	IIa	B
Routine use of distal protection devices is not recommended	III	C
Routine use of IABP (in patients without shock) is not recommended	III	A

BMS = bare-metal stent; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; IABP = intra-aortic balloon pump; PCI = percutaneous coronary intervention
[a]Class of recommendation
[b]Level of evidence

is still little new evidence after the publication of both guidelines on NSTE-ACS, future studies on the efficacy and safety issues remain warranted (Tables 2.4, 2.5).

Antiplatelet and anticoagulant therapies

Antiplatelet and anticoagulant therapies are of great importance in NSTE-ACS patients undergoing PCI, as they prepare patients for interventional procedures, reduce ischemic complications, and improve long-term prognosis. In this part, we'll focus on adding new evidences to recommendations with low-to-intermediate level of evidences.

a. ***Fondaparinux***

Fondaparinux is recommended as having the most favorable efficacy–safety profile regardless of the management strategy (I, B), according to ESC guidelines. Recently, in a relatively small study of Chinese NSTE-ACS patients treated with tirofiban which compared fondaparinux and enoxaparin, no statistical difference in ischemic or bleeding outcomes with the use of either fondaparinux or enoxaparin was found (Zhao et al. 2015). Ross Terres et al. (2015) reported in OASIS-5 trial that in Canadian hospital setting, fondaparinux is cost-effective when compared to enoxaparin for the treatment of NSTE-ACS. This result holds both in

Table 2.5 Risk criteria mandating invasive strategy in NSTE-ACS

Very-high-risk criteria
• 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-T wave changes, particularly with intermittent ST-elevation
High-risk criteria
• Rise or fall in cardiac troponin compatible with MI
• Dynamic ST- or T- wave changes (symptomatic or silent)
• GRACE score >140
Intermediate-risk criteria
• Diabetes mellitus
• Renal insufficiency (eGFR <60 mL/min/1.73 m^2)
• LVEF <40% or congestive heart failure
• Early post-infarction angina
• Prior PCI
• Prior CABG
• GRACE risk score >109 and <140
Low-risk criteria
• Any characteristics not mentioned above

. CABG = coronary artery bypass graft; eGFR = estimated glomerular filtration rate; GRACE = Global Registry of Acute Coronary Events; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; MI = myocardial infarction

the immediate post-event period and over the lifetimes of patients. With similar efficacy and safety level plus better cost-effectiveness, fondaparinux seems to be a wiser choice over enoxaparin. Nevertheless, according to AHA guidelines, fondaparinux should not be used as the sole anticoagulant to support PCI in patients with NSTE-ACS due to an increased risk of catheter thrombosis (III, B) (Table 2.6).

b. ***Bivalirudin***

Bivalirudin, a specific and reversible direct thrombin inhibitor (DTI), is recommended in both AHA and ESC guidelines to be a useful anticoagulant. Recent trials and meta-analysis are supportive of guideline recommendations. From the ACUITY trial that included 13,819 patients of NSTE-ACS treated with an early invasive strategy, Geisler et al. (2016) found that treatment with bivalirudin alone significantly reduced major bleeding and improved net clinical outcomes during the upstream medical management phase with comparable rates of MACE.

Table 2.6 Summary of main recommendations regarding pharmacological management from NICE, the ESC and ACCF/AHA

	ESC	ACC/AHA	NICE
Immediate relief	Short-acting nitrate	Sublingual nitroglycerin or nitroglycerin spray (I, B)	Short-acting nitrate
First-line therapy	β-Blocker and/or calcium channel blocker (I, A)	β-Blocker (I, B) non-dihydropyridines or long-acting organic nitrates. Use when BB contraindicated or clinical response is inadequate (I, B)	β-Blocker and/or calcium channel blocker
Second-line	Long-acting nitrate or ivabradine or nicorandil or ranolazine (IIa B)	Dihydropyridines (DHP) (IIa, B) Ranolazine: Use in combination with a BB (IIa, A) When BB used is contraindicated or not tolerated (IIa, B)	Long-acting nitrate or ivabradine or nicorandil or ranolazine
Event prevention	Aspirin 75–150 mg daily (I, A) Clopidogrel in cases of aspirin intolerance. (I, B) Target dose to achieve target LDL level (I, A) ACE inhibitor (or ARB) when LVEF <40%(I, A) or normal LVEF (IIa, B)	Aspirin 75–162 mg daily (I, A) clopidogrel when aspirin is contraindicated (I, B) Use high dose-potent statin (I, A) ACE inhibitor (or ARB) when LVEF <40%(I, A) or normal LVEF (I, B)	Low-dose aspirin Atorvastatin 80 mg to lower non-HDL-cholesterol by >40% ACE inhibitor for patients with diabetes

A meta-analysis of five trials found bivalirudin may confer an advantage over unfractionated heparin in NSTE-ACS while undergoing PCI, reducing major bleeding without increasing stent thrombosis (Farag et al. 2015).

