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Miao Wang *Editor*

Coronary Artery Disease: Therapeutics and Drug Discovery

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Chapter 1
Coronary Artery Disease: From Mechanism to Clinical Practice

Chunli Shao, Jingjia Wang, Jian Tian and Yi-da Tang

Abstract In most developed countries, coronary artery disease (CAD), mostly caused by atherosclerosis of coronary arteries, is one of the primary causes of death. From 1990s to 2000s, mortality caused by acute MI declined up to 50%. The incidence of CAD is related with age, gender, economic, etc. Atherosclerosis contains some highly correlative processes such as lipid disturbances, thrombosis, inflammation, vascular smooth cell activation, remodeling, platelet activation, endothelial dysfunction, oxidative stress, altered matrix metabolism, and genetic factors. Risk factors of CAD exist among many individuals of the general population, which includes hypertension, lipids and lipoproteins metabolism disturbances, diabetes mellitus, chronic kidney disease, age, genders, lifestyle, cigarette smoking, diet, obesity, and family history. Angina pectoris is caused by myocardial ischemia in the main expression of pain in the chest or adjoining area, which is usually a result of exertion and related to myocardial function disorder. Typical angina pectoris would last for minutes with gradual exacerbation. Rest, sit, or stop walking are the usual preference for patients with angina, and reaching the maximum intensity in seconds is uncommon. Rest or nitroglycerin usage can relieve typical angina pectoris within minutes. So far, a widely accepted angina pectoris severity grading system included CCS (Canadian Cardiovascular Society) classification, Califf score, and Goldman scale. Patients with ST-segment elevated myocardial infarction (STEMI) may have different symptoms and signs of both severe angina pectoris and various complications. The combination of rising usage of sensitive MI biomarkers and precise imaging techniques, including electrocardiograph (ECG), computed tomography, and cardiac magnetic resonance imaging, made the new MI criteria necessary. Complications of acute myocardial infarction include left ventricular dysfunction, cardiogenic shock, structural complications, arrhythmia, recurrent chest discomfort, recurrent ischemia and infarction, pericardial effusion, pericarditis, post-myocardial infarction syndrome,

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venous thrombosis pulmonary embolism, left ventricular aneurysm, left ventricular thrombus, and arterial embolism.

Keywords Epidemiology · Risk factors · Clinical presentation · Complication · Pathophysiology

1.1 Epidemiology

In most developed countries, coronary artery disease (CAD) is one of the primary causes leading death. The primary cause of CAD is the atherosclerosis of coronary arteries. The word "atherosclerosis" is the combination of two Greek words, "athero" and "sclerosis", which mean "gruel" and "hardening", respectively. Though during the last 40 years, a decrease in the global coronary heart disease (CHD) mortality has been seen. From 1990s to 2000s, mortality caused by acute MI declined up to 50%. Of all the cardiovascular disease (CVD) cases, nearly one-third to 50% were caused by CHD (Rosamond et al. 2008; LloydJones et al. 2010; Nichols et al. 2014). Each year, more than four million people die of CHD in the 49 countries of Europe and Northern Asia. Also, about 1.5 million Americans suffer from heart attack or stroke yearly, which results in around 250,000 deaths.

1.1.1 Prevalence

From the report on The 2010 Heart Disease and Stroke Statistics update of the American Heart Association (LloydJones et al. 2010), despite the significant increase in CVD deaths since 1990, age-standardized death rate of the same period fell by 22% instead, which was mainly contributed by shifting age demographics and causes of death worldwide.

In a 2009 report, which made use of the NHANES data, MI prevalence of middle-aged individuals (35–54 years) was compared by sex from 1988 to 1994 and 1999 to 2004 (Towfighi et al. 2009). In this report, it showed a greater MI prevalence in both time periods (2.5 versus 0.7 and 2.2 versus 1.0, respectively) in men than women. Prevalence of anatomic CHD of both general population and military personnel has been documented to decrease *over time* according to autopsy data.

Based on the comparison of autopsy data between the periods 1979 to 1983 and 1990 to 1994, the prevalence of significant anatomic CHD fell in both male and female aged 20–59 subjects, 42%–32% and 29%–16%, respectively (Roger et al. 2001). Yet the prevalence showed no difference for those over 60.

An autopsy analysis including 3832 United States military personnel, who died of combat or unintentional injuries between October 2001 and August 2011, and of whom 98% were male, with a mean age of 26, showed a 8.5% prevalence of CHD (Webber et al. 2001). Compared with the autopsy-documented CHD prevalence

shown during the Korean War in the 1950s (77%) and the Vietnam War in the 1960s (45%), a significant decrease would be seen.

1.1.2 Incidence Demographics

The original Framingham Study cohort with 44 years' follow-up displayed that the lifetime risk of developing CHD was 49% and 32% for 40 years old men and women, respectively, For CHD free people who were at age 70, the nontrivial lifetime risk of developing CHD was 35% and 24% for men and women, respectively.

Both the longevity and age-specific mortality from CVD, CHD, and stroke have been improved since 1975. Yet still, high prevalence and treatment cost are the principal features of CVD and its related complications. One cohort study, which included over 1.9 million people, who were 30 or above, free of known baseline CVD, suggested that neither myocardial infarction nor stroke were the majority of initial CVD presentations (Kannel 1987). Angina, heart failure, peripheral arterial disease, transient ischemic attack, and abdominal aortic aneurysm, along with some less common manifestations, represented 66 percent of the initial CVD presentations based on a median of six years' follow-up.

Though for both genders, the incidence increases greatly with age, women apparently lag behind men, 10 years for total coronary events and 20 years when it comes to more serious manifestations of coronary disease, such as MI and sudden death, yet as people grow older, the incidence of sex ratio narrows progressively (LloydJones et al. 2010). The incidence of women aged 65–94 tripled compared to ages 35–64, and it doubled in men. For women who are menopausal, the rates of incidence and severity of coronary disease tripled of those the same age.

1.1.3 Temporal Trends

In developed countries, the incidence of CHD has declined with time. An epidemiologic follow-up study of 10,869 patients from 1971 to 1982 and the other one that consisted of 9774 patients from 1982 to 1992 were included in NHANES I (Ergin et al. 2004), according to which the CHD incidence descended to 1.14% cases from 1.33%.

1.1.4 International Trends

The decline of heart disease mortality that has been seen in America and regions with relatively advanced economies and health care systems does not apply to the whole world. Despite their counties' income level, the number one cause of death

of patients is ischemic heart disease. And between 1990 and 2020, nearly 29% and 48% increase in coronary heart disease mortality, respectively, for women and men from developed countries could be expected according to the report. For women and men in developing countries, the corresponding estimated rises were 120 and 137% (Yusuf et al. 2001).

Together with the mortality associated with initial CVD event improvement is the rapidly increased prevalence of CVD in developing countries. Also along with the growth of population worldwide, the global burden of CHD was estimated to rise by 29% due to the increases in therapy and longevity (Goyal and Yusuf 2006). Furthermore, markedly regional variation was showed in CHD mortality; according to the 2010 data, while South Asia possess the largest number of CHD death, Eastern Europe and Central Asia have the highest rate of CHD mortality.

In China, what comes along with economic development is an epidemiological transition. Every year more than 1 million people die of ischemic heart disease (IHD), which means the mortality caused by IHD has risen more than double during the past two decades (Yang et al. 2013; Omran 1971). Number of individuals with myocardial infarction will rise to 23 million by 2030 based on the estimation of World Bank (The World Bank 2013), with the trend to accelerate. Improvements of implementing policies have been executed with financial barriers reduced, numbers of hospitals and physicians increased to develop the Chinese medical care system, while the epidemiology's changing (Chen 2009; Ministry of Health of People's Republic of China 2012). Yet during the last ten years, no definition of clinical profiles, management, and outcome of patients with this disorder found in any national representative studies, even though acute myocardial infarction being such crucial in China, particularly ST-segment elevation myocardial infarction (STEMI) accounting for 80% of such events in the country. A retrospective analysis of hospital records named China PEACE-Retrospective AMI Study and lasted from 2006 to 2011 assessed the trends in STEMI management and outcomes in China during the past decade. For both 30-day acute MI hospital mortality and readmission rate of Medicare beneficiaries 65 years of age, important regional differences was found existing. Thus, performance may be improved with the reasons of such differences understood.

1.1.5 STEMI or Non-STEMI

Over the past decade, incidence rate of STEMI has dropped whereas the rate of non-ST-elevation ACS ascended in the United States Community. MI presentations contribute approximately 25–40% STEMI so far. The non-ST elevation MI compared with ST elevation MI relatively increased over time (Furman et al. 1975; Rogers et al. 1990; Roger et al. 2010). A report including 2.5 million MIs from 1990–2006 from The National Registry of Myocardial Infarction (Rogers et al. 1990) showed that the proportion of NESTEMI, accounted for 59% of MIs, and that was 19% in 1994. And this variation was related to the incidence of STEMI's certain decline and rate of NSTEMI's increase or remain unchanged (Roger et al. 2010). The

mortality rates from STEMI, in-hospital (nearly 5–6%) and 1-year (nearly 7–18%), have declined remarkably in association with a significant raise in the frequency of care, which consist of guideline directed medical therapy (GDMT) and interventions ("defect-free" care).

1.2 Risk Factors

Risk factors of CHD exist among many individuals of the general population; for individuals with one or more risk factors, over 90% of CHD events would eventually happen (Yusuf et al. 2004; Vasan et al. 2005; Stamler et al. 1999). According to the report from three observational studies, systolic blood pressure ≥140 mmHg/diastolic blood pressure ≥90 mmHg, total cholesterol ≥240 mg/dL (≥6.22 mmol/L), diabetes, obesity, and smoking were defined as the five major CHD risk factors, which caused approximately an over 50% of cardiovascular mortality (Patel et al. 2015) 0.87% (men aged 40–59 in the MRFIT trial) to 100% (women aged 18–39 in the Framingham Heart Study) subjects dying of CHD exposed to at least one risk factor.

Meanwhile, a much lower incident rate of CHD can be predicted among people without major risk factors. In Framingham Heart Study and the Third National Health and Nutrition Examination Survey (NHANES III), the frequency and predictive value of the five major risk factors were evaluated. The percentage of patients having one to two elevated risk factors is nearly 60% for men and 50% for women, and for those with at least one borderline risk factor (defined as low density lipoprotein cholesterol (LDL-C) 100–159 mg/dL [2.6–4.1 mmol/L], high density lipoprotein cholesterol (HDL-C) 40–59 mg/dL [1.0–1.5 mmol/L], blood pressure 120–139/80–89 mmHg, smoking history and impaired fasting glucose without overt diabetes), is 26% and 41%, respectively. Apart from women aged 35–40 (8.9%) or 45–54 (3.7%), only 0–0.4% had none of elevated or borderline risk factor. This cohort also evaluates the frequency of "borderline" risk factors (Vasan et al. 2005). The incidence of CHD events is nearly 8% for patients with multiple borderline risk factors, while it rarely happens to patients with none.

Studies of both Western and Asian population display a rise in the risk when multiple risk factors exist (Vasan et al. 2005; Jackson et al. 2005; Lowe et al. 1998; Asia Pacific Cohort Studies Collaboration 2005). Take the general principles in ESTABLISHED RISK FACTORS FOR ATHEROSCLEROTIC CVD as example. Almost all cases of CHD are caused by atherosclerosis, which processes as follows: fatty streaks in adolescence, plaques in early adulthood, thrombotic occlusions, and coronary events in middle age and after. For coronary arteries and other arterial beds, when various factors take concerted actions, the risk of atherosclerotic plaques rises (Wilson 1994). Adult patients with dyslipidemia, hypertension, and diabetes can use risk factor assessment as therapy guidance, while risk of coronary disease events can be helpfully estimated by using multivariate formulations (Wilson et al. 1998; Ridker 1999).

1.2.1 Risk Factor Prevalence

It has been a long time that in emerging nations, the prevalence of risk factors remains strange and/or neglected in the literature. A national representative cohort of Chinese showed a low overall prevalence of CVD (1.8% and 1.1% in males and females, respectively) (Yang et al. 2012). Traditional CVD risk factors showed a much higher prevalence; followings are the prevalence of risk factors for male and female, respectively: overweight or obese—36.7 and 29.8%, hypertension—30.1 and 24.8%, dyslipidemia—64 and 67.4%, and hyperglycemia—26.7 and 23.6%. With the presentation of risk factors, the odds of CVD increased (odds ratio 2.4, 4.2, 4.9, and 7.2 for 1, 2, 3, and 4 or more risk factors, respectively, compared with no risk factors) (Yang et al. 2012). The result indicated that without medical intervention and effective lifestyle, the incidence and prevalence of CVD in China may rise significantly.

Despite the abstruseness of CVD risk factors prevalence, as the improvement of awareness and diet and lifestyle, prevalence of established risk factors has changed. Reports from NHANES show that from 1960 to 2000, the prevalence of obesity (body mass index $\geq$ 30 kg/m^2) rises to 30% from 15%. Meanwhile, the diagnosed diabetes increased to 5% from 1.8%, especially obvious in obese population. On the contrary, there are other cardiovascular risk factors declined significantly, with smoking 39–26%, hypertension (blood pressure $\geq$140/$\geq$90 mmHg) 31–15%, and serum total cholesterol $\geq$240 mg/dL (6.2 mmol/L) drop from 34 to 17%. These changes were associated with the improved usage of lipid-lowering drugs and antihypertensive medications, occurring among all weight groups. Also, seven ideal cardiovascular health metrics have been promoted by AHA, which includes physical activeness, no smoking, normal blood pressure, normal blood glucose level, normal total cholesterol level, normal weight, and healthy diet.

Among participations in NHANES (1988–1994), all seven metrics were achieved by only 2%. Compared to those achieving none or one metric, people with six or seven metrics had lower cardiovascular mortality (adjusted harzard ratio [HR] 0.24, 95% confidence interval [CI] 0.13–0.47) and overall mortality (adjusted HR 0.49, 95% CI 0.33–0.74). In NHANES (1999–2002), people with five or more metrics had lower cardiovascular mortality (adjusted HR 0.12, 95% CI 0.03–0.57) compared to people with none.

1.2.2 Hypertension

A well-established risk factor for adverse cardiovascular outcomes (mortality from CHD and stroke) is hypertension (Miura et al. 2001; Lewington et al. 2002). Patients with hypertension have higher lifetime risk of developing CVD. The INTERHEART study showed that of the population-attributable risk of first MI, hypertension contributed 18% (Yusuf et al. 2004). Both duration and degree of hypertension are risk factors.

1.2.3 Lipids and Lipoproteins

Lipids (mainly cholesterol and triglycerides) are compounds that involve in water. They need apolipoproteins or apoproteins to transport in blood. Also in the INTERHEART, 49% of the population-attributable risk of a first MI was contributed by dyslipidemia,which was defined as a raised apo B to apo A-1 ratio) (Yusuf et al. 2004). Lipoprotein metabolism Disturbances are usually familial, with Lp (a) excess (alone or with other dyslipidemia), combined hyperlipidemia, and hypertriglyceridemia with hypoalphalipoproteinemia being the most common ones. With the given of primary and secondary prevention, coronary events and mortality can be reduced as the total and LDL-cholesterol levels decrease (mainly all with statins) based on randomized trials (Shepherd et al. 1995; Downs et al. 1998; Sacks et al. 1996). Statins therapy contributes to LDL-cholesterol lowering may as well as other factors improvement.

1.2.4 Diabetes Mellitus

Atherosclerotic cardiovascular disease is related to all of insulin resistance, hyperinsulinemia, and elevated blood glucose (Kannel and McGee 1979a, b; Almdal et al. 2004; Reaven 1988; Zavaroni et al. 1989; Singer et al. 1992; Gerstein et al. 1999; Al-Delaimy et al. 2004). In the INTERHEART, of the population-attributable risk of a first MI, 10% was contributed by diabetes ((Yusuf et al. 2004). Other than being a risk factor, compared to nondiabetic, diabetics have a greater burden of hypertension, obesity, increased total-to-HDL-cholesterol ratio, hypertriglyceridemia, and elevated plasma fibrinogen. It has been elevated to the maximum risk kinds since it was pointed out in the 2002 National Cholesterol Education Program, specific diabetes was reported a CHD risk equivalent. According to the guidelines published by the National Cholesterol Education Program and the sixth Joint National Committee, coronary risk factors in diabetics should be treated aggressively (Miura et al. 2001; National Cholesterol Education Program (NCEP) 2002). Strong evidence shows the value of treating serum cholesterol and hypertension in patients with diabetes aggressively.

1.2.5 Chronic Kidney Disease

Mild to moderate renal dysfunction are now proved to be associated with substantial increase in CHD risk as well as end-stage renal disease (Gansevoort et al. 2013). According to the ACC/AHA 2004 practice guidelines, chronic kidney disease was a CHD risk equivalent (National Kidney Foundation 2002; Antman et al. 2006a). The annual cardiac death rate of patients with no chronic kidney disease (CKD) and ischemia was 4.5, 11% for those who had both.

1.2.6 Age and Genders

The contributions of CVD development appear to include age, and each additional decade of life was associated with an approximate doubling of the risk of vascular disease: 51–60 years 3.5%, 61–70 years 7.15, 71–80 years 13%, 81–90 years 22.3%, and 91–100 years 32.5%.

Male gender alone may contribute to the risk of CHD, although the potential mechanisms for such risk are not well understood. Several population studies have identified male gender as a risk factor for higher rates of CHD and CHD-related mortality. from the ONTARGET and TRANSCEND study populations, females had approximately 20% lower risk than males for all major cardiovascular endpoints including cardiovascular death, myocardial infarction (MI) and a combined endpoint of death, MI, stroke, and heart failure hospitalization (adjusted relative risk [RR] 0.81, 95% CI 0.76–0.87) (Kappert et al. 2012).

1.2.7 Family History

Family history alone also could contribute to CHD, especially for the young who have the family history of premature disease (Sesso et al. 2001; Andresdottir et al. 2002; Roncaglioni et al. 1992; Lloyd-Jones et al. 2004; Murabito et al. 2005; Sivapalaratnam et al. 2010; Otaki et al. 2013). It is generally agreed that first-degree relative such as parent or sibling suffering from atherosclerotic CVD or dead from CVD indicates a remarkable family history, even prior to age 55 (males) or 65 (females) (Patel et al. 2018). For people who have two or more first-degree relatives die of premature cardiovascular disease, the incidence of CVD increased 3 times before 50. The Framingham Offspring Study started an analysis to explore the reliability of self-reported family history of CHD and risk factors for CHD (Sivapalaratnam et al. 2010), and the findings were noted as follows: For family histories of hypertension, diabetes, and hypercholesterolemia, the positive statement's value for prediction was over 75%, while for cardiac death, it was 66% and 47%, respectively, for fathers and mothers. When it came to a negative statement, for family history of cardiac death or diabetes, the predictive value was over 90%, yet for family history of hypertension or hypercholesterolemia, less than 60%.

1.2.8 Risk Factors in Childhood

Cardiovascular risk factors in childhood can be recognized and used to predict the subsequent development of CHD (Li et al. 2003; Raitakari et al. 2003; Davis et al. 2001).

1.2.9 Lifestyle Factors—Cigarette Smoking

Cigarette smoking is an important and reversible risk factor for CHD. Compared with nonsmokers, subjects who smoke no less than 20 cigarettes every day have a higher incidence of myocardial infarction, six times increased for women while 3 times for men (Njølstad et al. 1996; Prescott et al. 1998). Of the population-attributable risk of a first MI, 36% was led by smoking in the INTERHEART (Yusuf et al. 2004). On the other hand, a study of smokers who had MI showed that the risk of recurrent infarction decreased by 50% for those with one year's smoking cessation; for those with two years, the risk was normalized to that of nonsmokers (Wilhelmsson et al. 1975). Patients benefit from smoking cessation no matter how long or how much they smoked previously.

1.2.10 Diet

The risk of CHD may also be contributed by high glycemic index (GI) or glycemic load (GL) diets. Increasing evidence points out that the risk of CHD and stroke and the consumption of fruit and vegetable have an inverse correlation. According to the meta-analysis of seven prospective cohorts, every additional daily portion of fruit could decrease the risk of stroke by 11%; yet no similar effect found in vegetable (Dauchet et al. 2005). While according to the INTERHEART study, 14% of population-attributed risk of first MI was caused by lacking of daily fruit and vegetables consumption (Yusuf et al. 2004). Significant controversy exists regarding the types of dietary fat and the associated risks of CHD (Chowdhury et al. 2014; de Souza et al. 2015). In a 2014 meta-analysis, no significant association was identified between types of dietary fat (i.e., saturated, monounsaturated, or polyunsaturated) and risk of CHD (Chowdhury et al. 2014). Higher risks of CHD have been associated with higher red meat and high-fat dairy products' consumption. Compared to low fiber consumption, the reduced risk of CHD and stroke is associated with high intake of fiber. The reduction in risk for MI was associated to an additional 10 g fiber intake per day (relative risk 0.81, 95% CI 0.66–0.99) (Rimm et al. 1996; Wolk et al. 1999). A neutral effect on the development of CVD was found in both caffeinated and non-caffeinated coffee intake (Floegel et al. 2012). Both risk of acute coronary events and CHD mortality have an inverse correlation with high serum concentrations of enterolactone and high diet putative biomarker of fiber and vegetables.

1.2.11 Obesity

It is reported that obesity is the risk factor for atherosclerosis, CHD, hypertension, insulin resistance and glucose intolerance, hypertriglyceridemia, and lower levels of

HDL-C (Eckel et al. 2004; Calle et al. 1999; Wolk et al. 2007; Tirosh et al. 2011). After adjusting for traditional risk factors, the occurrence of CHD and cerebrovascular disease can be predicted by obesity (measured by body mass index [BMI]) significantly and independently (Wilson et al. 2008). In addition to that, the risk of CVD increases along with the BMI linearly (Jensen et al. 2014; Twig et al. 2016). All atherogenic risk factors can be intensified or worsened by obesity, while only some can be aggravated by physical inactivity. Yet both obesity and physical inactivity would make patients of all ages more vulnerable to CHD events.

1.2.12 Exercise

Exercise was suggested that coronary heart disease and all-cause mortality can be effectively protected by exercise, even it is moderate degree (Yusuf et al. 2004). Exercise benefits variously–serum HDL-cholesterol elevated, blood pressure reduced, insulin resistance decreased, and weight loss. Besides the exercise amount, the decrease of coronary heart disease risk and overall cardiovascular mortality is also related to the degree of cardiovascular fitness, which is a measure of physical activity and determined by the exercise duration and the Maximal Oxygen Consumption on treadmill (Barlow et al. 2012; Mandsager et al. 2018). The INTERHEART study also found that 12% of the population-attributable risk of a first MI was contributed by lacking of regular physical activity (Yusuf et al. 2004).

1.2.13 Psychosocial Factors

All of sudden cardiac death, acute precipitation of MI and the early development of atherosclerosis may be promoted by psychosocial factors, including depression, anger, stress, and other factors, and all the above have a relationship with cardiovascular outcomes.

1.2.14 Inflammatory Markers

It has been reported that the increased risk of CVD is related to various numerous inflammatory markers (Emerging Risk Factors Collaboration et al. 2010), such as C-reactive protein (CRP), interleukin-6, myeloperoxidase, and other inflammatory markers. What else has been reported to be the markers of increased CHD risk are elevated levels of white blood cells, erythrocyte sedimentation rates, interleukin-18, tumor necrosis factor alpha, transforming growth factor beta, soluble intercellular adhesion molecule-1, P-selectin, cathepsin S, and lipoprotein-associated phospholipase A2.

1.3 Clinical Presentation

1.3.1 Characteristics of Angina

Angina pectoris is caused by myocardial ischemia in the main expression of pain in the chest or adjoining area, which is usually a result of exertion and related to myocardial function disorder. Angina is firstly described as a sense of "strangling and anxiety" in Heberden, and that is still *prominently* relevant. The sense is also described in the manner of heavy, squeezing, tight, suffocating, constricting, and crushing. The sensation for some patients is more vague including a mild pressure-like discomfort, a numb or burning sensation. Generally, the discomfort area is substernal, with the ulnar surface of left arm as a common radiant area, the outer of both arms and right arm sometimes. Patients may also have discomfort in Epigastric area alone or along with chest pressure. It is rare to find anginal discomfort above the mandible or below the epigastrium. Except angina, dyspnea, eructations, fatigue, and faintness are also the common symptoms of myocardial ischemia, defined as anginal equivalents, especially for older patients. For patients without angina or ECG (electrocardiogram)-proved CAD, abnormal exertional dyspnea history may be useful in indicating IHD. Severe ischemia may present dyspnea (at rest or with exertion), which results in increased left ventricular (LV) filling pressure (Abidov et al. 2005). In the case of nocturnal angina, sleep apnea should remain on high alert. Another possible marker of severe CAD is postprandial angina, which may be occur when the coronary blood supplied by the severely stenotic vessels is redistributed. Typical angina pectoris would lasts for minutes with gradual *exacerbation*. Rest, sit or stop walking are the usual preference for patients with angina, and reaching the maximum intensity in seconds is uncommon.

Angina can be indicated with a discomfort in the chest while walking uphill or in the cold. Manifestations like pleuritic pain, fingertip pain, pain that lasts for hours or only seconds, pain caused by movement, pain caused by chest wall, or arms palpation are not markers of angina pectoris. Another highly unusual angina pectoris expression is pain that radiated to the lower extremities.

Rest or nitroglycerin usage can relieve typical angina pectoris within minutes. Though nitroglycerin may cause esophageal pain and other syndromes, it can be used to diagnose angina pectoris. When the symptoms are not brought on by ischemia, or caused by severe ischemia as well as unstable angina or acute MI, with rest and nitroglycerin, relief would be delayed for more than 5–10 min. The ability of continuing same or greater level exertion without symptoms of exertion-led patients can be described using the symptom of first effort angina. With repetitive exertion, attenuation was observed in myocardial ischemia presumably for ischemic preconditioning; and it seems that the warm-up phenomenon could be induced with ischemia greater or equal to medium intensity.

1.3.2 Grading of Angina Pectoris

So far, a widely accepted angina pectoris severity grading system was proposed by CCS (Canadian Cardiovascular Society) (Kaul et al. 2009). And this system, which was modified by NYHA (New York Heart Association) functional classification, makes a more specific classification of patients possible. In addition to the above, there is also an angina score and a specific scale of activity, developed by Califf and Goldman with their associates, respectively.

Yet all these grading system would be limited without precise observation of patients or their diverse symptoms' tolerance. The reproducibility shown on the CCS was only 73%, and no positive correlation was found between that and objective measures of exercise performance. The indicator in the Goldman scale is the metabolic cost of particular activity, and it seems to be effective for both physicians and nonphysicians. While in the anginal score of Califf and coworkers, both ST and T wave changes on the ECG and clinical manifestations are combined, which becomes an independent prognostic factor except LV function, age, coronary angiographic anatomy, and gender.

1.3.3 AMI General Appearance

Anxiety and major distress are common clinical features of STEMI patients, who usually have anguished facial expression, with fist clenched and held against their sternums during description. While any activity was believed to aggravate their discomfort for severe angina pectoris patients, whose preferences are sitting, lying or standing still.

Clinical manifestations of typical LV failure and sympathetic patients include chest discomfort and suffocation. Their sputum is usually pink, frothy or blood-streaked. Thus sitting or propped up in bed are their typical position. And skin pallor and cold perspiration also may be obvious.

Features of cardiogenic shock are as follows: listless lying, pallor face, cold and humid skin, few or no autonomous movements, bluey or mottled extremities, and cyanosed nail beds and lips. Both normal conversation or confusion and disorientation could happen for patients in shock based on their cerebral perfusion level.

1.3.3.1 Heart Rate

Different degrees of LV failure and underlying rhythm make heart rate various, including bradycardia, rapid regular or irregular tachycardia. Premature ventricular beats are also ordinary. Rapid and regular pulse in these patients usually means sinus tachycardia at 100–110 beats/min. Relief of anxiety and pain would slow down the heartbeat.

1.3.3.2 Blood Pressure

Though the systolic and pulse pressure decreased and diastolic pressure elevated for tachycardia accompanied stroke volume reduction, the blood pressure for most patients with noncomplex STEMI is normal. For patients whose previous blood pressure is normal, probably due to the release of adrenergic, which is secondary to agitation, pain, and anxiety, occasional hypertension would be observed in the first few hours, and arterial pressure over 160/90 mmHg. Although 3–6 months postinfarction, elevated blood pressure would be recovered for many of those who have a history of hypertension, without post-STEMI therapy, the blood pressure of some often get normalized.

For patients with massive infarction, LV dysfunction and venous pooling resulted from morphine and/or nitrates administration would cause acute fall in arterial pressure, which inclines to back to preinfarction levels once they recover.

According to the definition of cardiogenic shock, the systolic pressure should be lower than 90 mmHg with proved end-organ hypoperfusion. Since for some inferior infarction patients who have activated Bezold–Jarisch reflex, a transient under 90 mmHg systolic pressure is also possible, hypotension is not a independent indicator for cardiogenic shock. For patients with slight hypotension, cardiogenic shock results from infarction extension and ischemia increasing. Their blood pressure may decline gradually and cardiac output reduce progressively in hours or days.

Hypertension, tachycardia, or both occur in half of both inferior and anterior STEMI patients, with excess parasympathetic stimulation occurring in former, sympathetic excess in the latter.

1.3.3.3 Temperature and Respiration

Within 24–48 h starting from onset, fever and nonspecific response to necrosis occur in most extensive STEMI patients. Following the development of STEMI may be mildly increased respiratory rate. Based on the fact that with therapy for physical and psychological discomfort, respiratory rate of non-HF patients was back to normal, its elevation was brought on by pain and anxiety, while respiratory rate in LV failure patients has correlation with the serious degree of failure. And the respiratory rate in pulmonary edema patients may over 40/min.

1.3.3.4 Chest

For STEMI patients who also have LV failure and/or LV reduction, moist rales are audible. For severe LV failure patients, diffuse wheezing exists. The occurrence of hemoptysis can also indicate pulmonary embolism with infarction. In 1967, based on STEMI patients' presence and severity of rales, a prognostic classification plan was suggested by Killip and Kimball (Barter et al. 2007). No rales or third heart sound was detected in Class I patients. A mild to medium rales (<50% of lung fields) and

a possible S3 in Class II patients. Rales in over 50% of each lung field and continual pulmonary edema in Class III patients, while cardiogenic shock occurs in Class IV patients.

1.3.3.5 Cardiac Examination

Auscultation

Murmurs
For patients with mitral valve regurgitation or tricuspid regurgitation or interventricular septum rupture, systolic murmurs usually are audible.

Friction Rubs
Pericardial friction rubs, most of which would be noticed in two or three days since infarction onset, are usually audible either along the border of left sternal or just inside the apical impulse for STEMI patients.

Laboratory Findings

Serum Markers of Cardiac Damage
The combination of rising usage of sensitive MI biomarkers and precise imaging techniques made the new MI criteria necessary. Compared to unstable angina (UA), more patients are diagnosed with MI when discharged.

For STEMI patients, who is urgent for reperfusion, the 12-lead ECG are recommended than biomarker assay for clinicians to start the treatment for STEMI. Serum creatine kinase (CK) concentration, which could be tested in most hospitals, is a sensitive indicator of STEMI. Yet a false-positive MI could be diagnosed in patients with alcohol intoxication, skeletal muscle trauma, convulsions, thoracic outlet syndrome, muscle disease, diabetes mellitus, after vigorous exercise, intramuscular injections, and pulmonary embolism, which could all result in an elevated serum CK concentration (Marcus et al. 2006).

Creatine Kinase Isoenzymes
CK has three isoenzymes: MM, BB, and MB. The BB isoenzyme mainly exists in brain and kidney extracts; major MM and some MB (1–3%) in skeletal muscle, while both MM and MB isoenzymes exist in cardiac muscle. There is also small amount of MB found in the following: tongue, uterus, small intestine, diaphragm, and prostate. For a given laboratory, several units over the reference limit above would generally be set as the cutoff value for abnormal elevated CK-MB.

Electrocardiography

Serial electrocardiographic changes occur in most of STEMI patients. Yet ECG has been limited with age of the infarct, presence of conduction defects, changes in electrolyte concentrations, extent of myocardial injury, its location, presence of previous infarcts or acute pericarditis, and administration of cardioactive drugs in the diagnosis and location of MI. ST segment and T wave changes, which are nonspecific, may be caused in the following cases: stable and unstable angina pectoris, acute and chronic pericarditis, early repolarization, shock, following the administration of digitalis, ventricular hypertrophy, myocarditis, electrolyte imbalance, and metabolic disorders; all the cases above could be differentiated from STEMI with the help of Serial ECG. With shock, persistent metabolic disorders and administration of digitalis eliminated, persistent changes prove infarction while transient changes support electrolyte disturbances or angina.

The electrocardiographic leads suggest that the infarction location, all of QRS duration and the extent of ST-segment elevation are related to poor prognosis. For most STEMI patients, electrocardiographic changes occur from the onset of infarction and last lifelong especially when they develop into Q waves. While for substantial minority, after several years, Q waves and even ECG are back to normal.

The Q wave patterns that may mimic MI in the following conditions: ventricular hypertrophy, preexcitation, pneumothorax, amyloid heart disease, traumatic heart disease, hyperkalemia, early repolarization, myocardial disease, conduction disorders, pulmonary embolus, heart tumors, pericarditis, intracranial hemorrhage, and cardiac sarcoidosis.

1.3.4 Right Ventricular Infarction

A fairly sensitive and specific evidence of infarction in right ventricular is the ST-segment elevation in the right precordial leads (V1, V3R to V6R) (Bhatt et al. 2007; Bangalore et al. 2007). Anterior ST-segment elevation caused by right ventricular injury usually would be inhibited by concurrent inferior wall injury. Likewise, the anterior ST-segment depression seems to be wakened by right ventricular infarction.

1.3.5 Imaging

Echocardiography

The fairly portable facility provides an ideal evaluation solution for coronary care unit (CCU) or even emergency patients with MI. Echocardiography, which favors myocardial ischemia, can also help with the diagnosis for MI patients with chest pain and nondiagnostic ECG based on the distinct area of disordered contraction. Similarly, it also help with the diagnosis of aortic dissection.

The echocardiograms' estimation in LV function is consistent with that of angiograms and it can be used in the post-MI prognosis establishment (Sipahi et al. 2007). Moreover, in the early diagnosis of congestive heart failure post-MI, MI mechanical complications, residual provocable ischemia, and stunned myocardium yet may still viable; echocardiography can also be helpful.

The blood flow across the cardiac valves and in the chambers can be evaluated with Doppler, whose combination with echocardiography can be used in the detection and assessment of post-STEMI mitral or tricuspid regurgitation. It can also possibly used to identify the position of acute ventricular septal rupture, calculate the shunt flow through the defect and assess the acute cardiac tamponade (Lee and Johnson 2009).

1.3.6 Other Imaging Modalities

Computed Tomography
Despite its relative inconvenience, compared to echocardiography, computed tomography is more sensitive in thrombus detection. Various applications of computed tomography include detection of LV aneurysms, assessment of cavity dimensions, and wall thickness and intracardiac thrombi in STEMI patients. Except that, MI patients' cross-sectional information can also be obtained.

Cardiac Magnetic Resonance Imaging
Compared to its narrow usage in acute phase, cardiac magnetic resonance imaging is widely used in subacute and chronic phases of MI, such as to localize and size the infarction area, to recognize early MI, and to assess the ischemic insult. Other than the above, it provides the assessments of infarcted and noninfarcted tissue perfusion, myocardium reperfusion, ventricular segmental wall motion and chamber size, also the identification of harmed but not infarcted myocardium, myocardial fibrosis, edema, hypertrophy, wall thinning, and the temporal transition between ischemia and infarction (Al-Mallah et al. 2006).

1.3.7 Estimation of Infarct Size

Electrocardiography
With the recognition that the infarcted myocardium volume implicate prognosis, interest has been concentrated on the accurate measurement of MI. However, the mortality rate is related to the number of electrocardiographic leads that display ST-segment elevation; for anterior MI patients, quantity of ST-segment elevations obtained from multiple precordial leads has a relationship with the myocardial injury extent. Compared to patients with only 2 or 3 leads with ST-segment elevation, the mortality rate of those with 8 or 9 are 2–3 times higher. A relationship also exists between the ischemia duration, which could be estimated by monitoring ST-segment

continuously, and IS (infarcted size), IS/AAR (area at risk) ratio, and subsequent abnormality in partial wall motion extent (Bonaa et al. 2006).

Serum Cardiac Markers
With its release ratio, volume of distribution, and amount of lost marker, the infarcted size can be estimated with the usage of serum cardiac markers. The measurement of MI size can use the help of serial calculations of proteins discharged from necrotic myocardium. Besides that, it can be estimated approximately with the crest value of CK or CK-MB, which has wide prognostic applications. Yet the washout kinetics of CK and other markers could be remarkably altered by the coronary artery reperfusion, which leads to overstated and premature peak levels and less the useful of the curves. Infarcted size may be responsibly determined with post-STEMI cardiac-specific troponin level test even after a successful reperfusion (Levonen et al. 2008).

Noninvasive Imaging Techniques
The infarct size can be assessed both experimentally and clinically with the help of the imaging modalities above. For patients whose arteries are occluded persistently, partial heterogeneity of infarction patterns can be displayed clearly in contrast-enhanced cardiac magnetic resonance.

1.3.8 The Presentations of Anginal Pain in NSTE-ACS Patients Are as Follows

Post-MI angina; new-onset (de novo) angina (class II or III of the Canadian Cardiovascular Society classification); prolonged (0.20 min) angina at rest; or previous stable angina become unstable in recent with at least Canadian Cardiovascular Society Class III angina characteristics (crescendo angina).

80 and 20% patients are found to have prolonged and de novo/crescendo angina, respectively. The elderly, female and patients with diabetes, chronic renal disease or dementia found are more likely to get anginal pain. One of the characters of typical chest pain refers to the retrosternal sensation of pressure or heaviness radiating to the left arm, sometimes to both arms or to the right arm, neck or jaw. A typical chest pain usually lasts for several minutes or persistent. What else possibly come along are sweating, nausea, abdominal pain, dyspnoea, and syncope. Epigastric pain, indigestion-like symptoms, and isolated dyspnoea are all included in the typical presentations. Intense physical activity and its relief afterword would aggravate the symptoms, which possibly lead to a higher the chance of myocardial ischaemia. Nitrites can relieve the symptoms, which according to a report of acute chest pain's other causes is not specific for angina.

There is very limited performance of chest pain characteristics to diagnose MI. The incidence of NSTE-ACS is possibly to be increased by many factors, including male gender, older age, diabetes, hypertension, hyperlipidaemia, renal insufficiency, and family history of CAD, previous manifestation of CAD as well as carotid artery

disease or peripheral. All of infection, fever, anemia, inflammation, and metabolic or endocrine (in particular thyroid) disorders may aggravate or facilitate NSTE-ACS.

1.3.8.1 Clinical Examination

The physical examination may be unremarkable or may support the diagnosis of cardiac ischemia. Signs suggesting that ischemia involves a large proportion of the left ventricle include sinus tachycardia, diaphoresis, pale cool skin, a third or fourth heart sound. In some patients, ischemia of a large area of myocardium reduces left ventricular dysfunction and causes hypotension.

Electrocardiography
ST-T changes occur in about half of the patients with UA/NSTEMI. Newly (or presumably new) ST-segment deviation ($\geq$0.1 mV) is a relatively reliable measure of ischemia and prognosis. When electrocardiograms preceding the acute event are available, further ST depression of only 0.05 mV is a sensitive although nonspecific finding of UA/NSTEMI. Transient (i.e., <20 min) ST elevation, which occurs in approximately 10% of patients with UA/NSTEMI, portends a high risk of future cardiac events. T wave changes are sensitive but not specific for acute ischemia unless they are marked (>0.3 mV).

1.3.8.2 Continuous Electrocardiographic Monitoring

Continuous electrocardiographic monitoring serves two purposes in UA/NSTEMI: (1) to identify arrhythmias and (2) to identify recurrent ST-segment deviation indicative of ischemia. Recurrent ST-segment deviation is a strong independent marker of adverse outcome, even in the presence of troponin release.

1.3.8.3 Markers of Cardiac Necrosis

Among patients presenting with symptoms consistent with UA/NSTEMI, elevations of markers of myocardial necrosis (i.e., CK-MB, troponin T or I) identify patients with the diagnosis of NSTEMI. With the use of troponins, which are more sensitive than CK-MB, a greater percentage of patients are classified as having NSTEMI, which is associated with a worse prognosis. Persistent elevation of troponin after an acute event also associates with worse clinical outcomes.

1.3.8.4 Laboratory Tests

The chest radiograph may be helpful to identify pulmonary congestion or edema, which occurs more frequently in patients with UA/NSTEMI in whom ischemia

involves a significant proportion of the left ventricle or in those with antecedent left ventricular dysfunction. The presence of congestion confers an adverse prognosis.

Transthoracic echocardiography (UCG) should be routinely available in emergency rooms, which is performed/interpreted by trained physicians in all patients during hospitalization for NSTE-ACS. It is useful to identify abnormalities suggestive of myocardial ischaemia or necrosis. Besides, UCG is helpful in other which is related with chest pain, such as aortic valve stenosis, pericardial effusion, acute aortic dissection, hypertrophic cardiomyopathy or acute pulmonary embolism. Moreover, UCG is the diagnostic tool for patients with hemodynamics instability of suspected cardiac origin. Evaluation of left ventricular (LV) systolic function is important to estimate prognosis.

1.3.8.5 Clinical Classification

Because UA/NSTEMI comprises such a heterogeneous group of patients, classification schemes based on clinical features are useful. Some clinical classifications or scores of UA/NSTEMI provide a useful means to stratify risk. *In NSTE-ACS*, it is superior to make quantitative assessment of ischaemic risk by means of scores that the clinical assessment alone. *The GRACE* risk score provides the most accurate stratification of risk both on admission and at discharge.

The TIMI risk score uses seven variables in an additive scoring system: age $\geq$ 65 years, three or more CAD risk factors, known CAD, aspirin use in the past 7 days, severe, angina, ST change $\geq$0.5 mm and positive cardiac marker. It is easy to use, but more accurate in discriminating risk levels than GRACE risk score.

1.3.8.6 Coronary Arteriographic Findings

The extent of epicardial CAD among patients with UA/NSTEMI randomized to the invasive arm of the TACTICS–TIMI 18 trial, who systematically underwent angiography, was as follows: 34% had significant obstruction (>50% luminal diameter stenosis) of three vessels; 28% had two-vessel disease; 26% had single-vessel disease; and 13% had no coronary stenosis >50%.

Approximately 10% had left main stem stenosis >50%. Women and nonwhites with UA/NSTEMI have less extensive coronary disease than their counterparts do, whereas patients with NSTEMI have more extensive disease on coronary angiography than do those who present with unstable angina alone.

1.3.9 Woman: Clinical Presentation

Compared to male's presentation time, it would generally be ten years later for female to get coronary heart disease (CHD), and burden of risk factors for women are greater

(Rutledge et al. 2009). Symptoms at the beginning would not be considered as the presentation of heart disease by women, which results in not prompt medical advice; they also will not be used in evaluating myocardial ischemia as early in women. Women under 45 years also have CHD and the prognosis is worse compared to men. CHD first presentation can be various, including sudden cardiac death (SCD), myocardial infarction (MI), heart failure (HF) or chest pain. The Reynolds risk score as alternative was developed for female patients since risk in women with early heart disease family history was underestimated.

1.4 Complications of Acute Myocardial Infarction

1.4.1 Left Ventricular Dysfunction

Left ventricular dysfunction is the most significant predictor of post-AMI mortality. Systolic dysfunction may happen alone or together with diastolic dysfunction (Pitt 2003; White et al. 2005). The diastolic dysfunction of LV causes pulmonary congestion and pulmonary venous hypertension, while systolic dysfunction mainly leads to cardiac output depression and ejection fraction depression. For these patients, except the necessity of hypoxemia improvement, ACEI/ARB, beta-adrenergic agonists, and diuretics are also significant. Afterload can be induced with the usage of nitroglycerin and other oral vasodilators, and systolic dysfunction can be improved by digitalis (Udelson et al. 2003).

1.4.2 Cardiogenic Shock

Cardiogenic shock, which is the most serious clinical manifestation of LV failure, contributes nearly 60% of total deaths after fibrinolysis for AMI. AMI patients who are older and have history of congestive heart failure or prior MI, sustained an anterior infarction, are more likely to have cardiogenic shock (Palmeri et al. 2005; Babaev et al. 2005).

1.4.3 Rupture of the Free Wall

Hemopericardium and death from cardiac tamponade are often caused by rupture of the free wall of the left ventricle (Antman et al. 2006b). There are mainly three types of rupture, including the catastrophic (an acute tear leading to immediate death), the subacute (nausea, hypotension), and the pericardial (discomfort) (Birnbaum et al. 2002a).

1.4.4 Rupture of the Interventricular Septum

The 30-day mortality of patients who had acute myocardial infarction and subsequent rupture of interventricular septum is high (Birnbaum et al. 2002b). The character of a ruptured interventricular septum is a new harsh, loud holosystolic murmur, which is usually together with a thrill and can be heard best at the lower left sternal border (Antman et al. 2006b). It has been reported that for critical patients with acute septal rupture after AMI, their conditions can be stabilized by catheter placing an umbrella-shaped device within the ruptured septum.

1.4.5 Rupture of a Papillary Muscle

Transmural MI is rarely complicated with partial or total rupture of a papillary muscle, which is often fatal. Severe (not immediately fatal) and sudden massive (rare, fatal) mitral regurgitation can be caused (Birnbaum et al. 2002b).

Surgical Treatment
For AMI and circulatory collapse patients, operative intervention for identifiable and repairable mechanical lesion, which is surgically correctable (ventricular septal defect or mitral regurgitation, for example), is most successful. And coronary revascularization is often in company with surgical reparations include prosthetic mitral valve insertion, ventricular septal defect closure, or mitral regurgitation correction (Antman et al. 2006b).

1.4.6 Ventricular Arrhythmias

1.4.6.1 Ventricular Premature Complexes

Frequent ventricular premature complexes (VPCs) are assumed to be over 5 per min, before reperfusion therapy, beta-blockers, intravenous nitrates, and aspirin were wildly used for STEMI management. Now it's been found out that patients who do and do not develop fibrillation have the same incidence of this "warning arrhythmias". For STEMI patients who have VPCs, instead of routine prescription of antiarrhythmic drugs, conservative course should be carried out and determine the presence of recurrent ischemia or electrolyte or metabolic disturbances (Antman et al. 2006b).

1.4.6.2 Accelerated Idioventricular Rhythm

As many as 20% STEMI patients have accelerated idioventricular rhythm, and in the first two days, it has frequent occurrence, which is the same for anterior and

inferior infarctions. Routine treatment for accelerated idioventricular rhythms is not necessary since it is believed not to influence the prognosis, unlike rapid ventricular tachycardia (Antman et al. 2006b).

1.4.6.3 Ventricular Tachycardia

It appears that for either during hospitalization or over the first year and non-sustained runs of ventricular tachycardia has no relationship with increased mortality risk. STEMI patients who have transmural infarction and left ventricular dysfunction usually have late yet maybe sustained ventricular tachycardia, which often causes significant hemodynamic deterioration and is related to both hospital and long-term mortality rates.

It's significant that the levels of serum potassium and magnesium be maintained above 4.5 mEq/l and 2 mEq/l, respectively. And for STEMI patients, it is compulsive to abolish the sustained ventricular tachycardia rapidly. An index episode of ventricular tachycardia is usually followed with several days' maintenance infusions of antiarrhythmic drugs, which is a common clinical practice. Specialized methods like surgery or antitachycardia devices implantation should be considered for recurrent or refractory ventricular tachycardia.

1.4.6.4 Ventricular Fibrillation

For hospitalized STEMI patients, ventricular fibrillation happens in three settings. Those who has none or few signs or symptoms of left ventricular failure have sudden and unexpected primary ventricular fibrillation, while patients in the progressive downhill course with left ventricular failure and cardiogenic shock have the secondary ventricular fibrillation as final event. The late ventricular fibrillation usually occurs over 48 h post-STEMI and it has regular but not solely occurrence in large infarcts and ventricular dysfunction patients. Ventricular fibrillation can be treated with unsynchronized electrical countershock (at least 200–300 j), which should be performed as fast as possible. The administration of intravenous amiodarone also promotes effective prevention of refractory recurrent episodes or interruption of ventricular fibrillation (Volpi et al. 1998).

1.4.6.5 Bradyarrhythmias

Sinus Bradycardia

Sinus bradycardia usually happens at the early stage of STEMI, especially for patients who have inferior and posterior infarction (Antman et al. 2006b). For patients whose extremely slow sinus rate (<40–50 beats/min) is in association with hypotension,

atropine can raise the heart rate effectively without the company of hypotension or ventricular ectopy, sinus bradycardia alone should firstly be observed instead of treatment.

Atrioventricular and Intraventricular Block

Specific treatment for first-degree AV block usually is not necessary. First-degree AV block may be caused by beta-blockers and calcium antagonists (other than nifedipine), since they can prolong AV conduction. Type I second-degree AV blocks, which are most common in association with occlusion of the right coronary artery and resulted from ischemia of the AV node, seem do not influence prognosis. With the absence of heart failure, premature ventricular contractions, and bundle branch block and ventricular rate over 50 beats/min, specific treatment for patients with second-degree AV block of the type I variety is unnecessary. Either anterior or inferior infarction patients can have the occurrence of complete (third-degree) AV block.

Patients with inferior wall infarction and complete AV block, which usually is transient, do not require pacing. Atropine has little value in patients with the followings: slow ventricular rate (<40–50 beats/min), presence of ventricular arrhythmias or hypotension, or development of pump failure. The abolishment of AV block or acceleration of the escape rhythm is likely to be led by atropine only when complete heart block develops within 6 h of symptoms onset, in which cases, AV block is probably transient and related to growth of vagal tone. While persistent block, which is more observed in the course of STEMI, usually needs cardiac pacing.

Intraventricular Block

Blood of the right bundle branch and the left posterior division are supplied from both anterior descending and right coronary arteries, whereas that of the left anterior division is supplied only from septal perforators, whose origin is left anterior descending coronary artery. Since nearly half of conduction blocks observed in STEMI patients are already present on the first ECG, they can't all be considered to be the complications of infarcts, and they may stand for the antecedent disease of conduction system (Di Chiara 2006; Wong et al. 2006).

Right Bundle Branch Block

Right bundle branch block, which is usually new and related to anteroseptal infarction, alone can cause AV block. It appears that for anterior STEMI patients, with the company of congestive heart failure, isolated right bundle branch block is related to an elevated mortality risk, even without the occurrence of complete AV block.

1.4.7 Atrial Flutter and Fibrillation

Atrial flutter, which commonly is transient and is the typical consequence of augmented sympathetic stimulation of the atria in STEMI patients, usually occurs in LV failure and pulmonary emboli patients, who has hemodynamic deterioration that aggravated by arrhythmia, or atrial infarction (Kober et al. 2006).

Fibrillation is commonly transient and likely to happen in LV failure patients just like atrial premature complexes. Yet patients who have pericarditis and atria ischemic injury and right ventricular infarction can also have that. The treatments for atrial flutter and fibrillation in STEMI patients and these conditions in other settings are similar. Oral anticoagulants should be administered in patients with recurrent episodes of atrial fibrillation. Beta-blocker should also be used in patients after STEMI if no contraindications exist. And these agents can also help to decrease the ventricular rate, should atrial fibrillation recurrence, except other several beneficial effects.

1.4.8 Other Complications

1.4.8.1 Recurrent Chest Discomfort

Both previous abnormalities on the ECG and patients' blurry description of discomfort sometimes make the evaluation of postinfarction chest discomfort complicated. Patients may either be too sensitive to transient discomfort or negative a potential recrudescence of symptoms. Diagnostic strategies can be used are as follows: repeat ECG reading, assessment of the response to sublingual nitroglycerin, 0.4 mg and repeat physical examination.

1.4.8.2 Recurrent Ischemia and Infarction

With a repeat ST-segment elevation on ECG within the first 18–24 h after the primary infarction, and abnormal serum cardiac markers, recurrent infarction is worth of serious consideration (Keeley et al. 2003). After 24 h, either re-elevated cardiac markers or newly appeared Q wave on ECG can be used to diagnose recurrent infarction. Catheterization and percutaneous coronary intervention, or repeat fibrinolysis if PCIs unavailable, should be considered for patients who have re-elevated ST segment. During the arrangement of other procedures, patients may be stabilized with an intra-aortic balloon pump being inserted (Scirica et al. 2006; Antman et al. 2006c).

1.4.8.3 Pericardial Effusion

Effusions are usually detected with echocardiography. And the incidence changes along with criteria, laboratory expertise, and technique. Patients with the presence of congestive failure, larger infarcts, and anterior STEMI are more likely to have effusions. Most post-STEMI pericardial effusions do not lead to hemodynamic compromise; and with the occurrence of tamponade, ventricular rupture or hemorrhagic pericarditis often induces effusions (Hombach et al. 2005).

1.4.8.4 Pericarditis

Pain caused by pericarditis may start in the first day and last 6 weeks post-STEMI. A higher dose of aspirin (650 mg orally every 4–6 h) is necessary to treat the pericardial discomfort. And nonsteroidal antiinflammatory agents and steroids should be prevented from using since their interference with the formation of myocardial scar (Abildstrom et al. 2005; Birnbaum and Drew 2003).

1.4.8.5 Post-myocardial Infarction Syndrome

Presentations of post-myocardial infarction syndrome include malaise, pericardial discomfort, elevated sedimentation rate, fever, leukocytosis, and pericardial effusion. Since glucocorticosteroids and nonsteroidal anti-inflammatory agents have the potential to weaken the infarct recovery, increase coronary vascular resistance, and lead to ventricular rupture in Dressler syndrome patients within 4 weeks of STEMI, it is best not to use them in such cases. Large doses of aspirin would be effective (Reinecke et al. 1998).

1.4.8.6 Venous Thrombosis Pulmonary Embolism

The origin of mainly all peri-MI pulmonary emboli is thrombi in the veins of the lower extremities; mural thrombi overlying an area of right ventricular infarction as the origin is rather uncommon.

1.4.8.7 Left Ventricular Aneurysm

Left ventricular aneurysm, which is often termed as true aneurysm, usually means discrete, dyskinetic area of the left ventricular wall with a broad neck. Compared to true aneurysms after STEMI, it is more common to see dyskinetic or akinetic areas of the left ventricle, which are known as regional wall motion abnormalities. The wall of the true aneurysm, which generally consists of fibrous tissue, necrotic muscle, and sometimes viable myocardium, is thinner compared to the rest wall of the

left ventricle. In contrast to patients without aneurysms, the mortality of those who have is six times higher. Ventricular reconstruction surgery is worth of consideration (Cheitlin et al. 2003; Vargas et al. 1999).

1.4.8.8 Left Ventricular Thrombus and Arterial Embolism

During the acute phase of infarction, a thrombogenic surface inside the left ventricle may be contributed by endocardial inflammation. Since the septum has been transmural-infarcted extensively, infarcted myocardium of both ventricles may be overlay with mural thrombi. When an embolic event has already occurred, or patient has a large anterior infarction with or without echocardiographically visualized thrombus, anticoagulation is recommended (intravenous heparin to increase the activated partial thromboplastin time to 1.5–2 times that of control, followed by at least 3–6 months of warfarin) (Rehan et al. 2006; Barbera and Hillis 1999).

1.5 Pathophysiology of Atherosclerosis

Atherosclerosis involves several highly interrelated processes, including platelet activation, thrombosis, lipid disturbances, endothelial dysfunction, oxidative stress, inflammation, altered matrix metabolism, vascular smooth cell activation, remodeling, and genetic factors (Libby 2002).

1.5.1 Platelet Activation and Thrombosis

Platelet activation and thrombosis are recognized as important components of atherosclerosis. Coronary thrombosis often occurs at sites of plaque rupture or erosion (Davies 1996). Subendothelial collagen, the lipid core, and procoagulants such as tissue factor and von Willebrand factor are exposed immediately to circulating blood after plaque rupture or erosion. Through the platelet glycoproteins (GP) Ia/IIa and GP Ib/IX20 (Rauch et al. 2001), platelets rapidly adhere to the vessel wall with subsequent aggregation to this initial monolayer through linkage with fibrinogen and the exposed GP IIb/IIIa on activated platelets. Platelets are a rich source of NO, which has been associated with thrombosis (Loscalzo 2001). Although thrombosis is an important process in ACS, it may have an even more critical role in modulating risk of acute ischemic events in peripheral arterial disease (PAD) (Makin et al. 2002). The findings of the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial demonstrated that in reducing the number of cardiovascular events in patients with PAD than in those with coronary artery disease, inhibition

of the platelet adenosine diphosphate receptor with clopidogrel (versus aspirin) is more effective (A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE) 1996).

1.5.2 Endothelial Dysfunction

The vascular endothelium is recognized as an important center of vascular control. The endothelium play an important role in regulation of nutrient delivery, vascular tone, inflammation, coagulation, and thrombosis.

Endothelial regulation of these processes stems primarily from production of autocrine and paracrine mediators including prostaglandins, NO, endothelin, endothelium-derived hyperpolarizing factors, and angiotensin II. These substances provide a balance between thrombosis and anticoagulation, vasodilation and vasoconstriction and modulation of inflammation. NO is the most potent vasodilator (Rees et al. 1989), which can be demonstrated by the wide variety of stimuli that modify its production and degradation. These activity modifiers differ from chemical to biomechanical stimuli and allow for the modulation of NO bioavailability (Luft 2002).

The decrease in the bioavailability of NO and the increase in production of vasoconstrictors such as angiotensin II can create a favorable environment for thrombosis and atherosclerosis (Loscalzo 2001). Besides to adversely affecting blood flow and nutrient delivery, another important aspect of endothelial dysfunction would likely be the increase in inflammation (Libby 2002). Endothelial cells are very important in the recruitment, adhesion, and diapedesis of leukocytes into the vascular wall through many chemokines and cytokines and intracellular transcription factors (Hawiger 2001; Berk et al. 2001; Rosenfeld 1996). Moreover, by enhancing vascular smooth muscle proliferation and migration, augmenting platelet activation and thrombosis, possibly participating in intravascular neovascularization, and favoring adverse lipid modification, decreased NO increases the tendency for lesion progression (Loscalzo 2001; Vallance and Chan 2001). After lesions have developed, endothelial dysfunction can exacerbate development of clinical events. Impaired endothelium may abnormally reduce vascular perfusion, produce factors that decrease plaque stability, and augment the thrombotic response to plaque rupture (Loscalzo 2001; Radomski et al. 1987; Diodati et al. 1998).

1.5.3 Inflammation

It is inflammation that plays a central role in atherosclerosis in a large body of experimental and clinical research studies (Libby et al. 2002). Inflammation and

accumulation of minimally oxidized LDL develop together in the arterial wall. Several adhesion molecules are expressed in the endothelial cell, including P- and E-selectins, intercellular adhesion molecule, and vascular cell adhesion molecule-1, which bind to circulating leukocytes (Hansson 2001). Chemoattractants such as monocyte chemotactic protein can mediate transmigration of leukocytes into the arterial wall, which leads to accumulation of inflammatory macrophages and T-cells within the arterial wall (Hansson 2001). Proteolytic enzymes and a variety of peptide growth factors and cytokines which can degrade matrix proteins and stimulate smooth muscle cells, endothelial cells, and macrophages are released by those activated leukocytes. Macrophage accumulation of oxidized LDL leads to foam cells aggregation. Several inflammatory cells, including macrophages, B and T lymphocytes, endothelial cells, vascular smooth muscle cells, and fibroblasts express CD40 receptor and CD40 ligand (Schonbeck and Libby 2001).