c. ***P2Y12 inhibitors***

It is well established that oral administration of P2Y12 inhibitors is important for NSTE-ACS management, and several novel P2Y12 inhibitors are listed in current AHA and ESC guidelines. A meta-analysis of four randomized clinical trials by Bavishi et al. (2015) found newer oral P2Y12 inhibitors decrease MACE and MI at the expense of a significant increase in the risk of bleeding. In terms of timing of initiation, it is suggested in both guidelines that initiation of P2Y12 inhibitor soon after the diagnosis of NSTE-ACS, namely the pre-treatment upon diagnosis of NSTE-ACS, is recommended. This line of recommendation is supported by multiple major clinical trials and is of rather high level of evidence. However,

there is little evidence comparing the difference between initiation of P2Y12 inhibitors at the time of diagnosis and at the time of angiography. Since no direct evidences are available, Gunton et al. constructed a decision analytic model based on clinical trial data, and concluded that pre-treatment with P2Y12 inhibition is unlikely to be beneficial to the majority of patients presenting with NSTE-ACS (Gunton et al. 2016). Evidences about P2Y12 inhibitors listed in the guidelines are generally consistent, and further clinical investigation into contradictory results is warranted.

d. ***GPIIb/IIIa inhibitors***
Glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitor is another important antiplatelet agent used during PCI. The ESC guidelines recommended that GPIIb/IIIa inhibitors should be considered for bailout situations or thrombotic complications (IIa, C), and that not to administer GPIIb/IIIa inhibitors in patients whose coronary anatomy is unknown (III, A). Recent studies on the effect of GPIIb/IIIa are rare.

e. ***Vorapaxar***
Vorapaxar, a thrombin receptor (protease-activated receptor, PAR-1) antagonist, is yet another novel anticoagulant that can be used in NSTE-ACS patients. There have been several large randomized trials testing the efficacy and safety of vorapaxar usage on NSTE-ACS patients, including the renowned Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial, the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2P-TIMI 50) trial, and so on. However, the results show that the benefit of vorapaxar in addition to aspirin and clopidogrel is modest, while vorapaxar increases bleeding events including intracranial hemorrhage (Roffi et al. 2016). The ESC guidelines made no specific recommendations on vorapaxar, but suggested to "carefully weigh the benefit of vorapaxar and the risk of bleeding". More recent evidence shows older patients had a greater risk for ischemic and bleeding events, while efficacy and safety of vorapaxar in NSTE-ACS were not significantly influenced by age (Armaganijan et al. 2016). Thus, vorapaxar should be used with caution according to current knowledge.

Statins

Both guidelines made clear and strong recommendations on statins usage for NSTE-ACS patients. Besides its lipid-lowering effects, statins have been discovered to have anti-inflammation and antithrombotic properties as well, which is a possible cause for its multiple beneficial effects. It is recommended in ESC guidelines to start high-intensity statin therapy as early as possible, unless contraindicated, and maintain it long term (I, A). Shehata et al. (2015) found in a small-scale study of 140 patients that intensive atorvastatin therapy in NSTE-ACS patients is associated with lower hs-CRP levels and with higher left ventricular ejection fraction after 6 months, with no significant impact on adverse cardiac events. Based on current knowledge, it is necessary to comply with the guidelines recommendations on statins.

Vasospastic angina

In terms of vasospastic angina, the ESC guidelines recommended that calcium channel blockers and nitrates should be considered and beta-blockers must be avoided (IIa, B) (Roffi et al. 2016). A review on pharmacotherapy of vasospastic angina confirmed this line of recommendation, saying that CCBs are recommended as first-line agents for treatment and prevention of vasospastic angina, and that some evidence has shown the benefit of combined non-DHP and DHP CCBs therapy (Harris et al. 2016). Similar recommendations corresponding to the ESC guidelines are also made in the review, with additional introduction of the effects of statins and alpha1-adrenergic antagonists. Further evidences are needed for clinical application of these new agents.

PCI versus CABG

Furthermore, the argument between coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention never stopped. In the setting of NSTE-ACS, PCI's main advantages are faster revascularization of culprit lesion, lower risk of stroke, and deleterious effect of cardiopulmonary bypass on the ischemic myocardium, while CABG more frequently offer complete revascularization in advanced multivessel CAD (Roffi et al. 2016). In the setting of STEMI, although CABG is comparatively rare, CABG may be indicated in patients with anatomy unsuitable for PCI but who have a patent infarct-related artery, as patency of this artery provides time for transferring to the surgical team (Task Force Members Steg et al. 2012). Detailed evidences are provided in both AHA and ESC guidelines. Medical practitioners should be adept at choosing different methods of revascularization according to various settings. Cooperation and consultation between interventional cardiologist and cardiac surgical teams should be well established in order to provide the most in-time, high-quality treatment possible to ACS patients.

Conclusion

Last but not the least, it's always important to remember that management of both STEMI and NSTE-ACS is an integrated body of multiple team works. Due to the length of this part, we chose to only focus on the most effective and core parts of ACS treatment, percutaneous coronary intervention, and protective medications. A complete management of ACS involves timely and accurate diagnosis, making strategic decisions based on risk assessment, pharmacological treatment or revascularization, early and late hospital care, post-hospital discharge care, and so on. Failure of any element above is detrimental to an ACS condition. Although PCI is widely available around the world nowadays, there are still some medical centers where thrombolysis using fibrinolytic agents is still favorable, and there are recommendations accordingly in the guidelines. When it is contraindicated to perform PCI, thrombolysis is once again essential for revascularization of occluded arteries.

The AHA and ESC guidelines on STEMI and NSTE-ACS provided in-depth up-to-date recommendations to the whole procedure of ACS management, and also pointed out evidence gaps that can be filled with later studies or new methods of treatment worth developing in the near future. These guidelines are carefully written and reviewed by experts worldwide, and are indeed worth referring to for most medical practitioners.

2.3 Part 3: Evidence in Guidelines for Treatment of Chronic Stable CAD

The objective of treatment is a combination of both symptomatic and prognostic improvement. Prominent progress has been achieved in medicine and revascularization, though there are controversies and limitations that warranted further investigation. Chronic as CAD is, the management course is a lifelong period. Thus, education, habitual modification, and social support matters a lot for retarding the progression.

2.3.1 Pharmacological Management (See Major Recommendations from Different Guidelines in Table 2.1)

2.3.1.1 Short-Acting Nitrates

Sublingual nitroglycerin or nitroglycerin spray is recommended for immediate relief of angina in patients with SIHD (I, B) (Fihn et al. 2012). Same administration also can be applied to prevent likely ischemic attacks before physical or sexual activity. As for gradually reducing the frequency of episodes, single or combing medicine should be administrated from beta-blockers, calcium channel blockers, long-acting nitrates, and so on.

2.3.1.2 First-Line Anti-anginal Drugs

Beta Adrenoceptor-Blocking Agents

Beta-blocking agents constitute a cornerstone of therapy for stable angina. They reduce myocardial O_2 demand by slowing the heart rate, myocardial contractility, and BP. Furthermore, the slower heart rate in turn increases diastole period, permitting greater coronary perfusion to improve O_2 supply.

Clinical Efficacy in SCAD

Overwhelming evidence has confirmed the effect of beta-blockers in controlling exercise-induced angina, improving exercise capacity, and limiting the frequency of both symptomatic and asymptomatic ischemic attacks. Furthermore, prior trials showed better prognosis of continuingly long-term administration of beta-blocker in either post-MI patients or patients with heart failure. With regard to SCAD, numerous trials (observational or interventional), systemic reviews, and meta-analyses tried to reach a conclusive result. Here we list some evaluations as follows:

1. The Atenolol Silent Ischemia Study (ASIST) trial, one of the most influential RCTs reported that, among asymptomatic or minimally symptomatic patients

with daily life silent ischemia due to CAD, atenolol reduced daily life ischemia and was associated with reduced risk for adverse outcome at 1-year follow-up (Shu et al. 2012).

2. A meta-analysis reviewed 26 trials up to 2010 and concluded that the therapy of beta-blockers has significantly decreased all-cause mortality comparing with no treatment (OR 0.40, 95% CI 0.20–0.79), but no statistical difference in all-cause mortality when compared with neither placebo (OR 0.92, 95% CI 0.62–1.38) nor calcium channel blocker (OR 0.84, 95% CI 0.49–1.44). Similar negative results were reported with regard to fatal and non-fatal acute myocardial infarction, revascularization, and quality of life (Ardissino et al. 1995).

In view of their multiple benefits (anti-ischemic, antihypertension, reinfarction prevention), it is reasonable to consider beta-blockers over CCBs as the initial choice in treating patients with SCAD. Nevertheless, it is reminded that the first-class recommendations in guidelines mostly came from trials performed in selective patients with former myocardial infarction or heart failure. It still lacks clear-cut proof from large randomized clinical trials concerning the efficacy in SCAD.

Calcium Antagonists

The calcium antagonists encompass two major classes: dihydropyridines (DHP) and non-DHP (phenylalkylamines, modified benzothiazepines). They act as non-competitive blockades of the L-type calcium channels in cardiac and smooth muscle membranes. Due to the effect of systemic and coronary vasodilatation, oxygen imbalance can be corrected by reducing afterload and improving myocardial blood flow. Non-DHP can significantly reduce heart rate and contractility, resulting in decrease of O_2 demand. Besides, it is hypothesized that CCB might inhibit atherogenesis for hyperlipidemia-induced changes in the permeability of smooth muscle cells and calcium may play a role in atherogenesis.

Clinical Efficacy in Chronic Stable Angina Several studies have demonstrated the effectiveness of CCBs (nifedipine, verapamil, diltiazem) in alleviating symptoms of angina, both classic angina pectoris and the less frequent vasospastic, or variant angina (Prinzmetal's angina). They improve exercise performance, time to onset of angina and time to ST-segment depression, and decrease the frequency of episodes of angina, or the need of nitroglycerin. Rather complicated results make it unclear to understand its work on outcome of SCAD and its equivalence with other drugs.