Plaque disruption and thrombosis can also be led to by the inflammatory process. A large lipid core, a thin fibrous cap, and inflammatory cells at the thinnest portion of the cap surface are characters of vulnerable plaques (Davies et al. 1993). Matrix metalloproteinases (MMPs) and other substances expressed by macrophages lead to degradation of the cap, resulting in an unstable plaque that is susceptible to rupture, which have been shown in several studies (Galis and Khatri 2002). Then, formation of a thrombus can be led to by exposure of the underlying atheroma and tissue factor to circulating platelets and thrombin. It is serum markers of inflammation such as high-sensitivity C-reactive protein that are elevated in patients with acute coronary syndromes and PAD, which independently predicts subsequent events (Ridker et al. 2001).

1.5.4 Oxidant Stress

Excess generation of reactive oxygen species (ROS) has been proved to be a critical pathological process in atherogenesis. Each component of the atherosclerotic blood vessel has been demonstrated to increase production of ROS, primarily superoxide anion (O_2) (Maytin et al. 1999). Important sources of ROS are endothelial cells, vascular smooth muscle cells fibroblasts, and infiltrating leukocytes (Zalba et al. 2000). The importance of oxidation can be seen by the presence of oxidized LDL in atherosclerotic lesions, although the mechanism of oxidative modification of LDL remains unknown. As measured by autoantibody titers, the amount of oxidized LDL is reflective of the atherosclerotic burden (Tsimikas et al. 2001). Oxidized LDL induces a series of atherogenic processes, including production of matrix metalloproteinases, transcription of proatherogenic genes and antagonism of endothelial cell production of NO, promotion of vascular smooth muscle cell apoptosis (Kita et al. 2001).

1.5.5 Smooth Muscle Cell Proliferation

The vascular smooth muscle cell (SMC) plays a critical role in atherosclerosis. The growth factor, the SMC undergoes a phenotypic change that leads to a migratory and secretory cell that migrates into the neointima after being activated by injury, (Rivard and Andres 2000). SMCs proliferate and secrete matrix proteins and enzymes through growth factor and cytokine stimulation.

The atherosclerotic plaque contains cellular elements and extracellular matrix. The constituents of the plaque's extracellular matrix include proteoglycans, glycosaminoglycans, collagen, elastin, fibronectin, vitronectin, laminin, and thrombospondin. Activated SMCs are closely related to the production of these matrix proteins (Raines 2000). Collagen provides the structural support and scaffold for the vessel wall, whose production and degradation are both increased in atherosclerosis (Rekhter 1999). Activated SMCs and macrophages secrete MMPs that degrade collagen and elastin, whereas SMCs produce collagen (Benjamin 2001). The entire vessel can enlarge or constrict in size during development of atherosclerosis. This is often referred to as geometric remodeling, which plays a critical role in determining luminal patency.

1.5.6 Genetic Factors

Genetic predisposition is an important risk factor for atherosclerosis. In some studies, up to 50% of the risk for atherosclerosis, which is attributable to genetic predisposition (Galis and Khatri 2002). It has been proved that this is a multifactorial disease. Over the next several years, atherosclerosis may be understood as a molecular disease. The challenge will be to identify better diagnostic and therapeutic strategies for these syndromes by using these findings (Ridker et al. 2001).

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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

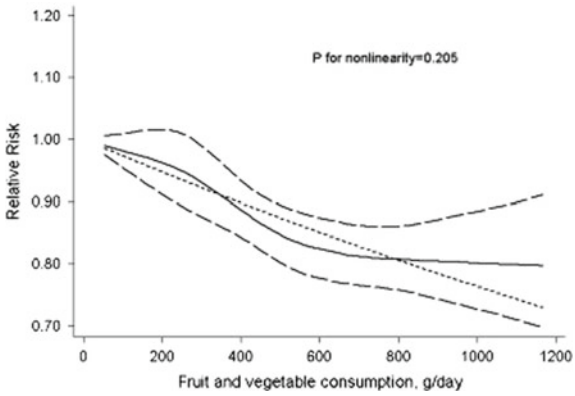

Fig. 2.1 Dose–response relation plots between fruit and vegetable consumption (g/day) and the risk of coronary heart disease (Gan et al. 2015), P for nonlinearity = 0.205

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

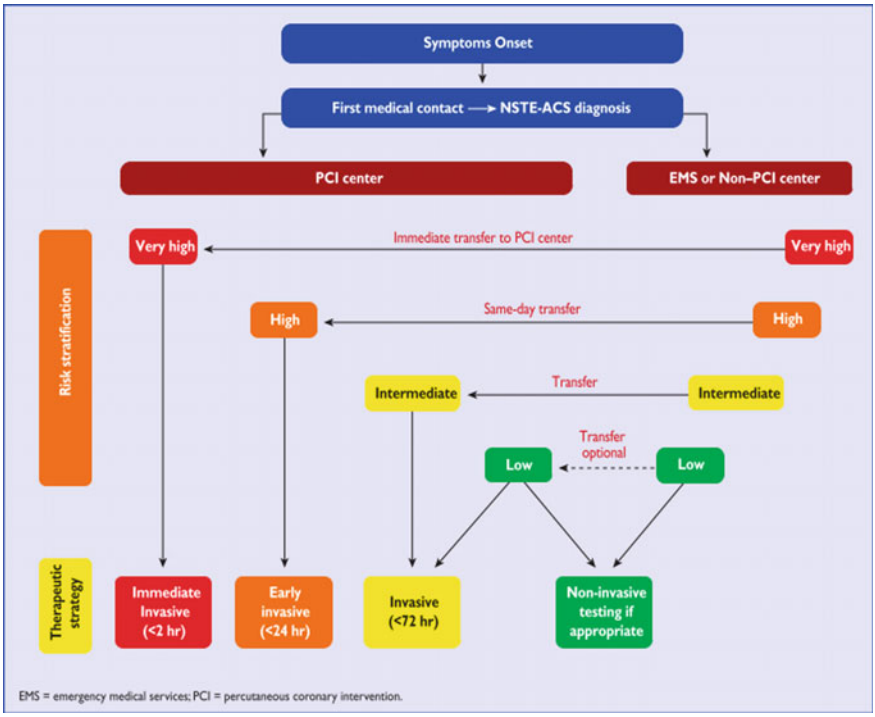

Fig. 2.2 Selection of non-ST-elevation acute coronary syndrome (NSTE-ACS) treatment strategy and timing according to initial risk stratification

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

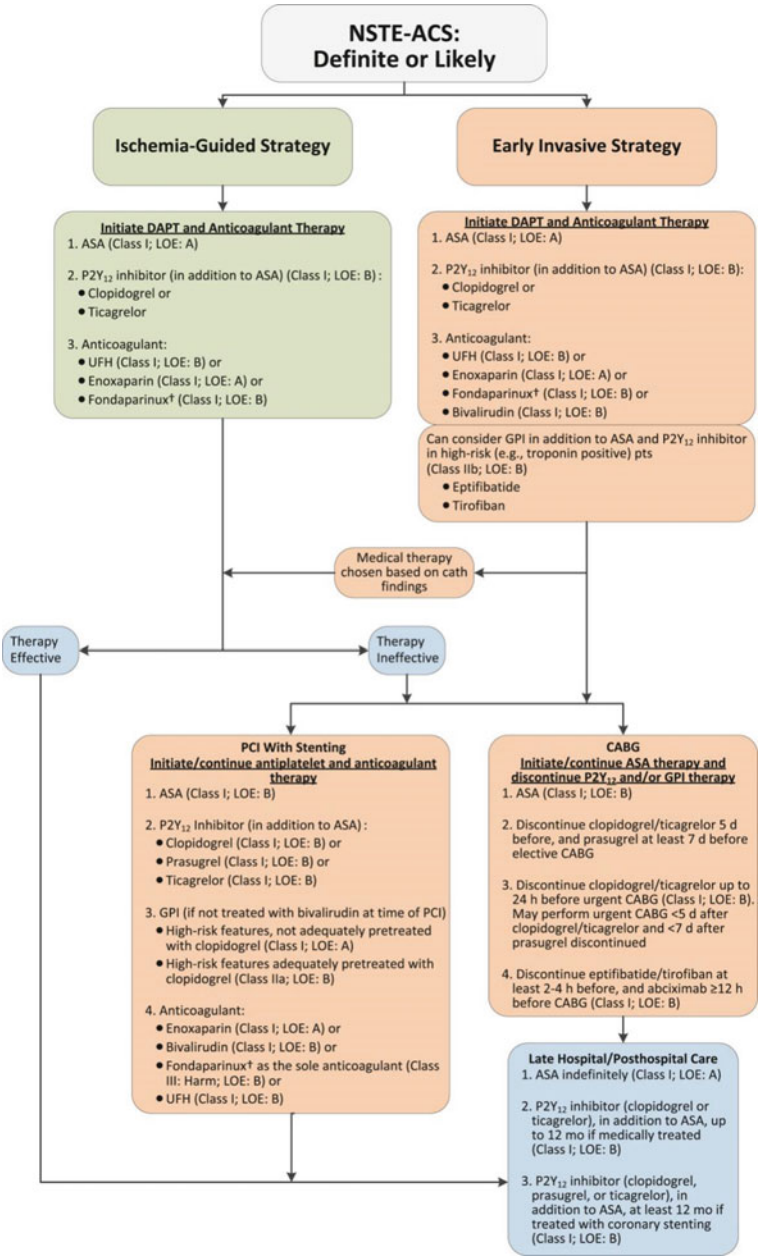

Fig. 2.3 Algorithm for management of patients with definite or likely NSTE-ACS (Worm et al. 2013) (In patients who have been treated with fondaparinux (as upfront therapy) who are undergoing PCI, an additional anticoagulant with anti-IIa activity should be administered at the time of PCI because of the 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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Chapter 3
Revascularization for Coronary Artery Disease: Principle and Challenges

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Abstract Coronary revascularization is the most important strategy for coronary artery disease. This review summarizes the current most prevalent approaches for coronary revascularization and discusses the evidence on the mechanisms, indications, techniques, and outcomes of these approaches. Targeting coronary thrombus, fibrinolysis is indicated for patients with diagnosed myocardial infarction and without high risk of severe hemorrhage. The development of fibrinolytic agents has improved the outcomes of ST-elevation myocardial infarction. Percutaneous coronary intervention has become the most frequently performed procedure for coronary artery disease. The evolution of stents plays an important role in the result of the procedure. Coronary artery bypass grafting is the most effective revascularization approach for stenotic coronary arteries. The choice of conduits and surgical techniques are important determinants of patient outcomes. Multidisciplinary decision-making should analyze current evidence, considering the clinical condition of patients, and determine the safety and necessity for coronary revascularization with either PCI or CABG. For coronary artery disease with more complex lesions like left main disease and multivessel disease, CABG results in more complete revascularization than PCI. Furthermore, comorbidities, such as heart failure and diabetes, are always correlated with adverse clinical events, and a routine invasive strategy should be recommended. For patients under revascularization, secondary prevention therapies are also of important value for the prevention of subsequent adverse events.

Keywords Coronary artery disease · Revascularization · Percutaneous coronary intervention · Coronary artery bypass grafting

Since the pathophysiology of coronary artery disease (CAD) was first established in the 1870s that impaired blood supply and caused the myocardial infarction

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(Diodato and Chedrawy 2014), cardiologists had always been striving for approaches for reconstructing coronary blood supply, which was later known as coronary revascularization, to radically resolve the problem.

In 1964, the first coronary artery bypass grafting (CABG) was performed, and 13 years later, percutaneous coronary intervention (PCI) was first available for myocardial revascularization. After decades of continuous advances, both procedures have become conventional therapies for CAD, with over 310,000 CABGs and 1.4 million catheterizations were performed in the United States in 2001 (Riley et al. 2011). In this article, we will introduce the approaches for revascularization and future challenges.

3.1 Evidence and Recommendations for Revascularization

Current guidelines have given recommendations on indications for myocardial revascularization. For patients with stable CAD (SCAD), optimal medical treatment was recommended before revascularization. SCAD with flow-limiting coronary stenosis is indicated to either PCI or CABG to reduce myocardial ischemia and terminate the adverse pathological process. Patients with persist symptoms despite optimal medical treatment and/or improved prognosis will more effectively benefit from revascularization. Revascularization by PCI or CABG is the most effective therapy for angina relief, and improvement of quality of life. These indications was based on randomized control trials (RCTs), in which patients that received revascularizations got better long-term survival benefits (Velazquez et al. 2011; Hlatky et al. 2009; Yusuf et al. 1994).

Revascularization is also recommended for patients with non-ST-segment elevation acute coronary syndromes (NSTEMI) for symptom relief and improvement of prognosis. In a meta-analysis of seven trials, invasive strategy significantly reduced the risk for all-cause mortality (RR = 0.75; 95% CI 0.63–0.90; $P < 0.001$) and myocardial infarction (RR = 0.83; 95% CI 0.72–0.96; $P = 0.012$), as compared with conservative therapy (Bavry et al. 2006).

Current evidence supported early invasive strategy for the NSTEMI, with most pronounced benefits in high-risk patients, but still emphasized risk stratification. Growing evidence suggested that early invasive strategy reduced the risk of recurrent syndrome by 41% for patients with NSTEMI. Intervention within 72 h after diagnosis was especially recommended for patients with higher risk (i.e., diabetes, renal insufficiency, reduced left ventricular function, recent revascularization, et al.) (Katritsis et al. 2011; Navarese et al. 2013).

For patients with onset of symptom with elevated ST-segment or new left bundle branch block on electrocardiography in less than 12 h, reperfusion therapy within the first 2–3 h is definitely recommended to save myocardium and improve prognosis. Reducing the time between symptom onset and provision of reperfusion therapy was the most important factor to improve medical quality and patient's prognosis. With an experienced team, PCI is the primarily recommended reperfusion strategy over

fibrinolysis. PCI was also recommended in patients with onset of symptom more than 12 h and the presence of continuing ischemia, life-threatening arrhythmias, pain, and electrocardiography changes. In patients with severe acute heart failure or cardiogenic shock, PCI is indicated no matter time delay.

3.2 Fibrinolysis

Thrombus in coronary arteries occludes the vessel, arrests blood flow, causes ischemic in myocardium, and provokes acute coronary syndrome. Targeting offending thrombus, thrombolytic therapy is an extensively used therapy for patient with acute ST-elevation (Q wave) myocardial infarction (STEMI), especially for those patients unavailable to PCI in 120 min.

Intravenous infusion of fibrinolytic drugs, commonly plasminogen activators, is utilized to activate the blood fibrinolytic system (Chapin and Hajjar 2015). These agents are highly specific to their substrate plasminogen, which was converted to active enzyme plasmin (Collen and Lijnen 2005). Free plasmin in the blood is very rapidly inactivated by α^2-antiplasmin, but plasmin generated at the fibrin surface is partially protected from inactivation (Collen et al. 1538).

3.2.1 Indications and Contraindications for Fibrinolytic Therapy

Patients with the following criteria are eligible for fibrinolytic therapy: (1) diagnosed of new developed myocardial infarction with confirmed symptoms and evidences; (2) cannot timely receive PCI for revascularization. Fibrinolytic therapy reduces the risk of mortality in patients with acute STEMI by 15–30%, as compared with placebo group and thus should be considered for all eligible patients, especially when PCI is not timely available. Early fibrinolytic therapy is recommended, better in 3 h after the outbreak of chest pain (Kolh and Windecker 2014).

Diseases with high risk of severe hemorrhage are absolute contraindications to fibrinolytic therapy that include previous intracranial hemorrhage (ICH), known structural cerebral vascular lesion, known malignant intracranial neoplasm, ischemic stroke within three months, suspected aortic dissection, active bleeding or bleeding diathesis, significant closed-head or facial trauma within three months, and major trauma or surgery or prolonged cardiopulmonary (>10 min) in less than 2 weeks.

Important relative contraindications include: hypertension with systolic blood pressure over 180 mmHg (Gore et al. 1995; Aylward et al. 1996); ischemic stroke in more than three months previously (Tanne et al. 1998); internal bleeding in the last 2 weeks; noncompressible vascular puncture; anaphylactic reactions to fibrinolytic

agents; prolonged cardiopulmonary (>10 min) in less than 3 weeks; pregnancy; active peptic ulcer; and current use of anticoagulant.

3.2.2 *Fibrinolytic Agents*

After decades of development, the index list of fibrinolytic agents has increased significantly and tends to reduce the risk of adverse events and increase the safety. Streptokinase is the first generation of fibrinolytic agent. Randomized trials have demonstrated that streptokinase reduced in-hospital and short-term mortality (Franzosi et al. 1998; Baigent et al. 1998). However, this early used agent was found to be associated with several adverse effects. Streptokinase is produced by beta-hemolytic streptococcus (Anderson and Willerson 1993; Marder and Sherry 1988) and is actually an antigenic that causes allergic reactions, especially under repeated administrations. Other events include hypotension and bleeding at puncture site. Risk of stroke is much lower but can cause catastrophic outcomes (GUSTO investigators 1993). Fibrinokinase is the other type of fibrinolytic agents (Astrup and Permin 1947), including tissue-type plasminogen activator (t-PA) (Rijken et al. 1979, 1980) and single-chain urokinase-type plasminogen activator (scu-PA or pro-urokinase). In the multisites randomized streptokinase-controlled GUSTO trial enrolling 41,021 patients with myocardial infarction, t-PA reduced 14% (95% confidence interval, 5.9–21.3%) of mortality (Investigators 1993). To date, t-PA is used worldwide in about 300,000 AMI patients every year, and has become a lifesaving drug for the treatment of evolving acute myocardial infarction and other thromboembolic diseases (Collen et al. 1538). Scu-PA is another agent for thrombolysis, which contributed to higher patency rate and reduced risk of complications (Meyer 1989; Spiecker et al. 1999; Bar et al. 1997; Tebbe et al. 1995; Zarich et al. 1995; del Zoppo et al. 1998; Furlan and Abou-Chebl 2002).

The third-generation fibrinolytic agents include recombinant plasminogen activator (r-PA), which is a nonglycosylated deletion mutant of wild-type recombinant tissue-type plasminogen activator (t-PA) (Wu et al. 1990). Early trials have demonstrated that r-PA has a higher rate of TIMI grade III flow at 60 and 90 min compared with t-PA. It was also associated with a reduced need for additional coronary interventions early after thrombolytic procedures. However, r-PA was not shown to get more benefit in either 35-day mortality or the overall incidence of TIMI grade III flow in these early trials (Bode et al. 1996; Smalling et al. 1995). Trials with much higher statistics power were conducted to compare the safety and effect of r-PA with other fibrinolytic agents.

GUSTO III trial compared r-PA with t-PA in 15,059 patients and showed no significant difference between the two drugs in the rate of mortality and stroke. There was no significant difference between r-PA and t-PA in mortality at one year (11.2 vs. 11.1%) (Topol et al. 2000). In INJECT trial, r-PA was compared with streptokinase in the treatment of acute MI (Wilcox 1995), and was shown to be equivalent to standard streptokinase in 35-day mortality, recurrent MI, in-hospital stroke rates, and major

bleeding events. T-PA was also associated with reduced risk of cardiogenic shock or hypotension and heart failure.

3.2.3 Complications

Bleeding and hemorrhagic stroke are two primary complications of all fibrinolytic agents, which raise concerns about risk of harm overwhelming benefits.

3.2.3.1 Bleeding

In GUSTO-I trial, 11.4% of the patients treated by streptokinase and t-PA had moderate bleeding, defined by the need for transfusion without influencing hemodynamic status or a need for interventions, while 1.8% had severe bleeding, defined by substantial hemodynamic compromise that required intervention or treatment (Berkowitz et al. 1997). Risk factors for bleeding include increased age, lighter weight, female sex, African ancestry, and experiencing invasive procedures. Bleeding also increases the risk of nonhemorrhagic adverse events, and accordingly is associated with increased length of hospital stay and mortality (Berkowitz et al. 1997).

3.2.3.2 Stroke

Stroke and intracranial hemorrhage (ICH) are severe complications of fibrinolytic therapy. In FASTRAK II project, stroke and intracranial hemorrhage (ICH) occurred in 1.2 and 0.7% of the patients with fibrinolytic therapy, respectively (Huynh et al. 2004). In patients who developed strokes after fibrinolysis, mortality rate increased to 41% and morbidity rate to 31% (Gore et al. 1995). Similar findings were noted in the (United States) National Registry of Myocardial Infarction-2 registry. Elderly age, female sex, prior history of stroke or transient ischemic attack, hypertension, weight $\leq$65 kg for women or $\leq$80 kg for men, international normalized ratio >4, or prothrombin time >24 s were independently associated stroke and ICH.

3.3 Percutaneous Coronary Intervention

Percutaneous coronary intervention (PCI) has become the most frequently performed therapeutic procedure in medicine. Balloon angioplasty provided a nonsurgical revascularization alternative to CABG, but was limited by acute arterial recoil, dissections, and restenosis. Coronary stents were developed to prevent abrupt artery closure following balloon angioplasty. Bare metal stents (BMS) improved procedural safety and

efficacy, however, was associated with arterial injury and elicited neointimal hyperplasia, leading to restenosis and adverse consequences. Drug-eluting stent (DES) was designed to decrease neointimal hyperplasia and reduced the rate of restenosis. In DES, metallic stent is coated with polymer and antiproliferative agents. The controlled local release of agents has reduced the local proliferative healing response and consistently reduced the risk of restenosis. Randomized trials and large registry studies have reported that DES significantly reduced the risk of repeat revascularization. In a meta-analysis involving 38 trials and 18,000 patients, early generation of DES significantly decreased the rate of repeat revascularization. In a large randomized trial, DES reduced the risk of stent thrombosis, repeat revascularization, and myocardial infarction. As a result, stenting has become the standard of care for PCIs, and DES is placed in most patients.

3.3.1 Type of Drug-Eluting Stents

Currently DESs have the same general components, which include stent platform, polymer, and antiproliferative agents. The difference mainly exists in the biologic characteristics and antiproliferative effects of coating agents.

The first commercially available DESs include the sirolimus-eluting stent and paclitaxel-eluting stent, and are now mostly replaced by second-generation DES with advanced stent platforms and polymer biocompatibility.

The "second-generation" DES, including zotarolimus-eluting stent and the everolimus-eluting stent, has undergone further modification. The stent platform is made of cobalt- or platinum-chromium alloy and is thinner and more deliverable than the first-generation DES. The new-generation DESs have polymer with better pharmacokinetics and are more biocompatible, generating less inflammatory response and more rapid vessel endothelialization, which may be associated with lower rates of myocardial infarction and stent thrombosis. In a meta-analysis of four randomized trials, DES reduced the risk of all-cause death (RR = 0.8, 95% CI 0.59–1.07), myocardial infarction (RR = 0.56, 95% CI 0.43–0.72), stent thrombosis (RR = 0.32, 95% CI 0.20–0.51), and repeat revascularization (RR = 0.57, 95% CI 0.46–0.71).

3.3.2 Indications for Use of Drug-Eluting Stents

DESs provide effective and relatively safe alternatives to CABG for patients with coronary artery disease. In FAME-2 trial, DESs significantly reduced the need for urgent revascularization as compared with medical therapy in patients with stable coronary artery disease (1.6% vs. 11.1%, $P < 0.001$). According to the 2014 guidelines of European Society of Cardiology for myocardial revascularization, use of DES has a class IA recommendation for patients with stable coronary artery disease.

Use of DES in patients with multivessel disease, unprotected left main disease, and diabetes is still a matter of debate.

Stent implantation has become standard reperfusion approach for patients with acute myocardial infarction. Several trials have shown that DES reduced the risk of repeat revascularization in patients with acute myocardial infarction as compared with BMS, but was associated with very late stent thrombosis. In the EXAMINATION study, everolimus-eluting stents reduced the risk of repeat revascularization and stent thrombosis as well. Larger studies with long-term outcomes will provide more detailed evidence on the use of DES for infarction. DES has a class IA recommendation for patients with acute infarction and do not have contradictions for dual antiplatelet therapy.

3.3.3 Periprocedural Complications

Improvements in devices, the use of stents, and aggressive antiplatelet therapy have significantly reduced the incidence of major periprocedural complications of PCI over the past 15–20 years. However, percutaneous and intracoronary procedure also have potential risk of coronary artery complications. The use of guidewires, catheters into the diseased artery, may lead to vessel injuries and consequent major complications.

3.3.3.1 Dissection and Abrupt Closure

Coronary arterial dissection and acute closure were once mostly occurred after percutaneous transluminal coronary angioplasty, without intentional stenting. This complication is commonly due to arterial dissection. Vigorous attempts by guidewire and the following catheters, and the "controlled injury" induced by inflation of the dilation catheter are the main cause of arterial dissection. Dissections occurred in up to 50% of patients who received coronary angioplasty, but were much less frequent since stents are generally used in most percutaneous coronary procedures.

Acute closure was mostly associated with large dissections (Huber et al. 1991; Ellis et al. 1988) and occurs in 4–9% of angioplasty cases. Dissection with reduced flow or total occlusion increases the risk mortality and nonfatal myocardial infarction by 10 times. Most occlusion (90%) can be reversed by stent implantation, but some patients still require bypass surgery to deal with persistent occlusion and ischemia.

3.3.3.2 Intramural Hematoma

Intramural hematoma is often caused by vessel injury after intracoronary procedure. Blood accumulated in the medial space between the internal elastic membrane and

the external elastic membrane. This complication occurs more commonly in coronary angioplasty than in stenting.

3.3.3.3 Perforation

Perforation and rupture of coronary arteries are serious complications that result from guidewire attempts, atherectomy devices, and balloons dilation. Coronary artery perforations occur in 0.2–0.6% of patients undergoing angioplasty and are 0.84% (Stankovic et al. 2004). After stent implantation. but are potentially catastrophic. Significant adverse events occurred in 35% (29 of 84) patients with a perforation, including 7 death (8.3%).

3.3.3.4 Failure of Stent Deployment

The risk of inability to deliver the stent to or expand it within the target lesion is higher for lesions in the left circumflex artery and other longer and complex stenosis. In patients with unsuccessful stent deployment, as much as 43% had major cardiac event in 30 days, as compared with 4% in those with successful deployment (Schuhlen et al. 1998). The risk of stent deployment is much lower for new generations of stents, which ranged from 0.4 to 2% (Bolte et al. 2001).

3.3.3.5 Stent Thrombosis

Stent thrombosis is an uncommon but catastrophic complication which significantly increases the risk of major cardiac events like death and myocardial infarction. The foremost and important risk factor of stent thrombosis is the absence of dual antiplatelet therapy. Acute stent thrombosis (within 24 h) and subacute thrombosis (within 30 days) is also potentially due to angiographic complications, such as residual dissection or slow flow. Late stent thrombosis (after one year) mostly occurs in DES and are related to delayed neointimal coverage and lasting vessel inflammation (Joner et al. 2006).

3.4 Coronary Artery Bypass Grafting

Coronary artery bypass grafting (CABG) is the most commonly performed cardiac surgery and most effective for the revascularization for stenotic coronary arteries. In patients with coronary artery disease caused by partially or completely obstructed atherosclerotic coronary arteries, CABG is used to relieve myocardial ischemia by constructing grafts to bypass culprit lesions and complement blood supply to distal coronary branches.

CABG is very effective in improving the patients prognosis after coronary artery disease, and selecting the eligible patients is a critical precondition for good outcomes. The evaluation of patients for CABG is based on the characteristics and comorbidity of the patient, the coronary anatomy, and, extent of coronary artery disease. CABG is performed primarily for patients with complex stable CAD including over 50% stenosis in left main disease with SYNTAX score over 33, and/or three-vessel disease ($\geq$50%) with SYNTAX score over 23. Patients with two-vessel CAD involving LAD artery and a SYNTAX score $\geq$23 is also recommended to undergo CABG. Patients with impaired left ventricular ejection fraction ($\leq$45%), diabetes, and ischemic mitral regurgitation are getting more survival benefit from CABG.

3.4.1 The Choice of Conduits

After a half-century development, the technique of CABG has undergone extraordinary evolutions. The choice of conduit for collateral blood supply was one of the most important issues associated with patients prognosis.

Left internal thoracic artery (LIMA) and the greater saphenous vein are the most commonly used bypass conduits. LIMA is preferable for grafting for lesions of the anterior descending coronary artery whenever indicated and technically feasible. LIMA was associated with lower mortality rate and much higher ten-year patency rate (Loop et al. 1986) with less progression of atherosclerotic plaque, fibrosis, and calcification within the proximal left anterior descending. The anatomic and histological structure of IMA has made it a favorable conduit for myocardial revascularization and quality indicator in CABG. Bilateral IMA has also been proposed to reduce myocardial infarction, reoperation and PCI after CABG. However, concerns have raised about technical difficulty and increased risk of delayed wound healing caused by postoperative reduction in sternal perfusion. Skeletonization of the IMA has also been suggested for added extra length, although without long-term benefits. Long-term data is still required for further confirmed evidence.

Saphenous vein is the most easily accessible graft for CABG. Besides arterial grafts, most patients who undergo CABG receive at least one saphenous vein graft (SVG). However, about 25% vein grafts failed in the first 12–18 month, and SVGs do not parallel with IMA grafts in their survival benefits, even with aggressive lipid lowering therapies.

Grafts from other arteries, such as the radial artery, the right internal thoracic artery, and the gastroepiploic artery, have been investigated and generally have been shown to have better patency than saphenous-vein grafts but are not routinely used (Suma et al. 2007; Desai et al. 2004). In a review on the choice of conduits in coronary artery bypass surgery, the authors provided opinions on the selection of conduits in accordance with technical accessibility, anatomic feature, angiographic factors, and patients characteristics. Patients with no major risk factors were eligible for bilateral IMA, and RA was indicated for severe target vessel stenosis (>70%),

GEA could be considered for revascularization for inferior wall. However, the author still emphasized that more evidence is needed.

3.4.2 Periprocedural Complications

3.4.2.1 Perioperative Myocardial Infarction

The risk of perioperative myocardial infarction with new Q wave on ECG after CABG ranges from 0 to 10% in different cardiac centers, and is higher in patients with cardiomegaly, long time cardiopulmonary bypass, repeat CABG, and combined cardiac surgery (Chaitman et al. 1983; Yokoyama et al. 2000; Stephan et al. 1996). A new Q wave myocardial infarction indicates poor myocardial perfusion distal to grafts anastomosis. The diagnosis of perioperative myocardial infarction, however, may be difficult, for the CABG-induced postoperative myocardial injury and inflammation also lead to ECG changes and cardiac enzyme elevation. The currently used diagnosis for MI was according to Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Health Federation Task Force definition, which requires increases of biomarkers greater than five times the 99th percentile of the upper reference limit plus either new pathologic Q waves or new left bundle branch block, angiographically documented new graft, native coronary artery occlusion, or imaging evidence of new loss of viable myocardium (Thygesen et al. 2007).

Perioperative myocardial infarction increases the risk of postoperative adverse events. The Coronary Artery Surgery Study (CASS) reported a in-hospital mortality of 9.7% in patients with perioperative new Q wave MI, as compared with 1.0% in those without MI.

3.4.2.2 Early Graft Occlusion

Graft occlusion within the first 30 days after surgery are generally due to suboptimal anastomosis technique and injured graft during harvesting, and occurs in 5–10% of saphenous vein grafts (Dauerman et al. 1996). Antiplatelet therapy, as important secondary preventive strategy, would reduce the risk of postoperative occlusion, and advanced surgical techniques like no-touch approach might also have potential benefits.

3.4.2.3 Low Cardiac Output

Low cardiac output is a relative frequent early postoperative complication. The incidence of low output syndrome is 6% in patients with preoperative left ventricular ejection fraction >40, 12% in those with LVEF between 20–40, and 23% in those

with LVEF <20% (Yau et al. 1999). The incidence of low cardiac output can result from perioperative factors including cardioplegic arrest and ischemic injury, reduced preload, excessive afterload, and perioperative complications like arrhythmias and MI (McKenney et al. 1994; Roberts et al. 1977), and often transient and response to fluid therapy and/or inotropic support. However, persistent low cardiac output for which pharmacologic therapy is ineffective, mechanical support is necessary.

3.4.2.4 Arrhythmias

Arrhythmias are common complications after CABG, and most often are tachyarrhythmias. Atrial fibrillation is one of the most important postoperative events, occurs in 15–40% of CABG cases. Atrial fibrillation after CABG is usually self-limited but is associated with increased risk of adverse outcomes including stroke, in-hospital and long-term mortality (Villareal et al. 2004; Bramer et al. 2010; Mariscalco et al. 2008). Perioperative beta blocker is considered the most effective therapy for the prevention of postoperative atrial fibrillation, and the current guideline recommended continued perioperative beta blocker therapy for patient without contradictions.

3.5 Decision-Making for Revascularization

3.5.1 Heart Team

The concept of Heart Team was first introduced in 2000s through randomized trials (Head et al. 2013). A Heart Team is made up of clinical or noninvasive cardiologists, cardiac surgeons and interventional cardiologists, provides a balanced, multidisciplinary decision-making process. The main job of Heart Team is to review the patient's medical condition and assess anatomy of coronary disease together, to develop the best revascularization options that combines local therapeutic capability and patient preferences. The 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery give a Class I (Level of Evidence: C) recommendations for Heart Team approach to revascularization in patients with unprotected left main or complex CAD (Hillis et al. 2011). Correspondingly, a Class I recommendation was made in 2014 ESC/EACTS Guidelines on myocardial revascularization (Kolh and Windecker 2014).

However, Heart Team has not yet been widely implemented for the novelty of concept, lack of experience and proven benefit, logistical issues, and doctors passive opinions. Moreover, the absence of reliable criteria or guidelines for Heart Team organization and involvement has made the formation and validation of Heart Team more difficult. The process of multidisciplinary decision-making by Heart Team also raised concerns on prolonged time delay before treatment and increasing expense. Therefore, it is crucial to design appropriate organizations and logistics to enlarge the

effect of Heart Team. A coordinator is helpful for acquiring all necessary information for decision making during Heart Team discussion. Leadership, but not dominance, is important for efficient team work, active participation, and innovation. Ad hoc meetings after coronary angiogram may be the best opportunity for Heart Team to collaborate and develop optimal strategy. The process of decision-making has three key points: sufficient information transfer, among physicians, from physicians to patients and patients to physicians; adequate discussion; and consensus.

We believe that a balanced multidisciplinary Heart Team has a promising future for interpret the available diagnostics, implement guideline directed therapy, consider local expertise and through shared decision-making take into account patient preferences, to provide a more objective and uniform decision-making process (Head et al. 2013). However, evidence on the benefit of Heart Team still requires updating. As a paucity of observational and randomized data, further study is still needed to provide insight to the Heart Team approach.

3.5.2 Left Main Disease

Significant left main coronary artery disease (LMCAD defined as a greater than 50% angiographic narrowing) is found in 4–6% of all patients who undergo coronary arteriography (Ragosta et al. 2006) and is associated with high morbidity and mortality owing to the large amount of myocardium at risk (at least 75% of the left ventricle) (Serruys et al. 2009). The optimal management of patients with left main coronary artery disease has been the subject of intense investigation for decades, both CABG and PCI along with best selected preventive therapies was recommended in the newest guidelines on myocardial revascularization for left main coronary artery disease in selective patients, and coronary artery bypass graft surgery (CABG) with best selected preventive therapies is recommended for all patients with significant left main coronary artery disease due to significantly improved survival.

CABG has a long track record of safety and efficacy in patients with LMCAD and is associated with significantly better cardiovascular outcomes, including mortality. In the 1970s, Veterans Administration Cooperative Study compared a strategy of initial CABG versus deferred CABG, substantial survival advantages were observed in patients underwent initial CABG at 2 years and 11 years, and also greater benefit was found in high-risk patients with more than 75% left main stenosis and/or left ventricular dysfunction, compared with patients with 50–75% stenosis and normal left ventricular function. The CASS Registry contained data from 1,484 patients with more than 50% left main CAD initially treated surgically or nonsurgically, median survival duration was 13.3 years in the surgical group, 6.6 years in the medical group (Caracciolo et al. 1995). With the development of surgical technology, Thirty-day mortality of CABG is now under 2% in some United States institutions, and in Fuwai hospital, this rate is lower than 1%.

The LMCAD once was a forbidden territory for percutaneous coronary intervention (PCI), however, the accumulation of experience, coupled with improved

technology and pharmacology, has led to this approach being rapidly evolved and broadly adopted in stenosis (Park et al. 2015), and also for cautiously selected patients with LMCAD. The NOBLE trial (Nordic-Baltic-British Left Main Revascularization) and EXCEL trial (Evaluation of XIENCE vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) were the latest published studies focus on the comparison of CABG with PCI for left main CAD. The NOBLE study, 1201 patients were randomly assigned, reported that CABG might provide a better clinical outcome for treatment of left main coronary artery disease than PCI, regard to the primary endpoint of major adverse cardiac and cerebrovascular events, with 46% excess hazard with PCI over CABG at 5 years ($P = 0.01$). However, the EXCEL trial, in which 1905 participants were enrolled, showed that the primary composite endpoint event of death, stroke, or MI at 3 years occurred in 15.4% of the patients in the PCI group and in 14.7% of the patients in the CABG group ($P = 0.02$ for noninferiority), leading to the conclusion that in patients with left main coronary artery disease and low or intermediate SYNTAX scores, PCI with everolimus-eluting stents was noninferior to CABG. In a 2016 meta-analysis examined the results of PCI versus CABG for unprotected left main coronary artery stenosis, the pooled data were numerically leveraged by EXCEL and varied in their definition of periprocedural MI, leading to a neutral result for the primary endpoint of all-cause death, MI, or stroke (odds ratio, 0.97; 95% confidence interval, 0.79–1.17; $P = 0.73$) (Nerlekar et al. 2016). Taken together, EXCEL and NOBLE confirmed that CABG is the most robust and durable therapy for coronary revascularization in the presence of LMCAD, and also, for the treatment of patients with left main coronary artery disease and low or intermediate SYNTAX scores, PCI with everolimus-eluting stents can be considered as another choice. Meanwhile, a professional Heart Team should also be involved, helps to balance the risks and benefits associated with each procedure in conjunction with the baseline risk profile and patient preferences, and finally make the best choice of the optimum revascularization strategy for an individual patient.

3.5.3 Multivessel Disease

Based on the basic CAD secondary prevention strategies including therapeutic lifestyle changes (TLCs) such as increased physical activity, dietary modification/weight loss, smoking cessation, and adjunctive drug therapies such as the routinely consumption of aspirin and statins, beta blockers and angiotensin converting enzyme inhibitors or angiotensin receptor blockers, patients with stable coronary artery disease involving 2 or 3 vessels should be assessed periodically to determine whether medical therapy or medical therapy with revascularization is a more appropriate strategy for effective relief of angina and improvement in long-term survival.

The choice between coronary artery bypass graft surgery (CABG) versus percutaneous coronary intervention (PCI) in patients with multivessel disease is dependent upon a number of factors, including the number of vessels involved,

the anatomic complexity of the lesions requiring revascularization, likelihood of complete revascularization, patient comorbidities such as diabetes, and patient preference.

The 2009 published SYNTAX trial (The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) enrolled 1800 patients with three-vessel or left main coronary artery disease to undergo CABG or PCI, after 1 years' follow-up, major adverse cardiac or cerebrovascular events (MACCE) were significantly higher in the PCI group (17.8%, vs. 12.4% for CABG; $P = 0.002$), and the rates of death and myocardial infarction were similar between the two groups, but stroke was significantly more likely to occur with CABG (2.2%, vs. 0.6% with PCI; $P = 0.003$), leading to the conclusion that CABG remains the standard of care for patients with three-vessel or left main coronary artery disease. Meanwhile, according to the SYNTAX score, a semi-quantitative tool based on the results of coronary angiography, the sub-group analysis showed that among patients with low (0–22) and intermediate (23–32) SYNTAX scores, the clinical outcomes were comparable with PCI and CABG (13.6 vs. 14.7 and 16.7 vs. 12.0, respectively), whereas in those with a high score (≥33), outcomes were better with CABG (23.4 vs. 10.9%, respectively) at 12 months (Serruys et al. 2009). Five years later, the SYNTAX trial five-year outcomes were reported, which showed that estimates of MACCE were 26.9% in the CABG group and 37.3% in the PCI group ($p < 0.0001$), estimates of myocardial infarction (3.8% in the CABG group vs. 9.7% in the PCI group; $p < 0.0001$) and repeat revascularization (13.7% vs. 25.9%; $p < 0.0001$) were significantly increased with PCI versus CABG, and all-cause death (11.4% in the CABG group vs. 13.9% in the PCI group; $p = 0.10$) and stroke (3.7% vs. 2.4%; $p = 0.09$) were not significantly different between groups. In addition, consistent results were observed in patients with different SYNTAX score risk stratification. Thus, the authors interpret that CABG should remain the standard of care for patients with complex lesions (high or intermediate SYNTAX scores), and for patients with less complex disease (low SYNTAX scores), PCI is an acceptable alternative. The author also suggested that all patients with complex multivessel coronary artery disease should be reviewed and discussed by both a cardiac surgeon and interventional cardiologist to reach consensus on optimum treatment (Mohr et al. 2013).

As noted in the studies above, for many patients with multivessel coronary artery disease, relatively well-preserved left ventricular systolic function, low complexity coronary anatomy, and no diabetes, or say, in a low or intermediate SYNTAX scores (≤32), CABG and PCI may have the same outcomes; for these patients with complex anatomy or diabetes and high SYNTAX scores (≥33), however, CABG is strongly recommended.

Hybrid coronary revascularization (HCR) has been defined as the combination of minimally invasive direct coronary artery bypass surgery and percutaneous coronary intervention (PCI) in selected patients with multivessel coronary artery disease, which is thought to bring together the excellent patency rates and survival benefits associated with the durable left internal mammary artery graft to the left anterior descending artery with the good patency rates of drug-eluting stents, and aims to reduce surgical trauma while preserving long-term survival and minimizing adverse

cardiovascular events. While it has achieved some measure of popularity, HCR has not been evaluated in reliable large-scale randomized trials comparing it with PCI or CABG. The largest observational study to date, published on JACC in 2016, compared 200 patients who underwent HCR and 98 patients who underwent multivessel PCI, and reported that the rate of primary outcome of major adverse cardiac and cerebrovascular events (i.e., death, stroke, MI, and repeat revascularization) within 12 months of the procedure was similar between the two groups after adjustment for baseline risk (0.142 vs. 0.119%, respectively; hazard ratio 1.063; $p = 0.80$) (Puskas et al. 2016). Until evidence from more well-designed randomized trials supporting its use is available, we believe HCR is a reasonable choice at centers with expertise.

3.5.4 CAD with Comorbidities

3.5.4.1 Heart Failure

Heart failure (HF) is a common clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood, and coronary artery disease or ischemic cardiomyopathy is a dominant cause of HF in developed countries. Thus, revascularization with CABG or PCI is indicated for symptomatic relief of angina pectoris in patients with heart failure. The Surgical Treatment for Ischemic Heart Failure (STICH) study (Velazquez et al. 2016) was designed to test the hypothesis that CABG plus guideline-directed medical therapy for coronary artery disease, heart failure, and left ventricular dysfunction would improve survival over that with medical therapy alone in a sample of 1212 patients with CAD and LV dysfunction (EF $\leq$ 35%). After 10 years' follow-up, the authors reported that the primary outcome event (death from any cause) occurred in 359 patients (58.9%) in the CABG group and in 398 patients (66.1%) in the medical therapy group (hazard ratio with CABG vs. medical therapy, 0.84; 95% confidence interval (Tanne et al. 1998), 0.73–0.97; $P = 0.02$ by log-rank test), and the median survival was 1.44 years longer in the CABG group (7.73 years among patients in the CABG group and 6.29 years among patients in the medical therapy group). Based on these results, the STICH supports a significant benefit of CABG plus medical therapy over medical therapy alone with respect to the rate of death from any cause among patients with ischemic cardiomyopathy. Meanwhile, since most studies refer to the revascularization strategies for patients suffering from coronary artery disease and set LV dysfunction as an exclusive criterion, the available data is insufficient to evaluate the efficacy of PCI and compare PCI with CABG in patients with LV dysfunction. A recent propensity score matching study compared PCI with everolimus-eluting stents versus CABG and concluded that in patients with multivessel disease and severe LV systolic dysfunction, PCI with an EES resulted in survival similar to that of CABG (Bangalore et al. 2016). However, we highly recommend that the choice between CABG and PCI should be made by the Heart Team after careful evaluation of the patient's clinical status and coronary anatomy, including SYNTAX score,

comorbidities, and expected completeness of revascularizations, and a specialist in heart failure should also be consulted.

3.5.4.2 Diabetes

Patients with diabetes comprise as many as 25–30% of those who undergo revascularization, and the short- and long-term results of revascularization with percutaneous coronary intervention or coronary artery bypass graft surgery are often worse in diabetic patients (Malmberg et al. 2000), emphasized by a higher risk of cardiovascular events and death than those without diabetes. The approach to revascularization in diabetic patients with left main or lesser degrees of coronary disease is similar to the broad population of patients; however, the optimal revascularization strategy for patients with diabetes and multivessel coronary artery disease remains to be deliberated.

BARI 2D trial (Group et al. 2009) (The Bypass Angioplasty Revascularization Investigation 2 Diabetes) was designed to address the effects of therapy on the rate of myocardial ischemia, a major cause of death in patients with diabetes, and of insulin resistance, the fundamental mechanism underlying diabetes with profound cardiovascular consequences. Overall, 2368 patients with type 2 diabetes mellitus and stable ischemic heart disease were enrolled, at 5 years, the primary endpoints of the rates of survival or freedom from major cardiovascular event death, myocardial infarction (Wu et al. 1990, or stroke) did not differ significantly between the revascularization group and the IMT alone group (88.3 vs. 87.8% and 77.2 vs. 75.9%, respectively). However, in sub-group analysis, the rate of freedom from major cardiovascular events was significantly higher in the CABG plus IMT stratum compared to the corresponding IMT stratum (77.6 vs. 69.5%), predominantly attributable to a reduction in nonfatal MI.

The FREEDOM trial (Farkouh et al. 2012) (Future Revascularization Evaluation in Patients with Diabetes Mellitus) compares CABG against PCI with the use of early-generation DES (94%) in diabetic patients undergoing elective revascularization for multivessel disease without left main coronary stenosis. A total of 1900 patients were enrolled at 140 international centers from 2005 through 2010 and were followed for a minimum of 2 years (median among survivors, 3.8 years). A more frequent primary outcome occurrence (a composite of death from any cause, nonfatal myocardial infarction, and nonfatal stroke) was observed in the PCI group ($P = 0.005$), with 5-year rates of 26.6% in the PCI group and 18.7% in the CABG group, driven by a borderline reduction of all-cause mortality ($P = 0.049$) and by a markedly lower rate of myocardial infarction in the CABG group ($P < 0.001$), leading to the authors' conclusion that for patients with diabetes and advanced coronary artery disease, CABG was superior to PCI in that it significantly reduced rates of death and myocardial infarction.

In the CARDia trial (Kapur et al. 2010) (Coronary Artery Revascularization in Diabetes), 510 diabetic patients with multivessel or complex single-vessel CAD at 24 sites were enrolled and randomly assigned to either CABG or PCI with the use of

either BMS or DES and routine use of abciximab. There were no differences between CABG and PCI for the primary endpoint of 1-year composite of death, myocardial infarction, or stroke (12.4% in the CABG and 11.6% in the PCI group), whereas repeat revascularization was more common among patients assigned to PCI, and also a higher rate of stroke in patients underwent CABG.

Hence, taking currently available evidence into consideration, for diabetic patients with multivessel CAD, CABG is the best revascularization choice; however, among diabetic patients with multivessel disease and low SYNTAX score, PCI can be considered as a treatment alternative.

3.5.5 Unstable Angina and Non-ST-Segment Elevation Acute Coronary Syndromes

Unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI) are part of the continuum of acute coronary syndrome (ACS), and the primary difference between UA and NSTEMI mainly lies in whether the ischemia is severe enough to cause sufficient myocardial damage to release detectable quantities of a marker of myocardial injury. After early risk assessment (TIMI risk score, GRAC 2E risk score, etc.) soon after the diagnosis is made to identify patients at high immediate- and long-term risk for death and cardiovascular events, whether and when coronary angiography and revascularization be performed should be determined. The invasive strategy of angiography followed by revascularization (PCI or CABG) is aimed at relieving symptom and improving long-term prognosis, and which approach to choose is based on comprehensive consideration regards to overall quality of life, length of hospital stays, and potential risk associated with invasive and pharmacological treatments.

The issue of whether patients should undergo early invasive or conservative strategy has long been studied. In general, unstable patients are referred for immediate angiography, high-risk patients are assigned to an invasive strategy, and low-risk patients are assigned to a conservative strategy. A meta-analysis of seven trials that compared early invasive against conservative approach showed a significant reduction in risk for all-cause mortality (early invasive vs. conservative approach, RR = 0.75; 95% CI 0.63–0.90; $P < 0.001$) and myocardial infarction (early invasive vs. conservative approach, RR = 0.83; 95% CI 0.72–0.96; $P = 0.012$) at 2 years without excess of death and myocardial infarction at 1 month (Bavry et al. 2006). A further meta-analysis of eight RCTs showed a significant lower incidence of death, myocardial infarction, or rehospitalization for ACS (OR = 0.78; 95% CI 0.61–0.98) for the invasive strategy at 1 year (O'Donoghue et al. 2008), and mainly attributed to improved outcomes in biomarker-positive (high-risk) patients. The results of these studies demonstrate that age, diabetes, previous myocardial infarction, ST-segment depression, hypertension, body mass index (<25 kg/m^2 or >35 kg/m^2), and treatment strategy were independent predictors of death and myocardial infarction during follow-up. Hence, a routine invasive strategy should be recommended but the

importance of risk stratification in the decision-making process management should be equally valued. For patients who are eligible for invasive strategy, the timing of angiography and revascularization should be based on patient risk profile. The 2014 ESC/EACTS guidelines on myocardial revascularization recommended that patients at very high risk (as defined above) should be considered for urgent coronary angiography (in less than 2 h) (Kolh and Windecker 2014). In patients at high risk, with at least one primary high-risk criterion, an early invasive strategy within 24 h appears to be the reasonable timescale. In lower-risk subsets, with a GRACE risk score of <140 but with at least one secondary high-risk criterion, the invasive evaluation can be delayed without increased risk but should be performed during the same hospital stay, preferably within 72 h of admission. In other low-risk patients without recurrent symptoms, a noninvasive assessment of inducible ischemia should be performed before hospital discharge (Kolh and Windecker 2014).

In stabilized patients, the choice of revascularization modality can be made in analogy to patients with SCAD. In approximately one-third of patients, angiography will reveal single-vessel disease, allowing ad hoc PCI in most cases. However, in patients found to have multivessel disease (including the culprit lesion) after coronary angiography, there are three major options for revascularization: culprit lesion/vessel PCI only, multivessel PCI (including the culprit lesion), or CABG. For patients whom multivessel revascularization is deemed necessary, the revascularization strategy should be determined early by the Heart Team and based on the patient's clinical status, as well as the severity and distribution of the CAD and the characteristics of the lesion. CABG is often preferred over PCI for the treatment of patients with left main or left main equivalent disease, or three-vessel disease involving the left anterior descending artery in patients with a reduced left ventricular ejection fraction or treated diabetes.

The AWESOME (Morrison et al. 2001) and ERACI II (Rodriguez et al. 2001) trials compared CABG with PCI in patients who are angiographically eligible for either approach. These studies came to similar conclusions: long-term mortality was comparable with both strategies but revascularization rates were higher with PCI as the primary strategy. A limitation to both trials is that they were performed before the availability of drug-eluting stents, which markedly reduce the rate of revascularization. The ACUITY trial (Ben-Gal et al. 2010) also compared CABG with PCI in a propensity-matched analysis among patients with multivessel disease. PCI-treated patients had lower rates of stroke, myocardial infarction, bleeding, and renal injury, similar 1-month and 1-year mortality, but significantly higher rates of unplanned revascularization at both 1 month and 1 year. However, only 43% of CABG patients could be matched and there was a strong trend for a higher rate of major adverse cardiac events (MACE) at 1 year with PCI, compared with CABG (25.0% vs. 19.5%, respectively; P 1/4 0.05).

In non-ST-elevation ACS (NSTEACS) patients with multivessel disease for whom PCI is chosen as the revascularization strategy, the operator must decide between culprit only or multivessel PCI. Culprit-lesion PCI does not necessarily require a case-by-case review by the Heart Team when, on clinical or angiographic grounds, the procedure needs to be performed ad hoc after angiography, such as continuing or

recurrent ischemia, hemodynamic instability, pulmonary edema, recurrent ventricular arrhythmias, or total occlusion of the culprit coronary artery requiring urgent revascularization. After culprit-lesion PCI, patients with scores in the two higher terciles of the SYNTAX score should be discussed by the Heart Team, in the context of functional evaluation of the remaining lesions and assessment of patients' comorbidities and individual characteristics (Kolh and Windecker 2014). A retrospective study of 1240 patients with NSTEMI investigated the safety and efficacy of multivessel stenting versus culprit-only stenting with bare metal stents. Multivessel stenting was associated with a significant reduction in the composite endpoint of death, MI, or revascularization during a mean follow-up of 2.3 years (hazard ratio 0.80, 95% CI 0.64–0.99). However, the difference was entirely attributable to a lower revascularization rate. Safety endpoints did not differ between the two groups. Since there have been no randomized trials directly comparing complete to incomplete revascularization (ICR) in NSTEACS patients with multivessel disease, we recommend the assessment of clinical status and disease severity to guide clinical practice until further studies inform decision making between culprit lesion only or multivessel PCI be conducted.

3.5.6 ST-Segment Elevation Myocardial Infarction

ST-elevation myocardial infarction (STEMI) is a clinical syndrome defined by characteristic symptoms of myocardial ischemia in association with persistent electrocardiographic (ECG) ST-elevation and subsequent release of biomarkers of myocardial necrosis (O'Gara et al. 2013). For patients with STEMI, prompt restoration of myocardial blood flow is essential to optimize myocardial salvage and to reduce mortality, and the decision must be made as soon as possible as to whether reperfusion will be achieved with fibrinolytic agents, primary (direct) PCI, or bypass surgery. Here we will mainly address the reperfusion strategy, including primary and secondary PCI and CABG.

Primary PCI is defined as percutaneous catheter intervention in the setting of STEMI, without previous fibrinolysis. It has replaced fibrinolysis as the preferred reperfusion strategy in patients with STEMI, provided it can be performed in a timely manner in high-volume PCI centers with experienced operators and 24-h, 7-day catheterization laboratory activation (Kolh and Windecker 2014). Compared with fibrinolytic therapy, primary PCI produces higher rates of infarct artery patency, TIMI 3 flow, and access site bleeding and lower rates of recurrent ischemia, reinfarction, emergency repeat revascularization procedures, intracranial hemorrhage (ICH), and death (Keeley et al. 2003). Earlier, successful PCI also greatly decreases the complications of STEMI that result from longer ischemic times or unsuccessful fibrinolytic therapy, allowing earlier hospital discharge and resumption of daily activities. Primary PCI has its greatest survival benefit in high-risk patients (Tebbe et al. 1995). For patients undergoing primary PCI, stenting should be preferred over

balloon angioplasty in the setting of primary PCI as it reduces the risk of abrupt closure, re-infarction, and repeat revascularization. Meanwhile, thrombus aspiration has been proposed as an adjunct during primary PCI, to further improve epicardial and myocardial reperfusion by prevention of distal embolization of thrombotic material and plaque debris.

Early, routine, post-thrombolysis angiography with subsequent PCI (if required) has been proven to reduce the rates of re-infarction and recurrent ischemia, which is referred as secondary PCI, compared with a strategy of "watchful waiting" (in this situation, angiography and revascularization were indicated only in patients with spontaneous or induced severe ischemia or LV dysfunction). In cases of failed fibrinolysis, or if there is evidence of re-occlusion or re-infarction with recurrence of ST-segment elevation, the patient should undergo immediate coronary angiography and rescue PCI (Gershlick et al. 2005).

CABG has a limited role in the acute phase of STEMI other than for cardiogenic shock, but it may be indicated for failed PCI, for coronary anatomy not amenable to PCI, and at the time of surgical repair of a mechanical defect, such as ventricular septal, papillary muscle, or free-wall rupture (O'Gara et al. 2013). The implementation of standard operative approach, such as on-pump beating-heart surgery, off-pump techniques, or adjunctive temporary mechanical circulatory support devices has led to improved survival rates after CABG in the acute hospital phase, but the timing of urgent CABG in patients with STEMI should be cautiously considered, and also an alternative antiplatelet strategy in patients with STEMI who may require urgent CABG during their index hospitalization (Hillis et al. 2011).

3.6 Secondary Prevention

Patients with established cardiovascular disease (CVD) have a high risk of subsequent cardiovascular events, including myocardial infarction (MI), stroke, and death; thus, we recommend that all patients with established coronary heart disease should receive interventions to prevent a subsequent CVD event. These are termed secondary prevention, including therapeutic lifestyle changes (TLCs) and adjunctive drug therapies, which can be briefly referred to as *ABCDE plan*; A for Aspirin and Anti-angina therapy, B for Beta-blockers and Blood pressure control, C for Cholesterol lowing and Cigarette quitting, D for Diet control and Diabetes treatment, E for Exercise and Education. The reduction of mortality and improvement of life quality due to effective secondary prevention has been determined by clinical studies and recommended by clinical guidelines (Smith et al. 2006). For patients at high risk (those with a prior CVD event as well as those whose 10-year risk is >10%), older adults, accompanied with diabetes mellitus, chronic kidney disease, interventions to prevent CVD events should be more emphasized and intensified.

3.6.1 Medical Therapy

Medical therapy focuses on comprehensive risk factor modification, including beta-blockers, antiplatelet agents, statins, and so on. Multiple clinical trials have shown that beta-blocker therapy can reduce recurrent MI, sudden cardiac death, and mortality in patients after MI, even in those who are normotensive; and the AHA has recommended that a beta-blocker regimen be initiated and maintained indefinitely for the secondary prevention of CAD in all patients after having an MI, unless contraindicated (Kulik et al. 2015). Antiplatelet agents are also recommended in all patients for the secondary prevention of CAD for peruse of net clinical benefits and reduction in ischemic events. Oral antiplatelet agents for secondary prevention include the cyclo-oxygenase-1 inhibitor aspirin, the ADP-dependent P2Y12 inhibitors clopidogrel, prasugrel and ticagrelor, and aspirin represents the cornerstone in secondary prevention of patients with stable CAD or ACS. The evidence is also well studied that reducing cholesterol levels decreases the risk of recurrent coronary events, and evidence-based cholesterol-lowering guidelines have been established, that statins should be the initial medication accompanied by beta-blockers and other medications for secondary prevention.

3.6.2 Exercise

Regular physical activity (PA) independently decreases the risk of cardiovascular disease (CVD) while also having a positive, dose-related impact on other cardiovascular risk factors. It has increasingly become a focus of CVD primary and secondary prevention (Varghese et al. 2016). Exercise-based cardiac rehabilitation (CR) is the cornerstone for secondary prevention of CVD. Indications include stable angina pectoris, myocardial infarction, undergone cardiac surgery (CABG, valve replacement and so on) and PCI. After pre-exercise screening is completed to identify those in whom exercise should be delayed or prohibited, the general recommendation for patients is 30–60 min daily of moderate-intensity PA for at least 5 days of the week and performed at an intensity of 40–80% of the peak heart rate (Fletcher et al. 2013). To note, some studies also suggest that extreme exercise may evoke acute elevations in troponin I and B-type natriuretic peptide and evidence of transient myocardial dysfunction, which means excessive exercise, may have some acute and/or chronic adverse effects (Trivax et al. 2010). It's more likely a J-curve or U-curve pattern regarding the exercise volume and clinical outcomes, where it is preferable to be in the middle of the distribution.