(1) Earlier small-scale clinical trials including the APSIS (Angina Prognosis Study in Stockholm), the TIBET(Total Ischaemic Burden European Trial), and IMAGE (International Multicenter Angina Exercise) all reported no difference between CCB and BB in mortality and CV death among patients with stable CAD (Fox K 1996; Rehnqvist 1995; Von 1995). Two trials (TIBBS, IMAGE) suggest beta-blockers were more effective in certain conditions (e.g. reducing morning peak of ischemic activity, applied for people in lower exercise tolerance) (Fox K 1996; Pepine 2003).

(2) The large International Verapamil-Trandolapril Study (INVEST) trial showed a more significant reduction in angina episodes with verapamil than with atenolol, in contrast with prior trials. More important, CCB-treated patients had comparable rates in primary endpoint, mortality, non-fatal MI, non-fatal stroke, CV-related death, and CV hospitalization as those in BB group (Brener et al. 2006).
(3) In The Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study, apart from confirming effectiveness of amlodipine in reducing CV events, it suggested a trend toward less progression of atherosclerosis presented by IVUS ($P = 0.12$), which was especially significant in the subgroup with systolic blood pressures greater than the mean ($P = 0.02$) (Stone et al. 2006).

2.3.1.3 Second-Line Antiangina Therapy

Long-Acting Nitrates

The effect of nitrates results from the vasodilator effect (both evident in systemic and coronary vessels) on ventricular preload reduction, which in turn reduces myocardial wall tension and O_2 requirements. Furthermore, nitroglycerin causes redistribution of blood flow from normally perfused segments to ischemic areas due to increasing collateral blood flow and lowering of LV diastolic pressure. Comparing with BB or CCB, there is no significant difference in the controlling of weekly angina onsets, time to ST-segment depression, total exercise time, and the frequency of sublingual nitroglycerin use.

There is no available evidence from RCTs about their influence on CAD outcomes. So, guidelines recommend long-acting nitrates be used for controlling ischemic occurrences when BB/CCB is contraindicated, intolerated or when it's necessary to add nitrates with them (Fihn et al. 2012).

Ranolazine

Ranolazine acts as an inhibitor of late inward sodium current, then prevents Ca^{2+} overload by inhibiting the sodium-dependent calcium channel, thus reducing ventricular diastolic tension and O_2 consumption.

(1) There is some evidence of its anti-ischemic work from original small-scale RCTs. The ERICA trial identified its work on significantly reducing angina episodes (2.88 ± 0.19 vs 3.31 ± 0.22, $p = 0.028$) and nitroglycerin consumption (2.03 ± 0.20 vs 2.68 ± 0.22, $p = 0.014$) (Chaitman 2004). Dose-related increase in improvement of exercise performance and time to ST-segment depression was observed in the MARISA (Monotherapy Assessment of Ranolazine In Stable

Angina) trial (Kosiborod et al. 2013). Besides, the TERISA trial found it especially significant for patients with high HbA1c to reduce the angina episodes (Melloni and Newby 2008).

(2) The MERLIN-TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes-Thrombolysis in Myocardial Infarction) trial designed to examine the long-term impact and safety of ranolazine in treating post-MI patients, confirmed its noticeable benefits of decreasing recurrent ischemia, but failed to find any difference in primary and major secondary endpoint (cardiovascular death, MI, or severe recurrent ischemia) in comparison with placebo (Vitale et al. 2012).

Trimetazidine

Trimetazidine targets the specific molecule, acetyl-CoA C-acyltransferase (commonly referred to as "3-KAT"), which is an important enzyme of fatty acid beta-oxidation. Thus by acting on 3-KAT, trimetazidine can inhibit fat oxidation and shift cardiac metabolism to more glucose oxidation. Some small RCTs (TRIMPOL II, VASCO-angina, and TACT) to evaluate the efficacy and tolerability in SCAD have been conducted (Vitale et al. 2012; Szwed et al. 2001; Chazov et al. 2005).

(1) In the TRIMPOL II trial, combination therapy of TMZ and metoprolol resulted in an improvement in time to ST-segment depression, total exercise workload, nitrate consumption, and angina frequency as compared to patients receiving placebo plus metoprolol. Equivalent results were found in the VASCO-angina study. Both doses of TMZ (140 and 70 mg/day) significantly increased total exercise duration ($p = 0.0044$ and $p = 0.0338$, respectively) as compared to placebo, albeit no significant difference was found between the two doses.

(2) Some pre-clinical experiments and observational research have pointed out its cardioprotective effects for inhibiting the activity of neutrophil and then improving pre- and pro-conditioning of ischemia (Fox et al. 2008).

Collectively, the present data conclude the consistent view on its benefit of reducing symptom. But due to lack of evidence from large RCTs, the prognostic effect of trimetazidine remains uncertain.

Ivabradine

This drug specifically inhibits sinus node I_f current, leading to lower heart rate and then decreasing oxygen demand without any effect on other aspects like cardiac function or blood pressure.

(1) Clinical trials have offered proof about the efficacy of ivabradine to attenuate ischemic symptom, reduce nitroglycerine use, and improve exercise tolerance during a stress test. In comparison with atenolol, ivabradine showed similar potentials of improving exercise capacity and reducing angina episodes.

(2) Whether ivabradine has advantage of improving outcomes appears to be indefinite. The large BEAUTIFUL trial found out that ivabradine could effectively reduce CV events, mortality, and hospitalization for MI or heart failure (Kolh 2014).

2.3.2 Revascularization

With great advances in technology and adjuvant medicine for periprocedural and long-term use, more CAD patients with various lesions are eligible for revascularization (PCI and CABG). Revascularization is conducted in patients for two similar purposes: symptom relief and events prevention. Albeit elaborate indications in guidelines, practical management must take individual characteristics, preference and compliance, and so on into consideration.

2.3.2.1 CABG

The merit of CABG in symptom attenuation has been revealed in several RCTs. The superiority of CABG to medical therapy in the management of specific subsets of CAD was firmly established in a meta-analysis of seven RCTs, which is still the major foundation for contemporary CABG. It demonstrated a survival benefit of CABG in patients with LM or three-vessel CAD, particularly when the proximal LAD coronary artery was involved (Shaw et al. 2008).

2.3.2.2 PCI

Still, there remains lot of debates over the necessity, the feasibility, and the efficacy of revascularization.

1. In the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation), PCI was at vantage of more freedom from angina at 1-year follow-up but was equivalent by 5 years. In the substudy of this trial, PCI manifested a greater reduction in myocardial ischemia (-2.7 vs -0.5%, $P < 0.0001$) than medical therapy, and more patients exhibited a relevant reduction in ischemia (33 vs 19%, $P = 0.0004$), particularly among those with moderate-to-severe ischemia (78 vs 52%, $P = 0.007$) (Hueb et al. 2004). In contrast, MASS II reported that for patients with multivessel CAD, after one-year follow-up, PCI was not superior to medical treatment owing to a higher rate of short-term events and an increased need for additional revascularization (13.3 vs 8.3%) (Trikalinos et al. 2009).
2. To date, few RCT or meta-analysis has proved survival improvement with application of PCI in SCAD. In the COURAGE trial, among patients with significant

one-, two-, and three-vessel CAD without left main stem (LMS) involved, there was no significant difference in the composite endpoint of death, stroke, or non-fatal MI between OMT and OMT plus PCI at a median follow-up of 4.6 years (HR for the PCI group 1.05, 95% CI 0.87–1.27, P = 0.62). An overview of 61 RCTs enrolling over 25,000 patients tested PCI for the treatment of non-acute CAD. While BMS and DES produced detectable reduction in the need for revascularization, no avail has found in the hard outcomes of death or MI, compared to medical therapy (De Bruyne et al. 2012). Notably, a recent RCT in patients with SCAD and functionally significant stenosis (FFR <0.80) proposed the competitive prognostic profit of FFR-guided PCI. A significant difference in primary endpoint event (4.3% in the PCI group vs 12.7% in the medical therapy group, hazard ratio 0.32; 95% CI 0.19–0.53; P < 0.001) was observed, driven by a lower rate of urgent revascularization in the PCI group than in the medical therapy group (1.6 vs 11.1%; hazard ratio 0.13; 95% CI 0.06–0.30; P < 0.001) (Cohen et al. 2014).

2.3.2.3 CABG Versus PCI

1. Left main CAD

Three RCTs (SYNTAX, LE MANS, and PRECOMBAT) suggested that major clinical outcomes in patients with left main CAD were similar between CABG and PCI at 1- to 2-year follow-up, yet PCI group was related to more revascularization. Further, meta-analysis of eight cohort studies and two RCTs reached the same conclusion in view of endpoints (death, MI, and stroke) and additional revascularization.

2. Multivessel CAD

In SYNTAX trial, at 12-month follow-up, DES implant had equivalent incidence of MACCE with CABG in those with a low SYNTAX score. Yet in those with an intermediate or high SYNTAX score, CABG was superior to DES in the incidence of MACCE. This difference between the two strategies increased with an increasing SYNTAX score. After 3-, 5-year follow-up, the mortality rate was higher in PCI-arm than that in CABG (Hueb et al. 2007).

The MASS II trial is a long-term comparative practice among three therapeutic strategies (medical therapy, CABG, and PCI) in multivessel CAD. At 1-year follow-up, 13.3% of PCI patients underwent additional interventions, compared to only 0.5% of CABG patients. At 5-year follow-up, the primary endpoints occurred in 21.2% of patients after CABG compared with 32.7% treated with PCI and 36% receiving MT alone (P = 0.0026). 15.3, 11.2, and 8.3% of patients experienced non-fatal myocardial infarction in the MT, PCI, and CABG groups, respectively (P < 0.001). But overall mortality showed no differences among three groups. At 10-year follow-up, CABG still remains the best of all in terms of incidence of MI, additional revascularization, and risk of combined events but not in survival (Trikalinos et al. 2009; Hueb et al. 2010; Farkouh et al. 2012).

3. Patients with diabetes

The BARI 2D trial evaluated whether revascularization combined with OMT would be better than OMT alone in patients with SCAD and type 2 diabetes mellitus. All-cause mortality at 5 years' follow-up didn't differ between the two treatments, nor did the rates of MI or stroke. Conversely, in the FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease), the balance tipped in favor of CABG in patients with diabetes and advanced three-vessel coronary artery disease, in that CABG significantly reduced 5-year rates of all-cause death (10.9 vs 16.3%) and myocardial infarction (6.0 vs 13.9%, $p < 0.001$), despite a higher rate of stroke (5.2 vs 2.4%, $p = 0.03$) (Pfisterer 2004).