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Chapter 4
Antithrombotic Drugs—Pharmacology and Perspectives

Tianyu Li, Deshan Yuan and Jinqing Yuan

Abstract Thrombosis, the localized clotting of blood that affects arterial or venous circulation, is one of the leading causes of death worldwide. Arterial thrombosis is commonly initiated by vascular endothelial injury, while venous thrombosis mainly stems from blood stasis. Despite these differences, platelet adhesion, activation and aggregation, and fibrin formation as a result of coagulation constitute the fundamental processes of thrombus formation. Antithrombotic drugs permitted on the clinical currently can dramatically reduce major adverse cardiovascular events; however, they can also increase the bleeding risk. Discovery of antithrombotic drugs that can effectively prevent thrombosis while sparing bleeding side effects remains unmet medical need. In this chapter, we provide an overview on the pathophysiology of thrombosis, followed by introduction of each class of antithrombotic drugs including their pharmacology, clinical applications and limitations. Practical challenges and future perspectives of antithrombotic drugs are discussed in the last part of this chapter.

Keywords Thrombosis · Antithrombotic drugs · Thrombolytic drugs

4.1 Hemostasis and Thrombosis

Hemostasis is the cessation of bleeding from an injured vessel consisting of three stages: vasoconstriction, platelet plug formation (primary hemostasis) and coagulation (secondary hemostasis). Vasoconstriction occurs immediately and markedly reduces blood flow to the injured area. Then, platelets stick together to form a temporary plug to seal vascular defects. Simultaneously, the coagulation cascade is activated, ultimately resulting in consolidation of the platelet plug with fibrin strands as well as some red and white blood cells. Later, as wound healing occurs, the blood clot

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is dissolved by plasmin, and this process is called fibrinolysis. Normally, hemostasis and fibrinolysis are finely regulated to ensure repair of vascular injury without thrombosis.

Under some abnormal circumstances, the mechanism of physiological hemostasis also contributes to pathological thrombosis, which causes tissue injury by local vascular occlusion or by distal embolization. Generally, platelet plug formation primarily contributes to arterial thrombosis, while coagulation cascade activation plays a prominent role in venous thrombosis. Thrombosis is usually related to one or more components of the Virchow triad: (1) Endothelial injury primarily underlies thrombosis in the arterial circulation; (2) Turbulence has a vital role in arterial thrombosis. Stasis is a major contributor in venous thrombosis; (3) Hypercoagulability is mainly associated with venous thrombosis.

4.1.1 Platelet

Platelets play a critical role in hemostasis by forming the primary plug and providing a surface that concentrates activated coagulation factors to enhance the rate of thrombin generation. There are three steps of platelet plug formation:

- Adhesion: When endothelial layer is disrupted, subendothelial adhesive glycoproteins, such as collagen and vWF, bind glycoprotein receptors expressed on platelet surface, thereby anchoring platelets to the site of injury.
- Activation: Shape change and release reaction are referred to collectively as platelet activation. After adhesion, platelets rapidly change shape accompanied by a conformational change in GPIIbIIIa, the dominant platelet receptor, allowing these receptors to bind fibrinogen. Adherent platelets also release substances (e.g., ADP, TxA_2 and 5-HT) that activate passing platelets, thereby recruiting them to the site of injury.
- Aggregation: Platelet aggregation occurs when fibrinogen binds simultaneously to GPIIbIIIa on two different platelets and bridge adjacent platelets together, leading to the formation of a platelet plug.

Activated platelets accelerate coagulation by translocating negatively charged phospholipids to the platelet surface, providing sites for the assembly of coagulation factor complexes.

4.1.2 Coagulation

Coagulation is the process by which blood changes from a liquid to a gel, which takes place in three essential steps:

- Coagulation cascade activation: At the same time as platelet activation, coagulation cascade is activated via intrinsic pathway (contact activation pathway) or/and extrinsic pathway (tissue factor pathway), each pathway involves a series of zymogen activation reactions. At each step, a coagulation factor zymogen is converted to an active protease which activates the next zymogen in the sequence. Finally, a complex of activated chemicals called prothrombinase complex (FXa, FVa, calcium and anionic phospholipids) is formed on the membrane of activated platelets and other cells.
- Generation of thrombin: Prothrombinase complex causes conversion of prothrombin into thrombin (FIIa). Thrombin activates platelets and upstream coagulation factors, including FV, FVIII and FXI, resulting in a burst of thrombin generation.
- Formation of blood clot: Thrombin converts fibrinogen to fibrin, allows soluble fibrin to polymerize and forms insoluble cross-linked fibrin fibers which reinforce the plate plug and entrap blood cells, leading to the formation of the blood clot.

Coagulation is precisely modulated by plasma coagulation inhibitors which downregulate coagulation to prevent massive thrombin generation in the absence of a substantial procoagulant stimulus. Some of the main physiological anticoagulants are as follows:

- Antithrombin attenuates coagulation by inactivating factors IIa, IXa, Xa, XIa and XIIa.
- Protein C system exerts anticoagulant effects by inactivating factors Va and VIIIa.
- Tissue factor pathway inhibitor (TFPI) specifically impedes extrinsic pathway by inactivating factor Xa and FVIIa-TF complex.

4.1.3 Fibrinolysis and Thrombolysis

4.1.3.1 Fibrinolysis

Fibrinolysis is the normal body breakdown of blood clots, which refers to the process of fibrin degraded by the fibrin-specific protease, plasmin.

Plasminogen, an inactive precursor of plasmin, is enmeshed within the blood clot when the clot is formed. After the clot has stopped bleeding (generally several days), plasminogen is converted by plasminogen activators to plasmin, which digests fibrin, limits the clot extension and removes the remaining unnecessary blood clot.

There are two endogenous plasminogen activators synthesized by endothelial cells and released in response to injury: tissue plasminogen activator (t-PA) and urokinase (u-PA); the former predominates under most conditions. Plasmin further stimulates plasmin formation by producing more activated t-PA and u-PA.

Fibrinolysis is regulated to remove unwanted thrombi while preserving fibrin in wounds to maintain hemostasis. t-PA and u-PA are inhibited by plasminogen activator

inhibitors (PAI)-1 and (PAI)-2. Plasmin activity is reduced by α_2-antiplasmin, α_2-macroglobulin and thrombin-activatable fibrinolysis inhibitor (TAFI).

Many small blood vessels occluded by clots are reopened spontaneously by this mechanism.

4.1.3.2 Thrombolysis

Thrombolysis is the breakdown of pathological thrombi using medication. Once thrombi acutely occlude major arteries or veins, fibrinolysis is often too slow to prevent subsequent tissue injury. The goal of thrombolytic therapy is to rapidly restore blood flow to an occluded vessel achieved by administering therapeutic doses of plasminogen activators, accelerating fibrinolytic proteolysis of the thrombus.

4.1.4 Arterial Thrombosis

Wall shear rates increase gradually from 300 to 800 s^{-1} in large arteries to 500–1600 s^{-1} in arterioles of the microcirculation. In pathologically stenotic vessels, the wall shear rates can reach 10,000 s^{-1} or even higher. Such a high-flow and high-stress arterial circulation is not suitable for coagulation factors to concentrate. In contrast, platelets can adhere to blood vessels, be activated to generate procoagulant properties on their cell surfaces and provide places for interaction of coagulation factors. Therefore, arterial thrombosis occurs mainly due to the formation of platelet plug. Factors that impel platelet adhesion, activation and aggregation promote formation of arterial thrombi.

- Endothelial injury exposes subendothelial prothrombotic substances (e.g., vWF, collagen and TF) to the blood, induces local activation of platelets and coagulation system. In arterial system, thrombi superimpose almost invariably upon pre-existing abnormal intimal surfaces, which typically are atherosclerotic lesions. Other vascular injuries such as vasculitis and trauma are likewise the causes.
- Turbulence (e.g., atherosclerotic vessel narrowing) usually compound increased shear stresses. High shear forces are sufficient to cause localized endothelial injury and direct activation of platelets, simultaneously.

Arterial thrombi, also known as white thrombi, tend to contain more platelets as the core and relatively few fibrin and red cells, with recruited white blood cells. Arterial thrombi are frequently occlusive in arterioles, and nonocclusive in large arteries (such as the aorta and common carotid arteries).

Arterial thrombosis most commonly develops in the coronary, cerebral and femoral arteries (in decreasing order of frequency), causing downstream ischemia of organs or extremities. Occlusive arterial thrombi can result in serious diseases, such as myocardial infarction (MI), stroke or critical limb ischemic necrosis.

The development of drug-eluting stents (DESs) successfully reduces coronary restenosis following the implantation of BMS, but increases the occurrence of stent thrombosis, a new form of arterial thrombosis, which is probably caused by eluting drugs interfering with endothelialization of the stent surface.

4.1.5 Venous Thrombosis

In the venous circulation, low shear forces are insufficient to directly activate platelets, while slow blood flow is conducive to the increase of local coagulation factors concentration. The initiation of venous thrombosis is thought to be caused by tissue factor, which leads to conversion of prothrombin to thrombin, followed by fibrin deposition. Therefore, intrinsic activation of the coagulation cascade plays a pivotal role in venous thrombosis. Any factor that directly or indirectly raises local coagulation factors concentration increases the risk of venous thrombosis.

- Stasis, referred to a condition of slow blood flow, is the most important risk factor for venous thrombosis, mostly caused by prolonged immobilization as well as any other mechanical factor that slows venous blood flow (e.g., atrial fibrillation (AF), congestive heart failure).
- Hypercoagulability includes acquired hypercoagulability (e.g., certain forms of cancer, use of oral contraceptives) and genetic hypercoagulability (e.g., factorVLeiden, a mutation in factorV resulting in activated protein C resistance), which also plays a role in venous thrombosis.
- Endothelial injury has little effect on venous thrombosis. The majority of venous thrombi form without any injured endothelium.

Venous thrombi are described pathologically as *red thrombi*. Formed in the sluggish venous circulation, they are composed predominantly of fibrin and red blood cells, with relatively few platelets which attach to downstream fibrin. Unlike arterial thrombi, venous thrombi are almost invariably occlusive and may form long casts of the vessels in which they arise.

Venous thrombosis often develops in deep veins, known as deep venous thrombosis (DVT), most commonly in the lower extremities (90% of cases). The most fatal consequence of DVT is pulmonary embolism (PE), which occurs when part or all of a deep venous thrombus travels through the bloodstream as an embolus and obstructs a pulmonary artery. DVT and PE are not separate disorders but a continuous syndrome of venous thromboembolism (VTE).

Atrial fibrillation is associated with stasis of blood in the left atria, which promotes the formation of mural thrombi and significantly increases the risk of cardiogenic thromboembolic stroke.

4.2 Principles of Antithrombotic Therapy

Broadly, the overall antithrombotic therapy includes antithrombotic drugs and mechanical approaches. Antithrombotic drugs are classified into antiplatelet drugs, anticoagulants and thrombolytic drugs based on their primary mechanism of action.

Antiplatelet drugs inhibit platelet function and are more effective in prevention and treatment of arterial thrombosis. Anticoagulants suppress blood clotting and are most commonly used in prevention of venous thrombosis and systematic embolization in patients with AF. Thrombolytic drugs act to dissolve established thrombi either in arterial or venous system, rapidly open occluded vessels and restore blood flow. Although there is overlap between their effects, each drug has its own features. The characteristics of diseases, patients' comorbidities and personal preferences, and properties of drugs should be taken into consideration for selecting the optimal antithrombotic strategy.

All antithrombotic drugs increase the risk of bleeding, especially when used in combination. Consequently, clinicians should carefully weigh the risks and benefits for each patient when deciding whether to perform antithrombotic therapy.

4.2.1 Antiplatelet Therapy

Platelets play an important role in hemostasis and thrombosis. The properties that make platelets useful in hemostasis also allow platelets to form pathological thrombi, particularly in arterial circulation with high shear forces, and subsequently lead to myocardial infarction, stroke and peripheral arterial thrombosis. Consequently, antiplatelet therapy is a cornerstone of secondary prevention in patients with established coronary, cerebrovascular or peripheral artery disease. It also has important applications for treatment of acute arterial thrombosis (Holbrook et al. 2012).

Platelet function mainly depends on their membrane receptors and is modulated by a variety of substances (Table 4.1).

Theoretically, all the receptors and substances above are potential targets for modulation of platelet function. Any agent that increases negative regulation or reduces positive regulation can act as an antiplatelet drug. Several targets for antiplatelet drugs that have been identified are as follows.

TxA_2 is a potent platelet agonist that exerts its effects via interaction with thromboxane prostanoid receptors (TP), and it also induces platelet aggregation by increasing expression of GPIIbIIIa on platelet surface. COX-1 inhibitors such as aspirin, the most widely used antiplatelet drug, suppress the production of TxA_2, thereby attenuating TxA_2-mediated platelet activation and aggregation.

ADP is a powerful platelet agonist that works through at least two receptors, $P2Y_1$ and $P2Y_{12}$. $P2Y_1$ binding to ADP directly induces platelet activation and aggregation, while $P2Y_{12}$ binding to ADP inhibits adenylyl cyclase, decreasing intracellular cAMP levels to weaken cAMP-dependent inhibition of platelet activation.

Table 4.1 The functions of important platelet membrane receptors and their corresponding ligands

Platelet membrane receptor	Ligands	Functions
GPIb/IX/V	vWF	Adhesion (under high shear forces)
GPIa/IIa	Collagen	Adhesion
GPVI	Collagen	Activation
TxA_2 receptor	TxA_2	Activation, aggregation
$P2Y_{12}$	ADP	Activation, aggregation
$P2Y_1$	ADP	Activation, aggregation
–	Ca^{2+a}	Activation, aggregation
5-HT_{2A} receptor	Serotonin	Activation, aggregation
V_1-type receptor	Vasopressin	Activation, aggregation
PAR-1	Thrombin	Activation
PAR-4	Thrombin	Activation
GPIb	Thrombin	Activation
AT_1-type receptor	Angiotensin II	Activation
α_2-Adrenergic receptors	Epinephrine	Activation
GPIIbIIIa	Fibrinogen, vWF	Aggregation, adhesion
EP_3	PGE_2 (at low concentrations)	aggregation
IP	PGI_2 (at low concentrations), PGE_2 (at high concentrations)	*Inhibits* activation
EP_4/EP_2	PGE_2 (at high concentrations)	*Inhibits* activation
–	NO[a]	*Inhibits* activation and aggregation
–	cAMP[a]	*Inhibit* activation
–	cGMP[a]	*Inhibits* activation and aggregation

[a]The substance acts within the platelet

Accordingly, $P2Y_{12}$ antagonists have effects on inhibition of ADP-mediated platelet activation and aggregation.

GPIIbIIIa is the most abundant platelet receptor. When platelets are activated, GPIIbIIIa undergoes a conformational change and binds to fibrinogen and vWF, then mediates platelet aggregation. Thus, GPIIbIIIa antagonists exert a vital function on blocking platelet aggregation.

cAMP inhibits platelet activation through decreasing intra-platelet Ca^{2+} and activating PKA, which phosphorylates specific target proteins such as TxA_2 receptor. Drugs that elevate intra-platelet cAMP levels enhance cAMP-dependent inhibition of platelet activation.

Thrombin induces platelet activation by interacting with thrombin receptors, such as PAR-1, PAR-4 and GPIb, among which PAR-1 mediates a substantial portion

of thrombin signaling. PAR-1 antagonist, vorapaxar, can inhibit thrombin-induced platelet activation.

These five types of antiplatelet drugs act by distinct mechanisms and achieve additive or synergistic effects when combined. That underlies dual antiplatelet therapy (DAPT), which usually refers to the administration of a $P2Y_{12}$ antagonist (most commonly clopidogrel) in addition to aspirin, to prevent stent thrombosis after stents implantation and reduce the incidence of systemic thrombotic events in patients with acute coronary disease (ACS).

Besides the classical view of platelets as effector cells in hemostasis, new roles of platelets played in arterial thrombosis are recognized recently. Platelets mediate a crosstalk between lipid metabolism, inflammation and thrombosis via platelet inflammasome, platelet microvesicles (PMVs) and noncoding RNA, and platelet function is modulated by lipid derivatives, neutrophil extracellular traps (NETs), etc (Elia et al. 2019). These substances may provide novel antiplatelet targets.

4.2.2 Anticoagulant Therapy

Blood coagulation greatly contributes to venous thrombosis, but it also plays an indispensable role in arterial thrombosis. Thus, anticoagulation therapy has been the standard for primary prevention of cardiogenic embolic stroke in patients with AF, and is the mainstay for (secondary) prevention and treatment of venous thrombosis. Furthermore, it is commonly used in the treatment of acute arterial thrombosis (e.g., myocardial infarction or peripheral arterial thrombosis).

Anticoagulants act to suppress blood clotting by attenuating the production and action of thrombin. Various substances in coagulation pathway and physiological anticoagulant system are listed in Table 4.2, some of which are targets for currently available anticoagulants.

Vitamin K is required for the synthesis of FII, FVII, FIX and FX. Vitamin K antagonists like warfarin attenuate coagulation by interfering with the formation of these vitamin K-dependent coagulation factors.

FX is activated by either FVIIa-TF complex (extrinsic pathway) or the FIXa-FVIIIa complex (intrinsic pathway). Then, FXa associates with FVa, calcium and anionic phospholipids to form prothrombinase complex, a potent activator of prothrombin. Agents directly inhibiting FXa have effects on inhibiting the production of thrombin.

Thrombin is the most critical factor for hemostasis, which converts soluble fibrinogen into insoluble strands of fibrin, as well as catalyzes many other coagulation-related reactions. Direct inhibition of thrombin can achieve a strong anticoagulant effect.

Among the most important anticoagulants in the blood is antithrombin, which inactivates FIIa, FXa, and other serine proteases such as FIXa, FXIa and FXIIa. However, antithrombin acts slowly and weakly in the absence of heparin. Heparin

Table 4.2 Features and functions of coagulant factors

Component or factor	Agonists	Inhibitors	Main functions
I(fibrinogen)			Induces platelet aggregation, forms fibrin
II(prothrombin)[a]	Prothrombinase complex	Antithrombin	FIIa (thrombin) activates platelets and FV, FVIII and FXI, converts fibrinogen to fibrin, activates Protein C, activates TAFI.
III(tissue factor, TF)			Initiates extrinsic pathway, cofactor of FVIIa
IV(calcium)			Cofactor
V(proaccelerin)	Thrombin, FXa	Proteins C	Cofactor of FXa
VII(proconcertin)[a]	FXa, FIXa, FVIIa	TFPI, antithrombin	FVIIa-TF activates FIXand FX
VIII(antihemophilic factor)	Thrombin, FXa	Proteins C	Cofactor of FIXa
IX(plasma thromboplastin component)[a]	FXIa, FVIIa-TF complex	Antithrombin	Activates FIX
X(Stuart-Prower factor)[a]	FVIIa-TF complex, FIXa-FVIIIa complex	Antithrombin, TFPI	Activates prothrombin
XI(plasma thromboplastin antecedent)	FXIIa, thrombin	Antithrombin	Activates FIX
XII(Hageman factor)	collagen	Antithrombin	Activates FXI
Antithrombin			Inactivates FIIa, FVIIa, FIXa, FXa, FXIa and FXIIa
Proteins C			Inactivates FVa and FVIIIa
Tissue factor pathway inhibitor (TFPI)			Inactivates FXa and FVIIa-TF complex

[a]The factor is vitamin K-dependent

and its derivatives accelerate the rate at which antithrombin inhibits coagulation factors, thereby indirectly exerting anticoagulant effects.

Anticoagulant therapy is sometimes monitored using coagulation testing because of (1) the narrow therapeutic window of some agents and (2) marked biologic variation in effect with some agents.

4.2.3 Thrombolytic Therapy

The basic principle of thrombolytic therapy is administration of sufficient plasminogen activator to achieve a high concentration at the site of the established thrombus, thereby initiating the fibrinolytic pathway, catalyzing the formation of plasmin from plasminogen and accelerating fibrin degradation.

The differences between arterial and venous thrombi are not absolute, since both types of thrombi contain different amounts of fibrin. Therefore, thrombolytic agents, from both recombinant and natural sources, are used for rapid lysis of both arterial and venous thrombi, all of which act as plasminogen activators. Thrombolytic therapy is indicated for acute management in patients with ST-segment elevation myocardial infarction (STEMI), acute ischemic stroke, severe VTE and thrombosis of catheters (e.g., peripherally inserted central catheters).

Thrombolytic therapy is associated with a higher risk of bleeding complications than treatment with either antiplatelet agents or anticoagulants. It is due to (1) dissolution of fibrin in protective hemostatic plugs as well as that in target pathological thrombi or (2) the lytic state that is triggered by the systemic generation of plasmin, which degrades several coagulation factors, especially factors V and VIII. Therefore, use of thrombolytic agents should be restricted to situations in which there is clear evidence of benefit.

4.3 Antiplatelet Drugs and Limitations

Antiplatelet drugs inhibit platelet adhesion, activation and aggregation, which include aspirin, ADP receptor antagonists, GPIIbIIIa receptor inhibitors, cilostazol and vorapaxar (Mega and Simon 2015; Wiviott and Steg 2015). The characteristics of these drugs are more or less different due to their discrete mechanisms of action, distinct chemical structures and different pharmacokinetics. Antiplatelet drugs can produce hemorrhage as their major side effect. Generally, they do not cause bleeding by themselves; instead, they exacerbate pre-existing bleeding or predispose to bleeding from pathologic lesions, particularly in the gastrointestinal or central nervous system.

4.3.1 Aspirin

Mechanism of action

Cyclooxygenase (COX)-1 is an intracellular enzyme that converts arachidonic acid released from membrane phospholipids to PGG_2, which is then converted to PGH_2 by a peroxidase. In activated platelets, PGH_2 is converted to TxA_2 which further activates new platelets, whereas in endothelial cells, PGH_2 is converted to prostacyclin (PGI_2), a potent inhibitor of platelet function by increasing intra-platelet cAMP.

Aspirin irreversibly acetylates COX-1, thereby blocking the formation of TxA_2 in platelets. Because platelets cannot synthesize new proteins, irreversible acetylation of COX-1 means that the inhibition persists for the lifespan of the platelet (7–10 days). Aspirin also inhibits the synthesis of prostacyclin in endothelial cells, but the effect is short-lived (6–12 h) because endothelium can synthesize new proteins.

Clinical applications

Aspirin is widely used for secondary prevention of thrombotic events in patients with established coronary artery disease, cerebrovascular artery disease or peripheral artery disease (PAD). It is also recommended for treatment of acute myocardial infarction (AMI) or acute ischemic stroke. However, using aspirin for primary prevention of cardiovascular events is controversial. Numerous clinical trials have shown that aspirin for primary prevention is not supported by sufficient evidence but it does increase bleeding risk. The results of two large trials published in 2018 (the ASCEND trial and the ARRIVE trial) also support the conclusion (Bowman et al. 2018; Gaziano et al. 2018). Aspirin and other antiplatelet drugs have little effect on prevention of cardiogenic embolic stroke in patients with AF.

Adverse effects

The main adverse effects of aspirin as antiplatelet doses are gastrointestinal intolerance, gastrointestinal ulceration and hemorrhage. Use of enteric-coated aspirin instead of plain aspirin does not eliminate gastrointestinal side effects.

Hepatic and renal toxicity, asthma and rash rarely if ever occur at antiplatelet doses.

Limitations

High on-aspirin platelet reactivity (HaPR), which is once known as aspirin resistance, refers to a reduction in aspirin's efficacy in protecting patients from ischemic events, frequently associated with high on-clopidogrel platelet reactivity (HcPR). There is no evidence that the resistance can be reversed by higher doses of aspirin (Guirgis et al. 2017).

The dose of aspirin that inhibits TxA_2 but not interferes in PGI_2 production has not been found.

4.3.2 ADP Receptor Antagonists

ADP receptor antagonists include thienopyridines (e.g., clopidogrel and prasugrel) and nonthienopyridines (e.g., ticagrelor and cangrelor).

4.3.2.1 Clopidogrel

Mechanism of action
Clopidogrel is a thienopyridine prodrug which irreversibly inhibits $P2Y_{12}$, thereby blocking the ADP pathway of platelets. It requires metabolic activation in the liver which leads to a relatively slow onset of action. Irreversible inhibition of $P2Y_{12}$ means that platelets are affected for the remainder of their lifetime.

Clinical applications
Clopidogrel is indicated for the reduction of thrombotic events (MI and stroke) in patients with ACS or recent stroke, or established PAD.

Contraindications

- Ongoing bleeds (such as gastrointestinal peptic ulcer or intracranial hemorrhage).
- Hypersensitivity to clopidogrel.

Adverse effects
The major adverse effect of clopidogrel is bleeding. Gastrointestinal upset has also been observed. Thrombotic thrombocytopenic purpura can occur but is rare.

Limitations
HcPR can occur in a substantial percentage of patients. Because clopidogrel requires activation via the cytochrome P450 enzyme isoform CYP2C19 in the liver, the effect of clopidogrel on inhibition of platelets considerably varies among patients. Individuals with CYP2C19 polymorphisms may have poor metabolism of clopidogrel, resulting in inadequate drug effect and ultimately leading to ischemic events. Randomized clinical trials have failed to show that higher doses improve the outcome in such patients. Other factors that affect the efficacy of clopidogrel include age and basal platelet activity. Further research is required to clarify the value of personalized antiplatelet therapy based on genetic detection and platelet function testing as a preventive strategy for HcPR.

Clopidogrel has a slow onset of action (6–12 h) and a slow offset of action (3–5 days), which could potentially limit the use of this drug in some clinical scenarios, such as when the need for surgery is uncertain before use.

4.3.2.2 Prasugrel

Mechanism of action
Like clopidogrel, prasugrel irreversibly blocks $P2Y_{12}$. Unlike clopidogrel, prasugrel is rapidly and completely absorbed and activated, and CYP2C19 polymorphisms do not influence its metabolism. Consequently, prasugrel acts more rapidly and effective than clopidogrel does.

Clinical applications
Prasugrel is only indicated in patients with ACS who are to be managed with percutaneous coronary intervention (PCI) to reduce thrombotic cardiovascular events (including stent thrombosis).

Contraindications

- Previous transient ischemic attack (TIA) or stroke.
- Previous intracranial hemorrhage.
- Ongoing bleeds.
- Hypersensitivity to prasugrel.

Adverse effects
Prasugrel is associated with higher rates of life-threatening bleeding than clopidogrel. Thrombotic thrombocytopenic purpura has been reported.

4.3.2.3 Ticagrelor

Mechanism of action
Ticagrelor produces reversible inhibition of $P2Y_{12}$, and does not require metabolic activation. Thus, ticagrelor has a more rapid onset and offset of action than clopidogrel does.

Clinical applications
Ticagrelor is indicated for the reduction of thrombotic events (including stent thrombosis) in patients with ACS who are managed with PCI or medication. Current guidelines give preference to ticagrelor over clopidogrel for patients with ACS.

Contraindications

- Previous intracranial hemorrhage.
- Ongoing bleeds.
- Hypersensitivity to ticagrelor.

Adverse effects
Ticagrelor has a higher risk of intracranial bleeding than clopidogrel. Dyspnea is reported in 14% of patients.

4.3.2.4 Cangrelor

Mechanism of action
Cangrelor is a parenteral reversible inhibitor of $P2Y_{12}$. It has an immediate onset of action and an offset of action within an hour.

Clinical applications
Cangrelor is indicated as an adjunct to PCI for the prevention of periprocedural MI, repeat coronary revascularization and stent thrombosis in patients undergoing PCI without prior $P2Y_{12}$ antagonist and GPIIbIIIa antagonist therapy.

Contraindications

- Ongoing bleeds.
- Hypersensitivity to cangrelor.

Adverse effects
The risk of bleeding with cangrelor is greater than that with clopidogrel during coronary intervention.

Limitations
Co-administered clopidogrel, prasugrel or ticagrelor will have no antiplatelet effect.

4.3.3 GPIIBIIIa Inhibitors

Mechanism of action
Blockade of GPIIbIIIa can be achieved with monoclonal antibodies or with peptide or nonpeptide inhibitors. Abciximab is a chimeric human-murine monoclonal antibody Fab fragment directed against the activated form of GPIIbIIIa. Eptifibatide is a cyclic peptide blocking the fibrinogen binding site on GPIIbIIIa. Tirofiban is a nonpeptidic, reversible inhibitor of GPIIbIIIa. They inhibit the final common pathway of platelet aggregation, providing the strongest antiplatelet effect. They act rapidly, and abciximab bound to platelets for up to 2 weeks, whereas eptifibatide and tirofiban have a short duration of action of a few seconds.

Clinical applications
Abciximab, eptifibatide and tirofiban are indicated as adjuncts to PCI for the prevention of cardiac ischemic complications (death, MI or refractory ischemia/repeat coronary revascularization) in patients undergoing PCI, particularly in those with AMI. Moreover, tirofiban and eptifibatide are used in high-risk patients with unstable angina. All of these presently available GPIIbIIIa antagonists are administered intravenously for short-term use.

Adverse effects
Bleeding is more likely to occur with GPIIbIIIa inhibitors than with oral antiplatelet drugs, but is easily controlled in most cases due to the drugs' short half-lives. In addition, thrombocytopenia is the most serious complication.

Limitations
Abciximab is immunogenic because of its mouse component and may induce anti-mouse antibodies, preventing repeated use in patients.

4.3.4 Cilostazol

Mechanism of action
cAMP is formed from ATP with catalysis by adenylate cyclase and degraded by cAMP phosphodiesterase (PDE). Therefore, drugs elevate intra-platelet cAMP levels through stimulating adenylate cyclase activity to promote the synthesis of cAMP, or through inhibiting PDE to suppress the degradation of cAMP.

Cilostazol selectively and reversibly inhibits PDE III activity in platelets and blood vessels, leading to inhibition of platelet aggregation and vasodilation, respectively.

Clinical applications
Cilostazol is FDA-approved to treat intermittent claudication. As it has been shown to reduce risk of stroke in Asian populations and the rate of stent thrombosis, cilostazol is also indicated for prevention of stroke, and is an alternative to aspirin for patients who require DAPT but cannot tolerate aspirin.

Contraindications

- Heart failure of any severity.
- Hypersensitivity to cilostazol.

Adverse effects
Headache is the most common side effect, and others include diarrhea, abnormal stools, peripheral edema, tachycardia, and so on.

Limitations
Cilostazol's cardiovascular side effects limit its indications. Another PDE inhibitor with vasodilator effects, dipyridamole, which also blocks the uptake of adenosine to increase adenosine plasma levels, further promoting cAMP production, is no longer recommended for patients with coronary vascular disease due to its severe cardiovascular adverse effects such as cardiac death, MI, ventricular fibrillation and hypotension.

4.3.5 Vorapaxar

Mechanism of action
Vorapaxar is a potent, long-acting, oral PAR-1 inhibitor. It selectively inhibits PAR-1, the major thrombin receptor on human platelets. The drug has a rapid onset of action, and its effect can persist for up to 4 weeks after the drug is stopped.

Clinical applications
Vorapaxar is indicated for the reduction of thrombotic vascular events in patients with a history of MI or PAD.

Contraindications

- Previous TIA or stroke.
- Previous intracranial hemorrhage.
- Ongoing bleeds.

Adverse effects
Vorapaxar increases the risk of bleeding.

4.4 Anticoagulants and Limitations

Anticoagulants are drugs that prevent blood clotting process by inhibiting coagulation factors, including parenteral and oral anticoagulants. Clinically, they are mainly used in the prevention and treatment of thromboembolic diseases. Currently available parenteral anticoagulants mainly include heparin, LMWH, fondaparinux and bivalirudin. Currently available oral anticoagulants mainly include dabigatran etexilate, an oral thrombin inhibitor; and rivaroxaban, apixaban, edoxaban and betrixaban, the oral factor Xa inhibitors.

4.4.1 Parenteral Anticoagulants

4.4.1.1 Heparin

Heparin is a sulfated polysaccharide, which is isolated from mammalian tissues rich in mast cells. Commercial heparin is mainly derived from beef lung or porcine intestinal mucosa and is a polymer of alternating D-glucuronic acid and N-acetyl-D-glucosamine residues. Heparin is a macromolecule with a lot of negative charges. It can hardly pass biomembrane. Heparin requires parenteral administration and is usually administered subcutaneously or by continuous intravenous infusion. In the circulation, heparin binds to the endothelium and to plasma proteins. The majority

of heparin is metabolized by heparinase through hepatic monocyte-macrophages system. Heparin and its degradation products are excreted from the body through the kidney. Because of its dose-dependent clearance mechanism, the plasma half-life of heparin ranges from 30 to 60 min with intravenous doses of 25 and 100 units/kg, respectively.

Mechanism of action

Heparin inhibits coagulation, both in vivo and in vitro, by activating antithrombin III and accelerating the rate at which it inhibits thrombin, factor Xa, XIa, XIIa and IXa. Synthesized in the liver, antithrombin plays as a plasma cofactor for heparin and is a member of the serine protease inhibitor superfamily. Once bound to antithrombin, heparin induces a conformational change in the reactive center of antithrombin that enhances the rate at which antithrombin inhibits its target clotting factors.

Clinical applications

- Thromboembolic diseases, such as deep vein thrombosis, pulmonary embolism and peripheral artery thromboembolism.
- DIC induced by various kinds of reasons, such as sepsis, placental abruption, dissolution of malignant tumors.
- Prevention and treatment of cerebral infarction, myocardial infarction, thrombosis after cardiovascular and peripheral venous surgeries.
- Anticoagulation in vitro.

Contraindications

- Patients allergic to heparin.
- Spontaneous bleeding tendency.
- Ulcer disease.
- Trauma.
- Postpartum hemorrhage.
- Severe hepatic insufficiency.

Side effects

- Hemorrhage. Bleeding risk increases with higher heparin dose, as well as the concomitant administration of drugs such as antiplatelet or fibrinolytic agents. Protamine sulfate can be used to neutralize heparin in patient with serious bleeding.
- Thrombocytopenia and thrombosis. Heparin-induced thrombocytopenia (Warkentin et al. 2005, 2010; Jaax and Greinacher 2012) is an antibody-induced process triggered by antibodies against neoantigens on PF4 that are exposed when heparin binds to this protein. PF4 is released by platelet 4 that binds with both circulating heparin and heparan sulfate of vascular endothelial cells forming complexes that trigger the antibody response predominantly through immunoglobulin G. The Fc segments of IgG are able to interact with the Fc γ

IA and Fc γ IIA receptors of the macrophages, which respectively result in the removal of the platelets and the platelet activation with the consequent thrombosis.
- Osteoporosis. Patients treated long term with heparin may have a reduction in bone density, partial of whom may have spontaneous fractures at the same time, which has been reported.
- Others, such as thrombosis, hypoaldosteronism, hypersensitivity reactions.

Limitations

- Poor bioavailability due to the limited absorption of long heparin chains.
- Dose-dependent clearance owing to the characteristics of heparin binding to endothelial cells.
- Variable anticoagulant response as a result of the fact that heparin can bind to plasma proteins, the levels of which vary from patient to patient.
- Reduced activity in the vicinity of platelet-rich thrombi because heparin can be neutralized by PF4 released from activated platelets.
- Limited activity against factor Xa incorporated into the prothrombinase complex and thrombin bound to fibrin because of the reduced capacity of heparin–antithrombin complex to inhibit factor Xa bound to activate platelet and thrombin.

4.4.1.2 Low-Molecular-Weight Heparin

Low-molecular-weight heparins (LMWHs) are the smaller fragments of heparin, the mean molecular weight of which is 5000. It can improve the action of antithrombin III on factor Xa but not its action on thrombin for the reason that its small molecules cannot bind to both enzyme and inhibitor, essential for inhibition of thrombin but not for that of factor Xa. LMWHs do not prolong APTT. In most patients, LMWH does not require monitoring of coagulation. LMWHs have a longer elimination half-life than heparin, so the effects are predictable and dosing less frequent. Because LMWHs are mainly eliminated by renal excretion, it is contraindicated in patients with kidney disease, and requiring LMWH monitoring in patients with renal insufficiency. But with this exception, LMWH are at least as safe and effective as heparin and more convenient to use (Quinlan et al. 2004). Because of its advantages over heparin, low molecular weight heparin has replaced heparin for many indications. The major complication of LMWH is bleeding, but the risk of major bleeding may be lower with LMWH than with heparin. Other side effects include thrombocytopenia and osteoporosis, the risks of both in which LMWHs are lower than unfractionated heparin.

4.4.1.3 Bivalirudin

Bivalirudin is a synthetic 20-amino acid analogue of hirudin and it can inhibit thrombin reversibly and directly. It can bind with plasmin both in blood circulation and in the form of combination. Bivalirudin interacts with the active site of thrombin with the NH_2-terminal portion, and its COOH-terminal tail binds to the substrate binding domain on thrombin called exosite1. Clinically, bivalirudin is used in selected patients undergoing percutaneous coronary interventions. It is contraindicated in patients with active hemorrhage or allergy to bivalirudin. And it can cause some side effects such as bleeding and hypersensitivity reactions.

4.4.1.4 Argatroban

Argatroban is a synthetic piperidine carboxylic acid derivative of L-arginine. It is a small molecular substance with high selectivity. Argatroban is administrated by continuous intravenous infusion.

It can reversibly and directly inhibit the activity of thrombin. Argatroban can bind rapidly with thrombin both in blood circulation and binding to blood clot to produce anticoagulant effect. The APTT is used to monitor argatroban's anticoagulant effect. Argatroban can be used for thrombosis associated with heparin-induced thrombocytopenia. It is contraindicated in patients with hemorrhage, severe disturbance of consciousness or hepatic dysfunction. The side effects include cerebral bleeding, gastrointestinal bleeding, shock and allergic reaction.

4.4.1.5 Fondaparinux

Fondaparinux is a synthetic analogue of the antithrombin-binding pentasaccharide sequence. It can catalyze inhibition of factor Xa by binding to antithrombin and does not enhance the rate of thrombin inhibition. It can be used in patients with acute coronary syndrome or the prevention and treatment of thromboembolism after surgeries (Büller et al. 2004). It is contraindicated in patients with active hemorrhage, severe renal insufficiency, acute bacterial endocarditis or allergic to fondaparinux. It has been reported that fondaparinux may induce the formation of HIT antibodies (Garcia et al. 2012), but there is no HIT occurs and fondaparinux has no cross-reactivity with HIT antibodies. The major side effect of fondaparinux is bleeding and there is no corresponding antidote.

4.4.2 Oral Anticoagulants

4.4.2.1 Warfarin

Warfarin is a water-soluble vitamin K antagonist (Ansell et al. 2008). It can act only in vivo. Its effect is delayed until preformed clotting factors are depleted. Because numerous medical and environmental conditions modify sensitivity to warfarin, its effect is monitored by measuring PT, which is expressed as an international normalized ratio (INR).

Mechanism of action
All the vitamin K-dependent clotting factors possess glutamic acid residues at their N-terminals. Warfarin interferes with the post-translational γ-carboxylation of glutamic acid residues in clotting factors II, VII, IX and X by inhibiting vitamin K epoxide reductase component 1. By blocking vitamin K epoxide reductase, warfarin inhibits the conversion of oxidized vitamin K into its reduced form. This inhibits vitamin K-dependent gamma-carboxylation of factors II, VII, IX and X because the reduced vitamin K serves as a cofactor for a gamma-glutamylcarboxylase, which catalyzes the gamma-carboxylation process, thereby converting prozymogens to zymogens capable of binding calcium and interacting with anionic phospholipid surfaces.

Clinical applications

- Prevention and treatment of thromboembolic diseases such as atrial fibrillation thrombotic embolism resulted from heart valve disease.
- Prevention of deep vein thrombosis after surgeries.

Contraindications

- Liver and kidney insufficiency.
- Severe hypertension.
- Coagulation dysfunction and hemorrhage tendency.
- Active ulcers.
- Trauma.
- Threatened abortion.
- Surgery recently.
- Gestation period.

Side effects

- Bleeding. Bleeding complications mainly occur when the INR exceeds the therapeutic range, which can be mild such as hematuria or epistaxis, or more severe such as gastrointestinal or retroperitoneal bleeding, even the life-threatening intracranial bleeding.

- Skin necrosis. Usually occurs at the beginning several days of therapy. Skin necrosis can form on the thighs, buttocks, breasts and the typical lesion has a progressive necrotic in its center. The reason for the skin necrotic results from the congenital or acquired deficiency of protein C or protein S.
- Pregnancy. Warfarin can cross the placenta and can cause fetal abnormalities or bleeding, especially in the first trimester of pregnancy.

Limitations
Warfarin and other vitamin K antagonists require frequent blood tests to individualize dose and are inconvenient as well as having a low margin of safety.

4.4.2.2 New Oral Anticoagulants

New oral anticoagulants target thrombin such as Dabigatran etexilate, or factor Xa such as rivaroxaban (Büller et al. 2012), apixaban (Agnelli et al. 2013a, b) and edoxaban. Compared with traditional anticoagulants, the NOACs have some advantages (Garcia et al. 2013). Firstly, the NOACs have a rapid onset of action and a short half-life that permit once or twice-daily administration. Secondly, they have less interactions with other drugs. Moreover, the new oral anticoagulants are more convenient to administer than warfarin because they are given in fixed doses without routine monitoring of coagulation. In addition, the NOACs have a low rate of intracranial bleedings. It has been proved that dabigatran etexilate can markedly reduce the risk of thrombotic and bleeding stroke and rivaroxaban can markedly reduce the risk of mortality and serious bleeding events. Rivaroxaban and edoxaban are taken once a day, while apixaban and dabigatran etexilate are taken twice a day, which can be a factor influencing the doctor's choices.

Mechanism of action
The new oral anticoagulants are small molecules which can bind to the active center of the target enzyme reversibly. Dabigatran etexilate, with a hydrophobic tail, is orally active direct thrombin inhibitor, and the pro-drug of dabigatran is a synthetic serine protease inhibitor. Dabigatran etexilate can bind to the specific fibrin site of antithrombin and block the dissociation of fibrinogen, thus blocking the key steps of thrombin enzymatic reaction and consequent thrombosis to play an anticoagulant role. Other kinds of NOACs, such as rivaroxaban, apixaban and edoxaban, are selective factor Xa inhibitors. They bind to the active site of the factor Xa and prevent the interaction of factor Xa with its substrate, which can inhibit the activity of thrombin and prolong the clotting time.

Clinical application

- Anticoagulation therapy of nonvalvular atrial fibrillation.
- Treatment of pulmonary embolism.
- Prevention and treatment of venous thromboembolism.

Contraindications

- Allergic reaction.
- Significant active hemorrhage.
- High risk of massive hemorrhage.
- Combined application of other anticoagulants.
- Hepatic dysfunction or liver diseases.
- Mechanical prosthetic valve.

Side effects

- Bleeding is the most common side effect of the new oral anticoagulants. The risk for gastrointestinal bleeding is higher with dabigatran and rivaroxaban than with warfarin.
- Nephrotoxicity. Rivaroxaban and apixaban is less harmful than dabigatran in kidney injury.
- Dyspepsia. Mainly occurs in patients treated with dabigatran.

Limitations

- Currently, there is no efficacious antagonist for NOACs and this may increase the risk of bleeding.
- Despite the wide therapeutic window, there is no specific laboratory index that can be observed to estimate the therapeutic effect of NOACs. And this may be a puzzled problem the doctors have to face with.
- Because of the short half-life, it will be dangerous if the patients forget to take NOACs.
- The patients with dysfunction of liver or kidney should be careful to take the NOACs.
- Limitation in the secondary prevention of acute coronary syndrome.
- The new oral anticoagulants are more expensive than warfarin, which may be a big problem for poor patients, especially in developing countries.

4.5 Thrombolytic Drugs and Limitations

Thrombolytic drugs, also called fibrinolytics, are able to convert plasminogen into plasmin, which can degrade fibrin and fibrinogen and consequently dissolve thrombus.

4.5.1 Streptokinase

Unlike other plasminogen activators, streptokinase is not an enzyme. Streptokinase is a kind of protein extracted from the culture medium of C-group β-hemolytic streptococcus and recombinant streptokinase can be prepared by genetic engineering technology (Huish et al. 2017; Thelwell and Longstaff 2014).

Mechanism of action
Streptokinase can bind with endogenous plasminogen in 1:1 ratio to form a complex, thereby inducing a conformational change in plasminogen which exposes its active site. This conformationally altered plasminogen converts additional plasminogen molecule to plasmin. The streptokinase–plasminogen complex activates both free and fibrin-bound plasminogen.

Clinical applications
Streptokinase is widely used in thrombotic diseases such as acute myocardial infarction, cerebral infarction, pulmonary embolism, deep vein thrombosis and acute or subacute peripheral arterial thrombosis.

Contraindications

- Bleeding, surgery or trauma within two weeks.
- Ulcer diseases or esophageal varices.
- Uncontrolled hypertension.
- Coagulation dysfunction and hemorrhage diseases.
- Severe liver and kidney dysfunction.
- Gestation period.
- Allergic reaction.

Side effects

- Allergic reactions. They may be manifested as a rash, fever, chills or rigors.
- Transient hypotension. This may be result from the release of bradykinin induced by plasmin.

Limitations
Streptokinase extracted from pathogenic hemolytic streptococcus may have certain antigenicity and cause systemic fibrinolysis, increasing the risk of bleeding.

4.5.2 Urokinase

Urokinase is a two-chain serine protease derived from cultured fetal kidney cells. It consists of two polypeptide chain with a molecular weight of 34,000.

Mechanism of action
Urokinase converts plasminogen to plasmin by specific cleavage of an Arg-Val bond in plasminogen.

Clinical applications
Like streptokinase, urokinase is mainly used in the thrombolytic therapy for thromboembolism diseases including acute extensive pulmonary embolism, coronary embolism and myocardial infarction occurs with 6–12 h, acute cerebrovascular embolism, retinal artery and peripheral arterial embolism, prevention of thrombosis after heart valve replacement surgeries.

Contraindications

- Acute visceral hemorrhage.
- Acute intracranial hemorrhage.
- History of brain infarction.
- Uncontrolled hypertension.
- Arteriovenous malformation.
- Arterial aneurysm.

Side effects

- Bleeding. Bleeding can occur in the superficial location such as skin, mucosa and vascular puncture site, as well as the visceral bleeding such as gastrointestinal bleeding, hemoptysis, hematuria, retroperitoneal bleeding, cerebral bleeding.
- Mild allergic reaction. Such as skin eruption, bronchial spasm and fever.
- Gastrointestinal reaction. Such as nausea, vomiting and inappetence.

Limitations
Like streptococcus, urokinase may activate fibrinolytic system and increase the risk of bleeding.

4.5.3 Tissue Plasminogen Activator, t-PA

t-PA is the physiological fibrinogen activator in the body and released by vascular endothelial cells into the blood circulation. Now recombinant tissue-type plasminogen activator such as alteplase has been prepared by method of genetic engineering (Longstaff et al. 2008).

Mechanism of action
t-PA binds with fibrin through its lysine residues at the location approaching fibrinogen-plasminogen binding site and converts the endogenous fibrinogen into fibrin (Silva et al. 2012).

Clinical applications

- Acute myocardial infarction occurs within 6–12 h.
- Acute large area pulmonary embolism.
- Acute cerebral ischemic stroke occurs within 3 h.

Contraindications

- High risk of hemorrhage tendency.
- History of hemorrhage stroke.

Side effects

- Blood system. Bleeding, including hematoma at the site of vascular injury or the puncture site, intracranial bleeding, aspiratory tract bleeding such as pharyngeal bleeding, epistaxis, hemoptysis, urogenital tract bleeding, such as hematuria, retroperitoneal bleeding, hemopericardium.
- Immune system, such as allergic reaction.
- Central nervous system, such as epileptic seizure, convulsion, aphasia, delirium, depression, confusion, acute brain syndrome.
- Cardiovascular system, such as cardiac arrest, cardiogenic shock, hypotension, thromboembolism.
- Gastrointestinal dysfunction, such as nausea and vomiting.

Limitations
Because of the short half-life, alteplase requires continuous intravenous administration.

4.5.4 Anistreplase

Anistreplase, also called ASPAC, anti-isolated plasminogen–streptokinase activator complex, is a complex formed by streptokinase which is mixed with equimolar amounts of Lys-plasminogen, a plasmin-cleaved form of plasminogen with a Lys residue at its N-terminal. Compared to the streptokinase, the anistreplase has some advantages. Firstly, the enzyme is slowly activated in vivo and can be injected intravenously. Intravenous injection increases the amount of anistreplase binding to fibrin. Moreover, it is not inhibited by α-antifibrinolytic enzyme in the blood. Secondly, anistreplase rarely causes enhanced systemic fibrinolytic activity, and consequently the risk of bleeding is reduced remarkably.

Mechanism of action
After the anistreplase enters the blood, it diffuses to the surface of thrombus containing fibrin, and binds to fibrin through the plasminogen lysine active center of the

complex. After slowly removing the acetyl group, the plasminogen on the surface of fibrin is converted into plasmin and plays a role of thrombolysis.

Clinical applications

- Acute myocardial infarction.
- Acute large area pulmonary embolism.
- Acute ischemic cerebral stroke.
- Other thrombotic diseases.

Side effects

- Blood system. Bleeding, including hematoma at the site of vascular injury or the puncture site, intracranial bleeding, aspiratory tract bleeding, such as pharyngeal bleeding, epistaxis, hemoptysis, urogenital tract bleeding, such as hematuria, retroperitoneal bleeding, hemopericardium.
- Immune system, such as allergic reaction.
- Nervous system, such as epileptic seizure, convulsion, aphasia, delirium, depression, confusion, acute brain syndrome.
- Cardiovascular system, such as cardiac arrest, cardiogenic shock, hypotension, thromboembolism.
- Gastrointestinal system, such as nausea and vomiting.

Limitations
The high cost of anistreplase may be a problem for poor patients.

4.5.5 Tenecteplase

Tenecteplase (Melandri et al. 2009) is a multisite variant of tissue-type plasminogen activator, the chemical formula of which is $C_{2558}H_{3872}N_{738}O_{781}S_{40}$. Known as the third-generation fibrinolytic drugs, tenecteplase was designed to have a longer half-life time than t-PA and to be resistant to inactivation by PAI-1.

Mechanism of action
Through its lysine residue, tenecteplase binds to fibrin and activates plasminogen binding to fibrin, which is consequently converted into plasmin. This effect is significantly stronger than that of t-PA in the activation of plasminogen in the blood circulation. Because tenecteplase is more fibrin specific than t-PA and selectively activates plasminogen, it does not cause bleeding complications, which is common in patients treated with streptokinase.

Clinical applications

- Acute myocardial infarction.
- Acute large area pulmonary embolism.
- Acute cerebral ischemic stroke.

- Deep vein thrombosis.
- Other vascular diseases, such as thrombosis in arteriovenous fistula.

Contraindications

- Hemorrhage diseases.
- Arteriovenous malformation or artery aneurysm.
- Acute ischemic stroke or subarachnoid hemorrhage.

Side effects

- Blood system. Bleeding, including hematoma at the site of vascular injury or the puncture site, intracranial bleeding, aspiratory tract bleeding such as pharyngeal bleeding, epistaxis, hemoptysis, urogenital tract bleeding such as hematuria, retroperitoneal bleeding, hemopericardium.
- Cardiovascular system, such as cardiac arrhythmia, vascular re-embolization.
- Central nervous system, such as epileptic seizure.
- Musculoskeletal system, such as hemorrhagic bursitis of knee.

Limitations
When used in conjunction with other drugs that affect clotting function, it increases the risk of bleeding significantly.

4.5.6 Reteplase

Reteplase (Simpson et al. 2006, 2007) is a recombinant nonglycosylated form of human tissue plasminogen activator, which has been modified to contain 357 of the 527 amino acids of the original protein. It can only be administered by intravenous injection. The modified reteplase has a longer half-life time. Reteplase also binds fibrin with lower affinity than alteplase, improving its ability to penetrate into clots.

Mechanism of action
Reteplase converts inactive plasminogen into plasmin by hydrolyzing the peptide bond between arginine at position 560 and valine at position 561 in the plasminogen peptide chain.

Clinical applications
Acute myocardial infarction in adults is caused by coronary artery obstruction.

Contraindications

- Active hemorrhage.
- History of hemorrhage stroke and ischemic stroke within six months.
- History of recent surgery or trauma.
- Arteriovenous malformation or artery aneurysm.
- Uncontrolled hypertension.

Side effects

- Bleeding. Including visceral bleeding such as intracranial bleeding, retroperitoneal bleeding, gastrointestinal bleeding, urinary tract bleeding and respiratory bleeding, as well as superficial location such as artery puncture site, vein cannula and surgical incision.
- Others, such as cardiac shock, cardiac arrhythmia, heart failure, pericarditis.
- Others, such as nausea, vomiting, fever or hypotension.

Limitations

The interaction of reteplase with other cardioactive drugs has not been studied. The use of heparin, vitamin K antagonists and antiplatelet agents before and after r-PA treatment may increase the risk of bleeding.

4.6 Challenges and Perspectives

4.6.1 Antiplatelet Drugs

Although the dual antiplatelet therapy of aspirin and clopidogrel has been the cornerstone of antithrombotic management for patients with acute coronary syndrome or undergoing percutaneous coronary intervention, the atherosclerosis thrombosis events still happen, which promotes the research of new antiplatelet. Currently, there are some new drugs targeting the multiple molecules in the signaling pathway of platelet aggregation that are on clinical trial, including P2Y12 receptor antagonists such as MRS2179, MRS2500; oral GPIIb/IIIa receptor antagonists such as MNS, RUC-1; platelet collagen antagonists such as GPVI antagonists kistomin, revacept and GPIb antagonists 6B4-Fab monoclonal antibodies; nitric oxide donors LA846, LA419; prostaglandin E receptor 3 antagonist DG-041; serotonin receptor antagonists, APD791; phosphatidylinositol 3-kinase inhibitor TGX-221, thrombin receptor PAR-4 inhibitors. Thrombin receptor PAR-1 antagonists such as vorapaxar, atopaxar can selectively interfere platelet activation induced by thrombin and inhibit pathological thrombosis. Because the PAR-1 signaling pathway is not so critical in the normal hemostatic process, it may not increase the risk of bleeding by inhibiting PAR-1, which means that PAR-1 antagonists can be the ideal antiplatelet drugs theoretically. The combination of dual antiplatelet therapy and PAR-1 inhibitors may thoroughly reduce the thrombosis induced by platelet.

With the gradual development of science and technology, we have a better understanding about the platelet functions and the factors or pathway associated with the platelet adhesion, activation, aggregation, and it is predicted that more effective and safer new antiplatelet drugs will come into being and bring more powerful help for the clinical practices. The accumulated clinical evidences about the superiority and limitations of antiplatelet drugs, as well as the emerging of new drugs and therapeutic technologies, will markedly improve the patients' antithrombotic therapies.

4.6.2 Anticoagulants

The application of anticoagulants increases the risk of bleeding complications due to its inhibition to the signaling pathway of physiologic hemostasis. In recent years, direct thrombin inhibitors and factor Xa inhibitors have been the research emphasis of the new anticoagulants. Known as the intersection of exogenous and endogenous clotting pathways, factor Xa can be selectively inhibited by factor Xa inhibitors and consequently reduce the amount of thrombin, which means the prolonging of clotting time. New factor Xa inhibitors include direct and indirect drugs. The direct factor Xa inhibitors can bind to the active site of factor Xa directly and inhibit the interaction with its substrate. The indirect ones play the role by inhibiting antithrombin III.

Traditional anticoagulants drugs like warfarin may cause high risk of serious bleedings in the anticoagulation process, which greatly limits its clinical application. It is no doubt that in the future new anticoagulants need to have a better balance in the security and efficacy, that is to say, the new anticoagulants should provide protective effects and reduce the bleeding complications at the same time. More attempts such as the reducing of drug dose, combined therapy or treatment time will be made in the future. Oral anticoagulants should have the following characteristics: specific inhibition against a single coagulation factor; good bioavailability; high security; predictable pharmacokinetics and pharmacodynamics; wide and effective therapeutic window; oral administration and without monitoring. There is no cross-reaction with food or drugs; fewer side effects. Rivaroxaban and dabigatran (Graham et al. 2015, 2016; Southworth et al. 2013) etexilate are known as the new generational anticoagulants used to prevent the stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and at the same time provide effective, predictable and stable anticoagulation, as well as less interactions with other drugs. Moreover, they don't need regular monitoring or dose adjustments.

Nowadays, with the advanced development in the field of anticoagulation applications, new oral anticoagulants can be regarded as the replacements of traditional anticoagulants and have a broad prospect because of the obvious advantages such as efficacy, security, cost and compliance. Considering the risk of bleeding and other unexpected adverse events in the treatment, it is critical to make effective risk estimations for special population. We have great confidence that the anticoagulation therapies will run into a new era with the constant process and breakthrough in the research of specific antagonists.

4.6.3 Thrombolytic Drugs

The discovery of streptokinase and urokinase can degrade fibrins and allows them to be used in thrombolytic therapy, but there is a systemic bleeding problem. The second-generational plasminogen activators, such as anistreplase and t-PA, partially alleviate bleeding problem. The third-generational thrombolytic drugs are mainly the

variants of t-PA, and have improved stability, security and efficacy. The ideal thrombolytic drugs have the following advantages: the specific selection of fibrin; good revascularized effect; low incidence of vascular re-embolization and hemorrhage; anti-PAI-1 effect, no antigenicity; reasonable price.

Although the thrombolytic drugs permitted on the clinical can dramatically reduce the mortality after acute myocardial infarction and are used to treat a variety of thromboembolic diseases, they have obvious shortages as well, including bleeding tendency, limited specificity on fibrin, excessive dose of treatment, vascular re-embolization. Some complementary drugs used with thrombolytic drugs also have associated side effects The third-generational thrombolytic drugs created by genetic engineering technology can not only improve the thrombolytic effects but also enhance specificity on the fibrin, as well as the prolonged plasma half-life time and resistance of PAI-1 inhibited effect, which contribute markedly to the security of the drugs.

Up till now, thrombolytic drugs cannot reach the perfect effect that make the 100% recovery of the coronary artery and totally avoid the systemic bleeding and vascular re-embolization. Therefore, it is necessary to create ideal thrombolytic drugs. The target drug delivery of plasmin variant combined with liposome technique is a developing direction in the future.

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Chapter 5
Lipid-Modifying Drugs: Pharmacology and Perspectives

Rui-Xia Xu and Yong-Jian Wu

Abstract Coronary artery disease (CAD) is one of the leading causes of death worldwide. It is well known that dyslipidemia is a major pathogenic risk factor for atherosclerosis and CAD, which results in cardiac ischemic injury and myocardial infarction. Lipid-modifying drugs can effectively improve lipid abnormalities including reducing low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) or increasing high-density lipoprotein cholesterol (HDL-C), and eventually decrease the incidence of cardiovascular events. This chapter will review basic principles of lipid metabolism and focus on the therapeutic strategies of lipids modifying drugs (statins, proprotein convertase subtilisin/kexin type 9 inhibitors, ezetimibe, niacin, polyunsaturated fatty acids, and so on) in patients with arteriosclerotic cardiovascular disease. Meanwhile, the challenges and perspectives of the lipid-lowering agents currently in clinical practice as well as their limitations will be outlined.

Keywords Coronary artery disease · Atherosclerosis · Lipids metabolism · Lipids modifying drugs

Coronary artery disease (CAD) is the leading cause of death worldwide, and the treatment and prevention of cardiovascular disease are facing severe challenges (Rosenson et al. 2014a). Lipid abnormalities usually persist in CAD patients. Low-density lipoprotein (LDL) cholesterol (LDL-C) is an established risk associated with the development of atherosclerosis and subsequent cardiovascular disease (CVD). High triglycerides (TG) levels are associated with high cardiovascular risk, the presence of CAD, and a higher mortality. Low high-density lipoprotein (HDL) cholesterol (HDL-C) levels are also associated with CAD in patients submitted to coronary angiography (Averna and Stroes 2017). The widespread availability, persuasive clinical database,

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and relative safety of the lipid-modifying drugs have established pharmacologic control of blood lipids as an increasingly acceptable strategy. Strategies to reduce cardiovascular risk in primary and secondary prevention focus on optimization of LDL-C levels. Primary prevention in patients without evident coronary disease remains a highly desirable aim. Lifestyle interventions (diet, smoking cessation, and physical activity) are the first line of treatment and may achieve cholesterol reduction in many patients. The national American campaign, promoting dietary management and other lifestyle measures, has resulted in a reduction of mean blood cholesterol levels and a fall in coronary heart disease (CHD) mortality rates. Clinical trials of lipid-lowering drugs such as hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins) in the past decade have demonstrated safety and clinical event reduction across the spectrum of cardiovascular risk (Nakamura et al. 2006). Still debated, however, are the fiscal and ethical issues related to the cost-effectiveness of lipid drug therapy in lower risk primary prevention (Taylor et al. 2011). Within secondary prevention, the latest guidelines from the American Heart Association (AHA) and American College of Cardiology (ACC) on secondary prevention support aggressive risk-reduction therapies for patients with established coronary and other atherosclerotic vascular disease (Smith et al. 2011). For patients at very high risk for future CHD, results from two clinical trials demonstrated the cardiovascular benefit of lipid lowering to levels significantly less than those prescribed by ATP III (LaRosa et al. 2005; Pedersen et al. 2005). Thus, the updated 2011 AHA-ACC guidelines support the recommended LDL-C goal of less than 100 mg/dL (2.6 mmol/L) for all patients with CHD and other clinical forms of atherosclerotic disease, but allow for an optional goal of less than 70 mg/dL (1.8 mmol/L) in such patients. These guidelines do not modify the ATP III recommendations for patients without atherosclerotic disease who have diabetes or multiple risk factors and a 10-year risk level for CHD greater than 20% (LDL-C: 100 mg/dL). Although drug-induced LDL-C reduction remains an essential component of cardiovascular risk factor management, total risk can also be modified through blood pressure control, dietary changes, increased exercise, weight loss, and strictly no smoking.

5.1 Lipids Metabolism (Cholesterol Metabolism, TG Metabolism)

Disorders of lipid metabolism play an important role in atherosclerosis and CAD. There is a clear-cut relationship between elevated serum cholesterol and myocardial infarction. Cholesterol deposits occur in areas of endothelial cell damage and are a prominent part of atherosclerotic lesions. Actually, cholesterol is a vital structural component of cell membranes and a precursor of steroid hormones and bile acids. Triglyceride is another lipid and it is a major source of energy for cells. Cholesterol and TG are the most important lipids in the study and management of CAD risk.

Projected trends in elevated total cholesterol would lead to a 9.2 million increase in annual cardiovascular disease events over 2010–2030 (Moran et al. 2010).

5.1.1 Cholesterol Metabolism

An elevated level of cholesterol carried by circulating apolipoprotein B-containing lipoproteins (non-HDL-C and LDL-C) is a root cause of atherosclerosis, the key underlying process contributing to most clinical atherosclerotic cardiovascular disease (ASCVD) events (Jacobson et al. 2015). Cholesterol cannot be metabolized by peripheral tissues and must be returned to the liver for excretion. HDL can transfer cholesterol from peripheral tissues to the liver and recycle or form cholic acid which is excreted in the stool. This process, known as reverse cholesterol transport, is a very complex process (Rosenson et al. 2012). Cholesterol reversal can be divided into several steps, including cholesterol efflux, cholesterol esterification, and cholesterol clearance (Shishehbor et al. 2003). Cholesterol efflux is the transfer of cholesterol in peripheral tissues in the form of free cholesterol, which can be divided into scavenger receptor class B type I (SR-BI) pathway, ATP binding cassette A1 (ABCA1) pathway, ATP binding cassette G1 (ABCG1) pathway, and passive diffusion pathway. The SR-BI pathway mainly uses HDL as a cholesterol receptor, and SR-BI mediates the release of free cholesterol to mature HDL particles. The cholesterol efflux of this pathway is related to the phospholipid composition and type of receptor. The ABCA1 pathway, which is the ATP binding cassette transporter A1 pathway, takes the fat poor apoA-1 as the receptor, which mediates the free cholesterol efflux to apoA-1. The ABCG1 pathway, the ATP binding cassette transporter G1, is based on HDL as a cholesterol receptor. ABCG1 mainly mediates cholesterol efflux to HDL to prevent cholesterol accumulation. The passive diffusion pathway, also known as water-soluble diffusion pathway, refers to the release of free cholesterol from the cell membrane and bind with the receptor in the aqueous phase. Lecithin cholesterol acyltransferase (LCAT), which is secreted into the blood by the liver, catalyzes the production of free cholesterol into cholesterol ester. Cholesterol esters are transported to the liver via HDL receptors, LDL receptors, and SR-BI to achieve the transfer of cholesterol from non-liver cells to hepatocytes, thereby removing excess cholesterol in the blood and surrounding cells.

5.1.2 TG Metabolism

The data showed that the risk of coronary heart disease was increased in patients with mild to moderate serum TG levels (Miller et al. 2011). Liver is the main organ of triglyceride metabolism and plays an important role in the regulation of energy metabolism (Tamura and Shimomura 2005). In the liver, absorption of fat from the gut, lipolysis-induced liberation of fat from adipocytes, and synthesis of fatty acids

from amino acids and carbohydrates are the three main sources of free fatty acids (FFA). TG are then formed following the etherification of FFA with glycerol. The liver cells secrete the TG in the form of very low-density lipoprotein (VLDL). Lipids accumulate in the liver in the presence of excess FFA; this results from an imbalance in the TG to VLDL ratio and is commonly a sequela of pregnancy, obesity, diabetes, corticosteroid use, or total parenteral nutrition. When inadequate amounts of protein are ingested or absorbed, the liver undergoes fatty alterations as the TG accumulate due to limited protein availability for lipoprotein synthesis (Aarsland et al. 1996). Elevated triglyceride and low HDL-C levels are believed to directly increase cardiovascular risk and should be treated initially with lifestyle modification, followed by niacin, a fibrate, or intensification of LDL-C lowering therapy if necessary.

5.2 LDL, HDL, Triglyceride, and Cardiovascular Risk

Lipoprotein is taking TC and cholesterol ester (CE) as the core, and the surface is covered with polar phospholipids, cholesterol, and a small amount of protein. Plasma lipoprotein can be divided into four categories by ultracentrifugation: chylomicrons (CM), VLDL, LDL, and HDL, where LDL is the highest level of cholesterol-rich lipoproteins (Gursky 2005).

Elevated plasma levels of LDL have been shown to be a common risk factor for coronary artery disease and other atherosclerotic diseases (Krauss 1995). Intervention trial data over the past two or three decades have demonstrated that cholesterol modification, especially reduction in LDL-C levels, is associated with favorable effects on reduction in CAD events. Clearance of LDL is mediated mainly by the LDL receptor (LDLR) mediated endocytosis of the liver, and the dysfunction of the LDLR is one of the major causes of coronary artery disease. The LDLR mediates the removal of LDL particles by binding to apo B100 and apo E (Brown and Goldstein 1979). In this process, if the ligand or receptor is abnormal, it will lead to the disorder of plasma cholesterol levels, resulting in atherosclerosis and other cardiovascular diseases. The most important site of LDLR expression is the liver, where its regulation is controlled by sterol regulatory element-binding proteins (SREBPs). In addition, the expression level of LDLR was also negatively regulated by oxidized LDL (ox-LDL), resulting in significantly increased LDL levels in the blood. And it can cause the accumulation of LDL in the blood vessel wall and promote the occurrence of coronary artery disease. A prospective meta-analysis of data from 90,056 individuals in 14 randomized trials of statins has shown that decreasing LDL-C level can significantly reduce the incidence and mortality risk of ASCVD (Baigent et al. 2005).

HDL is a highly heterogeneous lipoprotein in plasma, and it is mainly synthesized in liver and small intestine. HDL-C is a key factor in predicting cardiovascular disease risk. Clinical data show that a 1% increase in serum concentrations of HDL-C can decrease cardiovascular risk by 2–3% (Gotto and Brinton 2004). Although epidemiological studies have shown a significant negative correlation between HDL-C levels and cardiovascular risk (Expert Panel on Detection 2001), there is no cardiovascular

benefit in clinical trials with elevated HDL-C alone. Therefore, the researchers also proposed the HDL function hypothesis, that is, the HDL function and the existence of a causal relationship between the protection of atherosclerosis, and HDL function may not be assessed by the HDL-C level. HDL contributes to the elimination of cholesterol in foam cells during arterial disease, either by returning cholesteryl ester directly to the liver through the SR-BI receptor or through transfer to the apolipoprotein B (apo B)–containing lipoproteins in exchange for triglycerides. HDL also exerts anti-inflammatory and antioxidant effects (Rohrer et al. 2004). In addition, HDL also has the role of anti-thrombosis, endothelial repair, vascular regeneration, anti-diabetes, and anti-microbial infection. These are the main research directions of the HDL function hypothesis, in order to provide evidence for the correlation between HDL function and coronary artery disease.

After the failure of HDL-C test, some researchers began to shift their attention to the correlation between TG concentration and cardiovascular disease. Epidemiological evidence also showed that elevated lipoprotein TG, cholesterol, and triglyceride-rich lipoprotein may be another reason of increased cardiac death and all-cause mortality. Values of more than 150 mg/dL are considered elevated (Expert Panel on Detection 2001), and values below that level are associated with reduced cardiovascular risk even after major reduction of the LDL-C (Miller et al. 2008). TG are not directly affect the formation of atherosclerosis due to the large size of VLDL particles and chylomicrons, thus limiting their inability to penetrate the arterial wall and cause foam cell formation (Talayero and Sacks 2011). Elevated TG and low HDL-C levels are believed to directly increase cardiovascular risk. But there is a debate about whether triglyceride is an independent risk factor for cardiovascular disease. A study of more than 300,000 participants did not find an independent association between TG levels and CVD after adjustment for confounders (Emerging Risk Factors et al. 2009). These studies confuse the relationship between TG and cardiovascular disease.

5.3 Principles of Lipids Modifying Therapy

Effective and reasonable lipid regulation can significantly reduce and delay the incidence and progression of atherosclerosis, which is involved in hyperlipidemia, and effectively reduce the incidence and mortality of cardiovascular events. In clinical practice, the lipids modifying therapy should follow the principles of comprehensive, individualized medication, long-term stability, and safety monitoring. Treatment measures should be diversified to effectively regulate the metabolism of blood lipids and improve the status of other related diseases in order to achieve a better therapeutic effect. According to the level of risk assessment of patients with dyslipidemia, different treatment methods and drugs should be chosen. And the lipid-regulating process should be long-term adherence and moderate intensity. Safety monitoring is to strengthen the awareness of safe medication and timely monitor of relevant indicators, to find and evaluate the safety of medication. Possible drug interactions

should be reviewed when other treatment adjustments are made, especially with the introduction of drugs that interfere with catabolic pathways such as cytochrome P450.

5.4 Lipid-Lowering Drugs and Limitations

National clinical treatment guidelines recommend pharmacologic treatment in addition to therapeutic lifestyle modifications in patients with mixed dyslipidemia and multiple risk factors for coronary heart disease. The currently available lipid-lowering drugs mainly include statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, cholesterol absorption inhibitors, the bile acid sequestrant, nicotinic acid, the fibrates, etc.

5.4.1 Statins

Statins are the first-line treatment for hypercholesterolemia because of their relatively few side effects and predictable benefits for treating LDL-C. They decrease hepatic cholesterol synthesis by inhibiting HMG-CoA reductase, which is the rate-limiting step in cholesterol biosynthesis, resulting in increased LDL receptor activity with enhanced clearance of LDL particles and precursors. Statins reduce LDL-C concentration by up to 60% with more modest increases in HDL-C and decreases in triglyceride levels. They are highly effective in lowering lipids, and long-term safety and efficacy are now established.

The Scandinavian Simvastatin Survival Study (4S) clinical trials have shown for the first time that statins reduce the mortality and overall mortality of coronary heart disease (Scandinavian Simvastatin Survival Study Group 1994). The Cholesterol and Recurrent Events (CARE), the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID), and the Lescol Intervention Prevention Study (LIPS) trials have confirmed the important role of these drugs in the secondary prevention of coronary heart disease (Sacks et al. 1996; Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group 1998; Serruys et al. 2002). The West of Scotland Coronary Prevention Study (WOSCOPS), the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), the Collaborative Atorvastatin Diabetes Study (CARDS), the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), and the Heart Protection Study (HPS) trials have extended statin use from ASCVD patients to primary prevention and a wider population (Shepherd et al. 1995; Downs et al. 1998; Colhoun et al. 2004; Ridker et al. 2008; Heart Protection Study Collaborative G 2002). Studies of the pleiotropic effects of statins have suggested that they may also improve endothelial function, have antioxidant and anti-inflammatory effects, and stabilize atherosclerotic plaque. Statins can reduce the levels of cytokines and chemokines,

and decrease the expression of leukocyte adhesion molecules. Statins can also reduce the expression of interstitial collagenase, increase the level of interstitial collagen, decrease the level of ox-LDL, reduce the production of reactive oxygen species, inhibit thrombosis, and increase the fibrinolytic capacity.

Statins are the most widely prescribed agents for treatment of dyslipidemia and are the most effective medicines to reduce LDL-C and lower the risk of cardiovascular and cerebrovascular events. Statins are generally thought to be well tolerated, and their use is infrequently the cause of major complications in contemporary practice. However, statin dose dependently elevated aminotransferase levels, which incidence rate was about 0.5–3.0%, resulting in an abnormal liver function in patients (McKenney et al. 2006). Muscle complaints represent the most frequent adverse reports among patients treated with statins (Rosenson et al. 2014b). Preclinical studies show that statins decrease mitochondrial function, attenuate energy production, and alter muscle protein degradation, thereby providing a potential link between statins and muscle symptoms; controlled mechanistic and genetic studies in humans are necessary to further understanding (Stroes et al. 2015). And the problems are usually reversible when the dose of statin is decreased or the medication is discontinued or using a different statin. Among statins, pravastatin, fluvastatin, and rosuvastatin are hydrophilic and may be associated with fewer side effects of the muscle. Clinical trial data have suggested a modest, but statistically significant, increase in the incidence of new-onset type 2 diabetes mellitus with statin use (Maki et al. 2014). Multiple case reports and data from randomized trials have suggested a potential association between statins and cognitive impairment in some individuals (Rojas-Fernandez et al. 2014).

5.4.2 Cholesterol Absorption Inhibitor

Ezetimibe is currently the only available drug in the class of cholesterol absorption inhibitors. Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. Ezetimibe is a potent cholesterol absorption inhibitor, and it is able to selectively block the intestinal absorption of cholesterol and related phytosterols (Sudhop et al. 2002). Ezetimibe localizes at the brush border of the small intestine, and it inhibits the absorption of cholesterol, leading to a reduction in cholesterol from the small intestine to the liver. And this can reduce the hepatic cholesterol stores and increase the clearance of blood cholesterol. Monotherapy is primarily effective in reducing total cholesterol, LDL-C, and apo B, but its effects of reducing triglycerides or lowering HDL-C are not obvious and even increase the level of HDL-C. Ezetimibe lowers serum cholesterol concentrations by selectively inhibiting the absorption of cholesterol and related phytosterols by the small intestine (Sudhop and von Bergmann 2002). Ezetimibe has a mechanism of action that is complementary to that of the HMG-CoA reductase inhibitors, resulting in synergistic cholesterol-lowering effects when these drugs are used in combination (Sudhop and

von Bergmann 2002). Combining ezetimibe with statins therapy results in synergistic cholesterol-lowering effects and may lower LDL-C levels by an additional 15–20% than statin monotherapy (Gagne et al. 2002). Similarly, in a double-blind, randomized trial, when added to statin, ezetimibe resulted in incremental lowering of LDL cholesterol levels and improved cardiovascular outcomes (Cannon et al. 2015). The ENHANCE trial (Effect of combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) showed that coadministration of ezetimibe with simvastatin was safe, well tolerated, and provided higher LDL-C reduction compared with simvastatin alone in adolescents with HeFH (van der Graaf et al. 2008). Generally speaking, ezetimibe monotherapy is an option for patients with statin intolerance, and combination therapy with statins is effective in those requiring large LDL-C reductions. However, its clinical benefit in primary and secondary prevention has yet to be established.

The adverse effect profile for combined ezetimibe/statin therapy is similar to statin monotherapy, except for an increase in the incidence of hepatic enzyme elevations. In IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), 10 mg ezetimibe combine high-dose statin therapy further reduced LDL-C and decreased adverse cardiovascular outcomes without adverse effects in patients who were stable after an acute coronary syndrome (Spinar and Spinarova 2014). And pharmacokinetic differences for ezetimibe have been identified in patients with mild hepatic impairment; however, no dosage adjustments for ezetimibe are indicated.

5.4.3 PCSK9 Inhibitor

5.4.3.1 Proprotein Convertase Subtilisin/Kexin Type 9

Statins are the most effective therapy currently available for reducing the LDL-C level and preventing cardiovascular events. However, additional therapies are necessary for patients who cannot reach the target LDL-C level when taking the maximum-tolerated dose of a statin. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a secreted protease that promotes the degradation of the LDLR, but its catalytic activity is not required for receptor degradation. The discovery of PCSK9 represents a major milestone in the understanding of LDL metabolism. The PCSK9 protein can control the number of LDL receptors. When it binds to the LDLR, the latter is destroyed with the LDL particle. Interference with PCSK9's LDL receptor-binding capacity or silencing the gene for PCSK9 allows the LDLR to recycle to the cell surface to remove more circulating plasma LDL. Over a decade ago, individuals with gain-of-function mutations of the PCSK9 gene were found to underlie a rare form of autosomal dominant hypercholesterolemia. Human loss-of-function mutations in PCSK9 are associated with low levels of LDL and decreased risk of vascular disease (Kathiresan 2008; Cohen et al. 2006). These discoveries led to the development of monoclonal antibodies directed against PCSK9 as a novel cholesterol-lowering agent

(Stein and Raal 2014). Animal, genetic, and human modeling support PCSK9 inhibition strategies. Human mAbs bind to PCSK9 in the extracellular space preventing the binding of PCSK9 to the LDL/LDLR complex. PCSK9 inhibitor is able to reduce LDL cholesterol levels by at least 50%, whether or not they received diet therapy, statin therapy, or combined statin plus ezetimibe (Blom et al. 2014). In randomized trials, the use of monoclonal antibodies that inhibits PCSK9 significantly reduced LDL cholesterol levels and reduced the incidence of cardiovascular events (Sabatine et al. 2015; Robinson et al. 2015).

Among possible adverse effects, neurocognitive adverse events were uncommon, though the slight excess occurrence was not related to LDL cholesterol level. Compared to placebo, myalgia was slightly more common in alirocumab but not different in evolocumab groups. Common side effects include injection site reactions, nasopharyngitis, upper respiratory tract infection, influenza, and back pain. The risk-benefit ratio will become better defined as long-term and larger clinical trials are being completed. As a result, PCSK9 inhibition has implications for clinicians who manage patients with dyslipidemia or severe hypercholesterolemia through reduction of LDL-C levels and potential reduction of the risk of ASCVD events.

5.4.4 Niacin

In clinical medicine, nicotinic acid was the first hypolipidemic agent shown to decrease the incidence of secondary myocardial infarction (MI), and it is able to reduce total mortality in MI patients. Niacin, as a lipid-regulating drug, reduces TC, LDL, VLDL, and TG, and increases HDL cholesterol, making it a useful medication for monotherapy or in combination with statins or fibrates. It decreases hepatic production of VLDLs and apo B-100, inhibits free fatty acid release from adipose tissue, and stabilizes apo A-I from HDL-C, maintaining the structure and function of HDL-C. Nicotinic acid is effective at increasing HDL level even in patients whose only lipid abnormality is a low HDL value. But niacin has no affect on the fecal excretion of fats, sterols, or bile acids.

Clinical trials of niacin, alone or combined with other lipid-altering therapy, show that niacin use was associated with a significant reduction in the composite endpoints of any CVD event and major coronary heart disease event (Lavigne and Karas 2013). However, there are different perspectives; some studies have demonstrated that the combined use of niacin and statins did not have an incremental benefit on cardiovascular morbidity and mortality. In addition, the combination of niacin and simvastatin did not result in a greater reduction in the incidence of cardiovascular events than simvastatin alone in the AIM-HIGH trial, which randomized patients with stable cardiovascular disease (Investigators et al. 2011).

Furthermore, there was an increased risk of serious adverse events when niacin used in antilipemic doses, including an increased incidence of disturbances in diabetes control, as well as serious gastrointestinal, musculoskeletal, dermatological,

infectious, and bleeding adverse events. Some sustained-release nicotinic acid formulations have a lower incidence of flushing but a higher incidence of hepatotoxicity when compared to immediate-release forms.

5.4.5 PPAR Agonist

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors, and they belong to the nuclear receptor superfamily. There are three different isoforms of these nuclear receptors have been described in mammalian cells, namely, PPARalpha, PPARdelta, and PPARgamma. In the presence of a ligand, PPARs heterodimerize with RXR, a retinoid receptor, and modulate transcription of target genes by binding to PPAR response elements in the promoter region of target genes. Acting as molecular sensors, PPARs transactivate target genes in response to several endogenous ligands such as saturated and unsaturated fatty acids, derivatives of arachidonic acid, or synthetic hypolipidemic agents. Most of the identified PPAR target genes are implicated in various aspects of lipid metabolism and energy homeostasis. Over the last decade, the members of the PPAR subfamily of nuclear receptors have emerged as valuable pharmacological targets whose activation can normalize metabolic dysfunctions and reduce some cardiovascular risk factors.

PPARα agonists, such as the fibrates, can correct dyslipidemia. Fibrates such as gemfibrozil, fenofibrate, clofibrate, and ciprofibrate have been used for decades in the treatment of dyslipidemia and they can reduce HDL-C and increase TG levels through active the PPARα. PPARα is able to regulate the expression of genes involved in several respects of lipid and lipoprotein metabolism. In humans, activation of PPARα by fibrates causes a reduction of plasma TG and VLDL levels, and it can increase HDL-C levels through stimulating the expression of ApoAI and ApoAII, the major apolipoproteins of HDL (Staels et al. 1998). In addition, PPARα activation results in promoting reverse cholesterol transport via the stimulation of macrophage cholesterol efflux as a result of induction of the cholesterol transporter ABCA1 in macrophages (Chinetti et al. 2001). A large number of clinical trials have shown that fibrates can reduce the risk of cardiovascular disease associated with dyslipidemia, and can delay the progression of coronary atherosclerosis, resulting in reduced coronary events (Staels and Fruchart 2005).

PPARγ promotes the regression of foam cells by inducing cholesterol efflux via the upregulation of ABCA1, ABCG1, and ApoE. Activation of PPARγ contributes to remove the cholesterol, thereby preventing transformation of macrophages into foam cells and subsequent atherosclerosis development (Chinetti et al. 2001). At the same time, PPARγ agonists are able to activate the scavenger receptor and lipid transporters, such as SR-BI/CLA-1 and FAT/CD36, which can enhance uptake of lipids and cholesterol in macrophages (Chinetti et al. 2000).

PPARδ has an extensive expression, and it displays a higher level of expression in tissues controlling lipid metabolism, such as adipocytes, small intestine, heart,

skeletal muscle, and macrophages. PPARδ-specific agonists have revealed an important role for PPARδ in the regulation of lipid and lipoprotein metabolism. PPARδ agonist GW501516 can cause a significant rise in HDL-C, a reduction in LDL-C and VLDL-TG, and a normalization of insulin levels, but the mechanism is still unknown (Oliver et al. 2001). PPARδ may regulate cholesterol metabolism by promoting reverse cholesterol transport via the induction of ABCA1 in peripheral tissues (Sprecher et al. 2007). PPARδ agonists seem promising drugs for the improvement of parameters associated with the metabolic syndrome, such as dyslipidemia, obesity, insulin resistance, and vascular inflammation. However, activation of PPARδ is associated with some deleterious effects in preclinical animal models such as the development of small intestinal tumors (Gupta et al. 2004) and angiogenesis (Piqueras et al. 2007), as well as increased intima–media thickness as a consequence of an increase in smooth-muscle-cell proliferation (Zhang et al. 2002). Further studies are clearly necessary.

5.4.6 PUFA

Polyunsaturated fatty acids (PUFAs), including arachidonic acid and eicosapentaenoic acid (EPA), can be enzymatically converted to eicosanoids. A large number of data indicate that fatty acids not only regulate cell inflammation and immune function but also act as second messengers or regulators of signal-transducing molecules (Calder and Grimble 2002). Experimental evidences in isolated myocytes and animals point to a possible direct antiarrhythmic effect of PUFAs.

N − 3 PUFAs not only exert antioxidant, anti-inflammatory, and lipid-lowering effects, but also can block Na and L-type calcium channels and modulate membrane fluidity (Reiffel and McDonald 2006). Total cholesterol is not materially affected by n − 3 fatty acid consumption, low-density lipoprotein cholesterol concentrations tend to rise by 5–10% and high-density lipoprotein cholesterol by 1–3%, and serum triacylglycerol concentrations decrease by 25–30% (Harris 1997). Results from prospective cohort studies and randomized, controlled trials have provided evidence of a protective effect of n − 3 fatty acids against cardiovascular diseases, but these effects were not confirmed by subsequent clinical trials (Kromhout et al. 2010; Risk et al. 2013). Adverse reactions of n − 3 fatty acids are rare, with an incidence of about 2–3%, including gastrointestinal symptoms, and a small number of cases with elevated levels of transaminase or creatine kinase.

5.4.7 Combination Therapy

Combination therapy is now increasingly used to achieve goal lipid levels. The principle is to combine two different classes of agents with different mechanisms of action, such as a statin and a fibrate or nicotinic acid. Most sources warn against

these combinations because of the fear of muscle or renal damage or hepatotoxicity. Nonetheless, there is a growing consensus that judicious use of combination therapy, when required, is likely to confer more benefits than harm. Caution is still required, with regular clinical observation, patient education about side effects, and monitoring of creatine kinase and blood liver enzymes.

5.5 Challenges and Perspectives

Dyslipidemia is one of the major risk factors for atherosclerosis and CAD. A large number of epidemiological data and large-scale clinical trials show that correcting dyslipidemia is conducive to the prevention and treatment of arteriosclerotic cardiovascular disease. It is important to achieve greater understanding of treatment patterns in real-world patients by evaluating pharmacologic treatment of mixed dyslipidemia patients with CVD risk factors. Lifestyle and dietary interventions are integral parts of primary and secondary cardiovascular prevention and are recommended for all patients. Statin medications are the most effective and widely used agents for cholesterol lowering and have the most robust clinical trial data to support their use in lowering cardiovascular risk. Statins are generally well tolerated but the use may be limited by hepatotoxicity or muscle side effects. Combination with less dose statins and PCSK9 inhibitor, ezetimibe, or other lipid-lowering drugs as well as minimizing the side effects may achieve a recommended target LDL-C of lower than 100 mg/dL, and optimally lower than 70 mg/dL in patients with CHD or CHD risk equivalents or multiple CHD risk factors conferring an estimated 10-year risk for a cardiovascular event higher than 20%.

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Chapter 6
Hypertension Drug Therapy

Rutai Hui

Abstract Hypertension is still the number one global killer. No matter what causes are, lowering blood pressure can significantly reduce cardiovascular complications, cardiovascular death, and total death. Unfortunately, some hypertensive individuals simply do not know having hypertension. Some knew it but either not being treated or treated but blood pressure does not achieve goal. The reasons for inadequate control of blood pressure are many. One important reason is that we are not very familiar with antihypertensive agents and less attention has been paid to comorbidities, complications as well as the hypertension-modified target organ damage in patients with hypertension. The right antihypertensive drug was not given to the right hypertensive patients at right time. This reviewer studied comprehensively the literature, hopefully that the review will help improve antihypertensive drug selection and antihypertensive therapy.

Keywords Hypertension · Antihypertensive drugs · Organ damage · Cardiovascular risk · Hypertension treatment · Hypertensive emergency

Abbreviations

ABPM	Ambulatory blood pressure monitoring
ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
AHA	American Heart Association
ARB	Angiotensin II receptor blocker ARB
ASCVD	Atherosclerotic cardiovascular disease
BP	Blood pressure
BSA	Body surface area

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CCB	Calcium channel blocker
CK-MB	Creatine kinase-MB
DHP	Dihydropyridine
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
ENaC	Epithelial sodium channel
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ESKD	End-stage kidney disease
HBPM	Home blood pressure monitoring
HELLP	Hemolysis, elevated liver enzymes, and low platelets
HFpEF	Ejection fraction preserved heart failure
HMOD	Hypertension-modified organ damage
MAP	Mean arterial pressure
NEDD4L	Neural precursor cell expressed, developmentally down-regulated 4, like E3 ubiquitin Protein ligase
NO	Nitric oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
MRI	Magnetic resonance imaging
PWV	Pulse wave velocity
RAAS	Renin–angiotensin–aldosterone system
TIA	Transient ischemic attack
VSMC	Vascular smooth muscle cells

Introduction

Hypertension: Even though sustained increases in blood pressure (BP) above 115/75 mm Hg can increase cardiovascular disease morbidity and mortality (Sacks and Campos 2010), the average adult BP < 120/ < 80 mmHg is defined as normal BP as measured with a sphygmomanometer by using BP cuff around the upper arm while sitting according to ACC/AHA (American College of Cardiology/American Heart Association) guideline 2017 (Whelton et al. 2017). The European Society of Hypertension (ESH)/The European Society of Cardiology (ESC) guideline (2018) for the management of arterial hypertension (Williams et al. 2018) defined "a prehypertension status in two categories: (1) normal BP of 120–129 mm Hg or diastolic BP of 80–84 mm Hg; and (2) high-normal BP with systolic BP of 130–139 mm Hg or diastolic BP of 85–89 mm Hg." The definition of high-normal BP is not accepted widely because this may confuse patients that they are still at normal BP range, reluctant to take non-pharmacological or pharmacological management to control their BP. In adults, hypertension is generally defined as a sustained systolic BP $\geq$ 140 mm Hg and/or a sustained diastolic BP $\geq$ 90 mm Hg at office measurement, which is equivalent to a 24-h ambulatory blood pressure monitoring (ABPM) average

of at least 130/80 mm Hg, or a home blood pressure monitoring (HBPM) average at least 135/85 mm Hg (Whelton et al. 2017; Williams et al. 2018; James et al. 2014; Hypertension et al. 2013). The diagnosis of hypertension should be confirmed either by repeated office BP measurements over a number of visits or by out-of-office BP measurement using 24-h ABPM or HBPM if logistically and economically feasible.

The big human healthy burden by hypertension: It is well known that BP is increased with age. Before age of 50 years, most individuals diagnosed with hypertension will increase in both systolic BP and diastolic BP. After age of 50 years, only systolic BP increases with age in most people. According to ACC/AHA (Whelton et al. 2017), approximately 86 million adults (34%) are affected by hypertension in the United States alone. High BP affects approximately 1 in 3 adults and only about half of them have their BP under control (Whelton et al. 2017; James et al. 2014). The number of adults with hypertension at least reached 1.13 billion people worldwide (Hypertension et al. 2013). Overall, high-income countries have a lower prevalence of hypertension (35%) than other groups (at 40%) (Hypertension et al. 2013; World Health Organization 2008).

Hypertension remains one of the biggest single risk factors for cardiovascular disease, stroke and chronic kidney disease, and renal failure. Hypertension was responsible for 7% of death and disability-adjusted life years in 2010 (Lim et al. 1990). Even though there are 23 classes of antihypertensive agents available with over 100 different classes of antihypertensive drugs, nearly 40% of patients did not achieve their BP goal based on recent guideline of hypertension management in developed countries, and even worse in the developing countries (Whelton et al. 2017; Williams et al. 2018; James et al. 2014; Hypertension et al. 2013).

Adverse consequences of hypertension: Persons with prehypertension are at increased risk for cardiovascular diseases (Kokubo and Kamide 2009). Approximately, 17 million of global deaths were due to cardiovascular disease a year, constituted nearly one-third of the total worldwide death. Of these, complications of hypertension account for 9.4 million, responsible for at least 45% of deaths due to heart disease (total ischemic heart disease mortality and 51% of deaths due to stroke) (Hypertension et al. 2013). If left untreated or treated but BP level does not achieve to goal, hypertension can increase the risk of cardiovascular mortality and morbidity. Mild-to-moderate hypertension would increase 30% risk of atherosclerotic disease, and 50% of patients will have target organ damage within 8–10 years after hypertension onset (Carey et al. 2018).

Death from ischemic heart disease or stroke increases progressively with an increase in BP level. For every 20 mm Hg systolic or 10 mm Hg diastolic increase in BP above 115/75 mm Hg, the mortality rate doubles for both ischemic heart disease and stroke (Chobanian et al. 2003). So bringing BP under control goal is one of the most important strategies in preventing cardiovascular morbidity as well as mortality in patients with hypertension.

It is widely accepted that the higher the BP level, the greater the damage to hypertension-modified organ damage (HMOD). Three major target organ damages have been described (Whelton et al. 2017; Williams et al. 2018; James et al. 2014; Hypertension et al. 2013).

Heart disease: The high BP load is placed on the left ventricle, resulting in left ventricular hypertrophy. With pressure load being longer, the heart enlarges and dilates, and hypertrophy is more marked than dilation, until the left heart begins to fail, particularly when the heart reaches 500 g in size. Congestive heart failure and cardiac arrhythmias may result from the failing heart (Shenasa and Shenasa 2017; Olivetti et al. 2000).

Heart failure: In the Framingham Heart Study, comparing the highest BP with the lowest BP, the age-adjusted risk of congestive heart failure was 2.3 times higher in men and 3 times higher in women (Patrick et al. 1971).

Coronary artery disease: Data from multiple risk factor intervention trial showed that the relative risk for coronary artery disease mortality was 2.3 to 6.9 times higher in persons with mild to severe hypertension than in those with normal BP (Winkleby et al. 1997; Multiple Risk Factor Intervention Trial Group 1976; Stamler et al. 2012; Multiple risk factor intervention trial 1982; Culleton et al. 1999). The relative risk for stroke ranged from 3.6 to 19.2 times. The population-attributable risk for coronary artery disease varied from 2.3 to 25.6%, whereas ranged from 6.8 to 40% for stroke (Winkleby et al. 1997; Multiple Risk Factor Intervention Trial Group 1976; Stamler et al. 2012; Multiple Risk factor Changes and Mortality Results 1982; Culleton et al. 1999).

Central nerve systems: The effect of hypertension on small arteries and arterioles in the brain leads to thickening and loss of resilience. This hypertensive hyalinization may produce occlusion with resultant small lacunar infarcts. This arteriolar sclerosis also results in vessels that are more prone to rupture. The so-called hypertensive hemorrhage is one of the causes of a stroke.

Stroke risk: Huang et al. (2013) reported that compared with an optimal BP (<120/80 mm Hg), prehypertension was also associated with a 66% increased risk in stroke after adjustment for multiple cardiovascular risk factors in a meta-analysis of pooled data from 19 prospective cohort studies involving 762,393 patients (Huang et al. 2014). In subjects with low range of prehypertension (120–129/80–84 mm Hg), the risk of stroke increases 44%; in subjects with high range of prehypertension (130–139/85–89 mm Hg), the risk of stroke increases to 95%.

Renal complications: The renal vasculature shows changes with hypertension, including, but not limited to, hyaline arteriolosclerosis (thickening of small renal arteries and arterioles, so-called nephrosclerosis) and small cortical scars with a reduction in renal size. The changes seen in arterioles may include fibrinoid necrosis as a consequence of hypertensive emergency (malignant hypertension) when systolic BP is $\geq$180 mm Hg and/or diastolic BP $\geq$ 120 mm Hg along with signs of acute or ongoing end-organ damage. Nephrosclerosis is one of the possible complications of long-standing hypertension. The risk of hypertension-induced end-stage kidney disease (ESKD) is higher in black patients, even when BP is under well control. Furthermore, patients with diabetic nephropathy who are hypertensive also have a high risk for developing ESKD (Whelton et al. 2017; Williams et al. 2018).

Hypertension is the most important modifiable risk factor for coronary heart disease (the leading cause of death in North America), stroke (the third leading cause of death), congestive heart failure, ESKD, and peripheral vascular disease (Whelton

et al. 2017; Williams et al. 2018). The Framingham Heart Study found a 72% increase in the risk of all-cause death and a 57% increase in the risk of any cardiovascular events in patients with hypertension who were also diagnosed with diabetes mellitus (Chen et al. 2011).

Lowering BP can low cardiovascular disease risk. Since hypertension is the leading risk factor for cardiovascular disease morbidity and mortality worldwide, greater efforts should be devoted to improving hypertension control. Despite our tremendous scientific understanding of the cardiovascular risk factors that predispose to adverse health outcomes, pinpointing the BP for optimal risk reduction continues to evolve and be debated. Even we know for a long time that systolic BP over 110–115 mmHg increases cardiovascular risk in every age group. Most BP management guidelines remained focused on BP-lowering treatment in those patients meeting conventional hypertension definitions. The recent landmark clinical trial SPRINT (Systolic Blood Pressure Intervention Trial) provided strong evidence that high BP patients with high cardiovascular disease risk (SPRINT Research Group 2015). Achieving systolic BP between 120 and 124 mm Hg results in lower cardiovascular events and mortality than systolic BP between 125 and 129 mm Hg (Tajeu et al. 2017). It has been reported that with more than 7 years of follow-up, 63.0% incident cardiovascular events occurred in individuals with BP < 140/90 mm Hg (Ziaeian and Fonarow 2017).

These findings held for individuals either younger or older than 65 years of age, men or women, and across all race and ethnic groups studied. The conventional standard for controlled BP < 140/90 mm Hg is not enough in terms of cardiovascular disease prevention. The conventional definitions of hypertension may not adequately encompass the population having events, indicating that under-treatment of BP is a significant public health burden; a much larger population is at risk, with BP < 140/90 mm Hg but above optimal. Under this circumstance, adherence to guidelines must be improved and expanded for patients with unquestionable elevations in BP and lowering BP targets to SPRINT-defined levels is reasonable for selected populations along with the use of other effective cardiovascular risk reductions strategies.

It is well known that antihypertensive therapy reduces cardiovascular disease risk. It has been noticed that the cardiovascular disease event rate was nearly 3 times greater in patients not taking any antihypertensive medication than in those taking antihypertensive treatment (Gabriel et al. 2017).

The fundamental goal of treatment should be the prevention of the important endpoints of hypertension, such as heart attack, stroke, and heart failure. Although traditionally we reassured patients that they do not have hypertension at BP levels < 140/90 mm Hg or their hypertension was adequately controlled if BP < 140/90 mm Hg, more and more evidences support that the vast majority of cardiovascular events in the modern era occurred among individuals below that BP threshold. Identifying patients that would benefit from SPRINT targeted BP levels could effectively reduce event rates further.

Why should we actively lower BP? Most individuals diagnosed with hypertension will have increased BP as they age. Clinical trials demonstrated that antihypertensive therapy will benefit patients with lowering stroke risk 35–40%, myocardial infarction risk 20–25%, and heart failure risk more than 50%. It is estimated that one death can be

prevented if treating 11 patients with stage 1 hypertension which achieved a sustained decrease in systolic BP 12 mm Hg for 10 years as well as intervening concomitantly other cardiovascular risk factors. One death can be prevented if treating 9 hypertensive patients with cardiovascular disease or with end-organ damage by reducing systolic BP to the same level (Chobanian et al. 2003). Evidence suggests that BP reduction by 5 mm Hg can decrease the stroke risk by 34%, ischemic heart disease risk by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease (Arnett et al. 2019).

Patient's age, associated clinical conditions, and end-organ damage also play a very important role in determining dosage and type of antihypertensive drugs (Chobanian et al. 2003).

In this chapter, we are going to present hypertension diagnosis, risk factors for high BP, secondary hypertension, antihypertension agents, treatment of hypertension, and treatment hypertensive patients with special conditions.

6.1 Hypertension Ascertainment

BP measurement: Guidelines usually recommended the follow-up measurements of BP with standardized methods or electronic (oscillometric) upper arm devices, either ABPM or HBPM in individuals with white coat effect (Nerenberg et al. 2018).

Before BP measurement, subjects should be emptied their bladder and seat for five minutes with back supported and legs resting on the ground (not crossed). Arm used for measurement should rest on a table, at heart level. Use a sphygmomanometer/stethoscope or automated electronic device (preferred) with the correct size arm cuff.

Arm circumference	Usual cuff size
22–26 cm	Small adult
27–34 cm	Adult
35–44 cm	Large adult
45–52 cm	Adult thigh

Take two BP readings one to two minutes apart and average the readings (preferred). BP should be measured in both arms at initial evaluation. Consider checking standing readings after one and three minutes to screen for postural hypotension, especially in the elderly.

Hypertension is defined as office systolic BP at least 140 mmHg and/or diastolic BP at least 90 mmHg, which is equivalent to a 24 h ABPM average of at least 130/80 mmHg, or an HBPM average at least 135/85 mmHg. When hypertension is suspected because of an elevated screening BP, the diagnosis of hypertension should be confirmed either by repeated office BP measurements over a number of visits or

by out-of-office BP measurement using 24-h ABPM or HBPM if logistically and economically feasible. The diagnosis of hypertension is made at a subsequent visit one to four weeks after the first. If BP is very high (e.g., systolic 180 mmHg or higher), or timely follow-up unrealistic, treatment can be started after just one set of measurements (Williams et al. 2018).

Corresponding values of systolic BP/diastolic BP (mm Hg) for clinic, HBPM, daytime, nighttime, and 24-h ABPM measurements (Whelton et al. 2017; Williams et al. 2018).

Clinic	HBPM	Daytime ABPM	Nighttime ABPM	24-h ABPM
120/80	120/80	120/80	100/65	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/85	120/70	130/80
160/100	145/90	145/90	140/85	145/90

A meta-analysis of observational studies that included 13,844 individuals suggested that nighttime BP is a stronger risk factor for coronary heart disease and stroke than either clinic or daytime BP (ABC-H Investigators et al. 2014). The evaluation of hypertension involves accurately measuring the patient's BP, performing a focused medical history and physical examination, and obtaining results of routine laboratory studies. A 12-lead electrocardiogram should also be obtained. These steps can help determine possible causes of hypertension, target organ damage, coexistence of other cardiovascular risk factors, and comorbidities (Whelton et al. 2017).

The recommended BP classification system is most valuable in untreated adults as an aid in decisions about prevention or treatment of high BP. However, it is also useful in assessing the success of interventions to reduce BP. AHA/ACC 2017 guideline proposed a BP classification system (Whelton et al. 2017).

	Systolic BP	Diastolic BP
Normal BP	<120 mm Hg, and	<80 mm Hg
Elevated BP	120–129 mm Hg, and	<80 mm Hg

Hypertension

Stage 1	130–139 mm Hg or	80–89 mm Hg
Stage 2	≥140 mm Hg or	≥90 mm Hg

ESH/ESC 2018 guideline (Williams et al. 2018) proposed a classification of office BP and definition of hypertension grade as follows:

Category	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Optimal	<120	<80
Normal	120–129 and/or	80–84
High-normal hypertension	130–139 and/or	85–89
Grade 1	140–159 and/or	90–99
Grade 2	160–179 and/or	100–109
Grade 3	≥180 and/or	= 110
Isolated systolic hypertension	≥ 140 and	<90

ACC/AHA BP classification system is favored because it is simple and easy to apply for both clinicians and patients. High-normal BP classification by ESH/ESC 2018 guideline may confuse subjects who think that their BP is still in normal range, reluctant to actively control their BP by applying non-pharmaceutical intervention.

6.2 Hypertension-Modified Organ Damage (Williams et al. 2018; Corretti et al. 2002; Messerli et al. 2007)

The presence of HMOD further increases the risk of cardiovascular morbidity and mortality, and cardiovascular target organ damage should be screened as part of risk assessment in hypertensive patients.

Two classes of HMOD are subclinical and established cardiovascular and renal disease.

6.2.1 Subclinical Organ Damage

(1) Arterial stiffening (pulse pressure wide): In older people, pulse pressure ≥ 60 mm Hg; carotid–femoral PWV (pulse wave velocity) > 10 m/s;
(2) Left ventricular hypertrophy by using electrocardiogram: Sokolow–Lyon index > 35 mm, or RavL ≥ 11 mm, Cornell voltage duration product > 2440 mm * ms, or Cornell voltage > 28 mm in men or > 20 mm in women.
(3) Echocardiographic left ventricular hypertrophy: Left ventricular mass index > 50 g/m$^{2.7}$ (men) > 47 g/m$^{2.7}$(hight in m$^{2.7}$) (women); BSA (body surface area) normalization may be used in normal-weight patients: left ventricular mass index = left ventricular mass/BSA (g/m^2), men > 115 g/m^2, women > 95 g/m^2.
(4) Microalbuminuria: 30–300 mg/24-h urine collection, or elevated albumin/creatinine ratio 30–300 mg/g, or 3.4–34 mg/mmol (preferred on morning spot urine).
(5) Moderate chronic kidney disease with estimated glomerular filtration rate (eGFR) 30–59 ml/min/1.73 m^2.

(6) Ankle–brachial index < 0.9.
(7) Advanced retinopathy: hemorrhages or exudates, papilledema.
(8) Flow-mediated dilation to measure endothelial function in conduit arteries rather than resistant vessels. Flow-mediated changes in conduit artery diameter are caused by shear-stress-induced generation of endothelial-derived vasoactive mediators.

Although both carotid intima-media thickness values and coronary artery calcium scores have been associated with cardiovascular events, inadequate or absent data on the effect of improvement in these markers on cardiovascular events prevent their routine use as surrogate markers in the treatment of hypertension.

Left ventricular hypertrophy is an independent predictor of cardiovascular complications and most useful in adults who are young or have evidence of secondary hypertension, chronic uncontrolled hypertension, or history of symptoms of heart failure. At older ages, left ventricular hypertrophy measured by electrocardiography or magnetic resonance imaging (MRI) provides no independent contribution to the prediction of cardiovascular risk.

Left ventricular hypertrophy is commonly measured by electrocardiography, echocardiography, or MRI. Reduction in left ventricular hypertrophy can predict a reduction in cardiovascular disease risk, independent of change in BP. In TOMHS trial (Treatment of Mild Hypertension Study), chlorthalidone (a long-acting thiazide-like diuretics) was stronger than amlodipine, a calcium channel blocker (CCB), enalapril (an angiotensin-converting enzyme inhibitor, ACE inhibitor), doxazosin (alpha-receptor blocker), and acebutolol (beta-receptor blocker) in reducing left ventricular hypertrophy (Neaton et al. 1993).

Long-term high BP results in adverse effects on cardiac structure and function, documented with echocardiography, MRI, and other laboratory tests, including left atrial size enlargement both diameter and area, known as precursor for atrial fibrillation; diastolic dysfunction, and the precursor of ejection fraction preserved heart failure (HFpEF); left ventricular hypertrophy and left ventricular systolic dysfunction. Beta-blockers are the weakest agent in reducing left ventricular hypertrophy compared with either ARBs (angiotensin II receptor type 1 antagonist, ARB), or ACE inhibitors, or CCBs (Neaton et al. 1993).

6.2.2 Established Cardiovascular or Renal Diseases

High BP is the single biggest risk factor for cardiovascular disease. Hypertension can cause the following diseases:

(1) Cerebrovascular disease: Ischemic stroke, hemorrhage, TIA *(*transient ischemic attack).
(2) Coronary artery disease: Angina pectoris, myocardial infarction, and myocardial revascularization; and the presence of atheromatous plaque on imaging.
(3) Heart failure, including HFpEF.

(4) Peripheral artery disease.
(5) Atrial fibrillation.
(6) Severe chronic kidney disease with eGFR < 30 ml/min/1.73 m^2.

Cardiovascular disease in hypertension patients also includes asymptomatic atheromatous disease on imaging examination, diabetes (type 1 or type 2), and very high levels of individual risk factors (including grade 3 hypertension or chronic kidney disease at stages 3–5).

These mentioned above are automatically considered to be at very high 10-year risk (i.e., > 10% cardiovascular disease mortality) or high 10-year cardiovascular risk (i.e., 5–10% cardiovascular disease mortality). Such patients do not need formal cardiovascular risk estimation to determine their need for treatment of their hypertension and other cardiovascular risk factors.

6.2.3 Other Risk Factors

Sex (men > women), age, smoking (current or past), total cholesterol, HDL-C (high-density lipoprotein cholesterol), serum uric acid, overweight or obesity, family history of premature cardiovascular disease (men < 55 years and women < 65 years); family or parental history of early-onset hypertension, early-onset menopause, sedentary lifestyle, psychosocial and socioeconomic factors, and heart rate: rest > 80 beats/min.

6.3 Intervening Risk Factors of Atherosclerotic Cardiovascular Disease (ASCVD) Concomitantly

Majority of patients with hypertension usually have multiple cardiovascular risk factors in addition to high BP. These risk factors synergistically contribute to their absolute cardiovascular disease risk, but a cardiovascular event occurs in a defined period (Mancia 2006; Neaton et al. 1992; Thomas et al. 2002). Control of high BP should be a part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake (Whelton et al. 2017; Chobanian et al. 2003).

The prevalence of patients with ≥ 3 additional cardiovascular risk factors increased from 31.2% in 2000 to 34.2% in 2002 in Dutch population and from 31.1% to 39.3% in Italian population over the same period (Sturkenboom et al. 2008). According to AHA/ACC guideline 2017, hypertensive patients often carry cardiovascular risk factors (Whelton et al. 2017). NHANES (1999–2010) survey reported that 35.7% of obese individuals had hypertension (Saydah et al. 1999). On the other hand, 71% of US adults with diabetes mellitus have hypertension. In Chronic Renal

Insufficiency Cohort study (Denker et al. 2002), 86% of recruited participants had hypertension.

A meta-analysis from 18 cohort studies involving 257,384 patients identified a lifetime risk of cardiovascular death, nonfatal myocardial infarction, and fatal or nonfatal stroke, which was substantially higher in adults with ≥2 cardiovascular risk factors than in those with only one risk factor (Berry et al. 2012). Treating some of the modifiable risk factors may reduce BP and cardiovascular risk through modification of shared pathology.

6.4 Assessment of Cardiovascular Risk

Cardiovascular and renal complications are the most important outcomes of chronic hypertension. For individuals at age 40–70 years, each increment of 20 mmHg in systolic BP or 10 mmHg in diastolic BP across the entire BP range from 115/75 to 185/115 mmHg doubles the risk of cardiovascular disease (James et al. 2014). Treatment of hypertension should focus not only on BP readings.

ACC/AHA have published an online tool to calculate patients' 10-year and lifetime ASCVD risk [ACC: ASCVD Risk Estimator Plus]. ESH/ESC 2018 guideline (Williams et al. 2018) recommended to apply SCORE system to assess cardiovascular risk for patients with hypertension, but unfortunately, the SCORE system alone may underestimate the risk, such as when HMOD present, especially left ventricular hypertrophy, chronic kidney disease, and advanced retinopathy. HMOD further raises the risk of cardiovascular morbidity and mortality. Therefore, in all patients with hypertension, HMOD detection should be included in stratification of cardiovascular risk to improve diagnostic, prognostic, and therapeutic processes.

It has long been known that treating cardiovascular risk factors such as obesity, diabetes, hypercholesterolemia, and smoking are as important as managing hypertension in lowering overall cardiovascular risk. Meta-analysis has confirmed that lowering BP reduces cardiovascular disease and death in people with baseline systolic BP of 140 mmHg or higher (Brunström and Carlberg 2018). However, primary preventive BP lowering does not benefit people with lower baseline BP (except those with preexisting cardiovascular disease) (Brunström and Carlberg 2018). One Cochrane review found insufficient evidence to justify lower BP targets (≤135/85 mmHg) in people with hypertension and cardiovascular disease (Saiz et al. 2018).

Cardiovascular Risk in Patients with Hypertension

6.4.1 Cardiovascular Risk Assessment

SCORE is suitable for those who are not already at high or very high risk due to established cardiovascular disease, renal disease, or diabetes, a markedly elevated single factor (e.g., cholesterol) or hypertensive left ventricular hypertrophy.

6.4.2 Calculating Cardiovascular Age

The cardiovascular age can be automatically calculated using HeartScore (www.heartscore.org), especially young patients.

6.4.3 The Presence of Concomitant Disease

◦

6.4.4 Treated BP Value

The risk calculators are usually calibrated according to global risk factors, including office BP readings. Cardiovascular risk in patients with hypertension can't be completely reversed by BP lowering alone even BP goal was well achieved. If antihypertensive treatment has been long-standing, then the treated BP value will be used to calculate the risk which will be lower than the patient's actual risk. How to impute out-of-office BP values into risk calculators becomes another conundrum. In the estimation of cardiovascular risk, these various limitations should be kept in mind in clinical practice.

To screen major cardiovascular risk factors to provide rationale for optimizing lifestyle and to track risk factor progression to provide needed treatment.

6.4.4.1 Classification of Hypertension Stages

Presence of cardiovascular risk factors, HMOD, or comorbidities (Williams et al. 2018).

Classifications by ESH/ESC: (Williams et al. 2018).
High-normal systolic BP 130–139 mm Hg and/or diastolic BP 85–89 mm Hg.

Grade 1: Systolic BP 140–159 mm Hg and/or diastolic BP 90–99 mm Hg.
Grade 2: Systolic BP 160–179 mm Hg and/or diastolic BP 100–109 mm Hg.

Grade 3: Systolic BP ≥ 180 mm Hg, diastolic BP ≥ 110 mm Hg.

a. **Hypertension stage 1**: Uncomplicated hypertension

(1) No other risk factors:

Low risk: Hypertension disease stage 1: No other risk factors, high-normal systolic BP 130–139 mm Hg and/or diastolic BP 85–89 mm Hg, or grade 1 systolic BP 140–159 mm Hg and/or diastolic BP 90–99 mm Hg.

Moderate risk: Stage 1 hypertension: No other risk factors, grade 2 systolic BP 160–179 mm Hg and/or diastolic BP 100–109 mm Hg.

High risk: Stage 1 hypertension: No other risk factors, grade 3 systolic BP 180 mm Hg and/or diastolic BP 110 mm Hg.

(2) Hypertension stage 1, uncomplicated, having 1 or 2 risk factors:

Low risk: High-normal systolic BP 130–139 mmHg and/or diastolic BP 85–89 mm Hg.

Moderate: Grade 1 systolic BP 140–159 mm Hg and/or diastolic BP 90–99 mm Hg.

Moderate to high risk: Grade 2 systolic BP 160–179 mm Hg and/or diastolic BP 100–109 mm Hg.

High risk: Grade 3 systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg.

(3) Stage 1 hypertension (uncomplicated): Having ≥3 risk factors.

Low to moderate risk: High-normal systolic BP 130–139 mmHg and/or diastolic BP 85–89 mm Hg.

Moderate to high risk: Grade 1 systolic BP 140–159 mm Hg, diastolic BP 90–99 mm Hg.

High risk: Grade 2 systolic BP 160–179 mm Hg and/or diastolic BP 100–109 mm Hg. Grade 3 systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg.

b. **Stage 2** (asymptomatic disease): Presence of HMOD, chronic kidney disease grade 3, or diabetes mellitus without organ damage.

(1) Moderate to high risk: High-normal systolic BP 130–139 mm Hg and/or diastolic BP 85–89 mm Hg.
(2) High risk: Grade 1 systolic BP 140–159 mm Hg, diastolic BP 90–99 mm Hg, Grade 2 systolic BP 160–179 mm Hg and/or diastolic BP 100–109 mm Hg.
(3) High to very high risk: Grade 3, systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg.

c. **Stage 3** (established disease): Established cardiovascular disease, established cardiovascular disease, or chronic kidney disease damage grade ≥ 4, or diabetes mellitus with organ damage.

ESH/ESC 2018 pointed out: (Williams et al. 2018).

6.4.4.2 Very High Risk

(1) Ascertained clinical cardiovascular diseases, including but not limited to acute coronary syndrome, acute myocardial infarction, other arterial revascularization; stroke, transient ischemic attack; aortic aneurysm and dissection as well as peripheral artery disease.
(2) Confirmed cardiovascular disease on imaging (angiography or ultrasound), including atherosclerotic plaques (e.g., >50% of stenosis, not including only increase in the carotid intima-media thickness).
(3) Diabetes mellitus with target organ damage (i.e., proteinuria) or with a major risk factor (grade 3 hypertension or hypercholesterolemia).
(4) Severe chronic kidney disease (eGFR < 30 ml/min/1.73 m^2).
(5) Calculated 10-year ASCVD risk score >10% using the ASCVD algorithm (Arnett et al. 2019).

6.4.4.3 High Risk

Marked elevation of a single risk factor, particularly cholesterol, e.g., familial hypercholesterolemia, or Grade 3 hypertension (SBP $\geq$ 180 mm Hg and/or DBP $\geq$ 110 mm Hg); with diabetes, hypertensive left ventricular hypertrophy, moderate chronic kidney disease (eGFR 30–59 ml/min/1.73 m^2), a calculated 10-year risk score of 5–10%.

6.4.4.4 Moderate Risk

A calculated 10-year score of 1–5%. Grade 2 hypertension.

6.4.4.5 Low Risk

A calculated 10-year score of <1%.

ACC/AHA 2019 primary prevention of ASCVD guidelines recommended the risk-enhancing factors (Arnett et al. 2019). (1) Family history of premature ASCVD (occurred in male with age <55 years or in female with age <65 years); (2) primary hypercholesterolemia; (3) metabolic syndrome; (4) chronic kidney disease, not yet treated with dialysis or kidney transplantation; (5) chronic inflammatory disease, such as psoriasis, rheumatoid arthritis, systemic lupus erythematosus, HIV/AIDS; (6) history of premature menopause (before age 40 years) and pregnancy-related conditions which increase ASCVD risk, such as preeclampsia; and (7) Cardiovascular risk lipids/biomarkers.

Primary hypertriglyceridemia (non-fasting serum triglyceride $\geq$175 mg/dL) if measured; high-sensitivity C-reactive protein $\geq$2.0 mg/L, lipoprotein (a) $\geq$50 mg/dL,

apoB ≥ 130 mg/dl (corresponds to low-density lipoprotein-C, LDL-C > 160 mg/dL); ankle-brachial index <0.9. The available evidence suggests that many patients with hypertension would benefit from statin therapy, blood glucose-lowering therapy, antiplatelet therapy, and anticoagulant therapy (Williams et al. 2018; Arnett et al. 2019).

6.5 Antihypertensive Agents

6.5.1 Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors) (Arnett et al. 2019; Messerli et al. 2018)

ACE inhibitors suppress the activity of ACE; an enzyme is responsible for the conversion of angiotensin I into angiotensin II. At least 13 ACE inhibitors are available in clinical practice at present, including captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril, benazepril, cilazapril, imidapril, and zofenopril.