4. Elderly

Little competitive work of invasive treatment on long-term survival in comparison of medical therapy [91.5 vs 95.9% after 6 months, 89.5 vs 93.9% after 1 year, and 70.6% vs 73.0% after 4.1 years (P = NS)] was revealed in the TIME (Trial of Invasive vs Medical therapy in Elderly patients). Revascularization within the first year improved survival in both invasive strategy ($P = 0.07$) and medical strategy ($P < 0.001$) patients (Juul-Moller 1992).

In summary, guidelines acknowledge the efficacy of revascularization in patients with SCAD. Based on existing data, CABG seems to be more efficient than PCI in most conditions. Initial medical treatment is safe and beneficial for most patients. But patients with moderate-to-severe symptoms should be strongly considered for revascularization. Objective measurement of the lesion should be done with great caution.

2.3.3 Medicine of Prognosis Improvement

2.3.3.1 Antiplatelet Agents

Antiplatelet therapy is important in secondary prophylaxis for patients with cardiovascular diseases. Both AHA/ACC and ESC guidelines recommend low-dose aspirin daily in all SCAD patients (I, A) or clopidogrel as an alternative when aspirin is contraindicated (I, B) (Juul-Moller 1992).

Aspirin

The SAPAT (Swedish Angina Pectoris Aspirin Trial), initially prospectively examined low-dose aspirin in treating patients with stable angina, reported that, in contrast with placebo, aspirin had a significant reduction in primary outcome events of MI and sudden death (34, 95% CI 24–49%, $p = 0.003$) and secondary outcome events (vascular events, vascular death, all-cause mortality, stroke) decreased ranging from

22 to 32% (Berger et al. 2008). A meta-analysis assessed the efficacy and risk of aspirin in treating stable CAD. It was found that low-dose aspirin was associated with a 21% reduction in the risk of overall cardiovascular events (non-fatal MI, non-fatal stroke, and cardiovascular death) (95% CI 0.72–0.88), and similar advantage also worked in each single event, respectively, though with an increase in severe bleeding (odds ratio 2.2, 95% CI, 1.4–3.4) (Lancet 1996).

P2Y12 Inhibitors

Formal data from the CAPRIE trial has showed the equivalence of clopidogrel and aspirin in preventing CV events among patients at ischemic risks (Lemesle et al. 2016). A latest prospective registry study (the CONORO study) pointed out that clopidogrel tended to be used in higher-risk patients with SCAD compared with aspirin: composite of cardiovascular death, myocardial infarction or stroke at 5.8 versus 4.2% ($p = 0.056$). However, after propensity score matching, comparable event rates were observed between the groups (5.9% in clopidogrel vs 4.4% in aspirin respectively, $p = 0.207$) (Squizzato 2011).

To date, clinical trials testing prasugrel, or ticagrelor comparing with aspirin in treatment of SCAD have not been conducted. Thus only clopidogrel is chosen as the second-line therapy in patients with aspirin-intolerant patients or at high ischemic risks.

Dual Antiplatelet Therapy

A meta-analysis found only two available RCTs (CURE and CHARISMA) up to 2009 among patients with existing cardiovascular disease. It demonstrated that clopidogrel plus aspirin increased the risk of bleeding compared with aspirin alone, though yielded less incidence of cardiovascular events. Only the subgroup of patients with acute non-ST-elevated coronary syndrome obtained net benefit (Lamberts et al. 2014). Based on data in hand, dual antiplatelet therapy isn't favored in SCAD.

Antiplatelet Agents Plus VKA

A study aiming at atrial fibrillation patients with SCAD showed that the addition of antiplatelet therapy to VKA therapy was not reducing the risk of recurrent CV events or thromboembolism, but significantly adding more risk of bleeding (Yusuf 2000). With little information on this topic, combination therapy of antiplatelet therapy and oral VKA anticoagulation in certain risky patients calls for further investigation and prudent reassessment.

2.3.3.2 ACEI/ARB

ACEI

ACEI has proved to be effective in protecting cardiovascular system from further progression of atherosclerosis, LV hypertrophy and thrombosis. Hence ACEI are favored in treating patients with hypertension, acute coronary artery disease, and heart failure. As for patients with SCAD and normal LV function, many trials were conducted over the past decades. The HOPE, the EUROPA, and the PEACE trials, all showed that ACEI yielded the advantage of modifying the progression of primary endpoint (cardiovascular death, non-fatal MI, or all-cause death) (Fox 2003; Lindholm et al. 2002; Julius et al. 2004). Some have attributed the cardiovascular protective effects of ACEI to the lower BP level achieved; provided the greater body of supportive evidence, ACEI will probably remain the first line for reducing CV events and mortality in SCAD.