Mechanisms of action (Messerli et al. 2018): Under normal conditions, angiotensin II binds to angiotensin receptor Type 1 and has the following effects:

(1) Vasoconstriction and vascular smooth muscle hypertrophy, which lead to BP elevation and hypertension. Further, constriction of the efferent arterioles of the kidney leads to increased perfusion pressure in the glomeruli.
(2) Ventricular remodeling and ventricular hypertrophy of the heart by stimulating the proto-oncogenes c-fos, c-jun, c-myc, transforming growth factor beta through fibrogenesis and apoptosis.
(3) Stimulation of the adrenal cortex to release aldosterone, which acts on kidney tubules, causes sodium and chloride ions retention and potassium excretion. Sodium is a "water-holding" ion, so water is also retained, which leads to increased blood volume, hence an increase in BP.
(4) Stimulation of the posterior pituitary releases vasopressin (antidiuretic hormone), which acts on the kidneys to increase water retention. If antidiuretic hormone production is excessive in heart failure, Na^+ level in the plasma may fall (hyponatremia), and this is a sign of increased risk of death in heart failure patients.

ACE is located in the endothelial cells of large and small vessels, capillaries, and venules, and in pulmonary endothelial cells. ACE inhibitors target ACE, which catalyzes the conversion of angiotensin I to angiotensin II, leading to vasodilation of small resistance arteries, reduction in total peripheral resistance, and reduction of BP. Because cardiac output remains unchanged, despite BP lowering, heart rate remains unchanged, and no postural hypotension occurs, likely because ACE inhibitors reset baroreceptor function (Messerli et al. 2018).

Indications of ACE inhibitors: Hypertensive patients are indicated especially with left ventricular hypertrophy, coronary artery disease, chronic kidney disease, heart failure, cerebrovascular disease, and diabetes. ACE inhibitors reduce morbidity and mortality rates in patients with heart failure, patients with recent myocardial infarctions (Messerli et al. 2018). ALLHAT trial showed that ACE inhibitors were less effective in reducing BP compared to a CCB and had a 51% higher risk of stroke in black hypertensives when used as initial therapy (Davis et al. 2002).

Contraindication of ACE inhibitors: (Davis et al. 2002) The ACE inhibitors are contraindicated in patients with

(1) Previous angioedema associated with ACE inhibitor therapy.
(2) Renal stenosis.
(3) Hypersensitivity to ACE inhibitors.
(4) Pregnancy (Teratogenic): ACE inhibitors can cause injury or even death to a developing fetus. In pregnant women, ACE inhibitors should be discontinued as soon as possible.
(5) ACE inhibitors should be used with caution in patients with impaired renal function.
(6) Aortic valve stenosis or cardiac outflow obstruction.
(7) Hypovolemia or dehydration.
(8) Hemodialysis with high-flux polyacrylonitrile membranes.

Clinical outcomes: ACE inhibitors have been shown to effectively lower BP and improve clinical outcomes. These changes occur mostly in response to the reduction in BP, but a large number of evidences favor also a direct effect of ACE inhibitors on the cardiac, renal, and arterial tissue. ACE inhibitors have been ranked as the most effective antihypertensive drugs in reducing left ventricular hypertrophy, improving small artery remodeling and large artery stiffness. ACE inhibitors showed better outcomes than CCBs, diuretics, and beta-blockers in protection of target organ and in reduction of cardiovascular events. In long-term controlled studies, the ACE inhibitors exhibit the capacity to reverse aortic stiffening independently of BP lowering (Messerli et al. 2018).

Relaxation of large arteries by ACE inhibitors leads to less pressure wave reflection and a slower propagation of pressure waves along the aorta; thus, it is associated with a fall in central systolic and pulse pressures. Some clinical outcomes may result from an independent BP-lowering effect of ACE inhibitors, such as prevention of diabetic nephropathy, congestive heart failure, and prophylaxis of cardiovascular events (Messerli et al. 2018; Binkley et al. 1993).

Reno-protection is observed in various settings, i.e., established type 1 insulin-dependent diabetic nephropathy, early type 2 diabetic nephropathy, and type 1 diabetic patients without hypertension but with microalbuminuria (Laurent 2017; Xu et al. 2015). ACE inhibitors significantly reduced doubling of serum creatinine levels compared to other drugs (ARBs, alpha-blockers, beta-blockers.), suggesting a first line of antihypertensive drugs. ACE inhibitors have been found more effective at slowing down the decline of kidney function compared to CCBs and beta-blockers

(Hon-Yen et al. 2013; Sica 2003). As such, ACE inhibitors should be the drug treatment of choice for patients with chronic kidney disease regardless of race or diabetic status. ACE inhibitors (and ARB) should not be a first-line treatment for black hypertensives without chronic kidney disease (James et al. 2014). Results from the ALLHAT trial showed that thiazide-like diuretics and CCBs were both more effective as monotherapy in improving cardiovascular outcomes compared to ACE inhibitors for this subgroup (Davis et al. 2002; Wright et al. 2002).

ACE inhibitors have been shown to reduce the prevalence of malignant cardiac arrhythmias and the reduction in sudden cardiac death reported in large clinical trials (Binkley et al. 1993).

The BP-lowering effect of ACE inhibitors is supposed to maintain for months and years, because ACE inhibitors fail to suppress production of angiotensin II by alternative enzymatic pathways to ACE. The enzymatic pathway, such as chymase, trypsin, and cathepsin, can also convert angiotensin I to angiotensin II. On the long term, this alternative enzymatic pathway could up-regulate the production of angiotensin II, particularly in the vasculature and the myocardium, resulting in attenuation of the BP-lowering effect of ACE inhibitors (Kramkowski et al. 2007).

Since ACE is also responsible for the degradation of angiotensin (1–7), which is formed in the endothelial layer of human blood vessels, and angiotensin (1–7) acts as vasodilator and antiproliferative agent. Blocking ACE by ACE inhibitors suppresses the degradation of angiotensin (1–7), and accumulation of angiotensin (1–7) provides additional favored effect, protecting target organs. Indeed, long-term administration of ACE inhibitors is associated with a reduction of left ventricular hypertrophy, an improvement of endothelial function, a de-stiffening of large arteries, and a remodeling of large and small arteries (Russ et al. 2018).

Side effects: Compared with ARBs, ACE inhibitors have several-fold higher incidence of side effects at most doses (Law et al. 2003).

(1) The most common side effect of ACE inhibitors is a dry and irritating cough (5–35%). This is a class effect which can occur in patients taking any one of the ACE inhibitors and not dose-dependent. The exact mechanism of ACE inhibitor-induced cough is not known. It is likely multifactorial event, and most likely related to the inhibition of bradykinin and substance P breakdown that results in accumulation of these protrusive mediators in respiratory tract. Bradykinin also stimulates the production of prostaglandins which may contribute to cough as well (prostaglandin E2 via the EP_3 Receptor) (Arnett et al. 2019). Cessation of ACE inhibitor use is the only way to stop the cough (Messerli et al. 2018).
(2) The other reported adverse effects are hepatotoxicity and effect on the fetus (Sidorenkov and Navis 2014).
(3) Potentially life-threatening side effect is angioneurotic edema, a rare (0.55% of white patients and 1.62% of black patients), but greater risk for African-Americans, should pay extra-attention to the adverse effect because 20% of them may be fatal (Agostoni et al. 1999). Angioneurotic edema is explained by an increased in bradykinin concentrations, and/or increased concentration of other peptides such as substance P as well. In 26 trials with 74,857 patients,

0.30% of weighted incidence of angioedema with ACE inhibitors has been identified (95% CI: 0.28–0.32%) (Makani et al. 2012). The incidence of angioneurotic edema has been reported at about 1/2500 within the first week of taking ACE inhibitors (Israili and Hall 1992; Brown et al. 1997; Messerli and Nussberger 2000). However, it can first occur from a few hours to 8 years after an ACE inhibitor is initiated (Yusuf et al. 2008). The subsequent incidence of angioedema with ACE inhibitors is around 1 in 500 patients/year (Messerli and Nussberger 2000; Slater et al. 1988; Grossman et al. 2000).

(4) A moderate reduction in renal function: Angiotensin II constricts the efferent arteriole to a greater extent than the afferent one, blockade of ACE results in low production of angiotensin II, a fall in glomerular afferent arteriolar flow, and the vasodilatation of the glomerular efferent arteriole, such that GFR is maintained despite low perfusion. If patients with severe renal artery stenosis or solitary kidney, in case of dehydration, use of NSAIDs (non-steroidal anti-inflammatory drugs), heart failure, and microvascular disease, functional renal insufficiency occurs when using ACE inhibitors (Messerli et al. 2018).

Patients starting with an ACE inhibitor usually have a modest reduction in GFR which is stabilized after several days. Serum creatinine could be temporarily raised but not greater than 30% of the level before using ACE inhibitors, and then stabilized after a week of treatment. This change represents a hemodynamic (not a toxic) effect and is not a contraindication to continue ACE inhibitor. Indeed, ACE inhibitor treatment has been shown in some, but not all studies, to delay ESKD. Renal failure becomes especially problems when the patient is concomitantly taking ACE inhibitor with an NSAID and a diuretic; the risk of developing renal failure is significantly increased (Thomas 2000). In patients with decreased renal perfusion significantly, such as congestive heart failure, volume depletion, polycystic kidney disease, and renal artery stenosis, angiotensin II-dependent efferent vasomotor tone plays very important role in maintenance of GFR. In these patients, initiation of ACE inhibitor therapy blocks the production of angiotensin II and then could lead to a decrease in renal perfusion and may result in renal function deterioration. Therefore, it is necessary to monitor serum creatinine and electrolyte levels before and again 1 week after therapy (Messerli et al. 2018).

(5) Hyperkalemia: An ACE inhibitors suppress angiotensin II production and reduce plasma aldosterone levels. Since aldosterone is responsible for increasing the excretion of potassium, ACE inhibitors can cause retention of potassium and hyperkalemia. Hyperkalemia can slow the impulse conduction velocity in both nerves and muscle systems. Abnormal impulse conduction velocity may lead to arrhythmia and cardiac dysfunction in cardiac tissue and muscle weakness, paresthesia, nausea, diarrhea, and others in neuromuscular systems. In patients receiving ACE inhibitors, serum potassium level should be closely monitored in case of hyperkalemia (Sidorenkov and Navis 2014). ACE inhibitors usually do not lead to significant biochemical changes in patients with normal kidney function. In those with impaired kidney function, ACE inhibitors can raise the serum potassium concentration to the levels dangerous and requiring either a change

in therapy or increasing thiazide or loop diuretic dosage to promote potassium excretion. Such patients should restrict dietary potassium intake (Messerli et al. 2018).

The risk of hyperkalemia is also increased in patients with chronic kidney disease and heart failure or diabetes (who receive potassium-sparing diuretics or potassium supplements), previous history of angioneurotic edema or hyperkalemia, and bilateral renal artery stenosis (Messerli et al. 2018).

(6) ACE inhibitor-related anemia should be monitored when prescribing ACE inhibitors, likely due to the suppression of erythropoietin production.

The differences in how long these drugs act in the circulation are relatively small. Younger and white subjects are particularly likely to have an activated renin–angiotensin–aldosterone system (RAAS), whereas elderly and African American subjects are less likely. Diuretics enhance the action of ACE inhibitors, whereas ACE inhibitors themselves act on the kidney to retain some potassium, thereby reducing diuretic-induced adverse effect of hypokalemia (Messerli et al. 2018).

Recommended ACE inhibitor dose for hypertension treatment (Aram et al. 2003) (JNC-7)

Benazepril, equivalent daily dose 10 mg, starting from 10 mg, usually 30–40 mg, maximum daily 80 mg.

Captopril, equivalent daily dose 25 mg twice a day, starting from 12.5 to 25 mg twice a day, usually 25–50 mg twice a day, maximum daily 450 mg.

Enalapril, equivalent daily dose 5 mg, starting from 5 mg, usually 10–40 mg, maximum daily 40 mg.

Fosinopril, equivalent daily dose 10 mg, starting from 10 mg, usually 20–40 mg, maximum daily 80 mg once a day. Unlike most ACE inhibitors that are primarily excreted by the kidneys, fosinopril is eliminated by both renal and hepatic pathways, making it a safer choice in patients with renal failure and heart failure.

Lisinopril, equivalent daily dose 10 mg, starting from 10 mg, usually 10–40 mg, maximum daily 80 mg.

Moexipril, equivalent daily dose 7.5 mg, starting from 7.5 mg, usually 7.5–30 mg, maximum daily 30 mg.

Perindopril, equivalent daily dose 4 mg, starting from 4 mg, usually 4–8 mg, maximum daily 16 mg.

Quinapril, equivalent daily dose 10 mg, starting from 10 mg, usually 20–80 mg, maximum daily 80 mg.

Ramipril has been demonstrated to reduce mortality and to slow heart failure development in patients with myocardial infarction. The cardiovascular beneficial effects can also be observed in subjects regularly using ramipril without hypertension. Currently, ramipril is the only ACE inhibitors for which such effects are actually evidence-based (AIRE Study Investigators 1993).

Trandolapril, equivalent daily dose 2 mg, starting from 1 mg, usually 2–4 mg, maximum daily 8 mg.

Use in combination: There are warnings about the combination of ACE inhibitors with ARBs (Shelley 2014). Patients with heart failure may benefit from the combination in terms of reducing morbidity and ventricular remodeling (Krum et al. 2004; Solomon et al. 2005). In the treatment of nephropathy, this combination of ACE inhibitor with ARB therapy partially reversed the proteinuria and also exhibited a reno-protective effect in patients afflicted with diabetic nephropathy, and pediatric IgA nephropathy (Yang et al. 2012).

6.5.2 Angiotensin II Receptor Blockers (ARBs)

Nine types of ARBs are available in clinical practice, including losartan, candesartan irbesartan, olmesartan, telmisartan, valsartan, fimasartan, azilsartan, and eprosartan.

Mechanisms of action: ARBs antagonize the effects of angiotensin II at the level of the angiotensin II receptor type 1. All ARBs have high affinity for the receptor, which are found in high concentration in various tissues, particularly in smooth muscle cells, heart, kidney, and aorta (Messerli et al. 2018).

Because angiotensin II is a potent vasoconstrictor peptide, the blockade of its action at angiotensin II receptor type 1, thereby reducing effects of angiotensin II-induced vasoconstriction, sodium retention, and aldosterone release, leading to vasodilation of small resistance arteries and reduction in total peripheral resistance and BP. Cardiac output remains unchanged and no postural hypotension (Messerli et al. 2018).

It has long been noticed that chronic using ARBs had some favorable effects on cardiovascular system, including a reverse of hypertension-induced left ventricular hypertrophy, endothelial function improvement, and a de-stiffening of large arteries. These effects result in large artery relaxation and less pressure wave reflection when cardiac contracting; the wave propagation along the aorta is slowed; both the central systolic pressure and pulse pressure fall. The hemodynamic effects help reverse and slow down the remodeling of large as well as small arteries. Reno-protection of ARBs has been also observed in early type 2 diabetic nephropathy and proteinuria, independent of BP lowering (Messerli et al. 2018).

ARBs are generally used for patients who are unable to tolerate ACE inhibitors such as dry cough. But ARBs have nothing to do with ACE, so they don't disturb the metabolism of bradykinin; theoretically, no cough occurs. However, some cases of ARB-induced cough are reported especially with losartan which respond to discontinuation of losartan. Mechanism may be due to overexpressing unopposed angiotensin II receptor type 2 in central nervous system and some degree of ACE inhibitor-like property of losartan.

ARBs can be used alone to treat hypertension. If ARB monotherapy is insufficient to achieve BP goal, usually adding an antihypertensive diuretic. ARBs, like ACE inhibitors, can cause injury or even death to a developing fetus; therefore, they are prohibited for a childbearing woman who is planning to pregnancy or already becomes pregnant. A study by Harel et al. found that ARBs had a trend to cause

hyperkalemia, especially used concomitantly with aliskiren or ACE inhibitors (Harel et al. 2012). Under this circumstance, serum potassium level should be monitored closely. It has not been clearly established whether ARBs are more effective than ACE inhibitors in reducing proteinuria in diabetic nephropathy (Messerli et al. 2018).

ARB-related target organ protection occurs mostly in response to BP reduction, or a direct effect of ARBs on cardiac, renal, and arterial tissues. In addition, it has a BP-independent effect on arterial stiffness, mainly through long-term arterial remodeling and reduction of arterial wall fibrosis (Messerli et al. 2018).

As a consequence of angiotensin II receptor type-1 blockade, angiotensin II levels have been reported several-fold above baseline by uncoupling a negative-feedback loop. Increased levels of circulating angiotensin II result in unopposed stimulation of the angiotensin II receptor type-2 (Lévy 2004, 2005; Reudelhuber 2005). ARBs reduce cardiovascular events, including the risk of myocardial infarction, as effectively as but more safely than ACE inhibitors (Bangalore et al. 2011; Messerli and Bangalore 2017). In a Bayesian network meta-analysis of 119 randomized controlled trials with 564,768 people with chronic kidney disease, both ACE inhibitors and ARBs reduced the risk for kidney failure and cardiovascular events (Xie et al. 2016). In a network meta-analysis of 71 trials with 103,120 diabetic participants, no significant differences were documented between ACE inhibitors and ARBs with respect to all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, angina pectoris, hospitalization for heart failure, ESKD, or doubling of serum creatinine levels (Catala-Lopez et al. 2016).

Side effects: ARBs are generally well tolerated. By contrast to ACE inhibitors, cough and angioedema are much less common with ARBs since they have no effect on kininase II or other enzymes involved in the metabolisms of substance P or other peptides. Functional renal insufficiency is as common as with ACE inhibitors, since it has the same mechanisms. Dry cough has been very rarely noticed in patients with ARB, especially losartan (Mackay et al. 1999).

Contraindications: The same as ACE inhibitors.

Most guidelines for the management of patients with cardiovascular disease recommended ACE inhibitors as first-therapy choice, whereas ARBs are merely considered an alternative for ACE inhibitor–intolerant patients. Recent meta-analysis showed that no difference was identified in efficacy between ARBs and ACE inhibitors with regard to the surrogate endpoint of BP and outcomes of all-cause mortality, cardiovascular mortality, myocardial infarction, heart failure, stroke, and ESKD. Given the equal outcome efficacy but fewer adverse events with ARBs, so there is a trend that ARB will replace ACE inhibitors (Messerli et al. 2018).

Most Commonly Used ARB: (Chobanian et al. 2003).

Losartan: Losartan can be used alone with daily dose of 50 mg, maximum titrated up to 100 mg once a day. If BP is not well controlled, it can be combined with other antihypertensive agents, including diuretics. If combined with diuretics such as hydrochlorothiazide, lower losartan dose (e.g., 25 mg daily) can be initiated (Chobanian et al. 2003).

Valsartan: Valsartan has been approved to treat hypertension alone or in combination with other antihypertensive agents in adults as well as in children 6–16 years of

age, starting from 80 to 160 mg once a day in patients who are not volume depleted. If BP is not controlled well, valsartan is either titrated up to 320 mg daily or combined with an antihypertensive diuretic. It has been shown that valsartan combined with diuretics is better than dose increasing over 80 mg.

Olmesartan: Olmesartan can be used alone or combined with other antihypertensive agents such as diuretics. Starting from 20 mg daily, it can be titrated to 40 mg daily if BP was not well controlled. Dose greater than 40 mg once a day has not been shown greater effects.

Eprosartan: 400–800 mg once daily or twice daily in the treatment of patients with hypertension and not volume depleted, combined with other antihypertensive agents such as diuretics or CCBs if BP was not well controlled.

Azilsartan: 80 mg oral daily, used alone or combined with other antihypertensive drugs. In patients receiving high-dose diuretics, starting from 40 mg daily.

6.5.3 Direct Renin Inhibitor

Aliskiren is the only direct renin inhibitor product available in clinical practice. It blocks transformation of angiotensinogen to angiotensin I. Aliskiren reduces circulating angiotensin I as well as angiotensin II, producing a reduction in systolic and diastolic BP. It is contraindicated in patients with bilateral renal stenosis and during pregnancy. Compared with other blockers of RAAS, aliskiren has no dry cough side effect, but it can cause angioedema and small increase in creatinine as ACE inhibitors, and dose-dependent diarrhea.

Indications: Aliskiren has been approved as monotherapy or in combination therapy for hypertension. No outcome data are available in terms of reducing hypertension-related cardiovascular events. At present, it is often used as add-on drug, not as the first-line antihypertensive agent. One trial showed that aliskiren may have a potential reno-protection effect since the trial found that aliskiren combined with losartan reduces proteinuria compared with losartan alone in patients with type 2 diabetes (Parving et al. 2008).

ALTITUDE trial evaluated the combination of aliskiren with RAAS blocker on a primary endpoint consisting of combined cardiovascular and renal endpoints in diabetic patients with cardiovascular disease, chronic kidney disease, or both with a mean eGFR in the low 40s. The study was stopped prematurely because of a significantly higher risk of adverse effects and no decrease in primary endpoint among those taking aliskiren in combination with another RAAS blocker (Parving et al. 2012).

6.5.4 Thiazide-Type Diuretics

The most frequently used thiazide is hydrochlorothiazide, available as oral tablet or capsule in doses ranging from 12.5 to 50 mg. The usual dose is 12.5 mg given alone or in combination with other antihypertensive medication. Dose greater than 50 mg is often associated with hypokalemia. The onset of diuresis is within 2 h, peaking at 3–6 h, with a smaller effect after 12 h. Compared to placebo, thiazide diuretics have been confirmed to have antihypertensive effects and efficiency as well as favored cardiovascular protection effects: average reduction in congestive heart failure by 41–49%, stroke by 29–38%, coronary heart disease by 14–21%, total death by 10–11% (Psaty et al. 2003; Law et al. 2009; Wright et al. 2009; Ernst et al. 2009).

Mechanisms of action: Thiazide diuretics inhibit the coupled reabsorption of Na^+ and Cl^- in the nephron at the apical membrane in the early convoluted distal tubule, leading to a reduction in extracellular fluid volume similar to loop diuretics. In the circumstance of no-salt-added diet, the early response to thiazide diuretics is a net Na^+ loss of 100–300 mmol in a few days, which translates into a 1–2 L reduction in extracellular fluid volume. Plasma Na^+ concentration is unchanged. In response to an increased Na^+ excretion, the plasma volume, both venous return and cardiac output are decreased. The plasma volume reduction can stimulate the sympathetic nervous system and RAAS. In long-term use, thiazide diuretics lower peripheral vascular resistance (Ernst et al. 2009; JD and Cooper-Dehoff 2010).

Initially, diuretics lower BP by decreasing cardiac output and reducing plasma and extracellular fluid volume. Eventually, cardiac output returns to normal, and plasma and extracellular fluid volume return to the level slightly less than normal, but a reduction in peripheral vascular resistance is maintained, thus resulting in an overall lowering BP (Duarte and Cooper-Dehoff 2010).

Side effects of thiazide diuretics are resembled to those of loop diuretic, but dose-dependent, including hyponatremia (Na^+ depletion and dilution), hypokalemia, metabolic alkalosis, hypovolemia, hypotension, and to a lesser extent hyperuricemia (thiazide diuretics are contraindicated in patients with gout.), hypomagnesemia, and hyperglycemia (Duarte and Cooper-Dehoff 2010).

Thiazide diuretics induced the risk of diabetes that has been reported at 3–4% (Carter et al. 2008); low dosage can minimize or avoid the hyperglycemia effect.

Generally, dosage of diuretics causes average reduction in serum potassium level of 0.3–0.4 mmol/L. If combined with ACE inhibitors or ARBs, thiazide-induced hypokalemia can be prevented. Serum potassium should be monitored before and during administration of diuretics. If serum potassium level is lower than 3.8 mEq/L, potassium-sparing drugs may be added on.

Another side effect is impotence, which may disturb the sex life to sex actively male patients. Since thiazide diuretics increase in Ca^{2+} reabsorption at the level of distal tubule, hypercalcemia has been observed after thiazide diuretics, whereas hypocalcemia after loop diuretics. Thiazide diuretics can induce hyperlipidemia,

including high cholesterol and high triglyceride but do not have any clinically meaningful lipid change (Ernst et al. 2009; Durate and Cooper-Dehoff 2010; Carter et al. 2008).

Caution:

Breastfeeding: Thiazides pass into breast milk and can decrease the flow of breast milk. So, these drugs are classed as "drugs that have been associated with significant effects on some nursing infants and should be given to nursing mothers with caution" by the American Academy of Pediatrics Committee on Drugs (American Academy of Pediatrics Committee on Drugs 2001).

Pregnancy: It can be used in pregnant hypertension women but not a first-line choice (Gestational Hypertension and Preeclampsia 2019).

Athletes: Hydrochlorothiazide is prohibited in sports according to the regulations of the World Anti-Doping Agency (Helmlin et al. 2016) because of its ability to mask the use of performance-enhancing drugs.

Thiazide-type diuretics are associated with significant but small adverse glycemic effects. Treatment with a lower dose thiazide might reduce or avoid glycemic changes (Zhang et al. 2016; Scheen 2018).

ARIC (the Atherosclerosis Risk in Communities) study investigated the incidence of new-onset diabetes in 12,550 adults who did not have diabetes mellitus at the study beginning. After 3 years and 6 years of following up, new-onset diabetes risk was not significantly higher in patients receiving thiazide diuretic therapy than the subjects not receiving any antihypertensive therapy. The study only identified that new-onset diabetes risk was 28% greater in the individuals who were taking beta-blockers for hypertension for 6 years than in those with other antihypertensive agents. Low-dose thiazide-type diuretics (i.e., hydrochlorothiazide < 12.5 mg once a day) or thiazide-like diuretics (chlorthalidone or indapamide) can make these metabolic disturbances less marked. The data from subgroups of patients with hypertension and type 2 diabetes supported that the cardiovascular benefits from thiazides lowering BP were much greater than harm (Gress et al. 2000).

It is highly likely that the using an ACE inhibitor with diuretics could minimize or avoid the adverse glucose metabolism caused by thiazide diuretics (Kenneth et al. 2008; Shamiss et al. 1995). The negative effect on glucose metabolism of diuretics is dose-related, and it may also be related to hypokalemia. SHEP (The Systolic Hypertension in the Elderly Program) study indicated that each decrease of 0.5 mEq/L in serum potassium level during the first year of diuretics therapy was associated with an increase in adjusted diabetes risk 45% (SHEP Study 1991). This diuretic-induced diabetes risk can be prevented by either supplementation of potassium or by combination with ACE inhibitors or potassium-sparing agents (Jeunemaitre et al. 1988). If thiazide diuretics were combined with aldosterone antagonist, not only new-onset diabetes can be prevented by avoiding diuretic-induced hypokalemia, but also BP control will be improved greatly (Sharabi et al. 2006). Indapamide may not have a deleterious effect on glucose tolerance (Leonetti et al. 1990).

Diuretic-induced glucose changes may underline lesser prognostic significance. ALLHAT study showed that no significant association of fast serum glucose change

at 2 years with subsequent cardiovascular disease risk, including coronary heart disease, stroke, cerebrovascular disease, total mortality as well as end-stage renal disease. No significant association was identified between incident diabetes at 2 years and most clinical outcomes, except for coronary heart disease with risk ratio of 1.64 ($P = 0.006$). Chlorthalidone treatment showed a risk trend (risk ratio 1.46), but not statistically significant ($P = 0.14$). In ALLHAT study, the higher incidence of new-onset diabetes in the chlorthalidone group did not translate into a prognostic burden in this group, and a similar situation occurred in other studies (Barzilay et al. 2006).

Analysis of the 14.3 years of follow-up data from the SHEP study revealed that incident diabetes during the trial among participants randomized to placebo was associated with a >50% increase in cardiovascular mortality but not in individuals randomized to the diuretics (Kostis et al. 2005).

Summary: The strategy for lowering or preventing blood glucose elevation or new-onset diabetes caused by thiazide diuretics:

(1) Low dose of thiazide-type or thiazide-like diuretics.
(2) Used in combination with ACE inhibitors or ARBs.
(3) Taking in combination with a potassium-sparing diuretic. The combination of a low-dose thiazide diuretic with amiloride among the first-choice treatment strategies is recommended for hypertension (Brown et al. 2015). Supplement of potassium: hyperglycemic effect of thiazide diuretics is enhanced by potassium depletion and inversely related to the serum potassium concentrations.

6.5.5 Thiazide-like Diuretics Include Indapamide, Metolazone, and Chlorthalidone

They do not share the same chemical structure as benzothiadiazine-type diuretics, but they share the same pharmacologic mechanism of action and thus are formerly referred to as thiazide-like diuretics; however, in common practice, all diuretics that act on the Na–Cl cotransporter are called thiazides.

A thiazide-like diuretic is a sulfonamide diuretic that has similar physiological properties to thiazide diuretics but does not have the chemical properties of a thiazide, lacking the benzothiadiazine molecular structure. Thiazide-like diuretics should be reserved for use in combination with loop diuretics in patients with volume overload. In the treatment of hypertension, they are used alone or combined with other antihypertensive agents. Most of the research supporting the use of thiazide diuretics in hypertension was actually performed by using thiazide-like diuretics chlorthalidone. The results showed that chlorthalidone is better than thiazide-type diuretics in both antihypertensive effects and reduction of cardiovascular complications (Messerli et al. 2011).

Thiazide-like diuretics (chlorthalidone and indapamide) are more effective than the thiazide-type diuretics (such as hydrochlorothiazide) in reducing the risk of heart

attack, stroke as well as congestive heart failure in patients with hypertension (Olde Engberink et al. 2015).

Compared to the most prescribed thiazide-type diuretics such as hydrochlorothiazide, thiazide-like diuretics, indapamide, metolazone, and chlorthalidone, have an advantage in lowering both systolic BP and diastolic BP without significantly increasing the risks of hypokalemia and hyponatremia, or making a significant change of BP and serum total cholesterol. Antihypertensive effect of thiazide-related diuretics can be reduced by concomitant administration of NSAID, which block vasodilatory prostaglandin synthesis and therein negatively impact renal sodium handling. Even though indapamide is considered as a thiazide-like diuretics, but it does not necessarily have the same mechanism as other thiazide-like diuretics (James et al. 2014).

JNC-8 recommends both thiazide-type diuretics and thiazide-like diuretics as one of the four classes of first-line antihypertensive drugs, either as monotherapy or in combination with CCBs, ACE inhibitors, or ARBs (James et al. 2014). Fixed-dose combination drugs are widely available as well, such as combinations of an ACE inhibitor or an ARB with thiazide diuretics.

Recent meta-analysis results indicate that thiazide-type diuretics should be replaced by the thiazide-like diuretics, which possess higher efficacy of BP reduction and less risk of electrolyte disturbance and metabolic disorders (Liang et al. 2017).

Chlorthalidone is a longer acting thiazide with the duration of action for 24 to 72 h and can be given orally once a day, useful when a lengthier period of natriuresis is desired. Chlorthalidone can be used alone or combined with other antihypertensives. Starting from 25 mg once a day, dose can be titrated to 50 mg or even 100 mg daily if BP did not achieve goal. Usually, the dose of 100 mg or over 100 mg once a day does not increase antihypertensive effects further but increase serum uric acid level and hypokalemia risk over the range of 25–100 mg/day. So it may be better to add second antihypertensive agents instead of increasing dose if additional BP control is required (Madkour et al. 1996; Beckett et al. 2008). ALLHAT trial proved that chlorthalidone with longer and stronger antihypertensive effect and less side effects than thiazide diuretics, recommended chlorthalidone as favored choice of first-line diuretics if available (Barzilay et al. 2006).

Besides its diuretic properties, chlorthalidone presents some protective effects on vascular or organ damage in animal and human studies. In some clinical trials, it was effective in reducing left ventricular mass index in hypertensive patients and remarkably improving the renal function. In a recent clinical trial, use of a sustained-release indapamide-based regimen as initial therapy led to relative reductions of 39%, 64%, and 21% in the rates of fatal stroke, heart failure, and death, respectively, in patients older than 80 years of age (Madkour et al. 1996; Beckett et al. 2008).

Although much evidence demonstrated the effectiveness and advantages of indapamide, there is no large-scale immediate clinical trial and meta-analysis to evaluate the BP-lowering efficacy and safety between indapamide and hydrochlorothiazide (Liang et al. 2017; Tamargo et al. 2014).

The diuresis and antihypertensive effects of chlorthalidone are primarily through inhibiting the activity of Na^+/Cl^- symporter in the apical membrane of distal convoluted tubule cells in the kidney and then reduces the reabsorption of Na^+ and Cl^-. In addition, chlorthalidone also has a weak inhibiting effect on carbonic anhydrase in the proximal tubule responsible for the hydrolysis of bicarbonate, which then gets absorbed along with sodium. The inhibitory effects block the reabsorption of sodium and bicarbonate from the proximal tubule. Chronic exposure to chlorthalidone has a potential risk to decrease GFR. The diuretic effects of chlorthalidone will be diminished when renal function impaired. Chlorthalidone indirectly increases potassium excretion due to increased sodium delivery to the distal renal tubule via the sodium–potassium exchange mechanism (i.e., apical renal outer medullary potassium channel–ROMK/Na channels coupled with basolateral Na +/K ATPases). This can result in a low blood concentration of potassium and chloride as well as a mild metabolic alkalosis; however, the diuretic effect of chlorthalidone is not affected by the acid–base balance of the person being treated (Liang et al. 2017; Tamargo et al. 2014).

Both chlorthalidone and hydrochlorothiazide have a similar hypokalemia risk and other adverse effects at the usual doses prescribed in routine clinical practice. Unlike loop diuretics, chlorthalidone's diuretic effect is markedly diminished in patients with certain kidney diseases (e.g., chronic kidney disease). When chlorthalidone is used at lower doses (e.g., 12.5 mg per day), the frequency and severity of these adverse effects are substantially reduced (Liang et al. 2017; Tamargo et al. 2014). At the 12.5–25 mg doses of chlorthalidone, hypokalemia and hyperglycemia appear to be no clinical significance (Alderman et al. 2012; Barzilay et al. 2012). The incidence of hyponatremia for both chlorthalidone and hydrochlorothiazide is very strongly age related (van Blijderveen et al. 2014). Chlorthalidone was more effective in reducing visit-to-visit variability, which is a strong risk factor for cardiovascular disease (Muntner et al. 2014; 2015a, b).

Indapamide

Principal indications: Hypertension and edema are due to congestive heart failure. Indapamide is more effective than the thiazide-type diuretics in reducing the risk of heart attack, stroke, and heart failure in hypertensive patients. Adverse effects tend to be somewhat milder than with thiazides (Jaillon 1990; Hansson et al. 1983; ACOG Committee Opinion et al. 2019).

A minimum of 70% of a single oral dose of indapamide is eliminated by the kidneys and an additional 23% by the gastrointestinal tract, probably including the biliary route. The half-life of indapamide in whole blood is approximately 14 h, so the drug can be taken just once daily (Jaillon 1990; Hansson et al. 1983; ACOG Committee Opinion et al. 2019).

Indapamide is available generically as 1.25 and 2.5 mg non-scored tablets. It is now also available in sustained-release form. The adult dosage is 1.25 to 5 mg, orally, once daily, and usually in the morning. The drug decreases peripheral resistance, with little or no effect on cardiac output, heart rate, or cardiac rhythm. In hypertensive patients, daily doses of 1.25, 2.5, and 5 mg of indapamide have no appreciable cardiac

inotropic or chronotropic effect. Chronic administration of indapamide has little or no effect on GFR or renal plasma flow. So, indapamide keeps its antihypertensive effect in patients with varying degrees of renal dysfunction, although in general, diuretic effects declined as renal function decreased (Jaillon 1990; Hansson et al. 1983; ACOG Committee Opinion et al. 2019).

Clinical outcomes: HYVET trial proved that indapamide reduced stroke and all-cause mortality when given with or without perindopril to people over the age of 80 for the treatment of hypertension (Warwick et al. 2015). In a small number of controlled studies, indapamide taken with other antihypertensive drugs such as hydralazine, propranolol, guanethidine, and methyldopa, appeared to have the additive effect typical of thiazide-type diuretics (Jaillon 1990; Hansson et al. 1983; ACOG Committee Opinion et al. 2019).

Side effects: Hypokalemia, fatigue, orthostatic hypotension, and allergic manifestations. Hypokalemia is its most frequent side effects. At daily doses of 2.5 mg and 5 mg, the effects of indapamide on BP and edema are approximately equal to those obtained with conventional doses of other antihypertensive diuretics, and a mean serum potassium reduction was 0.5 and 0.6 mEq/L, respectively, uric acid increased by about 1 mg/100 mL. Electrolyte monitoring is essential, particularly in patients who would be at increased risk from hypokalemia, such as those with cardiac arrhythmias or who are receiving concomitant cardiac glycosides (Jaillon 1990; Hansson et al. 1983; ACOG Committee Opinion et al. 2019).

Hyponatremia was observed with indapamide 2.5 mg and 5 mg. Hyponatremia considered possibly clinically significant (<125 mEq/L) has not been observed in clinical trials with the 1.25 mg. Thus, patients should be started with 1.25 mg and maintained at the lowest possible dose. In general, diuretics should not be given concomitantly with lithium because they reduce its renal clearance and add a high risk of lithium toxicity.

Hyperuricemia and gout: Indapamide (1.25 mg once daily) may lead to an increase in serum concentration of uric acid by average of 0.69 mg/100 ml. Indapamide at dosage of 2.5 mg and 5 mg once daily may lead to an increase in serum concentration of uric acid by average of 1 mg/100 ml. Indapamide may precipitate gout in certain patients, so serum uric acid concentration should be monitored constantly during indapamide treatment (Jaillon 1990; Hansson et al. 1983; ACOG Committee Opinion et al. 2019).

Renal impairment: Indapamide should be given with caution in patients with severe renal diseases. Reduced plasma volume may worsen or precipitate azotemia. During indapamide treatment, as long as progressive impairment of renal function was identified, it is necessary to withhold or to discontinue it. At this circumstance, renal function should be tested periodically (Jaillon 1990; Hansson et al. 1983; ACOG Committee Opinion et al. 2019).

Glucose intolerance: A mean increase in glucose of 6.47 mg/dL was observed in patients treated with indapamide 1.25 mg, which was not considered clinically significant. Serum concentrations of glucose should be monitored routinely during treatment with indapamide. Lower incidence of new-onset diabetes was observed with indapamide though in the Prevention and Treatment of Hypertension with

Algorithm-based Therapy (PATHWAY) 3 study (Brown et al. 2016; Roush et al. 2015a).

Pregnancy Category B: No adequate and well-controlled studies were performed in pregnant women. This drug should be used during pregnancy only if clearly needed.

Breastfeeding: It is not known whether this drug is excreted in human breast milk. Because most drugs are excreted in human breast milk, if using this drug is deemed essential, the patient should stop nursing.

Contraindications: Contraindicated in known hypersensitivity to sulfonamides, severe kidney failure, hepatic encephalopathy or severe liver failure, and a low plasma potassium level (Jaillon 1990; Hansson et al. 1983; ACOG Committee Opinion et al. 2019).

Cautions: The combination of indapamide with lithium and non-antiarrhythmic drugs causing wave-burst arrhythmia (astemizole, bepridil, IV erythromycin, halofantrine, pentamidine, sultopride, terfenadine, and vincamine). Monitoring the serum levels of potassium and uric acid is recommended, especially in subjects with a predisposition or a sensitivity to low levels of potassium in the blood and in patients with gout (Jaillon 1990; Hansson et al. 1983; ACOG Committee Opinion et al. 2019).

Summary: Indapamide is thus far the most efficient and tolerable diuretic for hypertensive patients (Kaplan 2015). More efficient than hydrochlorothiazide was found in improving microalbuminuria (in diabetics), reducing left ventricular mass index, inhibiting platelet aggregation, and reducing oxidative stress (Roush et al. 2015).

Indapamide was also shown to reduce left ventricular hypertrophy more than enalapril. Importantly, indapamide does not share with thiazide diuretics their adverse effects on lipid and glucose metabolism, thereby it can be safely prescribed in diabetic patients (Kaplan 2015; Roush et al. 2015). Unlike other thiazides, indapamide appears to have less impact on glucose or lipid metabolism (Roush et al. 2015). In addition to its diuretic effects, indapamide acts to lower systolic BP via a calcium antagonist-like vasorelaxant effect and its potency is 5 mm Hg systolic BP lower than that of hydrochlorothiazide (Roush et al. 2015). The increased risk of negative metabolic effects does not appear to result in negative effects on outcomes (Remonti et al. 2016; Thomopoulos et al. 2017). For most patients, the risk of a clinically meaningful change in laboratory parameters is rather low, whereas the clinical benefits of diuretics are high.

Metolazone is a thiazide-like diuretic with half-life about 14 h; approximately, 65% of ingested metolazone is available in the bloodstream; Metolazone is slightly more efficacious than other thiazide diuretics because it has an additional diuretic effect in the proximal nephron, around 10 times as potent as hydrochlorothiazide. About 80% of metolazone was executed as a primary form through urine; the rest 20% is evenly split either excreted through biliary or metabolized into inactive form (Whelton et al. 2017; Rosenberg et al. 2005; Paton and Kane 1977; Freis 1989; Arnold 1984).

Moderate renal failure (GFR below 30–40 ml/min) did not influence the effects of metolazone. Since renal and heart failure often coexist and result in fluid retention in patients with hypertension, this characteristic makes metolazone to have considerable

advantage over other thiazide diuretics. Another distinct feature of metolazone is that it acts at the distal convoluted tubule instead of the loop of Henle which is the primary acting site of most other loop diuretics (Whelton et al. 2017; Arnold 1984). The drug indirectly decreases the amount of water reabsorbed into the bloodstream by the kidney, so that blood volume decreases and urine volume increases.

The usual dose of metolazone to treat edema of cardiac failure or renal disease is 5 mg to 20 mg once daily. To treat mild-to-moderate primary hypertension is 2.5 mg to 5 mg once daily.

Metolazone inhibits the function of the sodium–chloride symporter, preventing sodium and chloride, and therefore water too, from leaving the lumen to enter the tubule cell. Metolazone does not decrease GFR or the renal plasma flow. Metolazone is sometimes used together with loop diuretics such as furosemide or bumetanide to treat diuretic resistance in congestive heart failure, chronic renal failure, and nephrotic syndrome. These highly effective combinations can lead to dehydration and electrolyte abnormalities (Whelton et al. 2017; Rosenberg et al. 2005; Paton and Kane 1977; Freis 1989; Arnold 1984).

Side effects: Hyponatremia, hypokalemia, hypochloremia, hypomagnesemia, hypercalcemia and hyperuricemia, dizziness, headache, or heart arrhythmias. Serious, though rare, side effects include aplastic anemia, pancreatitis, agranulocytosis, and angioedema. Metolazone may unmask latent diabetes mellitus or exacerbate gout, especially by interacting with medicines used to treat gout. In addition, thiazide diuretics, including metolazone, are sulfonamides; those with hypersensitivity to sulfonamides may also be allergic to metolazone (Brisco-Bacik et al. 2018; Sullivan 1991; Leipzig et al. 1999; American Academy of Pediatrics Committee on Drugs 2001; Grosskopf et al. 1986).

6.5.6 Loop Diuretics: Bumetanide, Furosemide, Torsemide, and Ethacrynic Acid

Loop diuretics exert their effects in the nephron at the apical membrane in the thick ascending limb of the loop of Henle and lower BP through reducing extracellular fluid volume. Other major effects include a decrease in free water excretion during water loading and reabsorption during dehydration, because of reduced osmotic gradient in the medulla. An increased Ca^{2+} excretion is also observed in response to the inhibition of the paracellular Ca^{2+} transport across renal epithelia (Whelton et al. 2017; Williams et al. 2018; James et al. 2014; Chobanian et al. 2003).

In the following situations, loop diuretics are preferred to thiazide-type and thiazide-like diuretics in patients with acute coronary syndrome and heart failure or in patients with chronic kidney disease and an eGFR less than 30 mL/min/1.73 m^2. If persistent hypertension is not controlled with an ACE inhibitor (or ARB), CCB, and beta-blocker, thiazide-type or thiazide-like diuretics, loop diuretics may be added

accordingly, and then aldosterone antagonist (Whelton et al. 2017; Williams et al. 2018; James et al. 2014).

The most frequently used loop diuretics are furosemide, then bumetanide, and torsemide. The onset of diuresis with furosemide is rapid, within 1 h, peaking at 3–6 h, with a smaller effect after 12 h. In order to prevent rebound, loop diuretics should be given small dose, twice daily, or thrice daily in the treatment of hypertension (Whelton et al. 2017; Williams et al. 2018).

Loop diuretics are not as effective as thiazides in lowering BP. They are usually reserved for patients with renal insufficiency and remain benefit in case of chronic kidney disease with serum creatinine > 1.5 mg/dL or eGFR < 30 ml/min/1.73 m^2 (less effect for thiazide diuretics) (Malha and Mann 2016). **T**he use of loop diuretics was not mentioned in JNC-8 guideline (James et al. 2014). Meanwhile, 2013 ESH/ESC guideline recommended that a loop diuretic can only replace thiazide-type diuretics if there is renal function impairment (serum creatinine of more than 1.5 mg/dL or eGFR of less 30 ml/min/1.73 m^2) since loop diuretics are lack of long-term cardiovascular outcome data and appropriate dosing regimen of its use (Mancia et al. 2013). Unlike thiazides, loop diuretics are still effective in lowering BP or in treating edema in patients with poor kidney function (at stage 3 to 5, particularly with extracellular fluid volume expansion) (Whelton et al. 2017; Williams et al. 2018).

6.5.6.1 Torsemide

Torsemide is a pyridine-sulfonyl urea type loop diuretic, mainly used in the management of edema associated with congestive heart failure. As an antihypertensive agent, torsemide is available as an oral tablet or injection solution, used alone or combined with other antihypertensive agents. The dosage of torsemide can start from 5 mg once a day and may be titrated to 10 mg once a day. When reached to a dose of 10 mg per day, BP response is still not adequate, and additional antihypertensive drugs may be added instead of increasing torsemide dose.

Torsemide has advantages being longer action duration and once daily dosing, and more bioavailability (vs. furosemide). Torsemide and other loop diuretics appear to have less side effects (such as less hyponatremia, hypokalemia and glucose intolerance). Previous studies showed that high dose of thiazide diuretics (either thiazide-type or thiazide-like) was more effective in lowering BP than loop diuretics (Whelton et al. 2017; Williams et al. 2018; James et al. 2014; Chobanian et al. 2003).

The difference in efficacy among loop diuretics is probably related to the duration of action. Commonly used loop diuretics, such as furosemide and bumetanide, have a short duration of action (< 6 h); the antihypertensive efficacy of these medications may be limited since the initial fluid loss can be counteracted by activation of RAAS, leading to sodium retention during the period when the diuretic effect has worn off (Whelton et al. 2017; Williams et al. 2018). They are less effective than thiazide-type drugs in reducing BP in the non-edematous patient as has been shown in a recent Cochrane analysis, reporting the systolic BP/diastolic BP reduction of several loop diuretics in primary hypertension (Musini et al. 2015; Hermida et al. 2008).

Side effects of loop diuretics: Similar to thiazide diuretics, loop diuretics are contraindicated in patients with gout (Whelton et al. 2017; Williams et al. 2018). No evidence of torsemide-induced ototoxicity has been demonstrated in human. Low-dose torsemide (2.5–5 mg) produces no detectable effects on electrolytes, glucose, and lipids (and yet yields an antihypertensive effect comparable to thiazides) (Wargo and Banta 2009; Roush et al. 2014).

Since a smaller fraction of filtered load of Na^+ is reabsorbed at the distal tubular site where thiazides act, Na^+ excretion is associated with hypokalemia and mild metabolic alkalosis due to both an increased K^+ and H^+ excretion in the collecting tubule in response to the higher Na^+ concentration at this site. In response to hypovolemia, a significant secondary hyperaldosteronism can occur. Loop diuretics exert their effects in the more proximal site than do thiazide diuretics. Therefore, the natriuretic effect of loop is greater than that of thiazide diuretics. An increased Ca^{2+} excretion is also observed in response to the inhibition of the paracellular Ca^{2+} transport across renal epithelia (Whelton et al. 2017; Williams et al. 2018; James et al. 2014; Chobanian et al. 2003).

6.5.6.2 Furosemide

Furosemide, like other loop diuretics, inhibits the luminal Na-K-Cl cotransporter in the thick ascending limb of the loop of Henle, by binding to the chloride transport channel, thus causing an increase in excretion of sodium, chloride, and potassium loss in urine. Furosemide is primarily used for the treatment of hypertension and edema when eGFR < 30 ml/min/1.73 m^2. Furosemide takes diuresis effect within 1 h and completes within 6 h after oral administration, while intravenously administered it typically begins working within five minutes, peak effect within 30 min, and diuresis is complete within 2 h. It is excreted by tubular secretion; therefore, in severe kidney function impairment (e.g., GFR 5–10 ml/min), lower doses are required due to accumulation in the body. It also can cause further kidney damage and should be administered with caution (Schaefer et al. 2018; Grams et al. 2019).

Side effects: Common side effects of furosemide are dehydration and electrolyte imbalance, including loss of potassium, calcium, sodium, and magnesium. Excessive use of furosemide will most likely lead to a metabolic alkalosis due to hypochloremia and hypokalemia. Overdose may lead to dehydration, change in drinking patterns and urination, seizures, gastrointestinal problems, kidney damage, lethargy, collapse, and coma. Other side effects include ototoxic which usually occurs with large intravenous doses and rapid administration and in renal impairment, gout, caused by hyperuricemia and hyperglycemia (Schaefer et al. 2018; Grams et al. 2019).

Caution: Furosemide should be used with caution when combined with corticosteroids (as this increases the risk of electrolyte imbalance), aminoglycoside antibiotics (increases risk of kidney or ear damage), and trimethoprim sulfa (decrease platelet count). Furosemide may increase the risk of digoxin toxicity due to hypokalemia. The drug is best not used during pregnancy or in a lactating mother,

since studies with other species have shown that the medication could pass through the placenta and milk. Many studies have shown that the long-term use of furosemide could cause varying degrees of thiamine deficiency. For this reason, thiamine needs to be supplemented (Schaefer et al. 2018; Grams et al. 2019).

6.5.6.3 Bumetanide

Bumetanide is a loop diuretic of the sulfamoyl category. FDA approved for the treatment of edema. Its off-label use is for the treatment of hypertension in patients in whom high doses of furosemide or other diuretics are ineffective. The usual dosage is 0.5–2 mg/day given once or twice daily. Bumetanide is 40 times more potent than furosemide for patients with normal renal function. Bumetanide also masks other drugs, including steroids, by diluting the contents of the user's urine, yielding a lower concentration of filtered substances, which makes them less likely to be detected (Brunton et al. 2006).

6.5.6.4 Diuretic Resistance

Diuretic resistance is defined as a failure to achieve the therapeutically desired reduction in edema despite a full dose of diuretic. In human study, diuretic resistance was defined as that the diuretic effects fall by as much as 40% on the third day of furosemide treatment. Many factors contribute to the resistance to loop diuretics, including at least four aspects: (1) rebound sodium retention; (2) post-diuretic sodium retention; (3) the hypertrophied distal tubule and functional changes caused by increased delivery of sodium in this area over a period of time, promoted the capacity for sodium and fluid reabsorption; (4) diuretic braking: a phenomenon induced by long-term administration of loop diuretics. The body slowly adapts to their effects, the effectiveness of loop diuretics declined over time (Anderson 2016; Asare 2009).

To overcome diuretic resistance: (1) To restrict daily consumption of fluids and sodium intake. (2) To avoid taking NSAIDs. (3) To change the dose or the timing of diuretics such as furosemide 20–40 mg twice a day or thrice a day instead of once a day. (4) To use more than one type of diuretics such as a combination of thiazide (acting primarily on the distal convoluted of nephron) and loop diuretics (acting on the ascending limb of the loop of Henle). Their combination may improve the resistance (Anderson 2016; Asare 2009).

6.5.7 Potassium-Sparing Diuretics

This class of drugs includes spironolactone, eplerenone, and amiloride. Spironolactone and eplerenone are competitive aldosterone antagonists of mineralocorticoid receptors, present in the cytoplasm of tubular cells in the late distal tubule and the

collecting duct. The drugs act independently of aldosterone, including amiloride and triamterene, block ENaC (epithelial sodium channel) in the luminal membrane of the collecting duct (Dahal et al. 2015; Pelliccia et al. 2014). Only a modest natriuretic effect can be expected, since a smaller fraction of filtered load of Na^+ is reabsorbed at this distal site of action, compared to the more proximal site of action of loop diuretics and thiazide diuretics.

Amiloride blocks ENaC in the collecting tubule and thus blocks the reabsorption of water. Like spironolactone, amiloride is often used to counteract potassium wasting caused by other diuretics and also is the specific molecular target drug to treat Liddle's syndrome.

Side effects: The most common side effect is hyperkalemia with metabolic acidosis, particularly in patients with chronic kidney disease and heart failure or diabetes, receiving potassium-sparing diuretics or potassium supplements, or taking concomitantly an ACE inhibitor, an ARB, or an NSAID. Since spironolactone inhibits the binding of dihydrotestosterone to androgen receptors and increases the clearance of testosterone, the frequent complications are sexual side effects, including impotence, decreased libido, bilateral gynecomastia, and mastodynia. Eplerenone is a more selective aldosterone antagonist with much less sexual side effects (Pelliccia et al. 2014).

Potassium-sparing diuretics, particularly mineralocorticoid receptor antagonists, are contraindicated in patients with acute or severe renal failure (eGFR < 30 mL/min). Although spironolactone did not show an appropriate evidence for reducing cardiovascular events in hypertensive patients, it reduced total mortality in patients with advanced heart failure (Dahal et al. 2015). Moreover, its efficiency in resistant hypertension is well established (Pelliccia et al. 2014). Similarly, eplerenone has been shown to have greater impact on systolic BP and to improve endothelial function in hypertensive patients with similar rates of hyperkalemia (Fujimura et al. 2012; Hermida et al. 2008).

The following types of patients are at increased risk of developing hyperkalemia and should be monitored closely when using potassium-sparing diuretics:

(1) Patients receiving RAAS inhibitors.
(2) Patients receiving other drugs that can cause hyperkalemia, e.g., trimethoprim, sulfamethoxazole, amiloride, and triamterene.
(3) Patients with chronic kidney disease (eGFR < 60 mL/min/1.73 m^2).
(4) Baseline serum potassium > 4.5 mmol/L.

6.5.7.1 Triamterene

Triamterene is a member of potassium-sparing diuretic family, as a second-line antihypertensive drug, and used in combination with thiazide diuretics for the treatment of hypertension and edema. Triamterene directly blocks ENaC on the lumen side of the kidney collecting tubule (Qadri et al. 2012; Loffing et al. 2003). Serious side effects may include heart palpitations, tingling/numbness, fever, chills, sore

throat, rash, and back pain. Triamterene can also cause kidney stones through direct crystallization or by seeding calcium oxalate stones (Heran et al. 2012).

Caution with certain disease states: (Heran et al. 2012)

(1) Triamterene is best avoided in patients with chronic kidney disease due to the possibility of hyperkalemia. Patients using triamterene take salt substitute cautiously.
(2) The following situations, using triamterene, should be with caution: in patients with prediabetes and diabetes, hepatic function impairment, and kidney stones.
(3) In patients with creatinine clearance less than 10 ml/min, triamterene should be avoided.
(4) Kidney stones.
(5) Triamterene should be avoided if the creatinine clearance is less than 10 ml/min.

6.5.7.2 Amiloride

Amiloride has its principal antihypertensive effect by directly blocking ENaC (Qadri et al. 2012) and inhibits sodium reabsorption in the late distal convoluted tubules, connecting tubules, and collecting ducts in the nephron (Loffing et al. 2003). Onset of action is about two hours and lasts for about one day (Formulary 2008).

The drug is often used in conjunction with a thiazide diuretic to counteract the potassium-losing effect. Due to its potassium-sparing capacities, hyperkalemia may occur. The risk of developing hyperkalemia is increased in patients who are also taking ACE inhibitors, ARBs, other potassium-sparing diuretics, or any potassium-containing supplements.

Amiloride should be stopped using for more than 3 days prior to laboratory test in case of fatal hyperkalemia.

Indication:

(1) Amiloride is a second-line antihypertensive agent, and often used with a thiazide or other loop diuretic (e.g., furosemide), especially useful in patients with hypertension having potential hypokalemia or in patients for which maintaining a normal level of potassium is critically important, e.g., those taking digitalis (i.e., digoxin) are at higher risk for cardiac arrhythmia if their potassium levels get too low (Heran et al. 2012).
(2) For people with resistant hypertension, already taking a thiazide diuretic, an ACE inhibitor or an ARB, or a CCB, the addition of amiloride (or spironolactone) was better at reducing BP than adding a beta-blocker or an alpha-1 blocker (Han and Hee 2017). When combined with hydrochlorothiazide, amiloride had positive effects on BP and blood sugar tolerance, to prevent the metabolic side effects of thiazide diuretics, allowing for the use of higher thiazide doses (O'Riordan et al. 2018).

(3) Amiloride is also a specific agent for the treatment of Liddle's syndrome. Because Liddle syndrome usually involves an upregulation of ENaC channels, leading to hypokalemia, amiloride is useful as an ENaC channel inhibitor due to its potassium-sparing effects, restoring BP and potassium to normal levels (Tetti et al. 2018).

Side effects: Amiloride is generally well tolerated. Common side effects include hyperkalemia, vomiting, loss of appetite, mild skin rash, and headache and gastrointestinal side effects (nausea, vomiting, diarrhea, decreased appetite, flatulence, and abdominal pain). Mild symptoms of hypokalemia include unusual skin sensations, muscle weakness, or fatigue, but more severe symptoms such as flaccid paralysis of the limbs, bradycardia, and even shock can occur (Heran et al. 2012).

Caution: Paying extra-attention to the following commodities: (Heran et al. 2012)

(1) **Diabetes**: Patients with diabetes are at higher risk for kidney functional insufficiency, which increases their risk for hyperkalemia. So, when patients with diabetes use amiloride, their potassium and kidney function should be closely monitored. If performing glucose tolerance testing, amiloride must be discontinued for at least 3 days prior to the test, due to the risk for fatal hyperkalemia.
(2) **Kidney function insufficiency**: Patients with kidney function insufficiency (e.g., blood urea nitrogen > 30 mg/dL, or serum creatinine > 1.5 mg/dL) are at high risk for hyperkalemia.
(3) **Lactation**: No data are available on the use of amiloride in women who are breastfeeding. While diuretics can make lactation difficult, it is unlikely that amiloride would induce this effect in the absence of other diuretics.
(4) **Pregnancy**: Data from animal studies suggest that it does not pose a risk to the developing fetus. Limited human data from use during pregnancy suggest an association with a specific congenital penis abnormality if taken during the first trimester, as well as a risk for mild intrauterine growth restriction if taken throughout pregnancy.

Contraindication: Amiloride is contraindicated for the following people:

(1) In patients with kidney function insufficiency, such as anuria, acute or chronic renal insufficiency, or diabetic nephropathy. The situations are at increased risk for serum hyperkalemia, such as blood urea nitrogen more than 30 mg/dl, or serum creatinine level more than 1.5 mg/dl.
(2) In patients with plasma hyperkalemia (serum potassium concentration $\geq$ 5.5 mEq/L).
(3) In patients who are hypersensitivity to amiloride or any ingredients within the specific formulation.
(4) In patients who are already taking potassium-sparing drugs (e.g., spironolactone and triamterene) or taking potassium supplements (e.g., potassium chloride) in most circumstances.

Pharmacogenomics: A variants in the NEDD4L (Neural Precursor Cell Expressed, Developmentally Down-Regulated 4, Like E3 Ubiquitin Protein Ligase) may impact how amiloride affects a person's BP in hypertensive patients (McDonough et al. 2013).

6.5.8 Summary: Diuretics in the Treatment of Hypertension

Four types of diuretics are available in clinical hypertension treatment.

(1) Thiazide-type diuretics: Hydrochlorothiazide and chlorothiazide are the most popular thiazide diuretic in clinical management of hypertension.
(2) Thiazide-like diuretics: So named due to lack of the benzothiadiazine structure of thiazide-type diuretics but have similar action mechanisms and antihypertensive effects to thiazide-type diuretics. Most often used thiazide-like diuretics in hypertension therapy are indapamide, chlorthalidone, and occasional metolazone.
(3) Loop diuretics: Bumetanide, furosemide, torsemide, and only used in hypertensive patients with kidney failure or heart failure.
(4) Potassium-sparing diuretics: amiloride, triamterene, spironolactone, eplerenone.

More and more evidences, however, support that thiazide-type and thiazide-like diuretics need to be considered separately as they have different mechanisms of action, safety profiles, and possibly different efficacy profiles. While thiazide diuretics are more effective in patients with normal kidney function, loop diuretics are more effective in patients with impaired kidney function (Wile 2012).

Diuretics are efficient and quite safe antihypertensive drugs with several decades of clinical application. Diuretics are listed in hypertension guidelines as one of three equally weighted first-line treatment options. Since clinical differences are significant in terms of efficacy and safety among diuretics. Chlorthalidone and indapamide with less metabolic side effects and longer diuretic acting are recommended as first-line antihypertensive agents by some international guidelines.

Most suitable indications for diuretics treatment of hypertension alone or combined with other antihypertensive drugs are patients with obesity, elderly, salt-sensitive hypertension, Blacks, resistant hypertension irrespective of salt-sensitive status. Large meta-analyses have shown that low-dose diuretics are superior to other antihypertensive agents with the most favored clinical outcomes (Kokubo and Kamide 2009; Robert et al. 2018). Thus, most recent guidelines continue to recommend thiazide-related diuretics as a first-line antihypertensive choice.

In the setting of low renin hypertension, diuretics elevate renin activity in a dose-dependent manner and, therefore, would be expected to enhance the efficacy of ACE inhibitors as well as aldosterone receptor blockers.

6.5.9 Calcium Channel Blockers (CCBs)

CCBs block the entry of calcium ion into muscle cells in artery walls as well as in cardiac myocytes. There are two classes of CCBs in the treatment of hypertension, particularly effective against large vessel stiffness, one of the common causes of elevated systolic BP in elderly patients (Nelson 2010). CCBs are often less likely to cause side effects in people over the age of 65 years. CCBs are principally used to treat hypertension, arrhythmias, and chest pain related to angina. Certain groups of people may especially benefit from CCBs in combination with other medications, including African-Americans, individuals with kidney disease, the elderly, people with diabetes (Chen et al. 2010; Hockerman et al. 1997).

6.5.9.1 Dihydropyridine (DHP) CCB

Twenty types include amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, cilnidipine (Not available in US), clevidipine, efonidipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine (This substance can pass the blood–brain barrier and is used to prevent cerebral vasospasm), nisoldipine, nitrendipine, and pranidipine (Chen et al. 2010; Hockerman et al. 1997).

Mechanism of action and clinical indications: DHPs block the voltage-dependent L-type calcium channels (where "L" stands for long-lasting, referring to the length of activation) in vascular smooth muscle cells (VSMCs). Thus, DHPs have vascular selectivity and block the VSMC's calcium channel which are primarily dependent on Ca^{2+} influx. When acutely administered, DHPs reduce total peripheral resistance, BP, and increase cardiac output. Chronic administration of DHPs results in cardiac output returned toward pretreatment levels and mean arterial pressure (MAP) and systemic vascular resistance remained low and associated with a relaxation of large arteries, thus less arterial stiffness and wave reflection, a fall in central systolic BP, and pulse pressure (Chen et al. 2010; Hockerman et al. 1997).

JNC 8 recommended CCBs to be the first-line treatment either as monotherapy or in combination with thiazide-type diuretics, ACE inhibitors, or ARBs for all hypertensive patients regardless of age or race (James et al. 2014). They are especially effective as monotherapy in black patients and elderly patients. Some examples of DHPs include amlodipine, nifedipine, clevidipine, and felodipine (Chen et al. 2010; Hockerman et al. 1997).

Nifedipine: Extended-release nifedipine 30–90 mg (maximum of 120 mg) daily has been used to treat hypertension alone or combined with other antihypertensive drugs (Chen et al. 2010; Hockerman et al. 1997).

Amlodipine: Amlodipine has antianginal and antihypertensive effects. Amlodipine is a peripheral arterial vasodilator that acts directly on VSMC to cause a reduction in peripheral vascular resistance and reduction in BP. Recommended dosage is oral

5 mg once daily in the treatment of hypertension (Chen et al. 2010; Hockerman et al. 1997).

Felodipine: Felodipine inhibits the influx of extracellular calcium across the myocardial and VSMC membranes. These effects elicit an increased oxygen delivery to the myocardial tissue, a decreased total peripheral resistance, a decreased systemic BP, and a decreased afterload. Recommended dosage is oral 5 mg once daily in the treatment of hypertension (Chen et al. 2010; Hockerman et al. 1997).

Clevidipine: Clevidipine butyrate is a novel, ultra-short-acting DHP, rapidly metabolized in blood and tissues and does not accumulate in the body. It is indicated for the reduction of BP. Initial dose: 1 mg to 2 mg/h intravenous infusion (0.5 mg/1 mL) Dose titration: At hypertension emergency, dose can be doubled within 90 s. If BP goal was not achieved. After BP achieved goal, the drug dose titration should be less doubling and interval between dose adjustment can be increased to 5 min to 10 min. Every increase in dose of 1–2 mg per hour usually lowers systolic BP 2–4 mm Hg (Drugs.com, Clevidipine).

Maintenance dose: At the dose of 4 mg to 6 mg, most patients can have the desired therapeutic BP response. Patients with severe hypertension may require doses up to 32 mg/h (Drugs.com, Clevidipine).

Maximum dose: 16 mg per hour, not much experience with dose up to 32 mg per hour. Liquid should be restricted to less than 1000 ml per 24-hour period during drug therapy (Drugs com, Clevidipine).

Duration of therapy: There is little experience with infusion durations beyond 72 h at any dose (Drugs.com, Clevidipine).

Transition to an oral antihypertensive agent: To discontinue this drug or to titrate downward is established while appropriate oral treatment. Reduction of BP when oral treatment is not feasible or not desirable (Drugs.com, Clevidipine).

DHP-CCBs lowers BP with increased heart rate or even tachycardia but in the reduction of myocardial oxygen consumption, DHP-CCBs are less effective than non-DHP-CCBs such as verapamil and diltiazem which decrease heart rate. DHP-CCBs-induced tachycardia is caused by that baroreflex activation outweighs the direct effects on the sinus node. Chronic administration would lead to baroreflex that is less marked and heart rate can even be normalized (Chen et al. 2010; Hockerman et al. 1997).

Potent vasodilator DHP-CCBs usually have less cardio-depressant activity than non-DHPs-CCBs. Neither type of CCBs has direct effects on venous system and does not modify preload.

It is still inconsistent in the CCB effects on the progression of renal disease in patients with primary hypertension. Renal efferent arterioles do not express L-type channels, CCBs preferentially dilate renal afferent arterioles which can lead to an increase in glomerular pressure and accelerate glomerulosclerosis. On the other hand, CCBs may have renal protection effects, including retardation of the renal growth, dilating both afferent and efferent arterioles with new CCBs which block L-type and T-type channels, resulting in improving glomerular hypertension (Chen et al. 2010; Hockerman et al. 1997).

6.5.9.2 Non-Dihydropyridines (Non-DHP) CCB

Include mainly verapamil and diltiazem. Verapamil is a phenylalkylamine CCB. Its major mechanism of action is causing negative inotropy which is relatively selective for myocardium, reducing myocardial oxygen demand and reversing coronary vasospasm, and are often used to treat angina.

Diltiazem is a benzothiazepine class of compounds. By having both cardiac depressant and vasodilator actions, benzothiazepines are able to reduce arterial pressure without producing the same degree of reflex cardiac stimulation caused by dihydropyridines (Chen et al. 2010; Hockerman et al. 1997).

Non-DHPs CCBs bind to L-type calcium channels in the sinoatrial and atrioventricular node, as well as exerting effects in the myocardium and vasculature and more effective in black patients than in white patients. Both verapamil and diltiazem are bradycardic agents because of their direct inhibitory effect on the cardiac nodal tissue and lack of vascular selectivity, leading to bradycardia and impairment of atrioventricular conduction and depression of contractility. They have little, if any, effects on the automaticity of cardiac myocytes. Both verapamil and diltiazem are considered to be negative inotropic agents and should not be given to patients with preexistent bradycardia, atrioventricular conduction defects, or systolic heart failure, or combined with a beta-blocker, because they exaggerate the effects of beta-blockade on cardiac electrical and mechanical activity.

Verapamil and diltiazem have important drug interaction with digoxin, cyclosporine, dabigatran, atorvastatin, and simvastatin, among others.

Diltiazem produces its antihypertensive effect primarily by relaxation of VSMC and the resultant decrease in peripheral vascular resistance. The magnitude of BP reduction is related to the degree of hypertension. Extended-release capsules in the treatment of hypertension: Initial dose: 120–240 mg orally once a day, increasing the dose as needed. Maintenance dose: 120–540 mg orally once a day. Maximum dose: 540 mg/day (Drugs.com Diltiazem).

Verapamil: Verapamil produces its antihypertensive effect by a combination of vascular and cardiac effects. It acts as a vasodilator with selectivity for the arterial portion of the peripheral vasculature. As a result, the systemic vascular resistance is reduced, usually without orthostatic hypotension or reflex tachycardia. Sustained-release capsules: Initial dose: 240 mg orally once a day in the morning (usual dose in clinical trials). Alternatively, patients with small body size can start with 120 mg in the morning. The dosage can be up titrated to 480 mg per day, if desired BP response was not obtained after initial dose. Maximum daily dose: 480 mg. No evidences support that beyond 360 mg will provide additional BP-lowering effects.

Side effects: CCBs are generally well tolerated. High dose of DHPs often causes ankle edema, constipation, dizziness, headache, gingival overgrowth (all CCBs), flushing, and tachycardia. Ankle edema is more frequently observed with DHPs, neither due to sodium retention nor local hemodynamic changes, but it is due to fluid extravasation in response to an increase in transcapillary gradient, due to an imbalance between upstream arteriolar vasodilatation and downstream venoconstriction (Chen et al. 2010; Hockerman et al. 1997).

Caution: CCBs should not be taken with grapefruit products, neither whole fruit nor juice because grapefruit products interfere with the normal excretion of CCBs. It may be dangerous when a large amount of CCBs accumulated in body. Drinking grapefruit juice or eating grapefruit should be waiting at least 4 h after taking CCBs (Chen et al. 2010; Hockerman et al. 1997).

6.5.10 Adrenergic Receptor Blockers

Adrenergic beta-blockers have been used to treat hypertension, including atenolol, bisoprolol, betaxolol, carteolol, carvedilol, labetalol, metoprolol, nadolol, nebivolol, oxprenolol, penbutolol, pindolol, propranolol, and timolol.

Classes of beta-blockers:
Beta-1, nonselective: Alprenolol, bopindolol, bupranolol, carteolol, cloranolol, mepindolol, nadolol, oxprenolol, penbutolol, pindolol/iodopindolol, propranolol, sotalol, tertatolol, and timolol,

Beta-1, selective: Acebutolol, atenolol, betaxolol, bevantolol, bisoprolol, celiprolol, epanolol, esmolol, landiolol, metoprolol, nebivolol, practolol, atenolol, and talinolol.

Beta-1 selective/beta -2 selective: Butaxamine and arotinolol.

Beta selective + Alpha-1: Carvedilol and labetalol.

The mechanisms for beta-blockers lowing BP (Ripley and Saseen 2014): (1) Beta-blockers induced a reduction in cardiac output that is one of the most important factors for lowering mean BP. Since any BP lowering activates the baroreflex system which results in an increase in total peripheral resistance, this can be dampened by the baroreceptor resetting. (2) A reduction in sympathetic activity of central origin leads to a reduction in vasomotor tone. (3) A possible effect on pre-junctional beta-receptors leads to a reduction in norepinephrine release.

Beta-1 selective blockers with vasodilating effects act preferentially on the beta 1 receptor in heart and may also provide benefits from non-opposed beta-2 arteriolar vasodilation. BP-lowering effect-induced by vasodilating beta-blockers is accompanied by less reduction in heart rate and less total peripheral resistance than non-vasodilating beta-blockers (such as atenolol and metoprolol) (Ripley and Saseen 2014; Cruickshank 2017; Wright 2016).

Vasodilating beta-blockers, cicloprolol and nebivolol, have a partial agonist activity at beta-2 adrenergic receptor sites. Vasodilating beta-blockers, carvedilol and labetalol, have an antagonist activity at the alpha-1 adrenergic receptor sites. Nebivolol has potential NO (Nitric oxide) activity. These drugs lower BP with less increase in central BP than other non-vasodilating beta-blockers. These drugs can also improve arterial stiffness independent of their BP-lowering effects.

In summary, vasodilating beta-blockers effectively modify the peripheral and central hemodynamic components, resulting in vasodilation of both large arteries and small arteries, reduction of BP, heart rate and cardiac output, relaxation of large

arteries, and vasodilatation of small arteries (Ripley and Saseen 2014; Cruickshank 2017; Wright 2016).

Non-vasodilating beta-blockers may exert deleterious or at least neutral effects on the arterial system. For instance, it has been noticed that despite less deleterious effects of catecholamine on the heart, atenolol did not significantly decrease total peripheral resistance and sympathetic drive. Atenolol has also been found fewer protective effects on HMOD than RAAS blockers, including left ventricular hypertrophy and carotid intima-media thickness (Ripley and Saseen 2014; Cruickshank 2017; Wright 2016)

Non-vasodilating beta-blockers can even stiffen large arteries through a direct "profibrotic" effect, when the lowering of BP is not large enough to unload the stiff components of the arterial wall. This deleterious effect can be due to several mechanisms (Ripley and Saseen 2014; Cruickshank 2017; Wright 2016).

Beta-blockers lower BP and prevent heart attacks in people who have already had a heart attack but they do not have a positive benefit on endpoints as some other antihypertensives (James et al. 2014). In the United Kingdom, Management of Hypertension in Adults in Primary Care guideline of the National Institute for Health and Clinical Excellence (NICE 2006), first downgraded the role of beta-blockers due to their risk of provoking type 2 diabetes (NICE 2006). In addition, beta-blockers have been shown a less protective effect on stroke risk than other classes of antihypertensive agents (Nelson 2010). A systematic review of 63 clinical trial data covered 35,000 participants and showed that beta-blockers increased mortality compared with other antihypertensive agents (Wu et al. 2013). Therefore, beta-blockers are not first-line therapy for hypertension except for patients with coronary heart disease, heart failure, or tachycardia by European and US guidelines (Whelton et al. 2017; Williams et al. 2018; James et al. 2014; Chobanian et al. 2003).

Beta-blocker contraindications: (1) Moderate-to-severe asthma (adrenergic bronchodilatation requires intact beta-2 receptor function); (2) unstable systolic heart failure; (3) second- or third-degree atrioventricular block; and (4) sick sinus syndrome (with no pacemaker).

Used with caution: Diabetes milieus. Beta-blocker may worsen glucose intolerance and mask hypoglycemic symptoms.

Side effects: Vivid dream, insomnia, hallucination, and depression. These side effects are more often observed with the highly lipid-soluble beta-blockers such as propranolol, metoprolol, and pindolol. These lipid-soluble beta-blockers can penetrate the central nervous system easier than non-lipid-soluble ones, important but less frequently observed with vasodilating beta-blockers (Ripley and Saseen 2014; Cruickshank 2017).

Although beta-blockers are generally not recommended as first-line agents for the treatment of hypertension by NICE (2006) and JNC8 guidelines (James et al. 2014), however, they are suitable alternatives when a compelling cardiac indication is present. Nearly, all beta-receptor blockers can be nonselective at higher doses.

Caution should be taken when using beta-blockers in situations such as asthma or severe obstructive pulmonary disease regardless of beta-receptor selectivity profile. Abrupt discontinuance of beta-blocker may worsen angina or even myocardial

infarction in patients with coronary heart disease. If planning to discontinue beta-blocker, the best way is to reduce beta-blocker dose gradually in a few weeks (Ripley and Saseen 2014; Cruickshank 2017).

6.5.10.1 Beta-Blockers, Beta-1 Selective

Beta-1 receptor blockers may still be the first-line antihypertensive agent for patients less than 60 years age or with other indications such as coronary heart disease and sympathetic activity increase (heart rate over 85 beats/min) (Ripley and Saseen 2014; Cruickshank 2017; Wright 2016).

Atenolol: Used as a conditional antihypertensive agent either used alone or with other antihypertensive drugs, starting from 50 mg once a day. If the desired BP response was not obtained, it can be titrated to 100 mg daily. It has been shown that atenolol lacks specific potential for stroke prevention.

Metoprolol: Presently considered as conditional antihypertensive agent, either used alone or with other antihypertensive drugs, starting from 50 mg immediate-release formulation twice daily, maximum of 450 mg per day and extended-release formulation, started from 47.5 mg once daily, maximum of 400 mg per day.

Propranolol: At present, propranolol is considered as a conditional antihypertensive agent, either used alone or combined with other antihypertensive drugs (such as diuretics), starting from 40 mg twice daily. Maintenance dose: 120–240 mg per day; maximum of 640 mg per day. If planning to reduce the dose, reduced gradually over a few weeks because exacerbation of angina and even myocardial infarction have been reported following abrupt discontinuing propranolol therapy.

Bisoprolol: Except nebivolol, bisoprolol has more specific beta-1 blocking effect than any other beta-blockers available in clinical practice right now. Start with 5 mg once a day in the treatment of hypertension. The dose should be reduced to 2.5 mg for hypertensive patients with bronchospastic disease. Maximum dose: 20 mg per day if necessary.

Timolol: Used alone or combined with other antihypertensive agents such as diuretics in treatment of hypertension. Starting with 10 mg twice daily, maximum of 30 mg daily. Abrupt discontinuing may lead to the exacerbation of ischemic heart disease.

6.5.10.2 Beta-Blockers with Intrinsic Sympathomimetic Effects

Beta-blockers acebutolol and pindolol have intrinsic sympathomimetic effects and can be used to treat hypertension alone or combined with other antihypertensive agents such as diuretics.

Acebutolol: Starting with 400 mg daily in patients with uncomplicated, mild-to-moderate hypertension. Even though some patients obtained good BP response at as little as 200 mg daily, the optimal response is often achieved with 400 mg to 800 mg per day (Ripley and Saseen 2014; Cruickshank 2017; Jaillon 1990).

Pindolol: In the management of hypertension, the initial dose is 5 mg twice daily alone or in combination with other antihypertensive agents. An antihypertensive response is usually achieved within the first week of treatment. Maximal response, however, may take as long as 2 weeks or even longer (Ripley and Saseen 2014; Cruickshank 2017; Jaillon 1990).

6.5.10.3 Nebivolol, The Third Generation of Beta-1 Adrenergic Blocker

Lowering BP: Recommended starting dose is 5 mg once daily, with or without food, as monotherapy or in combination with other antihypertensive agents. For patients requiring further BP reduction, the dose can be increased up to 40 mg at 2-week intervals. A more frequent dosing regimen is unlikely to be beneficial. In patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed.

In patients with moderate hepatic impairment, the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed. Nebivolol has not been studied in patients with severe hepatic impairment, and therefore it is not recommended in that population.

Nebivolol has not been studied in patients receiving dialysis.

Nebivolol is not approved for use in children under 18 years of age.

It was not studied in patients with angina pectoris or who had a recent myocardial infarction. There are no randomized controlled trials to study whether it can reduce cardiovascular morbidity and mortality, demonstrating risk reduction with nebivolol.

Geriatric patients: Not necessary to adjust the dose (Gielen et al. 2006; Baldwin and Keam 2009; Pessina 2001; Weber 2005; Poirier et al. 2001).

Nebivolol proved to be the most beta 1-selective beta-blockers tested so far, being approximately 3.5 times more beta 1-selective than bisoprolol. The drug is highly cardio-selective at 5 mg. In addition, at doses above 10 mg, nebivolol loses its cardioselectivity and blocks both beta-1 and beta-2 receptors (Bundkirchen et al. 2003; Prescribing Information 2009; Nuttall et al. 2003).

Nebivolol is unique as a beta-blocker. Unlike carvedilol, it has NO potentiating, vasodilatory effect via stimulation of beta-3 receptors. Along with labetalol, celiprolol, and carvedilol, it is one of four beta-blockers to cause dilation of blood vessels in addition to effects on the heart (Agabiti and Rizzoni 2007; Galougahi 2016; Weiss 2006; Bakris 2009).

Nebivolol lowers BP by inhibiting peripheral vascular resistance with significant increase in cardiac stroke volume. The net hemodynamic effects of nebivolol are the balance of beta-blockade and maintaining cardiac output. Its antihypertensive effects have been proved in various groups of patients including black patients (Rosei and Rizzoni 2007; Galougahi 2016; Weiss 2006; Bakris 2009).

Common side effects include dizziness, feeling tired, nausea, and headaches. Serious side effects are heart failure and bronchospasm (Nebivolol Side Effects Site 2019; Nebivolol Hydrochloride Monograph for Professionals 2019; Nebivolol Pregnancy 2019).

Cautions: Like most other beta-blockers, abrupt stopping use of nebivolol may cause severe adverse effects such as severe exacerbation of angina pectoris, myocardial infarction, and ventricular arrhythmia in patients with or without coronary heart disease. When planned to stop nebivolol, dose is recommended to reduce over one to two weeks gradually; carefully monitor patients' clinical presentations and advise patient to minimize physical activity during the specific period of time. If angina worsens or coronary insufficiency occurs, restart nebivolol promptly (Nebivolol Side Effects Site 2019; Nebivolol Hydrochloride Monograph for Professionals 2019; Nebivolol Pregnancy 2019).

Contraindications: Severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), severe hepatic impairment (Child-Pugh class B), and hypersensitive to any component of this product (Nebivolol Side Effects Site 2019; Nebivolol Hydrochloride Monograph for Professionals 2019; Nebivolol Pregnancy 2019).

6.5.10.4 Beta-Blockers Bearing Alpha Activity

Beta-blockers, such as labetalol and carvedilol, have peripheral vasodilatory effects that act via antagonism of the alpha-1 receptor in addition to beta-receptor, leading to vasodilation and decreased total peripheral resistance, which results in decrease in BP without a substantial decrease in resting heart rate, cardiac output, or cardiac stroke volume.

Labetalol: Labetalol is often used as the first-line antihypertensive drug in the treatment of pregnant-related hypertension alone or combined with other antihypertensive agents, starting with 100 mg twice a day. After 2–3 day, if desired BP response was not achieved, increment of 100 mg twice a day can be considered every 2–3 days, maximum of 2400 mg per day (Gestational Hypertension and Preeclampsia 2019; MacCarthy and Bloomfield 1983).

Carvedilol: Carvedilol is approved for the management of primary hypertension as well as congestive heart failure as monotherapy or in combination with other antihypertensive agents, especially thiazide-type diuretics. The initial dose is 6.25 mg given twice daily. The dose can be titrated to 12.5 mg twice daily at intervals of 7–14 days, then to 25 mg twice daily as needed (maximum of 50 mg/day). Carvedilol lowers standing BP more than supine BP. Orthostatic hypotension may occur after taking this drug (Ripley et al. 2014).

6.5.10.5 Alpha-Adrenergic Receptor Blockers

Alpha-adrenergic receptor blockers include doxazosin, phentolamine, indoramin, phenoxybenzamine, prazosin, terazosin, and tolazoline.

Despite lowering BP, alpha-blockers have significantly poorer endpoint outcomes than other antihypertensives and are no longer recommended as a first-line choice in

the treatment of hypertension. However, they may be useful for some men with symptoms of prostate disease and for patients with pheochromocytoma and for resistant hypertension as add-on therapy (Whelton et al. 2017; Williams et al. 2018).

Most frequently used for treatment of hypertension are prazosin, terazosin, and doxazosin. They are particularly useful in BP lowering when BP is measured with standing position or during exercise. These drugs can significantly lower BP but with little or no change in cardiac output, heart rate, and cardiac index. The first-dose phenomenon limited their use as antihypertensive agents. The phenomenon often occurred during the first 90 min following the first dose, or the dose increased rapidly, presented as sudden severe symptomatic orthostatic hypotension. The incidence of syncope can be reduced by giving the drugs at bedtime or using gastrointestinal therapeutic system which provides a true 24-hour delivery (Whelton et al. 2017; Williams et al. 2018).

6.5.11 Aldosterone Antagonists (Also See Sect. 6.5.7 Potassium-Sparing Diuretics)

Aldosterone antagonists are known as potassium-sparing diuretics, mainly spironolactone and eplerenone, compete with aldosterone receptor sites, and decrease BP and sodium reabsorption, but they are not recommended as first-line antihypertensive agents. Both spironolactone and eplerenone can be used in the treatment of heart failure and resistant hypertension as well.

6.5.11.1 Spironolactone

Spironolactone is usually used in combination with other antihypertensive drugs for patients who cannot be treated adequately with other agents, such as resistant hypertension or for whom have special indications such as primary aldosteronism.

(1) Heart failure: Typically used at a low dosage of 25–50 mg/day (Bath et al. 2015; Warrell et al. 2003; Pitt et al. 1999; Ramrakha et al. 2012).
(2) Hypertension: Used from 25 to 200 mg once a day in the treatment of primary hypertension. Likewise, the maximal antihypertensive effect can be seen after 2–3 weeks (Bath et al. 2015; Ramrakha et al. 2012).
(3) Primary or secondary aldosteronism: It has been found that increased aldosterone levels even within the physiologic range can predispose to the development of hypertension. Primary hyperaldosteronism has been found occurring in at least 10% of all patients with hypertension (Lim et al. 1997; Schirpenbach and Reincke 2007). Spironolactone targets these people's primary cause of the elevated BP.
(4) Edematous conditions such as nephrotic syndrome or ascites in people with liver disease and low blood levels of potassium: On its own, spironolactone is

only a weak diuretic because it primarily targets the distal nephron (collecting tubule), where only small amounts of sodium are reabsorbed at collecting tubule. Spironolactone needs to be combined with other diuretics to increase efficacy. The clinical benefits of spironolactone as a diuretic can be typically observed after 2–3 days from dosing beginning. Spironolactone is also commonly used to treat symptoms of hyperandrogenism in polycystic ovary syndrome (Goodman et al. 2015).

Side effects and cautions:

(1) Hyperkalemia: therefore, potassium supplementation should not be given concurrently. Spironolactone together with trimethoprim/sulfamethoxazole increases the likelihood of hyperkalemia, especially in the elderly. The trimethoprim portion acts to prevent potassium excretion in the distal tubule of the nephron (Velázquez et al. 1993).
(2) Spironolactone directly blocks androgen signaling and also acts as an inhibitor of androgen production. Higher doses of spironolactone are not recommended in males due to the high risk of feminization and other side effects. Impotence can occur because spironolactone blocks the effects of the hormones aldosterone and testosterone and has some estrogen-like effects. This is the reason why often reluctant to give it to younger men. Spironolactone has not been well studied in pregnancy and should not be used to treat pregnant-related hypertension.

Breast change: Spironolactone frequently causes breast pain and breast enlargement in women (Kenneth 2001; Tsioufis et al. 2016) and in men. This is probably because of estrogenic effects on target tissue. At high doses, breast tenderness is reported to occur in up to 40% of women (Conn et al. 1998). Spironolactone also commonly produces gynecomastia (breast development) as a side effect in men, dose-dependently (Tsioufis et al. 2016; Seldin and Giebisch 1997; Side Effects of Drugs Annual 2014; McInnes 2008) with 5–10% at low dose and exceeding 50% at high dose (Tsioufis et al. 2016; Seldin and Gerhard 1997; Side Effects of Drugs Annual 2014; McInnes 2008; Ménard 2004; Thompson and Carter 1993; Eckman and Dobs 2008; Mathur and Braunstein 1997). The spironolactone-induced gynecomastia occurred at 27 $\pm$ 20 months after using the medication at low dose and at 9 $\pm$ 12 months at high dose (Rosenberg et al. 2005) and regressed within a few weeks after discontinuing the medication (van Blijderveen et al. 2014). Spironolactone-induced gynecomastia may become irreversible after a sufficient duration (e.g., 1 year) because hyalinization and fibrosis of tissue occurred (Eckman and Dobs 2008; Mathur and Braunstein 1997).

Menstrual disturbances: Spironolactone produces an irregular, anovulatory pattern of menstrual cycles. It is also associated with metrorrhagia and menorrhagia (or menometrorrhagia) in a large percentage of women. In any case, regardless of their mechanism, the menstrual disturbances associated with spironolactone can usually be controlled well by concomitant treatment with a birth control pill, due to its progestin component.

If GFR is below 30 mL/min or with a serum potassium of greater than 5.0 mEq/L, spironolactone doses should be adjusted according to the degree of kidney function as well (Pitt et al. 2014).

Pregnancy and breastfeeding: Spironolactone is able to cross the placenta and considered pregnancy Category C, meaning that it is unclear if it is safe for use during pregnancy. Likewise, it has been found to be present in the breast milk of lactating mothers. It is generally recommended that women may not take the medication while nursing.

I**nteraction with digoxin**: Licorice, which has indirect mineralocorticoid activity by inhibiting mineralocorticoid metabolism, has been found to inhibit the antimineralocorticoid effects of spironolactone (Armanini et al. 2016; Armanini et al. 2007; Salassa et al. 1962). Licorice may be used to reduce these side effects in women treated with spironolactone as an antiandrogen who are bothered by them (Armanini et al. 2016; Armanini et al. 2007). Spironolactone can reverse licorice-induced hypokalemia. Spironolactone-mediated diuresis and natriuresis can be attenuated by aspirin and other non-steroidal anti-inflammatory drugs (Omar et al. 2012; Lin et al. 2003; Parthasarathy and MacDonald 2007). Spironolactone may interfere with the antidepressant drug effects, but the data are still inconsistent (Holsboer 1999; Otte et al. 2010; Mostalac-Preciado 2011).

Contraindications: Hyperkalemia. When spironolactone was given in a typical dose in patients with heart disease, 10–15% of the patients will develop some degree of hyperkalemia, and 6% of them were severe hyperkalemia (fatal). In a higher than typical dose, the hyperkalemia rate increased to 24%, resulting in 0.2% to 11% of hospitalization, and 0.3/1000 to 2.0/1000 death between early 1994 and late 2001 (Lainscak et al. 2015; Juurlink et al. 2004). The risk of hyperkalemia is greatest in the elderly, in people with renal impairment, e.g., due to chronic kidney disease or diabetic nephropathy, in people taking certain other medications, including ACE inhibitors, ARBs, NSAIDs, and potassium supplements, and at higher dosage of spironolactone.

6.5.11.2 Eplerenone

Eplerenone is selectively blocking aldosterone at the mineralocorticoid receptors, more specific than spironolactone, in epithelial (e.g., kidney) and nonepithelial (e.g., heart, vessel, brain) tissues, thus decreasing BP and sodium reabsorption. Eplerenone is much more selective for the mineralocorticoid receptor but has 10- to 20-fold lower affinity for the mineralocorticoid receptors relative to spironolactone (Delyani 2000), less potent than spironolactone. Eplerenone does not possess any antiandrogen, progestogen, glucocorticoid, or estrogenic effects. Eplerenone differs from spironolactone in its extensive metabolism, with a short half-life (Struthers et al. 2008).

Principal cardiovascular indications:

(1) Hypertension: Used alone or in combination with other antihypertensive agents. Clinical trial has shown that eplerenone effectively lowers BP compared to agents such as spironolactone, enalapril, losartan, and amlodipine, but its effect on clinical outcomes like mortality is still generally unknown (Brown 2003).
(2) Heart failure: Since eplerenone belongs to a steroidal anti-mineralocorticoid of the spironolactone group, used as an adjunct in the management of chronic heart failure as well, specifically indicated for the reduction of risk of cardiovascular death in patients with heart failure and left ventricular dysfunction within 3–14 days of an acute myocardial infarction (Struthers et al. 2008).

Adverse effects: Similar to spironolactone, such as hyperkalemia, hypotension, dizziness, altered renal function, and increased creatinine concentration, but with a lower incidence than spironolactone of sexual side effects such as feminization, gynecomastia, impotence, low sex drive, and reduction of size of male genitalia (Struthers et al. 2008; Jennifer 2004).

Contraindication: Hyperkalemia, severe renal impairment (eGFR less than 30 ml/min), or severe hepatic impairment (Child-Pugh score C).

Drug interaction: Eplerenone is primarily metabolized by the cytochrome P450 enzyme CYP3A4. Potential adverse drug interactions can be seen with other drugs that induce or inhibit CYP3A4. Specifically, contraindicated to concomitantly using the CYP3A4 potent inhibitors, like ketoconazole and itraconazole, other CYP3A4 inhibitors, like erythromycin, saquinavir, and verapamil (McGraw et al. 2019). Other drugs that increase potassium concentrations may increase the risk of hyperkalemia associated with eplerenone therapy, including salt substitutes, potassium supplements, and other potassium-sparing diuretics.

6.5.12 Direct-Acting Vasodilators

Vasodilators act directly on the smooth muscle of arteries to relax their walls so blood can move more easily through arteries; Direct-acting vasodilators are a heterogeneous group of drugs, whose side effects are tachycardia and fluid retention. They are only used in hypertensive emergencies or when other drugs failed, and even so are rarely given alone. The most often prescribed in hypertension are minoxidil and hydralazine (van den Born et al. 2019).

6.5.12.1 Minoxidil

Minoxidil is used as a peripheral vasodilator in the treatment of hypertension. It opens sarcolemma adenosine triphosphate-dependent potassium channels on vascular smooth muscle cells, resulting in the relaxation of large and small arteries with no vasodilator effects. The vasodilator effects of the medication lead to activation of sympathetic nervous system and of renin–angiotensin–aldosterone system, fluid

retention which attenuate its BP-lowering effects (Whelton et al. 2017; Williams et al. 2018; Pettinger 1980).

Minoxidil may produce serious adverse effects, such as peripheral edema, pericardial effusion, occasionally progressing to tamponade, and exacerbation of angina pectoris, hypertrichosis which may require to discontinue minoxidil. Minoxidil should be reserved only for hypertensive patients who do not respond adequately to maximum therapeutic doses of other antihypertensive agents, particularly in patients with chronic kidney disease. It must be administered under close supervision, usually concomitant use with therapeutic dose of beta-adrenergic blockers to prevent tachycardia and increase myocardial workload and a diuretic acting in the ascending limb of the loop of Henle to prevent serious fluid accumulation. BP response to minoxidil is dose-dependent and proportional to the extent of hypertension. It is usually started with 5 mg once daily and can be titrated to a maximum of 100 mg per day in a divided dose (Whelton et al. 2017; Williams et al. 2018; van den Born et al. 2019).

6.5.12.2 Hydralazine

Hydralazine is a direct vasodilator of resistance arterioles. Its derivatives are also used in the treatment of severe hypertension, although they should be avoided in emergencies. Hydralazine is no longer indicated as first-line therapy for hypertension due to side effects and safety concerns but remains the choice in gestational hypertension. Hydralazine, like minoxidil, reduces total peripheral resistance with no effect on venous system. In response to its BP-lowering effect, hydralazine results in activation of sympathetic nervous system and of renin–angiotensin–aldosterone system and fluid retention which attenuates its antihypertensive effect (Sharma et al. 2017).

Side effects are dose-dependent. Most frequent side effects are fluid retention and tachycardia, which may limit the BP-lowering effect. Other adverse effects include hemolytic anemia, vasculitis, glomerulonephritis, and a lupus-like syndrome. Hydralazine now is most commonly recommended for pregnant-related hypertension combined with a beta-blocker, according to NHBPEP (Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000). Caution should be taken when hydralazine is administered in patients with concomitant coronary artery disease (Whelton et al. 2017; Williams et al. 2018; Sharma et al. 2017). For the first 2 to 4 days of treatment, 10 mg orally is taken 4 times a day alone or preferred with other antihypertensive drugs such as diuretics and beta-blockers, then 25 mg 4 times a day for one week (Sharma et al. 2017; Hirschl et al. 1997; Hardy et al. 2011).

6.5.12.3 Sodium Nitroprusside

Sodium nitroprusside is a very potent, short-acting vasodilator, most commonly used for the quick and temporary reduction of BP in hypertension emergencies (such as

malignant hypertension or aortic dissection). Nitroprusside has both venous dilating and arterial dilating effects, resulting in reduction in preload as well as in afterload. It is often used in hypertensive heart failure as well as hypertensive emergency such as hypertensive encephalopathy, aortic dissection with beat blockers (Somerville 2004; Hirschl et al. 1997; Hardy et al. 2011).

Intravenous infusion should be started with 0.25 μg to 1.0 μg/kg body weight/min in increment of 0.5 μg/kg body weight, to a maximum of 8 μg to 10 μg/kg body weight/min (infusion for 10 min or less in avoid of cyanide toxicity risk). Nitroprusside is rapidly broken down to the active moiety, cyanide, and nitric oxide, and detoxified to thiocyanate. The dose of more than 2 μg/kg body weight/min can lead to cyanide accumulation with toxicity to central nervous system and heart, including agitation, seizure, cardiac instability, and an anion gap metabolic acidosis (Hirschl et al. 1997; Hardy et al. 2011).

Accumulation of thiocyanate within the body can cause toxic side effects such as lethargy, tumor, abdominal pain, and vomiting, and transitory elevation of hair follicles if BP was reduced too rapidly. Accumulation of thiocyanate can be caused by using nitroprusside more than one week or in patients with kidney failure by using nitroprusside for 3–6 days (Hirschl et al. 1997; Hardy et al. 2011). So, usually after 3 consecutive days of nitroprusside, serum thiocyanate concentration should be monitored daily. If the concentration reached more than 12 mg/dL (or more than 2 mmol/L), the drug should be discontinued. The intravenous bag and tubing should be wrapped in an opaque covering in case of UV light-induced nitroprusside broken down. Some recent data showed that nitroprusside may increase mortality compared with other intravenous medications, including clevidipine, nitroglycerin, and nicardipine. It may not use nitroprusside when other alternatives are available (Hirschl et al. 1997; Hardy et al. 2011).

6.5.12.4 Nitroglycerine

Hypertensive subjects received intravenous nitroglycerin to lower BP at dosage of 10 μg, or 30 μg, or 100 μg min^{-1} for hypertension emergency which needs immediate BP reduction with intravenous drugs such as clevidipine, fenoldopam, nitroglycerin, nitroprusside, nicardipine, labetalol, esmolol, and hydralazine (van den Born et al. 2019; Hardy et al. 2011).

Nitroglycerin affects veins more than arterioles. It is especially suitable for managing hypertension during and after coronary artery bypass graft surgery, acute myocardial infarction, unstable angina pectoris, and acute pulmonary edema.

Since nitroprusside-related "steal mechanism" tends to decrease ischemic area flow, on the contrary, nitroglycerin increases coronary flow (Hirschl et al. 1997; Hardy et al. 2011). Started with 10 μg to 20 μg/min intravenous infusion, it can be titrated upward 10 μg/min by every 5 min until achieved desired BP response. Nitroglycerin is not for long-term BP control. The side effects include headache (2%), tachycardia, nausea, vomiting, apprehension, restlessness, muscular twitching, and palpitations (Hirschl et al. 1997; Hardy et al. 2011).

It has been shown that daily glyceryl nitrate patch, a daily glyceryl nitrate patch, could be safely used to lower BP for 7 days after acute stroke (Lancet ENOS trial) (Bath et al. 2015).

6.5.12.5 Fenoldopam

Fenoldopam is a peripheral dopamine-1 receptor agonist. It can cause systemic and renal vasodilation as well as natriuresis. The medication is an effective treatment for patients with severe hypertension and hypertension emergency, and it may continue maintenance infusion for up to 48 h. Fenoldopam has potential to become an effective alternative to nitroprusside because of its rapid antihypertensive effect (initial effect: 10 min, max effect: 30-120 min), short half-life (5 min), and not cross the blood–brain barrier. Intravenously started with 0.1 μg/kg body weight/min, titrated upward by 0.1 μg/kg body weight in every 15 min to a maximum of 1.6 μg/kg body weight/min (Somerville 2004; Hardy et al. 2011).

6.5.13 Epithelial Sodium Channel (ENaC) Inhibitors

Amiloride and Triamterene (Tetti et al. 2018; Rossier and Schild 2008).

ENaC is a membrane-bound ion channel, selectively permeable to the ions of sodium (Na+) and assembled as a heterotrimer composed of three homologous subunits α or δ, β, and γ. These subunits are encoded by four genes: *SCNN1A, SCNN1B, SCNN1G*, and *SCNN1D*. ENaC causes sodium to be reabsorbed in exchange for potassium (lost in urine). ENaC inhibitors have a weak diuretic effect, and therefore do not have a significant effect on BP. They are primarily used to counteract potassium loss from thiazide and loop diuretics. In general, when ENaC inhibitors are combined with thiazide diuretics, potassium increases in the range of 0.20–0.50 mEq/L can be expected.

No studies were found that ENaC inhibitors were used by themselves to treat hypertension. ENaC inhibitors are most commonly used for adjunct hypertension treatment. Triamterene is the substrate of enzyme CYP1A2. Six studies showed (4 with amiloride, 2 with triamterene) where ENaC inhibitors were added to hydrochlorothiazide. The analysis found that ENaC inhibitors had no significant effect on BP when added to hydrochlorothiazide. They are primarily used with thiazide diuretics to help prevent potassium loss. The highest doses were 5 mg for amiloride, and 50 mg for triamterene in the studies. ENaC inhibitors are the targeted drugs for Liddle's syndrome (first-line drug) (Tetti et al. 2018).

Side effects: Hyperkalemia. When ENaC inhibitors are prescribed with thiazide or loop diuretics, the combination can offset the hyperkalemia effect. When prescribing ENaC inhibitors, one needs to pay attention to the factors that may increase the risk of hyperkalemia, including kidney disease (GFR < 60 ml/min) or serum creatinine > 1.6 mg/dl, diabetes, dehydration (from diuretics, diarrhea, etc.), advanced age, and

some medications that have potential increasing serum potassium level. High dietary potassium salt substitutes, nuts, dried fruit, and potassium supplements may also increase hyperkalemia risk in patient taking ENaC inhibitors. For patients at high risk of hyperkalemia, taking ENaC inhibitors should have their potassium levels monitored appropriately (Tetti et al. 2018; Rossier and Schild 2008).

Kidney stones (Triamterene): Deposits of triamterene and its metabolites in kidney stone has raised concerns that triamterene may contribute to kidney stone formation. No evidences support this concern. Triamterene is typically prescribed with thiazide diuretics which are known to lower the risk of kidney stones (Tetti et al. 2018; Rossier and Schild 2008).

Uric acid/gout risk: Although the triamterene may elevate uric acid level, it does not appear to have a significant effect on uric acid levels (Tetti et al. 2018; Rossier and Schild 2008).

Magnesium retention: ENaC inhibitors appear to promote magnesium retention by the kidneys (loop and thiazide diuretics promote magnesium loss).

Contraindications: Hyperkalemia (>5.5 mEq/L), concomitant spironolactone or triamterene or amiloride, significant kidney disease (serum creatinine > 1.5 mg/dl), known hypersensitivity, and severe liver disease (Tetti et al. 2018; Rossier and Schild 2008).

Folic acid deficiency (triamterene): Triamterene is a weak folic acid antagonist. It may contribute to the appearance of megaloblastosis in cases where folic acid stores have been depleted (Tetti et al. 2018; Rossier and Schild 2008).

Drug Interaction: Lithium—ENaC inhibitors may reduce the clearance of lithium and should not be taken with lithium if possible. Lithium levels should be monitored closely in patients taking ENaC inhibitors. Salt substitutes typically contain a high amount of potassium. Cautions should be taken when consuming salt substitutes. ENaC inhibitors have the potential to raise potassium levels. When taken with other medications that raise potassium, the risk may be compounded. Medications have potential to cause hyperkalemia when concomitantly used with ENaC inhibitors, including ACE inhibitors, ARBs, aldosterone antagonists (spironolactone, eplerenone), aliskiren (renin inhibitor), cyclosporine, penicillin G potassium injection (1 million units contains 1.68 mEq of potassium), potassium supplements, tacrolimus, trimethoprim, and heparin. Heparin raises potassium secondary to inhibiting aldosterone synthesis (low molecular weight heparin does not appear to have the effect).

NSAIDs can block the therapeutic effect of ENaC inhibitors. Patients should be monitored for decreased effectiveness of ENaC inhibitors when taking NSAIDs for extended periods. Triamterene may potentiate the effect of muscle relaxants used during anesthesia, including preanesthetic and anesthetic agents and skeletal muscle relaxants (non-depolarizing) (Tetti et al. 2018; Rossier and Schild 2008).

6.5.14 Alpha-2 Agonists, Central-Acting

Centrally acting alpha-2-agonists stimulate pre-synaptic alpha-2-adrenergic receptors in the brain stem, which reduces sympathetic nervous activity. The decrease in plasma concentrations of norepinephrine is directly correlated with the hypotensive effect. The most frequently used centrally acting antihypertensive drugs are clonidine, an alpha-2 adrenergic agonist, rilmenidine, acting on non-adrenergic imidazoline receptors, and methyldopa.

6.5.14.1 Methyldopa

Methyldopa is used to lower BP by activating alpha-2 receptors in the central nervous system and by reducing the concentration of epinephrine, norepinephrine, dopamine, and serotonin. The hypotensive effect was greatest at standing position and also significant at supine position. The medication has postural hypotension effect but unlike clonidine, no rebound effects. It is the first-line antihypertensive agent for gestational hypertension. Side effects include sedation, fatigue, dryness of the mouth, reduction in libido, and less frequently but not rarely Parkinsonian symptoms, hyperprolactinemia, hepatotoxicity, and hemolytic anemia. Centrally acting agents are contraindicated in patients with severe depression (Whelton et al. 2017; Williams et al. 2018). The usual starting dosage of methyldopa is 250 mg twice or thrice daily in the first 48 h. The daily dosage then may be adjusted according to BP response. In order to minimize the sedation effects, start dosage increases in the evening.

6.5.14.2 Clonidine

Clonidine can be used alone or in combination with other antihypertensives in the treatment of hypertension. Clonidine is associated with a rebound effect, especially at higher doses or with more severe hypertension. It can be used orally or as extended-release skin patch. Transdermal clonidine comes as a patch to apply to the skin in every 7 days. Clonidine lowers BP by an effect on both cardiac output and total peripheral resistance. Side effects include sedation, fatigue, dryness of the mouth, reduction in libido, sleep disturbance with vivid dreams, symptomatic bradycardia, and atrioventricular blocks in predisposed patients (Sica and Grubbs 2005).

6.5.14.3 Guanfacine

Guanfacine is an orally active antihypertensive agent and may be given alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

6.5.14.4 Rilmenidine

Rilmenidine is the first example of a hypotensive drug which has more affinity for imidazoline preferring receptors than for classical alpha 2-adrenoceptors. Rilmenidine has two to three times higher selectivity than clonidine for the non-adrenergic imidazoline receptors within the nucleus reticularis lateralis. Rilmenidine dose-dependently decreases BP, Central side effects are significantly less frequent with rilmenidine than with clonidine or methyldopa. In contrast to clonidine, no sodium retention or weight gain is observed during chronic treatment with rilmenidine (Head and Burke 2000; Cobos-Puc and Aguayo-Morales 2019; Bousquet et al. 1992).

6.5.15 Peripherally Acting Adrenergic Agents

Reserpine is a peripherally acting adrenergic agent, indicated for mild hypertension or as an adjunct therapy with other antihypertensive agents in more severe forms of hypertension. Reserpine has been used as a second- or third-line therapy in some of those trials. The systolic BP effects were achieved with 0.5 mg/day or greater. Reserpine reduces BP by depleting sympathetic biogenic amines. The result of reserpine's effects on biogenic amines is sympathetic dysfunction, with a subsequent decrease in peripheral vascular resistance and a lowering of BP often associated with bradycardia. This agent may be associated with depression (Perez 2009).

6.5.16 Endothelin Receptor Blockers

Bosentan belongs to a new class of drug and works by blocking the receptors of the hormone endothelin. It is specifically indicated only for the treatment of pulmonary artery hypertension in patients with moderate-to-severe heart failure. It is a potential drug for treatment of hypertension in the future (Chen et al. 2018).

6.6 Hypertension Treatment

6.6.1 Purpose of Antihypertensive Therapy

Antihypertensive therapy seeks to prevent the complications of high BP, such as stroke, myocardial infarction, and renal failure. There are many classes of antihypertensives, which lower BP by different mechanisms. Among the most important and most widely used antihypertensive drugs are thiazide diuretics, CCBs, ACE

inhibitors, and ARBs. Which type of medication to use initially for hypertension has been the subject of several large studies and resulting national guidelines.

6.6.2 Drug Therapy Indications

As a conventional definition of hypertension as systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg, most BP guidelines have focused on BP-lowering treatment in those patients meeting conventional hypertension definitions.

Generally speaking, antihypertensive drug treatment should be initiated not only based on the basis of BP level but also on the level of total cardiovascular risk. BP-lowering treatment is associated with a reduced risk for death and MACE (major adverse cardiovascular events) if systolic BP is 140 mm Hg or above. If systolic BP is below 140 mm Hg, antihypertensive treatment is not associated with any benefit in primary prevention, but it may reduce the risk for several cardiovascular outcomes in people with previous coronary heart disease (marginal benefit) (Brunstrom and Carlberg 2018).

The guideline recommends the use of BP-lowering medications in the presence of the following indications: (Whelton et al. 2017)

(1) The hypertensive patients with cardiovascular diseases (e.g., coronary heart disease, heart failure, and stroke) and those who need secondary prevention of cardiovascular disease in patients with clinical cardiovascular disease whose BP is ≥ 130/80 mm Hg (Whelton et al. 2017).
(2) Adults with an estimated 10-year ASCVD risk of ≥ 10% and an average systolic BP ≥ 130 mm Hg or an average diastolic BP ≥ 80 mm Hg (Whelton et al. 2017) for primary prevention of cardiovascular disease.
(3) The following people will need two or more antihypertensive drugs: Those even at stage 1 hypertension (systolic BP 130–139 mm Hg and/or diastolic BP 80–89 mm Hg), but already had a cardiovascular event such as heart attack or stroke. Hypertensive patients are at high risk of cardiovascular disease with age more than 50 years, diabetes mellitus, chronic kidney disease, or high risk of atherosclerotic cardiovascular disease score (Whelton et al. 2017).
(4) Grade 1 hypertension (office BP 140–159/90–99 mm Hg) at low-moderate-risk, even they do not have HMOD, should now receive drug treatment if their BP is not controlled after a period of lifestyle intervention alone (Williams et al. 2018).
(5) Higher risk grade 1 hypertension, including those with HMOD, or with higher grades of hypertension (e.g., grade 2 hypertension, ≥160/100 mm Hg), drug treatment should be initiated alongside lifestyle interventions. These recommendations apply to all adults aged < 80 years (Williams et al. 2018).
(6) Age > 80 years, BP-lowering therapy reduces mortality, stroke, and heart failure as well. Antihypertensive drug therapy is recommended when their office

systolic BP is 160 mm Hg or above, provided that the treatment is well tolerated (Williams et al. 2018).

6.6.3 *Benefit from Lowering BP*

Control of BP in patients with hypertension led to 50% of reduction in heart failure, 40% of reduction in cerebrovascular disease, and 25% of reduction in myocardial infarction (Winter et al. 2013). In a large meta-analysis, it has been shown that BP reduction of 10 mm Hg in systolic BP or 5 mm Hg in diastolic BP reduce all major cardiovascular disease risk by 20%, all-cause mortality by 10–15%, stroke by 35%, coronary events by 20%, and heart failure by 40% in patients with hypertension. The above antihypertensive benefits are consistent, irrespective of baseline BP within hypertensive range, the level of cardiovascular risk, comorbidities, age, sex, and ethnicity (Grossman 2011).

Although it has been well established that a linear relationship exists between elevations in systolic BP > 110 or > 115 mm Hg and cardiovascular events in every age group (Lewington et al. 2002), many cardiovascular events occurred in individuals with BP above optimal but below conventional hypertension definition (Danaei et al. 2009; Murray et al. 2013). No guideline recommended that target BP should be <115/75 mm Hg (Whelton et al. 2017; Williams et al. 2018).

The recent landmark SPRINT trial (Systolic Blood Pressure Intervention Trial) provided strong evidence that the under-treatment of high BP for patients with high cardiovascular risk increases rates of death and cardiovascular events (Wright et al. 2015). Sprint trial did not include patients with diabetes. A meta-analysis of published trials demonstrated that the risk of cardiovascular events and mortality were lower in achieving systolic BP between 120 and 124 mm Hg than in achieving systolic BP between 125 and 129 mm Hg (Bundy et al. 2017). Based on the recent evidence, lower targets are beneficial for certain patients. BP goals must be lower, and treatment needs to be more intensive than prior guidelines recommended.

The long-standing US cohorts—With >7 years of follow-up, 63.0% of incident cardiovascular events occurred in individuals with BP < 140/90 mm Hg. These findings held for individuals younger and older than 65 years of age, men and women, and across all race and ethnic groups studied (Muntner et al. 2015; 3rd et al. 2017; Ambale-Venkatesh et al. 2017; McClelland et al. 2015). Patients with BP ≥ 140/90 mm Hg had an observed event rate that was 2.25 times the rate of cardiovascular events as those with BP < 140/90 mm Hg. The event rate was nearly 3 times greater in patients not taking any antihypertensive medication than in those taking antihypertensive medications (Booth et al. 2017; James et al. 2013).

These results support that BP < 140/90 mm Hg but above optimal level results in a much larger population at cardiovascular risk. Traditionally, if individuals have their BP < 140/90 mm Hg, they were told not having hypertension, or if the patient

with hypertension had their BP to be lowered to the level <140/90 mm Hg, they were told that their BPs were adequately controlled. This is not true.

In the modern era, hypertension is defined as office BP 130/80 or more (ACC/AHA 2017), and BP control goal is less than 130/80 (ACC/AHA 2017) or less than 140/90 mm Hg. Abundant epidemiological data have shown that the risk of cardiovascular disease rises with increasing BP, starting at ≥115/75 mm Hg, in a strong, independent, graded, and continuous manner, indicating that lowering BP in patients with BP more than 115/75 mm Hg but less than 140/90 mm Hg may further reduce cardiovascular risk (Bundy et al. 2017).

6.6.4 Goal of BP

Lowering office systolic BP to <140 mmHg is beneficial for all patient groups, including independent older patients. If tolerated, systolic BP may be targeted to 130 mm Hg or less, to reduce stroke risk further which can be potentially beneficial to most patients. Systolic BP lowered to less than 120 mm Hg may not be recommended concerning the balance between benefit and harm.

BP targets in old and very old patients. The desired systolic BP target range for all patients aged more than 65 years is 130–139 mmHg, but any BP lowering toward this target is likely to be beneficial, provided that the treatment is well tolerated. Achieving systolic BP goal of <130 mm Hg is often impossible in some older people, such as those with poor vascular compliance (i.e., pulse pressures more than 80 to 90 mm Hg, who typically have dizziness and poor mentation when their systolic BP approaches 140 mm Hg (Williams et al. 2018). For older patients, treatment target may be BP < 140/90 mmHg and for those ≥80 years, BP < 160/90 mm Hg.

For patients with diabetes, systolic BP is targeted to less than 140 mm Hg. If tolerated, to 130/80 mm Hg or less, but more than 120 mm Hg, this can reduce stroke risk further, but not other major cardiovascular events. For patients with chronic kidney disease, target BP range should be 130–139 mm Hg.

Target diastolic BP has not been very well studied. It is often recommended that diastolic BP should be targeted to 80 mm Hg (ACC/AHA 2017). In some patients with isolated systolic hypertension, their diastolic BP is already below the target. These patients are still encouraged to control their systolic BP to target level and well tolerated.

The optimal diastolic BP target has been less well defined, but less than 80 mm Hg is recommended. Some patients with stiff arteries and isolated systolic hypertension will already have diastolic BP levels below this target. These are high-risk patients, and the low diastolic BP should not discourage treatment of their elevated systolic BP to the recommended target, providing that treatment is well tolerated.

New definition of hypertension by the 2017 ACC/AHA Hypertension Guidelines (Whelton et al. 2017) is BP > 130/80 mm Hg.

For hypertensive patients with clinical cardiovascular disease or 10-year ASCVD risk is 10% or >10%, their BP was >130/80 mm Hg, and their BP should be brought to the goal of <130/80 mm Hg.

For hypertensive patients with no clinical cardiovascular disease and 10-year ASCVD risk <10%, BP is ≥140/90 mm Hg for initiation of pharmaceutical antihypertensive treatment and BP goal is <130/80 mm Hg.

For old persons of age ≥65 years, non-institutionalized, ambulatory, community-living adults, BP level for initiation of pharmaceutical antihypertensive treatment is systolic BP ≥ 130 mm Hg; systolic BP goal is <130 mm Hg.

Patients with hypertension have the following special situations, as long as their BP was ≥130/80 mm Hg, antihypertensive drug therapy should start with the BP goal <130/80 mm Hg, including all hypertensive patients with diabetes, with chronic kidney disease, with chronic kidney disease after renal transplantation, with heart failure, with stable ischemic heart disease, with secondary stroke prevention, and with peripheral artery disease.

6.6.5 The Rapidity of the Antihypertensive Treatment

It sis dependent on the patient's clinical presentation (presence of new or worsening target organ damage) and presence or absence of cardiovascular complications, but treatment should be initiated within at least 1 week after confirming hypertension diagnosis if not a hypertension emergency nor an urgency.

6.6.6 Strategy of Antihypertensive Therapy

Initial therapy for the majority of patients with hypertension should be a combination of two drugs. The only exception would be in a limited number of patients with a lower baseline BP close to their recommended target, who might achieve that target with a single drug, or in some frailer old or very old patients (>80 years) in whom more gentle reduction of BP may be desirable.

Single-pill combinations therapy has been shown to improve adherence to treatment and is now the preferred strategy for initial two-drug combination treatment of hypertension and for three-drug combination therapy when required.

6.6.7 Lifestyle Intervention of Hypertension

Many guidelines exist for the management of hypertension. Most groups, including the ESH/ESC, JNC, the American Diabetes Association, and the AHA/American Stroke Association (ASA), recommend lifestyle modification as the first step in

managing hypertension. In general, this approach is reasonable in older adults, those at high cardiovascular risk, or with significant elevations in BP (systolic BP > 20 mm Hg or diastolic BP > 10 mm Hg above target, respectively), medication is usually started even while the patient is pursuing lifestyle change.