ARB

1. ARBs manifested no inferiority to other types of antihypertensive agents.

The LIFE study compares losartan with atenolol in patients with hypertension and LV hypertrophy. There was a significant reduction of stroke (5 vs 7%; RR 0.87; 95% CI, 0.63–0.89) and composite primary endpoint of death, MI, or stroke in the losartan group (11 vs 13%; RR 0.87; 95% CI, 0.77–0.98). Equivalent result was also found in the subgroup of diabetic patients (Yusuf et al. 2008). In the VALUE study, there was no difference between valsartan and amlodipine in the primary combined endpoint of cardiovascular mortality and morbidity except for a 19% relative increase in MI ($p = 0.02$) and a 15% increase in stroke ($p = 0.08$) in valsartan arm (Lemesle et al. 2017).

2. Mixed results of the comparison between ARB and ACEI have been presented.

The ONTARGET study enrolling patients with stable IHD and preserved LV function provided evidence that ARBs are equal to ACE inhibitors in the prevention of clinical endpoints (RR, 1.01; 95% CI, 0.94–1.09), like cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure, but there was no additive benefit of combination therapy (RR, 0.99; 95% CI, 0.92–1.07) (Baigent 2010).

However, by analyzing different trials and groups of patients, meta-analyses showed controversial conclusions. Some stressed that ACEIs have favorable effects on all-cause mortality, non-fatal MI, and stroke, while ARBs are only associated with reduction of stroke. Others reputed that ARBs have the equivalent potential for reducing the risk of all-cause death, new-onset HF, stroke, and IHD. The latest result from a prospective registry on stable CAD (the CORONOR study) found that a significant proportion of stable CAD patients are treated with ARB rather than with ACEI in modern practice. ARB shows similar outcomes of the combined endpoint

(cardiovascular death, myocardial infarction, stroke) (HR 0.95, 95% CI 0.69–1.31, p = 0.765) (ACCORD Study Group 2010).

Overall, with a substantial amount of evidence, ARBs are recommended for patients with ACEIs intolerance.

2.3.3.3 Beta-Blockers

As mentioned above, beta-blocking agents demonstrate their combined advantages of not only alleviating symptoms but also preventing events (mortality reduction and reinfarction prevention). Treatment with beta-blockers after acute coronary syndrome proves to be associated with reduced MACE and mortality. However, no large trials aiming at the influence in prognosis of SCAD have been performed. From substantially direct and indirect proofs, guidelines acknowledge the effects of beta-blockers for better prognosis.

2.3.4 Risk Factors Management

Until now, there is no evidence from large RCTs, specifically in patients with SCAD, examining the benefit of lifestyle modifications, including regular physical activity, healthy diet, and weight loss, but overall results in other populations (like people with no CVD or post-MI patients) show consistent results. So these strategies are considered to be positive when applied to patients with SCAD.

2.3.4.1 Overweight and Obesity

Obesity is considered to predispose the development and progression of atherosclerosis and coronary heart disease (CHD). Although lacking large-scale RCT to specify the association between obesity and prognosis of SCAD, consistent proof within the patients with no CAD or post-MI calls for weight control for the same purpose.

2.3.4.2 Cigarette

Still, few large RCTs have been performed in SCAD, but formal results strongly suggest that cigarette cessation is an effective strategy of secondary prevention.

2.3.4.3 Dyslipidemia

Patients with SCAD are supposed to take good administration of serum lipid level, starting with both diet and lifestyle adjustment. Prognosis can be further improved

thanks to the cholesterol-lowering drug (statins in most condition). A total of 26 RCTs were included in the large cholesterol treatment trialists (CTT) analysis. The consequence of statin treatment is marked as 10% proportional reduction in all-cause mortality (RR 0.90, 95% CI 0.87–0.93; $p < 0.0001$), and 20% proportional reduction in CAD death (RR 0.89, 99% CI 0.81–0.98; $p = 0.002$) per 1.0 mmol/L (40 mg/dL) LDL-C reduction (Rosendorff et al. 2015).

Whether a goal of <70 mg/dL or <100 mg/dL is better has been called for question. According to the ESC/EAS guidelines, target of LDL-C is based on the risk stratification of cardiovascular disease.

Moreover, for patients with existing CAD (identified as high risk), international guidelines recommend same goals as LDL-C <1.8 mmol/L (70 mg/dL) or 50% LDL-C reduction when target level cannot be reached. For this purpose, the use of a high-dose statin is recommended by AHA/ACC and NICE guidelines.

2.3.4.4 Hypertension

BP Goal

Of what impact BP reduction acts on the balance of O_2 demand and supply is quite intricate. And whether the lower BP goal is appropriate for the treatment of CAD is still a heated debate.

The ACCORD trial compared two different BP goals in diabetic patients at high CVD risks. Intensive therapy (targeting a systolic pressure of <120 mmHg) failed to reduce the primary composite outcome (hazard ratio 0.88; 95% CI 0.73–1.06; $P = 0.20$) and overall mortality (hazard ratio, 1.07; 95% CI, 0.85–1.35; $P = 0.55$), as compared with standard therapy (targeting a systolic pressure of <140 mmHg), while the serious adverse effect of medicine occurred significantly more in the intensive treatment ($p < 0.001$) (Lima et al. 2013). Relevant committees reconsidered BP control as secondary prevention of diabetes and recommended a systolic pressure of <140 mmHg in replacement (Camafort 2011).