Healthy habits have been recommended by guidelines to lower BP, including, weight loss, limiting alcohol intake, reducing sodium intake, maintaining adequate intake of dietary potassium, maintaining adequate intake of dietary calcium and magnesium, stopping smoking and reducing intake of dietary saturated fat and cholesterol for overall cardiovascular health, and engaging in aerobic exercise at least 30 min daily for most days (Whelton et al. 2017; Williams et al. 2018). In terms of alcohol intake, recent systematic analysis showed that there is no safe dosage for alcohol drinking. It is better not to take alcohol anymore (GBD 2016). Lifestyle modifications are effective for young and patients with grade 1 hypertension to achieve the goal of BP in about 3 months. If not, drug therapy should be initiated immediately.

6.6.8 Selection of Antihypertensive Drugs for Initiation Therapy Based on

(1) The level of BP.
(2) Whether the presence of secondary hypertension.
(3) Risk factors for hypertension.
(4) Patient age.
(5) Associated medical conditions.
(6) End-organ damage.
(7) Pharmacogenomics.

Which class of antihypertensive drugs should be selected firstly? JNC 8 recommended 4-class antihypertensive agents as first-line antihypertensive drugs, thiazide-type diuretics, CCBs, ACE inhibitors, or ARBs. JNC 8 guideline (James et al. 2014) particularly pointed out that in blacks, thiazide diuretics and CCBs are more effective in BP lowering than beta-blockers, ACE inhibitors as well as ARBs when used as monotherapy. Tremor is indicated to use beta-blockers.

The patients with hypertension aged over 55 years and all patients who are African/Afro-Caribbean ethnicity start antihypertensive drug therapy with CCBs or thiazide diuretics. All other ethnic young patients start with ACE inhibitors or ARBs. If dual therapy needed, ACE inhibitors (or ARBs) in the combination of either a CCB or a thiazide diuretic can be selected. If BP did not achieve goal by using dual therapy, triple therapy may be tried, including ACE inhibitors (or ARBs), CCBs, and diuretics. Triple therapy is then of all three groups and needs to be added in a fourth agent, to consider either a further diuretic (e.g., spironolactone or furosemide), an alpha-blocker, or a beta-blocker (Acelajado et al. 2019). JNC 8 does not recommend β-blockers as the first-line drug for hypertension (James et al. 2014).

6.6.9 Management of Isolated Systolic High BP

Older people, especially after 60 years old, often have isolated systolic high BP with a low diastolic BP (<90 mm Hg, even <60 mm Hg). This situation brings some concerns about diastolic BP too low to meet coronary blood supply while lowering systolic BP (so-called J-curve) and created a debate regarding the optimal treatment targets for systolic hypertension in the elderly. SPRINT trial showed beneficial cardiovascular effects of intensive systolic BP of <120 mmHg in older patients (Joshua et al. 2006). ACC/AHA/ASH guideline (2017) recommends a systolic BP reduction of <130 mmHg (Whelton et al. 2017). JNC 8 recommends a systolic BP reduction <150 mmHg for the same age of patients (James et al. 2014).

It has been found that on-treatment diastolic BP yielded no relationships with the risk of cardiovascular disease or the risk of all-cause mortality. Systolic BP in the range between 130 mm Hg and 144 mm Hg was associated with minimal adverse outcomes but with a reduction in cardiovascular disease and in all-cause mortality among Japanese older adults with isolated systolic hypertension (Yano et al. 2017).

Although recent data support that a systolic BP reduction of <140 mm Hg for persons aged ≥60 years, with an attempt for systolic BP reduction to ≤130 mm Hg in healthier subjects and those with cardiovascular disease, diabetes mellitus, and chronic kidney disease, care should still be taken not to further reduce the systolic BP in older subjects if their diastolic BP is ≤60 mmHg for the fear of J-curve effect (Chrysant 2018).

6.6.10 Sexual Dysfunction

Since sexual function is an important aspect of quality of life for the individuals and a high prevalence of sexual dysfunction has been found in hypertensive men, attention should be paid to the problem. Hypertension per se, regardless of drugs, has been suggested to affect sexual function. Other cardiovascular risk factors, especially diabetes mellitus, have also been shown to correlate with impaired sexual function. It has been proposed that sexual and especially erectile dysfunction may, at least in part, represent just another manifestation of ASCVD or HMOD. The incidence of sexual dysfunction is exacerbated by antihypertensive drug treatment, most frequently occurred in using thiazide-class diuretics, β-blockers, and centrally acting sympathoplegics. The third generation of β-blockers like nebivolol, thiazide-like diuretics, and ARBs may improve erectile function, but this should be verified in large clinical trials before written in the guideline. CCBs and ACE inhibitors have been considered neutral with respect to this endpoint.

6.6.11 Antihypertensive Agent-Related Cough

ACE inhibitors (cough can also be caused by ARBs), beta-blockers, and CCBs have been associated with cough as a side effect. It is unknown what are the exact mechanisms of cough. The level of evidence is strongest with ACE inhibitors. ACE inhibitors are associated with a dry, persistent cough in 5–35% of patients who take them. Chinese seem to have more this side effect (Coates 2010). The mechanism of cough is likely multifactorial. This side effect is not dose-dependent and often precludes the use of all agents within the drug class. No one ACEI is any better or worse than another in terms of causing coughing. It is known that the coughing may occur within a week of starting ACE inhibitors or up to 1 year later. This cough is usually worse at night and when the person is lying down. Stopping ACE inhibitors is the best way to stop the cough. Cough will go away within 2 weeks to several months after discontinuing ACE inhibitors. If switched to ARBs, cough risk becomes significantly lower, but not for sure of completely gone (Messerli et al. 2018).

Beta-blockers: Blocking beta-2 receptors can cause bronchoconstriction (Whelton et al. 2017). Many commercially available beta-1 selective blockers have a high affinity for beta-2 receptors. Therefore, both selective and nonselective beta-blockers may cause bronchoconstriction, especially at high dosage, which can lead some patients to experience a cough reflex (Tiotiu et al. 2019; Morales et al. 2014).

CCBs: Although there are reported incidences of cough associated with CCBs, a literature search for drug-induced cough associated with CCBs yielded no relevant studies or case reports. The rates are low, estimated ranging from <1 to 6%. However, the search yielded studies on the potential antitussive benefits of CCBs (Düsing 2005; Khaja et al. 2016; Martínez-Salamanca et al. 2014; Angulo et al. 2010; Kamei and Kasyya 1992).

6.6.12 Withdrawal Syndrome

Sympathetic discharge and acute hypertension can occur on cessation of clonidine or beta-blockers acutely, so-called withdrawal syndromes. Although few studies describe risks of withdrawing beta-blockers in the perioperative time period, abrupt withdrawal of long-term beta-blockers is harmful. There are fewer data to describe whether short-term (1 to 2 days) perioperative use of beta-blockers, followed by rapid discontinuation, is harmful (Whelton et al. 2017).

6.6.13 Caution in Determining RAAS

If patients were suspected of having secondary hypertension, RAAS needs to be investigated. Before tests, diuretics should be withdrawn for at least 4 weeks and

other medications interfering with the laboratory test results should be stopped at least 2 weeks before test (preferably 4 weeks). Under the circumstance, BP will be controlled with medications which have less effects on renin-aldosterone measurement such as verapamil slow-release (with or without hydralazine) or prazosin (Whelton et al. 2017; Williams et al. 2018).

6.7 Hypertensive Emergencies and Urgency

Acute onset, severe hypertension that is accurately measured using standard techniques, persistent for 15 min or longer, is considered a hypertensive emergency. Hypertensive emergency is defined as severe elevations in BP (> 180/120 mm Hg) associated with evidence of new or worsening target organ damage. If left untreated, 1-year death rate is more than 79%, and the median survival is 10.4 months. With BP control and medication compliance, the 10-year survival rate approaches 70% (Whelton et al. 2017).

Hypertensive emergencies include the following conditions:

(1) Malignant hypertension, a typical presentation of a hypertension emergency, is characterized by severe hypertension (usually grade 3) associated with funduscopic changes (flame hemorrhages and/or papilloedema), microangiopathy, and disseminated intravascular coagulation, and it can be associated with encephalopathy (about 15% of cases), acute heart failure, and acute deterioration in renal function. The hallmark of this condition is small artery fibrinoid necrosis in the kidney, retina, and brain. The term "malignant" reflects the very poor prognosis for this condition if untreated.
(2) Patients with severe hypertension as well as other urgent clinical conditions requiring immediate to bring BP to a safe level, for example, acute aortic dissection, acute myocardial ischemia, or acute heart failure.
(3) Patients with pheochromocytoma present with severe hypertension or hypertensive crisis.
(4) Pregnant women with severe hypertension or preeclampsia.
(5) In patients with hypertensive encephalopathy, the presence of somnolence, lethargy, tonic seizures, and cortical blindness may precede a loss of consciousness. However, focal neurological lesions are rare and should raise the suspicion of stroke.
(6) Acute stroke, especially intracerebral hemorrhage, when associated with severe hypertension, a more cautious approach is now recommended for acute BP lowering in the emergency setting of acute stroke (Williams et al. 2018).

Target organ damage includes but is not limited to hypertensive encephalopathy, intracerebral hemorrhage, acute ischemic stroke, acute myocardial infarction, acute left ventricular failure with pulmonary edema, unstable angina pectoris, dissecting aortic aneurysm, acute renal failure, and eclampsia (Whelton et al. 2017).

Diagnostic in patients with a suspected hypertension emergency: Common tests for all: Fundoscopy, critical, 12-lead ECG (electrocardiogram), hemoglobin, white blood cell count, platelet count, fibrinogen; creatinine, eGFR, electrolytes, lactate dehydrogenase, haptoglobin; urine albumin: creatinine ratio, urine microscopy for red cells, leucocytes, casts, pregnancy test for in women of childbearing age. Specific tests by indications: troponins, CK-MB (creatine kinase-MB), NT-proBNP (The N-terminal prohormone of brain natriuretic peptide), chest X-ray, echocardiography (aortic dissection, heart failure, or cardiac ischemia), brain CT or brain MRI (magnetic resonance imaging), renal ultrasound, and urine drug screen (Williams et al. 2018).

Acute management of hypertension emergency: Hypertensive emergencies are often life-threatening and require immediate but careful intervention to lower BP, usually with intravenous therapy, demand immediate reduction of BP (not necessarily to normal) to prevent or limit further target organ damage. No RCT evidences inform clinicians which first-line antihypertensive drug provides more benefit than harm in hypertensive emergencies. However, from clinical experience, it is highly likely that antihypertensive therapy is an overall benefit. However, two trials have demonstrated that nicardipine may be better than labetalol in achieving the short-term BP target (Whelton et al. 2017).

ESH/ESC 2018 guideline recommended that drug treatments for specific hypertension emergencies are as follows according to six specific clinical presentations:

(1) Malignant hypertension with or without acute renal failure: Timeline: several hours, target for BP reduction to reduce MAP by 20–25%. First-line antihypertensive agents: Labetalol, Nicardipine. Alternative drugs: Nitroprusside or Urapidil.
(2) Hypertensive encephalopathy: Timeline and target for BP reduction: Immediately to reduce MAP by 20–25%. First-line antihypertensive agents: labetalol, nicardipine. Alternative drug: Nitroprusside.
(3) Acute coronary events: Immediately reduce systolic BP to <140 mm Hg. First-line antihypertensive agents: Nitroglycerine, labetalol. Alternative drug: Urapidil.
(4) Acute cardiogenic pulmonary edema: Timeline and target for BP reduction: Immediately reduce systolic BP to <140 mm Hg. First-line treatment: Nitroprusside or nitroglycerine (with loop diuretic). Alternative drugs: Urapidil (with loop diuretic).
(5) Acute aortic dissection: Timeline and target for BP reduction: Immediately reduce systolic BP to <120 mm Hg and heart rate <60 beats/min. First-line antihypertensive agents: Esmolol or nitroprusside or nitroglycerine or nicardipine. Alternative drugs: Labetalol or metoprolol.
(6) Eclampsia and severe preeclampsia/HELLP (hemolysis, elevated liver enzymes, and low platelets): Timeline and target for BP reduction: Immediately reduce systolic BP to <160 mm Hg, diastolic BP < 105 mm Hg. First-line treatment: Labetalol or nicardipine and magnesium sulfate. Alternatives: Consider delivery.

ESH/ESC 2018 recommended possible drug dosage: (Williams et al. 2018).

Esmolol: Onset of action: 1–2 min. Duration of action: 10–30 min. Dose: 0.5–1 mg/kg intravenous bolus; 50–300 μg/kg/min intravenous infusion. Contraindications: Second- or third-degree atrioventricular block, systolic heart failure, asthma, and bradycardia. Adverse effects: Bradycardia.

Metoprolol: Onset of action: 1–2 min. Duration of action: 5–8 h. Dose: 2.5 mg–5 mg intravenous bolus over 2 min; may repeat every 5 min to a maximum dose of 15 mg. Contraindications: Second- or third-degree atrioventricular block, systolic heart failure, asthma, bradycardia. Adverse effects: Bradycardia.

Labetalol: Onset of action: 5–10 min. Duration of action: 3–6 h. Dose: 0.25–0.5 mg/kg intravenous bolus; 2 min–4 mg/min, intravenous infusion until goal BP is achieved, thereafter 5 mg–20 mg/h. Contraindication: Second- or third-degree atrioventricular block; systolic heart failure, asthma, bradycardia. Adverse effects: Bronchoconstriction, fetal bradycardia.

Fenoldopam: Onset of action: 5–15 min. Duration of action: 30–60 min. Dose: 0.1 μg/kg/min, intravenous infusion, increase every 15 min with 0.05 μg to 0.1 μg/kg/min until goal BP is achieved. Caution in glaucoma.

Clevidipine: Onset of action: 2–3 min. Duration of action: 5–15 min, 2 mg/h intravenous infusion, increase every 2 min with 2 mg/h until goal BP achieved. Side effects: mainly headache and reflex tachycardia.

Nicardipine: Onset of action: 5–15 min. Duration of action: 30–40 min. Dose: 5 mg–15 mg/h intravenous infusion, starting dose 5 mg/h, increase every 15–30 min with 2.5 mg until achieving goal BP, then decrease to 3 mg/h. Contraindication: Liver failure. Adverse effects: mainly headache and reflex tachycardia.

Nitroglycerine: Onset of action: 1–5 min. Duration of action: 3–5 min. Dose: 5–200 μg/min intravenous infusion, 5 μg/min increase every 5 min. Adverse effects: Headache, reflex tachycardia.

Nitroprusside: Onset of action: Immediate. Duration of action: 1–2 min. Dose: 0.3–10 μg/kg/min intravenous infusion, increase by 0.5 μg/kg/min every 5 min until goal BP. Contraindication: Liver/kidney failure (relative). Adverse effects: Cyanide intoxication.

Enalaprilat: Onset of action: 5–15 min. Duration of action: 4–6 h. Dose: 0.625 mg–1.25 mg intravenous bolus. Contraindication: History of angioedema.

Urapidil: Onset of action: 3–5 min. Duration of action: 4–6 h. Dose: 12.5–25 mg intravenous bolus; 5 mg–40 mg/h as continuous infusion.

Clonidine: Onset of action: 30 min. Duration of action: 4–6 h. Dose: 150–300 μg intravenous bolus over 5–10 min. Adverse effects: Sedation, rebound hypertension.

Phentolamine: Onset of action: 1–2 min. Duration of action: 10–30 min. Dose: 0.5 mg–1 mg/kg intravenous bolus or 50 μg–300 μg/kg/min intravenous infusion. Adverse effects: Tachyarrhythmias, chest pain.

In hypertensive emergencies, the BP should be aggressively lowered to not more than 25% within minutes to an hour, and then lowered to 160 mm Hg/100–110 mm Hg within the next 2–6 h (Law et al. 2003).

For hypertension emergency, antihypertensive drugs are recommended to be given through intravenous route. ACE inhibitors, ARBs, or beta-blockers may be very

effective in the management of malignant hypertension due to the activation of RAAS by renal ischemia, starting with low dose because of very sensitive to these agents in these patients (Williams et al. 2018).

6.8 Hypertensive Urgencies

Hypertensive urgencies are situations associated with severe BP elevation in otherwise stable patients without acute or impending change in HMOD or target organ dysfunction. Many of these patients have withdrawn from or are noncompliant with antihypertensive therapy. These patients should be treated by reinstitution or intensification of antihypertensive drug therapy and treatment of anxiety as applicable (Williams et al. 2018). While these patients require BP reduction, they usually do not require admission to hospital, and BP reduction is best achieved with oral medication (James et al. 2014). However, these patients need to be monitored closely to make sure that their BP is under control.

Ingestion of sympathomimetics such as meta-amphetamine or cocaine can sometimes induce acute and severe increase in BP, namely, hypertension emergency. It is emphasized that many patients in an emergency department with acute pain or distress may experience an acute elevation in BP that will be restored to normal when the pain and distress are relieved, rather than requiring any specific intervention to lower BP.

Prognosis and follow-up. The survival of patients with hypertension emergencies should be screened for secondary hypertension. After discharge from hospital, when BP has reached a safe and stable level on oral drug therapy, frequent visits in a specialized setting at least monthly until the optimal target BP is achieved and long-term specialist follow-up thereafter (Williams et al. 2018).

6.9 Specific Hypertensive Emergencies

6.9.1 Hypertensive Encephalopathy

This is a symptom complex of severe hypertension with headache, vomiting, visual disturbance, mental status changes, seizure, and papilledema. Cardiac symptoms such as angina, myocardial infarction, and pulmonary edema may occasionally be the main presenting symptoms (Whelton et al. 2017; Williams et al. 2018).

6.9.2 *Hypertensive Left Ventricular Failure*

Symptoms are those of decompensated cardiac failure with shortness of breath, pulmonary edema, lethargy, paroxysmal nocturnal dyspnea, and orthopnea. A cough productive of frothy pink sputum may be reported. Left heart failure can lead to biventricular failure, and there may be signs of peripheral edema and hepatomegaly. An echocardiogram will usually be indicated, and imaging of the coronary arteries may be helpful as reversible cardiac ischemia may improve symptoms and prognosis (Whelton et al. 2017; Williams et al. 2018).

6.9.3 *Acute Aortic Dissection*

Typically presents with acute, severe chest pain with "ripping" or "tearing" characteristics. It may radiate to the back or jaw. Syncope, altered cognition, and anxiety are common neurologic symptoms. A BP difference of >20 mmHg is suggestive but not diagnostic of an acute aortic dissection. Treatment will depend on the portion of the aorta that is affected and may include surgical repair, endovascular stenting, or medical therapy alone. All patients require close monitoring and intensive treatment of BP and pulse, usually in a high-dependency or intensive care unit with appropriate specialist input (Whelton et al. 2017; Williams et al. 2018).

6.9.4 *Preeclampsia*

Preeclampsia is new-onset persistent hypertension, with either proteinuria or evidence of systemic involvement, that occurs in pregnant women after 20 weeks' gestation. Women with preeclampsia require specialist obstetric care. The details of diagnosis and management are beyond the scope of this review. For further information, please see the Best Practice topic on Preeclampsia (Sacks and Campos 2010; Williams et al. 2018).

6.10 Patients with Diabetes and Hypertension

ALLHAT trial showed that long-term use of diuretics induced more new-onset diabetes than CCBs, ARBs, and ACE inhibitors. Diuretics may increase plasma glucose level and even new diabetes risk but did not worse clinical outcomes. The net effect is beneficial to patients at least during the trial (Barzilay et al. 2012).

In 2016, the American Diabetes Association issued Standards of Medical Care in Diabetes, the following recommendations were made in the control of high BP in patients with diabetes:

(1) All diabetic patients with confirmed office-based BP > 140/90 mm Hg were recommended to start antihypertensive pharmacotherapy.
(2) The first-line antihypertensive medication is either ACE inhibitors or ARBs.
(3) If BP did not achieve goal, multiple drug therapy was generally initiated, and thiazide diuretics should be added to the regimen of ACE inhibitor/ARBs at maximal doses.
(4) Serum creatinine/eGFR and serum potassium levels should be monitored frequently in patients receiving ACE inhibitors, ARBs, or diuretics (Williams et al. 2018; ADA 2016). Beta-blockers also have risk of new-onset diabetes, especially used with diuretics. Vasodilating beta-blockers, carvedilol, nebivolol, and labetalol seem not to have unfavorable effects on metabolic profile, especially glucose level or diabetes risk (Wiysonge and Opie 2013).

6.11 Metabolic Syndrome

The prevalence of metabolic syndrome was 34.2% in the United States (Moore et al. 2017). The metabolic syndrome is linked to several other disorders, including nonalcoholic steatohepatitis, polycystic ovary syndrome, certain cancers, chronic kidney disease, Alzheimer's disease, Cushing's syndrome, lipodystrophy, and hyperalimentation.

No clinical proved therapy for metabolic syndrome is available now. Lifestyle modification, with an emphasis on improving insulin sensitivity by means of dietary modification, weight reduction, and exercise constitute the foundation of metabolic syndrome treatment. It has not been clearly defined for the optimal antihypertensive drug therapy for hypertensive patients with metabolic syndrome. No data are currently available that diuretics can worsen cardiovascular and renal outcomes even there is risk for high plasm glucose and new-onset diabetes (Whelton et al. 2017).

ALLHAT trial showed that chlorthalidone was associated with only a small increase in fasting glucose levels (1.5–4.0 mg/dL), and this increase did not translate into increased cardiovascular risk. Similarly, high-dose ARB therapy reduces arterial stiffness in patients with hypertension with the metabolic syndrome but did not provide outcomes data (Barzilay et al. 2012).

Beta-blocker therapy increased diabetes risk by 33% compared with placebo and 22% compared with nondiuretic antihypertensive agents. In looking at specific beta-blockers, the researchers found that atenolol and metoprolol increased diabetes risk by 30% and 34%, respectively, compared with other antihypertensives (Bangalore et al. 2007). The newer vasodilating beta-blockers, such as labetalol, carvedilol, and nebivolol, have shown neutral or favorable effects on metabolic profiles compared

with the traditional beta-blockers but no clinical trials showed that these vasodilating beta-blockers improve cardiovascular outcomes (Zullo et al. 2018; Bell 2004).

6.12 Antihypertensive Treatment in Patients with Acute Ischemic Stroke

It has been reported that patients with cerebral hemorrhage have a history of chronic hypertension accounted for 89%, and these people's systolic BP is generally in 160 mm Hg ~ 240 mm Hg, diastolic BP between 90 mm Hg ~ 160 mm Hg.

Observational studies showed that raised BP on ischemic stroke onset is prognostically associated with excess risk for early adverse events and mortality. Benefit or harm effects were still uncertain within the first 48–72 h to initiation or re-initiation of antihypertensive treatment in ischemic stroke (Whelton et al. 2017).

ACC/AHA 2017 guideline (Whelton et al. 2017) recommended indications for antihypertensive therapy in patients with ischemic stroke:

(1) The first antihypertensive therapy indication was when patient's BP was > 220 mm Hg/120 mmHg and gradually to lower BP by 15% during the first 24 h after onset of stroke (Whelton et al. 2017).
(2) Those eligible for therapy with intravenous tissue plasminogen activator (tPA) but their BP was > 185/110 mmHg. Before tPA, BP should be controlled to less than 180/110 mm Hg. During tPA therapy, BP should be maintained at <180/105 mm Hg at least for the first 24 h (Whelton et al. 2017).

Otherwise, acute and aggressive BP responses within 24-h of stroke onset should be avoided, because the results from randomized controlled trials and recent meta-analyses did not show that effectively controls elevated BP in the acute stage of ischemic stroke could be translated into improvement in the risk of death or dependency (Georgianou et al. 2018).

Maintenance of cerebral perfusion pressure provides physiologic support for the safety of BP reduction in intracerebral hemorrhage (Tamm et al. 2016).

6.13 Antihypertensive Management of Acute Intracerebral Hemorrhage

Antihypertensive indications: Only systolic BP > 220 mm Hg, or MAP > 150 mm Hg, continuous intravenous infusion of antihypertensive agents is indicated. Systolic BP needs to be monitored closely not too lower every 5 min (Whelton et al. 2017). When elevated intracranial pressure is suspected and there are evidences which support the diagnosis, monitor intracranial pressure **and** keep intracranial pressure at 60–80 mm Hg by using intermittent or continuous intravenous infusion of antihypertensive agents.

Recent data from some clinical trials support that intensive BP lowering to levels < 140 mmHg for systolic BP is safe and lowers the risk of hematoma expansion in patients with acute intracerebral hemorrhage (Verdecchia et al. 2016). Intensive BP lowering in patients with acute cerebral hemorrhage is still controversial. The treatment of participants with intracerebral hemorrhage to achieve a target systolic BP of 110 mm Hg to 139 mm Hg did not result in a lower rate of death or disability than standard reduction to a target of 140 mm Hg to 179 mm Hg (Qureshi et al. 2016). If systolic BP is >180 mm Hg or MAP is >130 mm Hg and there is a possibility of elevated intracranial pressure, then consider monitoring intracranial pressure and reducing BP using intermittent or continuous intravenous medications while maintaining a cerebral perfusion pressure >60 mm Hg.

BP goal:

(1) Lowering BP 15–30%; first systolic BP achieved to 180 mm Hg and diastolic BP to 105 mm Hg within first 6 h.
(2) Then BP lowered to the level before hemorrhage or systolic BP $\leq$ 160 mm Hg, diastolic BP $\leq$ 90 mm Hg.
(3) When cerebral edema disappears *and* intracranial bleed is stopped completely, clinical conditions are improved and stable, and BP can be lowered to 135/85 mm Hg or even less to prevent hemorrhage recurrence.
(4) If the patient's systolic BP was more than 180 mm Hg or MAP more than 130 mm Hg with no evidence of elevated intracranial pressure, MAP can be lowered to 110 mm Hg, or target BP to 160/90 mm Hg by intravenous infusion of antihypertensive drugs. The patients should be clinically monitored for every 15 min (Morgenstern et al. 2010).

Studies have shown that BP control in intracranial hemorrhage can be more aggressive: Goal systolic BP was set to less than 160 mm Hg. It's "probably" safe, even systolic BP was lowered to less than 140 mm Hg. From onset of spontaneous intracerebral hemorrhage to 6 h, patients have their systolic BP of 150–220 mm Hg, if their systolic BPs were lowered to a level of less than 140 mm Hg, no reduction in the rate of death or disability. Lowering BP to this level may be harmful (Anderson et al. 2013).

For the patients with ischemic stroke and also tPA candidate: BP goal is <185/110 mm Hg. Once tPA started, maintain BP $\leq$ 180/105 mm Hg (Anderson et al. 2013).

Antihypertensive agents used intravenously in patients with hemorrhagic stroke: Labetalol 5–20 mg, intravenous infusion (2 mg/min), repeated in every 15 min if BP did not achieve to target level (maximum dose of 300 mg/24 h) or nicardipine: intravenous infusion at rate 5–15 mg/h;

or Esmolol: intravenous loading dose 250 μg/kg; maintaining dose 25–300 μg/kg/min.
or Enalapril: 0.625–5 mg by every 6 h, intravenous injection.
or Hydralazine: 5–20 mg intravenous injection by every 30 min; maintaining dose 1.5–5 μg/(kg/min).

or Sodium nitroprusside: 0.1–10 μg/(kg/min).
or Nitroglycerin: 20–400 μg/min.
Daily glyceryl nitrate patch: a daily glyceryl nitrate patch could be safely used to lower BP for 7 days after acute stroke (Lancet ENOS trial) (Bath et al. 2015).

6.14 Secondary Prevention of Stroke (Toschke et al. 2011; Lakhan and Sapko 2009; Progress Collaborative Group 2001; Liu et al. 2009)

The presence of elevated BP increases the risk of recurrent stroke, and antihypertensive drug treatment to lower BP has been linked to a reduction in 1-year recurrent stroke risk by approximately 30%.

Specific antihypertensive agents that have shown benefit include diuretics, ACE inhibitors, and ARBs. Reduction in BP appears to be more important than the choice of specific agents used to achieve this goal. Thus, if diuretic and ACE inhibitor or ARB treatment do not achieve BP target, other agents, such as CCB and/or mineralocorticoid receptor antagonist, may be added (Whelton et al. 2017).

Achieving a systolic BP level <130 mm Hg was not associated with a lower stroke risk, and systolic BP levels achieved <120 mm Hg did not show benefit. Patients with a lacunar stroke treated to a systolic BP target of <130 mm Hg versus 130 mm Hg to 140 mm Hg may be less likely to experience a future intracerebral hemorrhage (Whelton et al. 2017).

6.15 Hemodialysis Patients with Hypertension

Up to 90% of patients with maintenance hemodialysis have hypertension and contribute to adverse cardiovascular outcomes, including the development of left ventricular hypertrophy, left ventricular dilation, heart failure, and death (Agarwal et al. 2003; Amar et al. 2000; Mazzuchi et al. 2000; Takeda et al. 2005; Foley et al. 1996). Recent studies demonstrated that control of BP of hemodialysis patients results in regression of left ventricular hypertrophy and reduces cardiovascular morbidity and mortality (London et al. 2001; Agarwal and Sinha 2009; Heerspink et al. 2009).

A meta-analysis of randomized controlled trials in hemodialysis patients showed that lowering BP was associated with a 29% reduction of cardiovascular events, a 29% reduction of cardiovascular mortality, and a 20% of all-cause mortality (Heerspink et al. 2009).

Extracellular fluid volume is a key determinant of BP in hemodialysis patients (Robert et al. 2018). Achieving "dry weight" should be the first step for BP control (Chobanian et al. 2003). Nonpharmacologic interventions are very important, such

as minimizing sodium intake and ensuring adequate sodium solute removal during hemodialysis (Inrig et al. 2007; Agarwal et al. 2009).

Despite these interventions, pharmacologic therapy is usually required to control BP to goal in hemodialysis patients. Most classes of antihypertensive agents are appropriate, and a combination of agents is typically required.

First-line antihypertension agents: The preferred antihypertensive agents in hemodialysis patients are RAAS inhibitors (either ACE inhibitors or ARBs), particularly those with diabetes mellitus or a history of heart failure (National Kidney Foundation 2005).

RAAS inhibitors are both effective (their documented benefits on left ventricular hypertrophy, pulse wave velocity, and potentially cardiovascular events) and safe. The USRDS Wave 2 Study identified that the use of ACE inhibitors at baseline was associated with a ~30% reduction of loss of residual renal function at 1 year (Moist et al. 2000). Among ACE inhibitors, lisinopril has been proved to effectively lower BP with no increase in intradialytic hypotension (Agarwal et al. 2001).

ARB—Clinical trials have also demonstrated ARBs to be safe and well tolerated in hemodialysis patients and relatively effective at lowering BP. Clinical trial demonstrated that candesartan therapy significantly reduced cardiovascular events and mortality rates in this trial (Takahashi et al. 2006; Suzuki et al. 2008). No single ARB can be dialyzable and once daily. These make ARBs very attractive as first-line antihypertensive drugs in patients with dialysis.

Atenolol is also reported as first-line therapy on the basis of the results of the HDPAL Trial (Agarwal et al. 2014).

Second-line agents: Beta-blockers, particularly in patients with coronary artery disease), combined alpha- and beta-blockers in patients with heart failure, CCBs, and direct vasodilators. A long-acting DHP-CCB, such as amlodipine or felodipine, is second-line therapy (Georgianos and Agarwal 2016). In patients with contraindications to ACE inhibitors or ARBs or cardiac conduction defects, these drugs are sometimes used as first-line agents.

Nocturnal dosing: In order to minimize the risk of intradialytic hypotension, and nocturnal hypertension in many patients with hemodialysis, nocturnal dosing of antihypertensive drugs is recommended.

Monitoring serum potassium concentration: Clinical trials have also shown ACE inhibitor therapy to be relatively safe in hemodialysis with no significant effect on serum potassium and <3% incidence of symptomatic hypotension. Other studies suggest that RAAS inhibitors are associated with potential hyperkalemia due to inhibiting extrarenal potassium loss (Armanini et al. 2007; Garthwaite and Bhandari 2009). Thus, considering the effects of RAAS inhibitors on potassium handling in patients with hemodialysis is uncertain, and monitoring of serum potassium following initiation of RAAS inhibitors is suggested.

Except for fosinopril, most ACE inhibitors are dialyzable. To avoid intra-dialysis hypertension, dialyzable ACE inhibitors should be replaced by un-dialyzable ARBs or other un-dialyzable antihypertensive agents.

Beta-blockers, α-/β-blockers (labetalol, carvedilol, arotinolol (Almarl 10 mg twice a day). Overall, β-blockers are effective and well tolerated in hemodialysis populations.

Water-soluble beta-blockers are mainly excreted through kidney. Water-soluble beta-blockers, such as atenolol, nadolol, and acebutolol, are dialyzable and need to be supplemented for patients with dialysis to prevent arrhythmia following dialysis. Their half-life is prolonged in patients with renal failure. Lipid-soluble beta-blockers (such as metoprolol) are mainly metabolized in liver; these drugs do not need to adjust dose if used in dialysis patients. Labetalol, propranolol, and nadolol are nonselective beta-blockers, which may increase the risk of pre-dialysis, fasting hyperkalemia. Combined α- and β-blockers (labetalol and carvedilol), twice daily, are not significantly removed by hemodialysis and thus provide the added benefit of not requiring additional dosing following hemodialysis.

Alpha-adrenergic blocking agents, such as doxazosin, prazosin, and terazosin. These alpha-receptor blockers can be safely used in hemodialysis patients with no additional dosing. These medications are contraindicated in patients with intradialysis hypotension and cannot be combined with midodrine, a peripheral *alpha*-adrenergic agonist.

CCBs are not removed by hemodialysis and thus do not require additional post-dialysis dosing. In addition, once daily dosing of most CCB makes them attractive for use in hemodialysis patients.

Aldosterone antagonists have not been fully investigated to date in patients with hemodialysis. As most dialysis patients are anuric, hyperkalemia resulting from aldosterone blockade could occur because of its effects on extrarenal potassium handling (such as inhibiting the intestinal elimination of potassium).

Centrally acting sympathetic agonists: methyldopa, guanabenz, guanfacine, and clonidine. These medications are less frequently used to control BP nowadays because of their high side effects such as dry mouth, erectile dysfunction, fatigue, and rebound hypertension. Clonidine is still used to treat difficult-to-treat hypertension in hemodialysis patients. Clonidine patch has been found to be effective and well tolerated without multiple dosing like oral formulation.

Direct vasodilators: hydralazine, isosorbide dinitrate, and minoxidil. Hydralazine and isosorbide dinitrate can be used to lower BP effectively in patients with resistant or refractory hypertension. Even though it has been proved that the combination of hydralazine and isosorbide dinitrate improved heart failure outcomes in African-Americans, this combination has not been tested in dialysis patients (Taylor et al. 2004).

Hydralazine is un-dialyzable, but isosorbide dinitrate can be removed by hemodialysis and requires extra-dosing around dialysis. Because of reflex stimulation of the sympathetic nervous system with vasodilators, these drugs should be administered simultaneously with a β-blocker to offset tachycardia.

Minoxidil is a vasodilator more potent than hydralazine and not extensively removed by hemodialysis. It can be used to treat hypertension once or twice daily

in dialysis patients with resistant hypertension. The most frequent side effect is significant fluid retention, including pleural and pericardial effusion. If fluid retention cannot be controlled with hemodialysis, minoxidil may be discontinued.

Diuretics are not used frequently in patients with hemodialysis. It has been found that diuretics use was associated with lower interdialytic weight gain and lower relative risk of cardiac death in patients with higher residual renal function (Bragg-Gresham et al. 2007). This study supports that diuretics can be helpful at controlling interdialytic weight and BP in patients with higher residual renal function. If used before dialysis, it is not necessary to stop diuretics upon initiation of hemodialysis (Stirnadel-Farrant et al. 2019).

6.16 Treatment of Hypertension After Renal Transplantation

Hypertension after transplantation is often associated with altered circadian BP rhythm with loss of the normal nocturnal BP fall and, in some, a nocturnal BP rise. These changes may return to normal after a longer period of follow-up (Whelton et al. 2017). BP targets change over time in patients with kidney transplantation. Right after transplantation to the first month after transplantation, less stringent BP target such as <160/90 mm Hg and >130/80 mm Hg (avoiding hypotension) is important for maintaining ample organ perfusion and preventing from graft thrombosis (Whelton et al. 2017). After the first month, BP goal is the same as non-transplantation patients in the prevention of target organ damage (Taler et al. 1999). Maintaining BP to goal of less than 130/80 mmHg in patients after renal transplantation, antihypertensive drugs can be selected as the following: CCBs can also improve GFR and kidney survival. Use of calcineurin inhibitor-based immunosuppression regimens after transplantation is associated with a high (70–90%) prevalence of hypertension (Taler et al. 1999).

No trials comparing different BP targets have been performed in post-transplantation patients. BP targets after kidney transplantation should be similar to general population with chronic kidney disease because kidney transplant recipients generally have a single functioning kidney and chronic kidney disease.

Antihypertensive agent selection: First-line drugs are CCBs to minimize graft loss and keep GFR higher. ACE inhibitors are only indicated when additional comorbidities are present such as proteinuria or heart failure after transplantation. If using ACE inhibitors, serum potassium and creatinine should be monitored closely (Whelton et al. 2017).

6.17 Antihypertensive Therapy of Hypertension in Patients with Chronic Kidney Disease

Chronic kidney disease was defined as an estimated GFR less than 60 mL/min/1.73 m^2 and/or urine albumin-to-creatinine ratio of 30 mg/g or more, among three times tests during previous 3 months, two times are higher than normal that can be ascertained as chronic kidney disease (National Kidney Foundation 2002). Clinical features of chronic kidney disease: hyperkalemia, resistant hypertension, and dialysis.

The prevalence of hypertension was much higher in patients with chronic kidney disease than in general populations. It has been reported that the prevalence of self-reported hypertension in patients with chronic kidney disease was 86%, only 29% in the general population (Lash et al. 2009; Egan et al. 2010). Furthermore, BP becomes more difficult to control with advancing chronic kidney disease stage (Cai et al. 2013).

Masked uncontrolled hypertension is more prevalent among individuals with chronic kidney disease, from 40 to 70% (Pogue et al. 2009; Bangash and Agarwal 2009).

Without an assessment of ambulatory or home BP, masked uncontrolled hypertension will be missed, and this group of individuals is at a high risk for both cardiovascular events and initiation of dialysis. Hypertensive patients with chronic kidney disease and masked hypertension whose BP was not controlled to goal had a threefold higher risk of fatal and nonfatal cardiovascular events and increased to nearly fourfold after initiation of dialysis compared with those BP controlled both at home and in the clinic during a median 5.2-year follow-up (Bakris et al. 2000).

Therapy: The aim of medical treatment is to slow the progression of chronic kidney disease by reducing BP and urinary albumin levels (Wright et al. 2002; Kent et al. 2007).

JNC-8 panel members found moderately strong evidence to recommend initial or add-on treatment with ACE inhibitors or ARBs for hypertension in all patients with chronic kidney disease to improve kidney outcomes (James et al. 2014). The recently published AHA/ACC guidelines on hypertension similarly recommend ACE inhibitors or ARBs in chronic kidney disease stage 3 or higher or those patients with albuminuria of at least 300 mg/day or 300 mg/g creatinine on spot check (Whelton et al. 2017).

Hyperkalemia: ACE inhibitors and ARB therapy. When the two classes of drugs are combined, this side effect is even more common. Furthermore, in those with higher baseline potassium and among those with chronic kidney disease stage 3B or more, the incidence of hyperkalemia is even greater (Brenner et al. 2001; Lewis et al. 2001).

Diuretics may have a greater role in patients with advanced chronic kidney disease (Arjun D. Sinha and Rajiv Agarwal. Clinical Pharmacology of Antihypertensive Therapy for the Treatment of Hypertension in CKD. CJASN May 2019).

Beta-blockers: Activation of sympathetic system contributes to hypertension in patients with chronic kidney disease, especially in patients with end-stage kidney disease. Majority of clinical trials excluded patients with end-stage kidney disease or even those with chronic kidney disease. A randomized and controlled clinical trial provided useful data in comparing lisinopril with atenolol in patients with hemodialysis. Thus, atenolol seems to be superior to lisinopril in BP reduction and possibly, in the reduction of a cardiovascular event in this hemodialysis population (Agarwal 1999). As with lisinopril, atenolol can be effectively removed by hemodialysis and thus, the medication should be dosed after hemodialysis. The burden of cardiovascular disease is high in patients with chronic kidney disease, and beta-blocker use is common in this population, however, so far lacking any definitive data to guide beta-blocker prescription in chronic kidney disease. Beta-blockers may not be as first-line antihypertensive agents in this population. However, the HDPAL Trial raised the question of whether beta-blockers may be especially efficacious for managing hypertension and its complications in pre-dialysis chronic kidney disease, and further study is, therefore, warranted.

Even lacking large trials specifically examining antihypertensive effects of DHP-CCBs in chronic kidney disease, DHP-CCBs have been found very effective in lowering BP in a volume-expanded state. In addition, DHP-CCBs are highly protein-bound and removed almost exclusively by hepatic metabolism; therefore, their dosing is not affected by renal dysfunction. DHP-CCBs combined with ACE inhibitors (or ARBs) lower BP more than any of these medications alone.

Mean nocturnal systolic BP predicts the risk of ESKD or death (Minutolo et al. 2011), and non-dipping is associated with the severity of interstitial fibrosis and tubular atrophy by kidney biopsy (Haruhara et al. 2014). Therefore, the findings from Mojon and colleagues that dipping patterns are blunted in individuals with chronic kidney disease is concerning and particularly relevant for management of hypertension in patients with chronic kidney disease (Mojon et al. 2013; Hermida et al. 2014)., At least one medication dosed at bedtime had an adjusted risk for a composite outcome of cardiovascular death, myocardial infarction, and stroke of approximately one-third than that of patients who took all their antihypertensive medications in the morning (adjusted hazard ratio, 0.28; 95% CI, 0.13–0.61) (Hermida et al. 2011).

Based on results from similar trials in patients with diabetes mellitus, the American Diabetes Association included a level A recommendation to administer one or more antihypertensive medications at bedtime in the 2013 guidelines for the care of diabetes mellitus (American Diabetes Associations 2013).

Many conditions disturbed salt excretion in patients with chronic kidney disease, including sodium–chloride handling in distal nephron, endothelial dysfunction or structural as well as functional abnormalities in renal mass, sympathetic nervous system, RAAS. Under these circumstances, high dietary sodium intake not only exacerbates hypertension but may also directly damage renal function in patients with chronic kidney disease, which highlights the importance of salt restriction in the management of hypertension in patients with chronic kidney disease (Fellner et al. 2014; Smyth et al. 2014). The combination of a low salt diet with hydrochlorothiazide

reduced proteinuria by 70% from baseline (Vogt et al. 2008). High salt intake diminishes nighttime dipping of BP in salt-sensitive hypertension. Importantly, obstructive sleep apnea may contribute to nocturnal hypertension as well as BP non-dipping in individuals with chronic kidney disease.

BP goal for hypertensive patients with chronic kidney disease: Expert consensus recommended that a BP goal of less than 130/80 mm Hg for individuals with chronic kidney disease and moderate-to-severe albuminuria (e.g., urine albumin-to-creatinine ratio > 30 mg/g) either with or without diabetes mellitus. The available evidence is inconclusive but does not prove that a BP target of less than 130/80 mm Hg improves clinical outcomes more than a target of less than 140/90 mm Hg in adults with chronic kidney disease (de Carvalho et al. 1977; Shah et al. 1978).

In a cohort of over 650,000 Veteran Americans with chronic kidney disease, mortality was associated with two extreme BP groups (the lowest BP and the highest BP), concluding that in patients with diastolic BP < 70 mm Hg, it may be harmful to try to reduce systolic BP to <130 mm Hg (Kovesdy et al. 2013). Conversely, a high salt diet offsets the antihypertensive efficacy of diuretics and blockers of RAAS as well as their anti-proteinuria efficacy.

Diuretics use in advanced chronic kidney disease

Thiazide-type, thiazide-like diuretics, and loop diuretics: Guidelines recommended switching from thiazides to loop diuretics when GFR falls below 30 ml/min/1.73 m^2. As a class, loop diuretics are relatively short-acting, limited their widespread adoption to treat chronic hypertension compared with readily available thiazide diuretics (Chobanian et al. 2003; Hayashi et al. 2008). The doses of furosemide as high as 250 mg intravenously have been found ineffective (Pitt et al. 1999). Thus, the role of the use of loop diuretics in end-stage kidney disease is marginal at best, being limited to only those patients with significant residual kidney function.

When using diuretics, chlorthalidone or torsemide is often selected due to their long durations of action and greater potency, and chlorthalidone is preferred to metolazone because of its lower cost.

The evidence against thiazide use is weak in advanced chronic kidney disease. The JNC8 (James et al. 2014) and the AHA/ACC recommendations (Whelton et al. 2017) take no position on the use of thiazides versus loop diuretics in chronic kidney disease. The position of the Kidney Disease Improving Global Outcomes guidelines considered that although many clinicians switch from thiazides to loop diuretics, the antihypertensive benefit of thiazides may still be preserved at low levels of GFR. The short-acting effect of many loop diuretics hinders their efficacy in long-term BP control. For all these reasons, clinicians may again turn to thiazide diuretics as an alternative or loop diuretics as add-on in advanced chronic kidney disease (estimated GFR < 30 mL/min/1.73 m^2) where they traditionally have been thought to be ineffective (Kramkowski et al. 2007). Clinical trial proved that the combination of thiazide diuretics (such as Chlorthalidone) with a loop diuretic showed more effective in lowering BP than using each alone in advanced chronic kidney disease (stages 4 and 5), especially in patients with excess volume (Agarwal and Sinha 2012).

Patients in later stages of chronic kidney disease are likely to have resistant hypertension. However, if chronic kidney disease was at stage 3, mineralocorticoid receptor antagonist raised serum potassium by an average of 0.4 mEq/L and serum creatinine levels from a mean 1.5 mg/dl to 1.8 mg/dl. Mineralocorticoid receptor antagonists should not be used in advanced chronic kidney disease (such as chronic kidney disease stage 4 or higher) (Pisoni et al. 2012).

In proteinuric chronic kidney disease and hypertension (Judd and Calhoun 2015): First-line antihypertensive drugs are ACE inhibitors or ARBs (Whelton et al. 2017). Second-line drugs are a DHP-CCB or a diuretic. Diuretics for the patient have signs of volume overload or if we judge that a mineralocorticoid receptor blocker will be urgently necessary to manage uncontrolled proteinuria and wish to lower potassium before starting the mineralocorticoid receptor blocker. Third-line antihypertensive drugs are ACE inhibitors or ARBs + CCBs + diuretics. On three antihypertensive agents including one diuretic, BP remains not to achieve treatment target; this is called resistant hypertension, and mineralocorticoid receptor blocker should be added on. If the presence of chronic kidney disease and impaired renal function pay more attention to plasma hyperkalemia, thiazide or loop diuretics may be used to prevent hyperkalemia.

Spironolactone has been found to effectively lower BP as well as urinary protein. It should be cautioned in patients with baseline serum potassium greater than 4.6 mEq/L. It is contraindicated in acute kidney injury or in creatinine clearances of less than 10 ml/min. Eplerenone is contraindicated when the creatinine clearance falls to less than 30 ml/min. End-stage renal failure is defined as GFR declined to less than 15 ml/min/1.73 m^2. Uncontrolled hypertension has been identified as the second major cause of end-stage renal failure (National Kidney and Urologic Diseases Information Clearinghouse 2010).

Although it is well known that lowering BP protect from cardiovascular disease, the protective effect of BP reduction on kidney function can be less obvious and only restricted to patients with diabetes or chronic kidney disease, in whom there is a faster rate of disease progression (Velázquez et al. 1993). In most hypertensive patients, BP reduction does not very often reduce the development of chronic kidney disease, nor the slow rate of decline in renal function. On the other hand, some, but not all RCTs (randomized clinical trials), have also shown a protective effect of BP lowering on the progression of chronic kidney disease toward end-stage kidney disease in both diabetic and nondiabetic nephropathy (Whelton et al. 2017). RCTs based on clinical outcomes have limitations, such as that these trials largely limited to older and high-risk patients, and over a relatively short duration of follow-up, rarely beyond 5 years.

6.18 Hypertensive Disorders in Pregnancy (Gestational Hypertension)

Gestational hypertension is defined as systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg at two or more measurements after 20 weeks of gestation and returning to normal by 12 weeks' postpartum.

6.18.1 Classifications of Pregnant-Related hypertension (Chobanian et al. 2003)

Chronic hypertension: Pregnancy or before 20 weeks' gestation; most of them are primary hypertension, either predating pregnancy or developing before 20 weeks' gestation. Systolic BP is equal to or more than 140 mm Hg or diastolic BP is equal to or more than 90 mm Hg that persists for >12 weeks' postpartum.

Preeclampsia and Eclampsia
Preeclampsia was defined as systolic BP of 140 mm Hg or more and/or diastolic BP 90 mm Hg or more with proteinuria (more than 300 mg/24 urine collection) after 20 weeks' gestation. Preeclampsia may be progressed to eclampsia. Risk factors for preeclampsia included nulliparous women, multiple pregnancies, women with hypertension more than 4 years who got pregnancy, preeclampsia family history, previous hypertension in pregnancy and renal disease, and new-onset proteinuria after 20 weeks in hypertensive woman.

Prevention of preeclampsia is the main focus of the clinical management of chronic hypertension in pregnancy. However, currently no evidence support that which specific BP targets in pregnancy or specific antihypertensive agents can modify the risk of superimposed preeclampsia in women with preexisting hypertension.

Preeclampsia may develop suddenly in young pregnant women with previous normotension. Prevention of preeclampsia consequence by antihypertensive medications, such as cardiovascular and cerebrovascular diseases, is the most important goal in management of preeclampsia.

Chronic hypertension superimposed preeclampsia occurred in about 25% of pregnancies in women with chronic hypertension. **HELLP syndrome** is a variant of preeclampsia characterized by hemolysis, elevated liver enzymes, and a low platelet count.

Gestational hypertension: Gestational hypertension is a temporary diagnosis with hypertension after gestation of 20 weeks without proteinuria. About 15–45% of women with gestational hypertension may develop preeclampsia or even cause premature delivery and growth retardation relative to mild preeclampsia. Gestational hypertension occurs in the latter half of pregnancy not associated with the systemic features of preeclampsia (e.g., proteinuria). Laboratory tests remain normal and BP decreases postpartum, and then the diagnosis is gestational hypertension. The patients

are more likely to suffer from preeclampsia in those who have early hypertension presentation, previous miscarriage, and previous pregnancy having hypertension (Carey et al. 2018; Chobanian et al. 2003). Although no evidences support that BP control to target level can prevent preeclampsia, antihypertensive medications should still be the choice to prevent the maternal consequence of severe hypertension.

Transient hypertension: Diagnosis made retrospectively. BP returns to normal by 12 weeks' postpartum. It may recur in subsequent pregnancies.

6.18.2 Female Hypertension Patients Are Planning Pregnancy

Female patients with hypertension who are at childbearing age can get pregnant. Hypertension needs to be appropriately controlled by using antihypertensive agents with no fetotoxic before conception. Goal of systolic BP 140 mm Hg to 159 mm Hg/diastolic BP 90 mm Hg to 109 mm Hg is appropriate if there are no other complications. Drugs are indicated for acute elevation of diastolic BP $\geq$ 105 mm Hg; the diastolic BP goal is gradually reduced to 90 mm Hg to 100 mm Hg (American College of Obstetricians and Gynecologists 2013; Regitz-Zagrosek et al. 2011; Committee on Obstetric Practice 2015).

6.18.3 Pregnant-Related Hypertension

Hypertension during pregnancy affects about 6–8% of pregnant women, who are at a higher risk of stroke and complications during delivery. As in women with chronic hypertension, antihypertensive medications should be prescribed with the goal of preventing maternal consequences of severe hypertension, because there is no evidence that targeted BP control prevents preeclampsia (Whelton et al. 2017; Williams et al. 2018; American College of Obstetricians and Gynecologists 2013; Regitz-Zagrosek et al. 2011; Committee on Obstetric Practice 2015).

Approximately, 15–45% of women initially diagnosed with gestational hypertension will develop preeclampsia, and this is more likely with earlier presentation, previous miscarriage, and previous hypertensive pregnancy, as well as higher BP. Preeclampsia can damage pregnant women's organs and be very dangerous to pregnant women's healthy if it isn't properly treated.

Besides high BP, preeclampsia can also cause proteinuria, which is a sign of kidney damage, headaches, changes in vision, upper abdominal pain, and decreased urine output. If a pregnant woman is suspected of having preeclampsia, antihypertensive medicines must be prescribed to control BP and prevent complications. Controlling high BP is an important part of the treatment for preeclampsia. Medications can help treat it, but the only way to cure the disorder is to deliver a baby. Depending

on the severity of symptoms and how near to term, the doctor may decide when necessary to deliver a baby right away (Whelton et al. 2017; Williams et al. 2018; American College of Obstetricians and Gynecologists 2013; Regitz-Zagrosek et al. 2011; Committee on Obstetric Practice 2015).

Additionally, much of the obstetric literature focuses on diastolic BP rather than systolic BP in contrast to hypertension guidelines in adults which emphasizes the importance of systolic BP.

During pregnancy, the challenge is to decide when to use antihypertensive medications and what level of BP to target. Untreated mild-to-moderate hypertension is unlikely to lead to unfavorable long-term maternal outcomes during the 9 months of pregnancy. In this setting, antihypertensive agents are mainly used to prevent and treat severe hypertension; to prolong pregnancy safely for as long as possible, thereby maximizing the gestational age of the infant; and to minimize fetal exposure to medications that may have adverse effects (Whelton et al. 2017; Williams et al. 2018; Chobanian et al. 2003; American College of Obstetricians and Gynecologists 2013; Regitz-Zagrosek et al. 2011; Committee on Obstetric Practice 2015).

6.18.4 Therapeutic Indications

(1) Severe hypertension (defined as ≥160/110 mm Hg, rather than stages as most guidelines).
(2) Preeclampsia.
(3) Eclampsia.

No antihypertensive has been proven safe for use during the first trimester. Drug therapy was indicated for uncomplicated chronic hypertension when diastolic BP was ≥100 mm Hg (Korotkoff V). Treatment at lower levels may be indicated for patients with diabetes mellitus, renal disease, or target organ damage.

6.18.5 Treatment of Pregnancy-Related Severe Hypertension

Pregnancy-related severe hypertension was defined as BP > 160/110 mm Hg for a pregnant woman. These patients are at risk of intracerebral hemorrhage, encephalopathy, and eclampsia. Risk of maternal death can be decreased by using treatment with parenteral agents to lower mean arterial pressure by 25% over minutes to hours, and then further lower BP close to 160/100 mm Hg over subsequent hours (Whelton et al. 2017; Williams et al. 2018; American College of Obstetricians and Gynecologists 2013; Regitz-Zagrosek et al. 2011; Committee on Obstetric Practice 2015).

In patients with severe pregnant-related hypertension, full functional autoregulation for placental blood flow has not been established yet, and aggressive BP lowering may cause fetal distress at the situation. Intravascular volume may also be depleted in

these patients who are at an increased risk of hypotension if aggressive lowering BP. Antihypertensive medications such as parental labetalol, hydralazine, or oral nifedipine should be started with a lower dose to minimize maternal and fetal adverse effects (Whelton et al. 2017; Williams et al. 2018; American College of Obstetricians and Gynecologists 2013; Regitz-Zagrosek et al. 2011; Committee on Obstetric Practice 2015).

In women with preeclampsia, consideration should be given to initiating agents for the treatment of acute severe hypertension at lower doses, because these patients may be intravascularly volume depleted and may be at increased risk for hypotension. A recent meta-analysis of 24 trials (2949 women) in which different antihypertensive drugs were compared for the treatment of severe hypertension in pregnancy concluded that there is insufficient data to favor one agent over another, although others have concluded that agents other than parenteral hydralazine (e.g., parenteral labetalol or oral nifedipine) are preferable because of reduced maternal and fetal adverse effects (Whelton et al. 2017; Williams et al. 2018; American College of Obstetricians and Gynecologists 2013; Regitz-Zagrosek et al. 2011; Committee on Obstetric Practice et al. 2015; Veerbeek et al. 2015).

6.18.6 BP Goals

Systolic BP $\leq$ 140 mm Hg and diastolic BP $\leq$ 90 are acceptable. Mild hypertension was defined as systolic BP 140–159 mm Hg/diastolic BP 90–109 mm Hg. No evidence-based data are available for management of mild-to-moderately elevated BP in pregnancy ($\leq$160/110 mm Hg), either chronic or pregnancy-induced (Whelton et al. 2017; Williams et al. 2018; American College of Obstetricians and Gynecologists 2011, 2013; Committee on Obstetric Practice 2015).

Therapy is recommended in the United States for a BP of $\geq$160/105 mm Hg^2 but no treatment target set. In Canada, the threshold for initiation of antihypertensive therapy is different, for non-severe hypertension in pregnancy (systolic BP 140–159 mm Hg and/or diastolic BP 80–109 mm Hg). BP targets: a diastolic BP of 85 mm Hg. A similar target could be considered for pregnant women with preeclampsia. Severe hypertension (systolic BP $\geq$ 160 mm Hg and/or diastolic BP $\geq$110 mm Hg) requires urgent antihypertensive therapy to reduce maternal, fetal, and newborn adverse outcomes (Veerbeek et al. 2015).

When the diagnosis is preeclampsia, the factors that influence the use of antihypertensive therapy are the gestational age as well as the level of BP. At term, women with preeclampsia are likely to be delivered, treatment of hypertension (unless severe) can be delayed, and BP can be reevaluated postpartum. If preeclampsia develops remote from term, severe hypertension should be treated, and BP can usually be safely lowered to 140/90 mm Hg with oral medications, usually in the range of 140–155/90–105 mm Hg (Whelton et al. 2017; Williams et al. 2018; American College of Obstetricians and Gynecologists 2013; Regitz-Zagrosek et al. 2011; Committee on Obstetric Practice 2015; Butalia et al. 2018).

6.18.7 The Choice of Antihypertensive Agents

Only a small proportion of currently available drugs have been adequately evaluated in pregnant women, and many others are contraindicated.

First-line of antihypertensive agents used in pregnant-related hypertension: methyldopa, labetalol, and long-acting nifedipine (Butalia et al. 2018). The combination of nifedipine with magnesium sulfate may cause excessively low BP and negative effects on the patient's muscle and nerves. Hydralazine is another drug that can be given orally or intravenously (very severe cases of hypertension) to control hypertension in pregnancy. Its main side effect is tachycardia arrhythmia (Magee et al. 2003).

The American College of Obstetricians and Gynecologists has issued a task force report, including recommendations for prevention, taking aspirin in selected cases, and treatment of severe hypertension with magnesium in patients with hypertension in pregnancy (American College of Obstetricians and Gynecologists 2013). A report detailing treatment of hypertensive emergencies during pregnancy and postpartum has also been released (Regitz-Zagrosek et al. 2011; Committee on Obstetric Practice 2015).

Methyldopa, starting dosage: 750 mg orally loading dose, then 250–500 mg PO twice a day; maximum dose: 2000 mg/day in up to 4 doses. Safety after the first trimester has been well documented, including 7 years follow-up of offspring.

Labetalol, direct Vasodilators, starting dose: 100–200 mg orally bid; maximum dose: 1200 mg/day in up to 4 doses. The medication may be associated with fetal growth restriction. For intravenous infusion: 1–2 mg/min. Because of a lower incidence of maternal hypotension and other adverse effects, labetalol is replacing hydralazine. It is avoided in women with asthma or with congestive heart failure.