Based on considerable amount of the statistics from epidemiological studies, observational, or interventional trials, a commonly admitted BP goal is <140/90 mmHg in general, <140/80 mmHg in patients with DM, and <130/80 mmHg in those with CKD (Camafort 2011).

Drug Choice in SCAD

AHA/ACC/ASH scientific statement on treatment of hypertension in patients with coronary artery disease recommends: The patients with hypertension and chronic stable angina should be treated with a regimen that includes: (a) Beta-blocker in patients with a history of prior MI; (b) An ACE inhibitor or ARB if there is prior MI, LV systolic dysfunction, diabetes mellitus, or CKD; and (c) A thiazide or thiazide-like diuretic (Class I; Level of Evidence A) (Camafort 2011).

2.3.4.5 Diabetes

Adverse Effects

From the MASS II study, patients with stable multivessel CAD and preserved left ventricular ejection fraction, all of the three therapeutic regimens (medical therapy, CABG, and PCI) had higher rates of overall mortality (32.3 vs 23.2%, $p = 0.024$) and cardiac-related deaths (19.4 vs 12.7%, $p = 0.031$) among diabetic than those in non-diabetic patients (Frasuresmith and Lespérance 2008).

Glucose Goal

It is concluded from the FRENA registry that the incidence of subsequent ischemic events was significantly lower in patients with mean HbA1c levels <7.0% (<53 mmol/mol) than in those with HbA1c levels >7.0% (>53 mmol/mol) in patients presenting with coronary artery disease (rate ratio 0.4; 95% CI 0.2–0.8) (Shibeshi et al. 2007).

Several meta-analyses revealed 15–17% reductions in the incidence of non-fatal myocardial infarction in those exposed to tight glucose control.

All in all, HbA1c levels <7.0% still remains the general target for good glucose control. In some situations, aiming for lower HbA1c levels may be appropriate.

2.3.4.6 Psychological Problems

Patients suffering from psychological problems seem to have increased CV risk and mortality. Depression, anxiety, panic attacks, stress are all revealed to be more or less related to increase onset CAD and worsen its prognosis (Chen et al. 2013; Frasuresmith and Lespérance 2003; Blumenthal et al. 2003).

Most common and concerning of them is major depression. Depression appears to increase the risk for cardiac morbidity and mortality in patients with ACS, or undergoing PCI or CABG (Frasuresmith et al. 1993; Burg et al. 2003; Whooley et al. 2011; Li et al. 2013; Gurfinkel et al. 2004; Udell et al. 2013). Numerous observational studies have also demonstrated an association between depression and SCAD. Possible mechanism lies in biological change in immune (inflammatory factors), endocrine (HPA axis), and neural system on the one hand. On the other hand, depression is often linked with other coexisting risk factors like smoking, unhealthy diet, less exercise and lack of adherence. Thus it is thought to be a potential mediator in some opinions. But contrary conclusions were reported in different cohort studies even after covariates being adjusted.

Until now, there is little supportive evidence from RCTs on the protective effect of either counseling or antidepressant treatment. From the ENRICHD trial, for acute MI patients with depression and/or low social support, those receiving invention

(psychotherapy and/or medicine) got significantly reduction in depressive symptoms (49 vs 33%), but not in reinfarction or death as compared with usual care people.

2.3.4.7 Alcohol Consumption

Light-to-moderate drinking assumes benefit of decrease in CV events and death, whereas multiple risks exceedingly outweigh potential benefits in people who have alcohol abuse. Thus patients are encouraged to limit their daily alcohol consumption as 1 drink (4 oz of wine, 12 oz of beer, or 1 oz of spirits) for women and 1 or 2 drinks for men (Fihn et al. 2012). Moreover, it is not an excuse for non-drinkers to start it in case of the potential addition risk.

2.3.4.8 Influenza Vaccination

A number of epidemiologic surveys and observational studies found MI occurred more frequently during the annual influenza season, suggesting that influenza vaccine may act as a method of secondary prevention in coronary disease. The FLUVACS (flu vaccination in acute coronary syndromes and planned percutaneous coronary interventions Study), focusing on the outcome of vaccine in MI patients, showed that vaccination had significantly reduced the primary endpoint of CV death (6 vs 17%, RR 0.34; 95% CI 0.17–0.71; P = 0.002) at 1-year follow-up. Triple composite endpoint were also lower as compared with control group (22 vs 37%, hazard ratio 0.59, 95% CI 0.4–0.86 P = 0.004) [106]. Further analysis from a meta-analysis of six RCTs also admitted the relationship between vaccination and a lower risk of major adverse cardiovascular events (2.9 vs 4.7%; RR 0.64, 95% CI 0.48–0.86, p = 0.003, from published trials), which is more significant among patients with recent ACS. Nevertheless, a large RCT is warranted to provide sound evidence on whether influenza vaccine protects against ischemic episodes and acute coronary syndromes (Udell et al. 2013).

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