Hydralazine is a director vasodilator. Long experience of safety and efficacy is in the treatment of pregnant-related hypertension. The greatest use is in the urgent control of severe hypertension or as a third-line agent for multidrug control of refractory hypertension. It has been widely used for chronic hypertension in the second and third trimesters, but its use has been supplanted by agents with more favorable adverse effect profiles. A meta-analysis of the use of intravenous hydralazine in severe hypertension in pregnancy concluded that parenteral labetalol or oral nifedipine were preferable first-line agents, with hydralazine as a suitable second-line agent (Butalia et al. 2018).

Hydralazine is effective orally, intramuscularly, or intravenously (bolus or infusion). Parenteral administration is useful for rapid control of severe hypertension, starting dose: 10 mg orally, 4 times a day; maximum dose: 200 mg/day in up to 4 doses. Few controlled trials and long experience with few adverse events are documented. It is useful in combination with sympatholytic agent. Hydralazine may cause neonatal thrombocytopenia. Usually, 5 mg is given through intravenous or intramuscular injection, then 5–10 mg for every 20–40 min; once BP controlled, it is repeated for every 3 h. For intravenous infusion: 0.5–10.0 mg/h; if not satisfied with BP goal, 20 mg intravenous injection or 30 mg orally taken, or consider another class drug

(American College of Obstetricians and Gynecologists 2013; Regitz-Zagrosek et al. 2011; Butalia et al. 2018).

Hydralazine has been safely used in all trimesters of pregnancy. Adverse effects of hydralazine are very frequently observed, such as headache, nausea, flushing, or palpitations. These adverse effects are mostly due to excessive vasodilation or secondary activation of sympathetic system. In rare cases, chronic use can cause hydralazine-induced lupus syndrome, other immunologic reactions as well as a pyridoxine-related polyneuropathy. Intravenous hydralazine has been successfully used for severe hypertension in later pregnancy but with more maternal and perinatal adverse effects than intravenous labetalol or oral nifedipine, such as maternal hypotension, cesarean section, and placental abruption (American College of Obstetricians and Gynecologists 2013; Regitz-Zagrosek et al. 2011; Butalia et al. 2018). Apgar score <7 and oliguria.

Apgar scores <7, and oliguria. The Apgar score was developed in 1952 by Virginia Apgar, an obstetric anesthesiologist, and has become a standard tool in quick, overall assessment of well-being of newborn babies. Apgar scores range from 0 to 2 for each condition with a maximum final total score of 10.

Some postnatal care must be applied to the newborn baby according to Apgar score, Score at one minute, score 7 to 10: routine post-delivery care; score 4–6, need some assistant breathing; score <4, require prompt life-saving measures. Apgar score at 5 min: score 7–10 as normal, score <7, continuously monitoring the baby is necessary and reexamined the score every 5 min until stable (up to 20 min) (Caughey 2017).

Long-acting nifedipine, a slow-release preparation, starting dose: 20–30 mg taken orally; maximum dose: 120 mg/day in one dose. It may inhibit labor and have synergistic action with magnesium sulfate in BP lowering. Little experience with other CCBs has been recorded (Chobanian et al. 2003).

Hydrochlorothiazide: Hydrochlorothiazide may be continued during pregnancy if it has been taken before conception; 12.5–25.0 mg daily, may minimize untoward metabolic effects, such as impaired glucose tolerance and hypokalemia. Majority of controlled studies were performed in normotensive pregnant women rather than in hypertensive patients; can cause volume contraction and electrolyte disorders; may be useful in combination with methyldopa and vasodilator to mitigate their compensatory fluid retention (American College of Obstetricians and Gynecologists 2013; Regitz-Zagrosek et al. 2011; Committee on Obstetric Practice 2015; Bozzo et al. 2009).

Hydrochlorothiazide, triamterene, and amiloride are not teratogenic according to a small number of case reports (Bozzo et al. 2009).

Spironolactone is not recommended because of its antiandrogenic effects during fetal development, although this was not borne out in an isolated case.

6.18.8 Contraindications

First-trimester use of ACE inhibitors and ARBs should be avoided since first-trimester exposure to ACE inhibitors has been associated with a greater incidence of malformations of the cardiovascular and central nervous systems. It may be best to counsel women to switch to alternate agents while attempting to conceive, in other terms, need to replace antihypertensive drugs with either methyldopa, or labetalol, or hydralazine or long-acting nifedipine or combined for at least 3 months before attempting to conceive (Regitz-Zagrosek et al. 2011; Committee on Obstetric Practice 2015; Butalia et al. 2018).

ACE inhibitors and ARBs lead to fetal loss in animals; human use associated with cardiac defects, fetopathy, oligohydramnios, growth restriction, renal agenesis, and neonatal anuric renal failure, which may be fatal. ACE inhibitors and ARBs are fetotoxic and not approved for use before and during pregnancy. Both ACE inhibitors and ARBs have been shown fetotoxic in the second and third trimesters of pregnancy. For ARBs, case reports with effects have been published similar to ACE inhibitors (Committee on Obstetric Practice 2015; Veerbeek et al. 2015).

Beta-receptor blockers, depending on specific agent, may decrease uteroplacental blood flow; impair fetal response to hypoxic stress; risk of growth restriction when started in the first or second trimester (atenolol); and may be associated with neonatal hypoglycemia at higher doses. Propranolol is a beta-blocker that lowers BP by reducing heart rate and the amount of blood pumped by the heart. It's been associated with birth defects, such as fetal bradycardia, or slow heartbeat, slowed development, and neonatal hypoglycemia (Committee on Obstetric Practice 2015; Veerbeek et al. 2015).

Generally, diuretics such as furosemide and hydrochlorothiazide should be avoided during pregnancy.

6.18.9 The Principal in Management of Pregnant-Related Hypertension

JNC-7 has proposed the principal in management of pregnant-related hypertension (Chobanian et al. 2003). First, making correct diagnosis of gestational hypertension or preexisting hypertension; second, classified as mild hypertension (BP 140–159/90–109 mm Hg) and severe hypertension ($\geq$160/110 mm Hg) instead of stage (as JNC7, 8); third, in contrast to hypertension guidelines in adults, which emphasize the importance of systolic BP, much of the obstetric literature focuses on diastolic rather than systolic BP, in part because of the lack of clinical trials to support one approach versus another.

6.18.10 Preeclampsia

Preeclampsia, defined as gestational hypertension plus significant proteinuria (≥0.3 g per 24 h), is a multisystem disorder that can affect maternal brain, kidneys, liver, and the blood clotting system (Duley 2009). Preeclampsia has implications in future maternal health (Carty et al. 2010), particularly in an increased risk of cardiovascular disease (Chen et al. 2014; Scantlebury and Hayes 2014), and mortality, with the prevalence of 0.2–9.2% worldwide (Carty et al. 2010; Umesawa and Kobashi 2017). Antihypertensive therapy is mandatory for high BP control in preeclampsia (Duley 2009), including methyldopa, nifedipine, hydralazine, and labetalol. These antihypertensive drugs allow the prolongation of gestation, thereby decreasing fetal and maternal adverse outcomes.

Diagnostic criteria for preeclampsia

(1) BP is ≥140 mm Hg systolic or ≥90 mm Hg diastolic on two occasions at least 4 h after 20 weeks of gestation in a woman with a previous normal BP.
(2) BP is ≥160 mm Hg systolic or ≥110 mm Hg diastolic, hypertension can be confirmed within minutes to facilitate timely antihypertensive therapy.
(3) Proteinuria: protein in urine ≥300 mg/24-h urine collection, or urinary protein/creatinine ratio of 0.3 mg/dL. If no proteinuria, new-onset hypertension with newly occurred thrombocytopenia (platelet count less than 100,000/microliter), renal insufficiency (serum creatinine concentration >1.1 mg/dL or doubling of serum creatinine concentration in absence of other renal disease), and impaired liver function (transaminases increased to twice normal concentration) (Townsend et al. 2016).

Preeclampsia complicates 2–8% of all pregnancies, contributes to 15% of preterm deliveries, is the cause of 9–26% of global maternal mortality, and maternal and neonatal morbidity. Early confirming diagnosis is very important to treat before target organ damage and to prevent complications.

New tools for early detection, prevention, and management of preeclampsia have the potential to revolutionize practice in the coming years.

For women with a medical history of early-onset preeclampsia and preterm delivery at least less than 34 0/7 weeks of gestation or preeclampsia in more than one prior pregnancy, initiating the administration of daily low-dose (60–80 mg) aspirin beginning in the late first trimester is suggested. The updated Cochrane Review identified 51 trials with over 36,500 pregnant women, evaluating antiplatelet agents, principally low-dose aspirin, for the prevention of preeclampsia; the results showed a small reduction in the incidence and morbidity of preeclampsia and no evidence of acute risk, although long-term fetal effects could not be excluded (Rolnik et al. 2017; Askie et al. 2007; Tong et al. 2017).

6.18.11 *Hypertension Arising During Pregnancy or in the Puerperium*

The lowest postnatal hypertension risk of 33% was found in patients with antenatal preeclampsia (proteinuric hypertension), then severe antenatal hypertension (>160/100 mm Hg), hypertension requiring antenatal treatment, to the highest risk of >75% in patients with pre-termed delivery (before 37 weeks of gestation) triggered by maternal hypertensive disease (American College of Obstetricians and Gynecologists 2013; Committee on Obstetric Practice 2015; ACOG 2018).

The perceived advantages of starting treatment in the early postnatal period are that episodes of severe hypertension will be reduced and discharge to the community will not be delayed unnecessarily.

Nice guidelines for postpartum care are recommended that BP should be measured within 6 h of delivery. All maternal women should be aware of preeclampsia manifestations and how to urgently contact an appropriate health professional (ACOG 2018; NICE guideline 2019). New patients should have a thorough history taken and physical examination, full blood count, electrolytes, and liver function tested to exclude impending eclampsia (American College of Obstetricians and Gynecologists 2013; Carty et al. 2010; Tong et al. 2017; Lewis 2003; National Institute for Health and Clinical Excellence 2010).

Regardless of whether antihypertensive agents are prescribed immediately following delivery, all women should be closely monitored with regular recordings of BP and fluid balance. It is anticipated that the introduction of modified obstetric early warning system charts might facilitate the detection of women who require further medical review (Lewis 2003).

Follow-up: Once discharged, BP should be measured on alternate days for the first 2 weeks and refer for medical review if two measurements >150/100 mmHg are obtained more than 20 min apart. If patients have preeclampsia symptoms or if patient's BP is more than 160/100 mm Hg, hospital review will be required. In most postnatal hypertension women, antihypertensive therapy should continue for at least 2 weeks and for some with early and severe hypertension, antihypertensive therapy should continue beyond 6 weeks. These patients may need further medical review to investigate their underlying causes. When BP achieves the levels of 130–140/80–90 mm Hg, the dose of antihypertensive agents can be reduced. If medication is required beyond 6 weeks, then further medical review should be arranged to investigate the possibility of an underlying cause. The 6-week postnatal visit is an opportunity to establish the diagnosis and to discuss implications for future pregnancies. All women who have had a diagnosis of preeclampsia should have their blood pressure measured and the urine tested for proteinuria (American College of Obstetricians and Gynecologists 2013; Committee on Obstetric Practice 2015).

6.18.12 Postnatal Hypertension

To advise women with hypertension who wish to breastfeed that their treatment can be adapted to accommodate breastfeeding and that the need to take antihypertensive medication does not prevent them from breastfeeding (NICE guideline 2019).

Enalapril could be offered to treat hypertension in women during the postnatal period (Hypertension et al. 2013), with appropriate monitoring of maternal renal function and maternal serum potassium (NICE guideline 2019). For black African women or Caribbean family origin with hypertension during the postnatal period, antihypertensive treatment could start with nifedipine or amlodipine if the woman previously used the medication to successfully control her BP. The NICE guideline on hypertension in adults recommended (NICE guideline 2019), if BP did not achieve the goal with a single medicine in the postnatal period in women with hypertension and try the combination of nifedipine (or amlodipine) with enalapril. If the combination still did not achieve BP goal or not tolerated, labetalol or atenolol can be added to the combination. Where possible, avoid using diuretics or ARBs to treat hypertension in women with postnatal hypertension who are breastfeeding or expressing milk (NICE guideline 2019).

When treating women with antihypertensive medication during the postnatal period, drugs are taken once daily when possible. Diuretics or ARBs are better to be avoided in women in the postnatal period who are breastfeeding or expressing milk (NICE guideline 2019).

In the treatment of women with postnatal hypertension who are not breastfeeding or not planning to breastfeed, NICE guideline for postpartum care recommended that BP should be measured within 6 h of delivery, be aware of preeclampsia symptoms, and how to urgently contact an appropriate health professional for all postnatal women.

NICE postnatal guidance (National Institute for Health and Clinical Excellence 2006) recommends medical review if diastolic BP is more than 90 mm Hg sustained over 4 h, associated with any symptoms of preeclampsia. Any new patients should have a thorough medical history taken and physical examination and laboratory tests to exclude eclampsia or HELLP syndrome.

NICE guidance (National Institute for Health and Clinical Excellence 2010) recommends that the platelet count, transaminases, and serum creatinine are checked 48–72 h after birth, or step down from Level 2 care, and only repeated thereafter if abnormal or clinically indicated.

Given that up to 44% of eclampsia fits occur in the postnatal period, usually within first 48 h following delivery (Douglas and Redman 1994). Hospitalized women with preeclampsia are better to delay discharge until the day when their BP is less than 150/100 mm Hg.

In situations where hypertension predates the pregnancy, it is advisable to discontinue methyldopa following delivery and switch back to antihypertensive medications and dose used at the pre-pregnant stage. If wishing to breastfeeding, or to taking any new drugs, the best way is to get advice from a pharmacologist before delivery.

Women taking diuretics should consider an alternative if they wish to breastfeed their babies.

There is a paucity of data available in the treatment of postnatal hypertension. Cautions must be taken because most subjects with postnatal hypertension may have to breastfeeding, and the antihypertensive drugs may appear in breast milk and have effects on lactation, and then on neonates.

The following antihypertensive medications can be selected for postnatal hypertension therapy and safely used in breastfeeding women as well.

Beta-blockers: The most commonly used are labetalol and atenolol. The high lipid solubility of beta-blockers, such as metoprolol, can be concentrated in breast milk with a possibility to transfer to neonate. Data are so far not enough to make the conclusion. Respiratory symptoms should be monitored after commencing a beta-blocker since respiratory symptoms may appear after a few days of beta-blockers. As long as respiratory symptoms are identified, the beta-blocker should be changed to an alternative medication.

Labetalol: 100–200 mg four times daily, contraindication: asthma, cardiac failure, bradycardia, II–III degree atrioventricular block. Side effects: postural hypotension, headache.

Atenolol: 25–100 mg orally taken, daily contraindication: Third-degree atrioventricular block, side effects: urinary hesitancy, fatigue.

CCBs: Nifedipine: 10–40 mg twice daily, contraindications: advanced aortic stenosis.

Amlodipine: 5–10 mg daily.

ACE inhibitors: Enalapril: 5–20 mg twice daily, avoid in acute kidney injury.

Breastfeeding: Antihypertensive agents can be used in breastfeeding women: Labetalol 100 mg bid or 200 mg once a day. Nifedipine 10–40 mg bid, Enalapril, 5–20 mg bid. Captopril, Atenolol, 25–50 mg daily. Metoprolol. Nifedipine (slow release) is the most commonly prescribed CCBs for breastfeeding women with hypertension and can initially be prescribed at a dose of 10–20 mg twice daily. Once BP is controlled, prescriptions may be converted to a sustained-release preparation of 30–60 mg daily. A second-line alternative is amlodipine 5–10 mg once daily.

The antihypertensive drugs with insufficient evidence can be safely recommended to infants: ARBs, amlodipine, and ACE inhibitors other than captopril and enalapril. NICE 2019 guideline (NICE guideline 2019) mentioned the opinion from MHRA (Medicines and Healthcare products Regulatory Agency: ACE inhibitors and angiotensin II receptor antagonists: recommendations on how to use for breastfeeding, Drug Safety Update May 2009, vol 2 issue 10: 3. Published 11 December 2014) that ACE inhibitors and ARBs are generally not recommended to breastfeeding mothers, but ACE inhibitors, captopril, enalapril, or quinapril, have been recommended to breastfeeding mother but the infant should be monitored carefully to avoid infant hypotension (NICE guideline 2019).

Treatment for hypertension Emergency in postnatal hypertension: Hydralazine, 5–10 mg intravenously or intramuscularly, repeated if necessary. Labetalol, 20 mg intravenously repeated when it is necessary at 20 min interval.

Nifedipine 10 mg sublingual, repeated when it is necessary at 20 min interval (NICE guideline 2019).

6.19 Resistant Hypertension

Resistant hypertension is typically defined as having an uncontrolled BP (≥140/90 mm Hg) on three or more antihypertensive medications, including a diuretic. An estimated prevalence is about 10–20% of treated hypertensive patients. The mechanism is proposed as persistent excess fluid retention (Calhoun et al. 2008).

Treatment: A standardized 3-drug regimen for resistant hypertension includes ACE inhibitors or ARBs, amlodipine, and the thiazide diuretics such as chlorthalidone or thiazide-like diuretic such as indapamide. It should be emphasized that intensification of diuretic therapy is far more important, especially with the combined use of chlorthalidone and spironolactone.

Use of spironolactone as the fourth agent for treating resistant hypertension: Volume overload and aldosterone excess have been noticed as a common cause of resistant hypertension. Multiple studies indicate that true, classical primary aldosteronism is present in ≈20% of patients. Given that excess aldosterone is a common cause of antihypertensive treatment resistance, mineralocorticoid receptor antagonists block the action of aldosterone. These agents are especially effective for the treatment of resistant hypertension (Calhoun et al. 2008; Acelajado et al. 2019).

6.20 Refractory Hypertension

Patients with refractory hypertension were identified after routine clinical follow-up of ≥3 visits for ≥6 months, had uncontrolled BP in spite of being adherent to a regimen of >5 classes of antihypertensive agents, including chlorthalidone 25 mg daily and mineralocorticoid receptor antagonists (spironolactone, 25 mg daily, ≤50 mg per day or eplerenone, 50 mg bid) without evidence of underlying secondary causes of hypertension. Its prevalence is approximately 5% of patients with uncontrolled resistant hypertension. This is a recently proposed phenotype of antihypertensive treatment failure and an extreme subtype of resistant or difficult-to-treat hypertension (Acelajado et al. 2019).

Mechanism: Refractory hypertension may be more likely attributable to heightened sympathetic output as opposed to inappropriate fluid retention (Acelajado et al. 2019).

Treatment: Effective sympathetic inhibition, either with medications or device-based approaches (Acelajado et al. 2019). To first select chlorthalidone because its superiority over hydrochlorothiazide to reduce BP, particularly nighttime high BP, is likely related to its longer half-life. However, chlorthalidone use is more frequently associated with adverse metabolic effects, particularly hypokalemia and

hyponatremia than with hydrochlorothiazide, so it is important to monitor electrolytes regularly when prescribing chlorthalidone. Side effects of spironolactone: most frequent side effects are gynecomastia or hyperkalemia. The risk of spironolactone-induced hyperkalemia is low in patients with normal renal function, particularly if they are already receiving chlorthalidone, which promotes potassium excretion (Bobrie et al. 2012). However, risk of hyperkalemia increases with declining renal function. Gynecomastia can be minimized or avoided by eplerenone replacement of spironolactone (Acelajado et al. 2019).

Sequential therapy of diuretics has been proposed for refractory hypertension: ARB/ACE inhibitors + amlodipine + chlorthalidone + spironolactone + furosemidum (10–20 mg bid) + amiloride (10–20 mg once a day) (Bobrie et al. 2012). This regimen has not been proved able to improve BP reduction as well as clinical outcomes by clinical trial.

6.21 Secondary Hypertension

All patients with new hypertension and resistant hypertension should be ruled out of secondary hypertension.

6.21.1 Renovascular Hypertension

Renovascular hypertension is defined as an elevated BP caused by renal hypoperfusion, usually resulting from anatomic stenosis of the renal artery and activation of RAAS. Renovascular disease includes renal artery stenosis, renovascular hypertension, and ischemic nephropathy (azotemic renovascular disease). Renovascular hypertension accounts for 1–2% of all cases of hypertension in the general population and 5.8% of secondary hypertension, but it plays a major role in treatable causes of hypertension in young individuals (Samadian et al. 2017).

It is often with clinical manifestations, including progressive loss of kidney function from ischemic nephropathy, and recurrent episodes of flash pulmonary edema (meaning acute/abrupt onset pulmonary edema). However, renal artery stenosis can also be completely asymptomatic.

Renovascular hypertension is the most frequent form of secondary hypertension. The risk of cardiovascular events and death risk increase 16% per year, six times more than the risk of end-stage renal disease in patients of 67 years of age and older (Kalra et al. 2005).

Causes: Renovascular disease remains a major cause of secondary and treatment-resistant hypertension. Major causes of renovascular disease are renal artery stenosis secondary to atherosclerosis and fibromuscular dysplasia. Other common causes are Takayasu's arteritis and mid-aortic syndrome (abdominal coarctation). Other less common forms of acquired renovascular hypertension are renal artery trauma or

thrombosis, thrombosis secondary to anti-thrombin deficiency, Kawasaki disease, and an anastomotic stenosis, as is seen occasionally in renal transplants, arterial dissection, stent occlusion, and embolic disease can produce the same syndrome, congenital or acquired causes including arterial hypoplasia or aplasia; neurofibromatosis and Williams syndrome which includes manifestations of supravalvular aortic stenosis, peripheral vascular stenosis (particularly in the subclavian and renal arteries), hypercalcemia, and elfin facies, tuberous sclerosis, and tumors.

Stenosis: Renal artery stenosis will be diagnosed when a main renal artery with >75% narrowing of the diameter or a luminal narrowing >50% with a post-stenotic dilatation. Hypertension is not a necessary clinical manifestation for patients with renal artery stenosis. Renovascular hypertension results from ischemic nephropathy, and surgical removal of small kidneys only can result in BP normalization in 25% of these patients, indicating that 75% of them are persistent damage. The following conditions can cause severe deterioration of renal function referred to ischemic nephropathy, including renovascular stenosis affected entire renal parenchyma such as bilateral stenosis, stenosis to a solitary kidney, as well as atherosclerotic renal artery disease progressed to complete occlusion. These constitute a frequent cause of end-stage renal disease with a poor prognosis even after renal transplantation therapy. That is why very important in early detection and management.

Atherosclerosis accounts for nearly 90% of renovascular hypertension. In selected populations displaying atherosclerotic disease of other vascular territories, prevalence is around 10–30% (Murphy and Lloyd 2013).

Fibromuscular dysplasia is a noninflammatory, nonatherosclerotic vascular disease that preferentially affects small- to medium-sized arteries. Most FMD lesions are caused by medial fibroplasia, consisting of banded lesions in the mid-portion of the renal arteries. Screening potential kidney donors with angiography showed that such lesions are often asymptomatic and can be detected in 3–6% of normotensives (Neymark et al. 2000). Screening patients with resistant hypertension found that the prevalence of fibromuscular dysplasia was 16% (Garovic and Textor 2005). Fibromuscular dysplasia mostly affected women at the age between 15 and 50 years. Renovascular hypertension was only overt when hemodynamic severity reached a sufficient degree (Garovic and Textor 2005).

Screening: Renal artery stenosis must be considered in any patient with a history of severe or resistant hypertension, especially in those associations of a decline in renal function or significant atherosclerosis in other vascular territories. Feature suggestive of renal artery stenosis includes (1) abrupt onset of hypertension at a relatively young age (30 years old) or older age (>50 years old), (2) worsening control of previously well-controlled hypertension, (3) recurrent episodes of flash pulmonary edema, (4) renal failure precipitated by initiation of antihypertensive therapy, especially ACE inhibitors or ARB, (5) unexplained kidney failure, and (6) unilateral atrophic kidney (Herrmann and Textor 2018).

Ascertain tests for renal artery stenosis: Simple greyscale ultrasound studies, catheter angiography, CT angiography, MR angiography, captopril isotope renography, the captopril test, and Doppler ultrasound.

Therapy: The purpose of therapy in patients with renal artery disease is to control blood pressure and preserve renal function. If hypertension control cannot be achieved or a decline in renal function is evident, revascularization should be more strongly considered (endovascular angioplasty and surgery) (Badila et al. 2014).

Angioplasty: Renal artery stenosis is a potentially reversible cause of hypertension. Randomized controlled trials comparing medical therapy with medical therapy and renal artery stenting have failed to show a benefit for renal artery stenting. Angioplasty is still the first-line treatment for renovascular stenosis secondary to fibromuscular dysplasia. Renal artery stenting is presently very often used in the treatment of atherosclerotic renal artery stenosis, but its clinical efficacy is inconsistent. Renal denervation is promising in the treatment of drug-resistant hypertension, and technical standard and clinical outcome need to be confirmed before it becomes clinical routine (Minocha 2016; Gornik et al. 2019).

The renal percutaneous transluminal angioplasty is an accepted and durable treatment strategy when the etiology of renovascular hypertension is fibromuscular dysplasia. Currently, correction of renal arterial inflow stenosis is reserved for patients with renal artery stenosis of >80% with a significant trans-lesional pressure gradient; difficult to control BP with more than three antihypertensives, especially in younger patients; and those with truncal rather than ostial stenosis; patient with a rapid deterioration of renal function; flash pulmonary edema; and post-transplant renal artery stenosis (Mohan and Bourke 2015; Mousa et al. 2017).

The rate of restenosis has been reported in the range of 5–11% after 1 year (Safian and Textor 2001). Interventional therapy is still controversial for atherosclerotic renal artery stenosis. The angioplasty response was poorer in patients with ostial lesion, sequential stenosis of single artery, or stenosis in multiple renal arteries on the same side. Endovascular treatment of renal artery stenosis may be considered in patients with impaired renal function (Safian and Textor 2001; Gray et al. 2002; Durros et al. 1068).

Surgical revascularization: A meta-analysis of 47 retrospective or nonrandomized studies compared the outcomes in patients subjected to surgical revascularization versus patients subjected to endovascular procedures. The results showed similar technical success rates, and surgical revascularization had better long-term BP control and renal function, but slightly higher perioperative mortality (attributed to concomitant aortic surgery) (Abela et al. 2009).

Medical treatment: No matter whether patients with renovascular hypertension need revascularization management or not, antihypertensive medical therapy is necessary either before or after surgery. Better control of BP before the operation can improve surgical outcomes. Continued medical treatment after revascularization can maintain improved BP results or help control refractory hypertension due to irreversible target damage imposed by long-term hypertension. Preferred choice of agents is adrenergic receptor blockers and diuretics. In patients with malignant hypertension, arterial dilators can be added to the management. CCBs are not used widely. Both ACE inhibitors and ARBs are contraindicated because of their renal function unfavored effect. Medical therapy remains the cornerstone of treatment for renal artery stenosis. The intensification of antihypertensive therapy and the control

of additional risk factors (smoking cessation, glycemic control, pharmacologic therapy using aspirin, statins) (Rocha-Singh et al. 2008) should be applied to all patients with atherosclerotic renal artery stenosis according to the European Guidelines (Perk et al. 2012; Dworkin and Cooper 2009).

ACE inhibitors, ARBs, and CCBs reduce BP significantly in 86–92% of patients with unilateral renovascular hypertension and may slow down the progression of renal disease. Thiazides, hydralazine, and beta-blockers are also effective in achieving target BP in individuals with renal artery stenosis. ACE inhibitors and ARBs are contraindicated in bilateral renal artery stenosis and when this lesion affects a single functional kidney (Plouin 2003; Eirin et al. 2019).

These drugs are often very well tolerated. Only 5% of patients have to stop using these three classes of drugs during the first 3 months of treatment. During the period of treatment, renal revascularization can only be considered if GFR decreased more than 30% or serum creatinine rising more than 0.5 mg/dL.

Bilateral renal artery stenosis is commonly contraindicated, especially when the affected kidney function impaired (Plouin 2003; Eirin et al. 2019).

ACE inhibitors induce vasodilation in both afferent and efferent arterioles, generally resulting in an increase in GFR. However, in hypoperfusion states, e.g., renal artery stenosis, aggressive diuresis, and decompensated congestive heart failure, GFR may fall because of unopposed prostaglandin vasodilation. Experience with using ARBs to treat renovascular hypertension. It is still very limited (Plouin 2003; Eirin et al. 2019).

Adrenergic blockers tend to be some of the most effective medicines for prolonged treatment of renovascular hypertension. Higher dose of alpha-adrenergic receptor blockers may cause sodium and fluid retention. As a result, concurrent diuretic therapy should be added to maintain the hypotensive effects of the alpha-receptor blockers. Beta-blockers, such as atenolol and metoprolol, can also be selected to treat renovascular hypertension (Plouin 2003; Eirin et al. 2019).

Diuretics, as an adjunct to other medications for renovascular hypertension, were used in renovascular hypertension, especially during acute hypertensive crises. Furosemide is especially effective in managing pulmonary edema associated with hypertensive crises and may be particularly useful in patients unresponsive to other diuretics or those who have severe renal function impairment. Nitroprusside is mainly used when a patient presents with a hypertensive emergency secondary to renovascular hypertension (Plouin 2003; Eirin et al. 2019).

6.21.2 Screen and Treatment of Other Secondary Hypertensions

The prevalence of secondary hypertension is 5–10% in all patients with hypertension (Benjamin et al. 2017). All new patients with hypertension should be screened

for secondary hypertension with a history, physical examination, and laboratory investigations before initiation of treatment.

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Chapter 7
Pharmaceutical Treatment for Heart Failure

Xue Lin and Ligang Fang

Abstract Heart failure (HF) is defined as a clinical syndrome resulting from structural or functional impairment of ventricular fillings or ejections of blood. Currently, HF is divided into three groups which include HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF) and HF with midrange EF (HFmrEF). Even though major advances have been made in treating HFrEF during the past decades, heart failure is a fatal disease. In this review, we briefly summarize the current advances in pharmaceutical managements for heart failure, which includes drugs used in acute heart failure as well as those that prevent heart failure progression, in each category major clinical trials are also described. In addition, information about some of potential new drugs are also mentioned. Traditional Chinese medicine also shows its potential in treating HF, and we are still lack of medicine to treat HFpEF.

Keywords Heart failure · HF with reduced ejection fraction · HF with preserved ejection fraction · Pharmaceutical management

7.1 Definition and Epidemiology

The definition of heart failure (HF) varies with time. The current American College of Cardiology (AHA) guidelines defines HF as a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood. According to this guideline, HF with reduced ejection fraction (HFrEF) is defined as an ejection fraction $\leqslant$40%, whereas HF with preserved ejection fraction (HFpEF) is defined as an ejection fraction $\geqslant$50%. (Yancy et al. 2013). ESC 2016 heart failure guideline advocates a new term for patients with HF and a left ventricular ejection fraction (LVEF) that ranges from 40 to 49%—"HF with midrange EF

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(HFmrEF)," this group of patients have better outcome and the underlying characteristics, pathophysiology and treatments are worthy of further studying (Ponikowski et al. 2016).

During the process of fighting this deadly disease, major advances have been made in understanding the pathophysiology of HFrEF which lead to a sophisticated system of life support, medications, and mechanical devices that reduce morbidity and mortality and improve life quality of heart failure patients during the past four decades; however, there are major unmet needs. Nowadays, HF is regarded as a rising global epidemic (Bui et al. 2011; Vos et al. 2012). Over 1 million patients are hospitalized for HF each year in the USA alone, and the prevalence of HF will increase ≈50% between 2012 and 2030, resulting in >8 million people ⩾18 years of age with HF (Mozaffarian et al. 2015; Heidenreich et al. 2013). At the same time, HF is still ranking one of the top reasons for death in middle-income and low-income countries (Mortality GBD and Causes of Death C 2015; Dokainish et al. 2015). Besides the great burden of HFrEF, our little understanding of pathophysiology of HFpEF which account nearly 50% of HF syndrome prevents effective treatment to HFpEF, up-to-now all of pharmaceutical treatment to HFpEF are neutral. There is still a long way to go before we can effectively treat HFpEF.

In this review, we will briefly describe the clinical manifestations of heart failure, focusing on the major pharmaceutical therapy of well-established medications as well as some of promising new drugs to heart failure from clinical management views; the device therapy and mechanical support of HF are referred to other comprehensive reviews (Gustafsson and Rogers 2017; Mitter and Yancy 2017).

When a physician facing a patient suspected with HF, she/he might ask themselves the following questions: Can the patient be diagnosed as heart failure? Is the HF acute or chronic? What is the etiology of the HF? Can we find out and correct the exacerbating factors? How can we treat the symptoms? How can we prolong the patient's survival?

7.2 Evaluation of a Patient with Heart Failure

When suspecting a patient with HF, a physician should collect complete medical history and perform careful physical examination that provide fundamental information of etiology of HF and exacerbating factors.

7.2.1 Recognizing Heart Failure Symptoms

7.2.1.1 Symptoms

Some symptoms provide important information for HF diagnosis. Worsening dyspnea is a core symptom of HF. Dyspnea ranges from exertional dyspnea, dyspnea

at rest, paroxysmal nocturnal dyspnea to orthopnea. Shortness of breath developing in recumbence is one of the most reliable indicators of HF (Solomonica et al. 2013). These symptoms all reflect pulmonary congestion, while weight gain, abdominal satiety, and the onset of edema in dependent organs indicate right heart failure. Fatigue is another cardinal symptom of HF, an indication of reduction in cardiac output as well as abnormal skeletal muscle metabolic responses to exercise (Jones et al. 2012). For some patients with advanced left HF, extreme fatigue might be the only chief complaint. None of these symptoms is specific to HFpEF versus HFrEF (Mann et al. 2014).

Physical examination is generally consisting of two key components: detection of reduced cardiac output and systemic hypoperfusion. Measurement of jugular venous pressure (JVP) is a reliable method to detect the presence of volume retention (Mann et al. 2014). Presence of a pleural effusion by dullness percussion and reduced breath sounds, lower-extremity edema are often very common findings in HF patients with volume overloading (Gheorghiade et al. 2010). Volume overloading might not be seen in severe left heart failure patients, for the fluid is mainly congested in lung, but not in any dependent organs.

7.2.1.2 Routine Assessment

Chest Radiography

Chest radiography could provide the information whether the patient has pulmonary edema or other pulmonary diseases in emergency room. The classic chest radiograph appearance of pulmonary edema of acute decompensated heart failure is a "butterfly" pattern of interstitial and alveolar opacities bilaterally fanning out to the periphery of the lungs. Many patients are also present with increased interstitial markings including Kerley B lines (thin horizontal linear opacities extending to the pleural surface caused by accumulation of fluid in the interstitial space), peribronchial cuffing, and evidence of prominent upper lobe vasculature (indicating pulmonary venous hypertension) (Mann et al. 2014; Gehlbach and Geppert 2004).

The Electrocardiogram

Most of ECG findings are nonspecific in HF patients, but some of ECG changes provide important information for clinical management. Arrhythmia could be the reason for acute heart failure such as atrial arrhythmia with fast ventricular response, and tachycardiomyopathy. Sinus tachycardia might indicate activating sympathetic nerve which would be the management aim for long-term treatment. And also, evaluation of the QRS complex has become a critical part to identify patients needing cardiac resynchronization therapy (Writing Committee et al. 2013), as well as anticoagulation for atrial fibrillation, or pacing for bradycardia.

Biomarkers

Natriuretic peptide biomarkers are useful biomarkers to assist the diagnosis of heart failure, especially when the cause of dyspnea is unclear. B-type (i.e., brain) natriuretic peptide (BNP) and its amino-terminal cleavage pro-peptide equivalent, N-terminal pro–B-type natriuretic peptide (NT-proBNP) are most commonly measured natriuretic peptides; both of these two biomarkers are released from cardiomyocytes in response to stretch (McQuade et al. 2017). While BNP, not NT-proBNP, is a substrate for neprilysin. Angiotensin receptor–neprilysin inhibitor (ARNI) (valsartan/sacubitril), a dual blockade of renin–angiotensin–aldosterone system (RAAS) and the natriuretic peptide system to treat HFrEF (Jhund and McMurray 2016), increases BNP levels (Packer et al. 2015), but not NT-proBNP levels (Zile et al. 2016), therefore only NT-proBNP should be tested when ARNI is used. BNP and NT-proBNP might be in normal range in stable HF patients, and the changes of their values with the symptoms can provide useful and instant information about the change of the heart functions.

Even though not used clinically, circulating concentrations of soluble ST2 (a member of the interleukin receptor family) and Galectin 3, as promising myocardial fibrosis markers, have been shown to be strongly linked to progressive HF and death in patients across the different stages of HF (Yancy et al. 2017; Santaguida et al. 2014). Combined with natriuretic peptide, these markers could provide valuable information of heart function and tissue characteristics to assist HF management in the near future.

Echocardiography and Other Imagine Modalities

Transthoracic echocardiography is an important part of the evaluation of HF. It is suitable for evaluating both the structure and function of heart, and also provides information about intracardiac pressures and flows. For measurement of LVEF, the modified biplane Simpson's is recommended. The Teichholz and Quinones methods of calculating LVEF from linear dimensions, as well as a measurement of fractional shortening, are not recommended (Ponikowski et al. 2016). As to HFpEF, the diagnosis might be more complex. The American association of echocardiography provides a systemic and official evaluation of diastolic heart failure in 2016 (Fig. 7.1) (Nagueh et al. 2016). Advanced echocardiography skills, for example, three-dimensional echocardiography can provide more detailed information of heart and facilitate cardiac surgeons to select more proper way for heart operations. Stress echocardiography can help diagnosis of microcirculation dysfunction in a fordable and reliable way (Porter and Xie 2010). Magnetic resonance imaging is excelling in evaluating myocardial tissue and assessing myocardial viability (Mahrholdt et al. 2005). Cardiac computed tomography is mainly to help determine whether or not obstructive coronary artery disease is present in HF patient particularly for patients with lower likelihood of coronary artery disease (Ghostine et al. 2008).

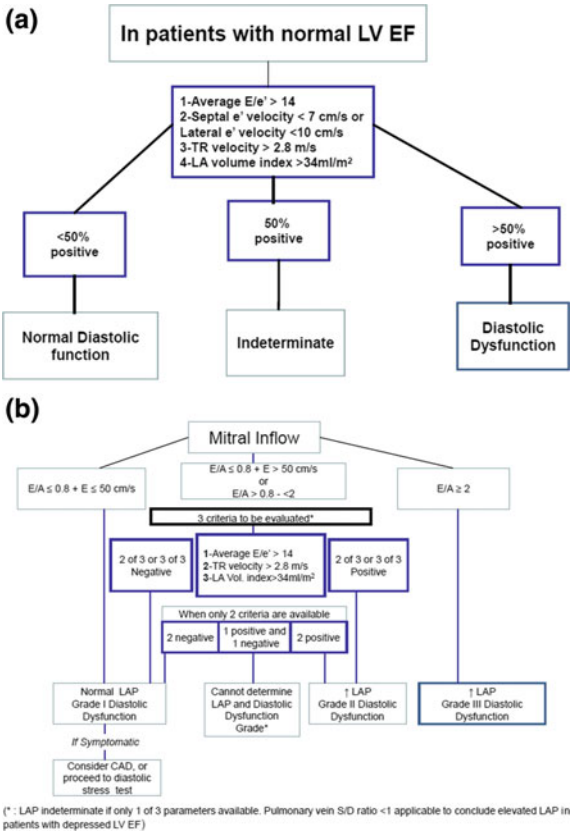

Fig. 7.1 Recommendations for the evaluation of left ventricular diastolic function by echocardiography (Nagueh et al. 2016)

The combination of symptoms, X-ray, and an elevated biomarker can assist the diagnosis of HF, the pathway of diagnosing heart failure is shown in Fig. 7.2.

7.2.2 Identify the Etiologies of HF

To identify and correct the cardiac structural and/or functional abnormalities responsible for HF is the first step to treat HF.

Heart function could be damaged by different ways. 70% HF patients have coronary heart disease as the initial cause of HF, valve disease accounts for 10%, and cardiomyopathies for another 10%. Some drugs such as ß-blockers, calcium antagonists, anti-arrhythmic, cytotoxic agents are also related to HF. Usage of toxins including alcohol, cocaine, some trace elements (mercury, cobalt, arsenic) might also cause HF. The heart is also involved in some systemic diseases including endocrine system (diabetic mellitus, hypo/hyperthyroidism, excessive hormone, pheochromocytoma) and immunological disease (lupus, vacuities, etc.). Sometimes but not often we had

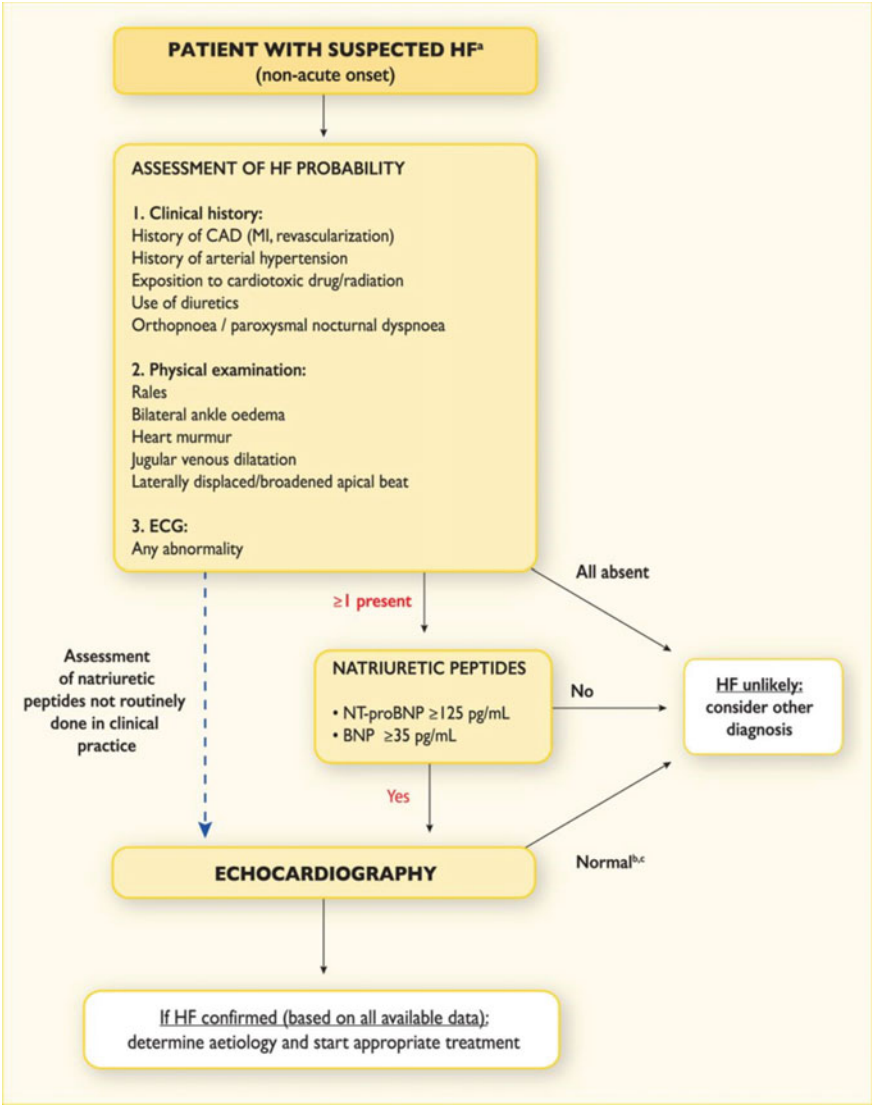

Fig. 7.2 Diagnostic algorithm for diagnosis of heart failure of non-acute onset. BNP: B-type natriuretic peptide; CAD: coronary artery disease; HF: heart failure; MI: myocardial infarction; NT-proBNP: N-terminal pro-B type natriuretic peptide. Adopted from 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure (Ponikowski et al. 2016)

seen causes including nutritional, infiltrative, and other diseases (Ponikowski et al. 2016; Fonarow et al. 2008; Dickstein et al. 2008).

7.2.3 Assessment of the Exacerbating Factors Responsible for Worsening HF

Most of HF patients could have stable heart function unless under stress. The most common precipitating factors are pneumonia/respiratory diseases (15.3%), ischemia/acute coronary syndrome (14.7%), arrhythmia (13.5%), and uncontrolled hypertension (10.7%). Non-adherence to medications was identified in 8.9% and non-adherence to diet in 5.2% of patients (Fonarow et al. 2008; Nieminen et al. 2005; Mysliwiec and Bonita 2017). These exacerbating factors generally cause volume overloading either in lung or in dependent organs leading to clinical manifestations of heart failure.

7.3 Pharmaceutical Management for Heart Failure

The main goals of treatment for HF are to reduce symptoms, prolong survival, improve the quality of life, and prevent disease progression.

Reducing the water retention is always the first step to improve symptoms as well as to increase the heart contractility and blood vessels dilation. Therefore diuretics, inotropes, and vasodilators are first-line medications to stabilize the decompensated vital signs.

When symptoms are reduced, physicians would consider how to prolong the survival of patients. The core compensation mechanisms of heart failure is continuous activating adrenergic nervous system and the renin–angiotensin system (RAS), which secret biologically active molecules exerting on the heart and circulation and ultimately result in heart remodeling (Mann et al. 2014). Consequently, anti-neurohormonal system drugs such as angiotensin-converting enzyme inhibitors (ACE inhibitor), beta blockers and aldosterone antagonists become the cornerstone to treat HFrEF.

7.3.1 Management of Acute Heart Failure

7.3.1.1 Diuretics

Diuretics are the first choice to reduce the symptoms of acute HF. Diuretics increase the urine volume by enhancing the excretion of water, sodium chloride, and other

ions, leading to a decrease in plasma and extracellular fluid volume and a decrease in peripheral congestion. The aim of diuretic therapy is to achieve and maintain euvolaemia with the lowest achievable doses.

Loop Diuretics, potassium-sparing diuretics, and thiazide diuretics and metolazone are three classes of diuretics and newly appeared water diuresis ("aquaretics") are gaining more attention. Loop diuretics are the primary pharmacologic agents and typically produce rapid symptom relief in most patients.

Loop Diuretics

Our bodies maintain the chemical balance and are cleansed by glomerular filtration, tubular reabsorption and tubular secretion in kidney; among them, formation of the medullary gradient by acting at the ascending limb of the nephron loop is a major step to form the urine in reasbsorption process (Marieb and Hoehn 2007). Loop diuretics, including furosemide, bumetanide, and torsemide, act by reversibly inhibiting the action of the sodium-potassium-chloride cotransporter in the thick ascending limb of the loop of Henle thereby preventing sodium reabsorption and the obligatory water reabsorption that normally follows. Loop diuretics also induce the synthesis of prostaglandins, resulting in renal and peripheral vascular smooth muscle relaxation and vasodilatation increase in renal blood flow and redistribution of renal cortical blood flow. Up to now, furosemide is still the most widely used loop diuretic orally or intravenously, furosemide reduces right atrial and pulmonary capillary wedge pressure within minutes when given intravenously (0.5–1.0 mg/kg) (Felker 2012; Michael 2010).

Thiazide and Thiazide-like Diuretics

Thiazide diuretics inhibit the sodium-chloride transporter in the distal tubule. This transporter normally only reabsorbs about 5% of filtered sodium, therefore these diuretics are less efficacious than loop diuretics, but they have synergistic effects with loop diuretics. So it is very common that physicians use a loop diuretic and a thiazide together. Thiazide diuretics' effectiveness is limited in patients with reduced glomerular filtration. Metolazone, an oral quinazoline diuretic, is much more potent than hydrochlorothiazide and remains effective even when the glomerular filtration rate is <30 mL/min, making it a useful adjunct to loop diuretics in patients with diuretic resistance or severe renal insufficiency (Mann et al. 2014; Sica 2003).

Potassium-Sparing Diuretics

The most often used potassium-sparing diuretics are the aldosterone receptor antagonists spironolactone and eplerenone. Even though spironolactone and eplerenone

are classified as diuretics, their roles in HF are far beyond just diuretics, as important medication to anti-remodeling, they will be discussed in the following part PREVENTION OF DISEASE PROGRESSION Aldosterone Antagonists.

Vasopressin Antagonists

All four antidiuretic hormone arginine vasopressin (AVP) antagonists, or "vaptans," which can block selectively the V2 receptor (e.g., tolvaptan, lixivaptan, satavaptan) or nonselectively block both the V1a and V2 receptors (e.g., conivaptan), increase urine volume, decrease urine osmolality, and have no effect on 24 h sodium excretion (Finley et al. 2008). Currently, conivaptan and tolvaptan are approved by U.S. Food and Drug Administration (FDA) to treat clinically significant hypervolemic and euvolemic hyponatremia (serum Na+ $\leqslant$125) that is symptomatic and resisted correction with fluid restriction in patients with HF (Gheorghiade et al. 2007). Currently, most of physicians use vaptans when other diuretics are not very effective in HF patients and strictly monitor the changes in serum electrolytes and volume, which is necessary. Generally speaking it is not recommended to restrict fluid intake during the first 24 h of therapy.

In EVEREST trial, 4133 HF patients with LVEF $\leqslant$40% and volume overloading were randomized either to take tolvaptan 30 mg once daily or placebo in addition to standard therapy, and they were followed up for 9.9 months. Tolvaptan 30 mg did not reduce mortality but was safe in patients with advanced HF. Dry mouth and thirst were the most common adverse effects (Konstam et al. 2007).

Adverse Reactions of Diuresis

Diuresis is notoriously known for their side effects including electrolyte and metabolic disturbances, volume depletion as well as azotemia. Potassium depletion is the most common side effect when using loop diuresis, and physicians generally advocate that the serum K^+ should be maintained between 4.0 and 5.0 mEq/L. Oral potassium supplements in the form of KCL extended-release tablets or liquid concentrate should be used whenever possible. The excessive use of diuretics can lead to hypotensive symptoms and azotemia which usually resolve after a decrease in the dosage or frequency of diuretics (Mann et al. 2014). Acceptable elevated blood serum creatinine may be necessary to maintain control of heart failure symptoms in some advanced patients.

One of the inherent limitations of diuretics is diuretic resistance, even though the underlying mechanism is not fully clarified, some of clinical strategies might help (Bowman et al. 2016). The major strategy in outpatient is to combine two classes of diuretic concurrently. Adding a proximal tubule or a distal collecting tubule diuretic to a loop diuretic is often effective. Alternative method is administration of short-acting diuretics several times per day or continuous intravenous infusion of a loop diuretic usually furosemide through a constant-infusion pump (Mann et al. 2014).

7.3.1.2 Vasodilators

In the absence of hypotension, vasodilators can be used as first-line agents in combination with diuretics in the management of patients with AHF to improve congestive symptoms (Dickstein et al. 2008; Metra et al. 2009).

Vasodilators can be classified as (1) venous dilator to reduce preload; (2) arterial dilators decreasing afterload; and (3) balanced vasodilators, with combined action on both the venous and the arterial system. Currently available vasodilators include the organic nitrates (nitroglycerin [NTG] and isosorbide dinitrate), sodium nitroprusside (SNP), and nesiritide (Mann et al. 2014).

All of these drugs act by activating soluble guanylate cyclase (sGC) in the smooth muscle cells, leading to higher intracellular concentrations of cyclic guanosine monophosphate (cGMP) and consequent vessel relaxation (Mann et al. 2014).

Even though few studies proved vasodilator can improve short- and long-term outcomes (Alexander et al. 2015), most of the physicians still use them to stable decompensate heart failure in case of life danger.

Nitrates

The ability to dilate vessels of nitrates changes with the dosages: Vasodilation is achieved in low dose and arteries and coronary arteries would dilate in higher dosage. The starting dose of nitroglycerin usually is 20 μg/min with rapid uptitration every 5–15 min in either 20 μg/min increments or doubling of the dose (Mann et al. 2014; den Uil and Brugts 2015).

Sodium Nitroprusside

Sodium nitroprusside (SNP) is recommended in patients with severe heart failure, and in patients with increased afterload such as hypertensive heart failure or mitral regurgitation. The initial dosage of SNP is 0.3 μg/kg/min up-titrating carefully to 1 μg/kg/min up to 5 μg/kg/min. The most common complaints with nitroprusside are related to the cyanide metabolite, including nausea, abdominal discomfort, dissociative feelings, and dysphoria (Nieminen et al. 2005).

Nesiritide

Nesiritide (recombinant human B-type [brain] natriuretic peptide) can cause potent vasodilation in the venous and arterial vasculatures, resulting in significant reductions in venous and ventricular filling pressures and mild increases in cardiac output (Mann et al. 2014).

The effectiveness of Nesiritide in decompensated Heart Failure (ASCEND-HF) was tested in 7,141 patients with either reduced or preserved ejection fraction. The

drug failed to significantly improve dyspnoea or decrease death or HF-related re-hospitalization within 30 days (O'Connor et al. 2011).

Because of its high cost and lack of clear clinical benefit, most of the physicians would try Nesiritide only if functions of the first line diuretics are limited. Hypotension is more common in patients with volume depletion; consequently, nesiritide use should be limited to those with congestive signs and symptoms. Headache might occur. Nesiritide did not improve urine output or renal function in patients with AHF in whom creatinine levels were increasing (Wang et al. 2004).

7.3.1.3 Inotropes and Inodilators

The inotropic drugs and inodilators (inotropic drugs with vasodilatory properties) increase cardiac output through cyclic adenosine monophosphate (cAMP)-mediated inotropy and reduce PCWP through vasodilation (Hasenfuss and Teerlink 2011). However, even the short term use of intravenous inotropes (except for digoxin) is associated with significant side effects such as hypotension, atrial or ventricular arrhythmias, and an increase in in-hospital and possibly long-term mortality (Felker et al. 2003). The use of these drugs should be limited to patients with dilated ventricles and reduced ejection fraction who are present with low SBP (<90 mmHg) or low measured cardiac output in the presence of signs of congestion and organ hypoperfusion. Additionally, intravenous inotropes may be used in cardiogenic shock as a temporary therapy to prevent hemodynamic collapse or as a life-sustaining bridge to more definitive therapy for those patients awaiting mechanical circulatory support, ventricular assist devices, or cardiac transplantation (Heart Failure Society of A et al. 2010; Jessup et al. 2009). These agents should be used with close telemetry monitoring and be stopped as soon as adequate organ perfusion is restored (Jaarsma et al. 2009; Teerlink et al. 2009).

Dobutamine

Even though dobutamine might increase the mortality of heart failure, it is the most commonly used positive inotrope (Tacon et al. 2012). Dobutamine has multiple actions through an agonist of both beta1 and beta2 adrenergic receptors with variable effects on the alpha receptors. Stimulation of Beta receptor results in increased inotropy and chronotropy by increasing intracellular cAMP and calcium. At low doses, stimulation of beta2 and alpha receptors causes vasodilation, resulting in decreased systemic vascular resistance and indirect increases in cardiac output. At higher doses, effects would include vasoconstriction, decreased venous capacitance and increased right atrial pressure. Many patients will experience improved renal perfusion with dobutamine doses of 1–2 μg/kg/min, while higher doses (5–10 μg/kg/min) may be necessary for profound hypoperfusion (Mann et al. 2014).

Adverse effects of dobutamine include tachycardia, atrial fibrillation, ventricular arrhythmias, myocardial ischemia, and possibly cardiomyocyte necrosis mediated by direct toxic effects and induction of apoptosis (Adamopoulos et al. 2006).

Dopamine

Dopamine, as a precursor to the synthesis of norepinephrine, an agonist of both adrenergic and dopaminergic receptors, and an inhibitor of norepinephrine uptake, has complex effects that vary significantly with dose (Mann et al. 2014).

Low-dose dopamine ($\leqslant$2 μg/kg/min) causes selective dilation of renal, splanchnic, and cerebral arteries, increasing renal blood flow, as well as promoting natriuresis through direct distal tubular effects.

Intermediate-dose dopamine (2–10 μg/kg/min) increases norepinephrine release with inotropy effect and peripheral vasoconstriction. But in patients with severe systolic dysfunction, dopamine is a poor inotrope for the depletion of myocardial catecholamine stores in advanced heart failure.

High-dose dopamine (10–20 μg/kg/min) causes peripheral and pulmonary artery vasoconstriction, mediated by direct agonist effects on alpha1-adrenergic receptors. These doses might cause limb and end-organ ischemia and should be used cautiously (Mann et al. 2014).

Epinephrine

Epinephrine acts by binding to a variety of adrenergic receptors. Epinephrine is a nonselective agonist of all adrenergic receptors, including the major subtypes α1, α2, β1, β2, and β3. Its actions are to increase peripheral resistance via α1 receptor-dependent vasoconstriction and to increase cardiac output via its binding to β1 receptors (Shen 2007). The direct effect of epinephrine on increasing inotropy independent of myocardial catecholamine stores makes it a useful agent in the treatment of transplant recipients with denervated hearts (Mann et al. 2014).

Phosphodiesterase Inhibitors

Many specific inhibitors of phosphodiesterase IIIa (PDE IIIa), such as milrinone and enoximone, can increase myocardial and vascular smooth muscle cell cAMP concentrations, and they are suitable for use in patients with LV dysfunction and pulmonary hypertension or in transplant recipients.

Milrinone therapy may be initiated with a 25–75 μg/kg bolus over 10–20 min, infusions typically are started at 0.10–0.25 μg/kg/min and may be uptitrated to hemodynamic effect with 15 min effect delay after dosage adjustment. Also patients

who have had prolonged administration of milrinone may experience delayed deterioration, so they should be observed for at least 48 h after cessation (Mann et al. 2014).

Levosimendan

Levosimendan acts by dual mechanism on heart, as a calcium sensitizer it directly binds troponin C in cardiac myocytes to function as a positive inotrope, and also it activates ATP dependent potassium channels in peripheral vessel smooth muscle to decrease cardiac afterload (Gheorghiade et al. 2005).

The efficacy and safety of levosimendan had been proved by series of phase II and phase III trials which showed levosimendan significantly increased cardiac output, reduced PCWP and afterload, as well as decreased dyspnea (Hasenfuss and Teerlink 2011). In the largest phase III clinical trial: the Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) trial which enrolled 1,327 patients with severe HF (85% with NYHA class IV, mean LVEF 24%), levosimendan had similar effects on the primary outcome of all-cause mortality at 180 days with dobutamine, and levosimendan group had reported higher rates of atrial fibrillation, electrolyte disturbances, and headaches, while dobutamine group showed increased incidence of cardiac failure (Mebazaa et al. 2007). While it is still debated whether levosimendan would have long-term survival benefit compared with dobutamine (Schumann et al. 2018).

7.3.1.4 Vasopressors

Vasopressors could be used for patients with marked central organ hypoperfusion. These agents will redistribute cardiac output centrally at the expense of peripheral perfusion and increased afterload. Phenylephrine is a selective alpha1 receptor agonist with potent direct arterial vasoconstrictor effects. Norepinephrine also is a potent agonist of the beta1 and the alpha1 receptors but is a weaker agonist of beta2 receptors. These agents may be used in case of severe hypotension, particularly when the hypotension is related to systemic vasodilation, rather than to a decrease in cardiac output. Both of these agents may induce end-organ hypoperfusion and tissue necrosis (Mann et al. 2014).

7.3.1.5 Potential New Therapies

Relaxin

Relaxin (RLX) is a member of the insulin superfamily, a major hormone of pregnancy with powerful systemic and renal vascular effects. It also has beneficial effects on

vasodilatory action and effects on cardiac fibrosis and remodeling, cardiac preconditioning and ischemia, inflammation. Chemically, it is a 6-kDa polypeptide produced by the mammalian corpus luteum and placenta. These functions along with increased GFR and cardiac output make relaxin a potential candidate for treatment of acute heart failure. Serelaxin (recombinant human relaxin-2) mediates vasodilatation by multiple NO-mediated mechanisms, in addition to VEGF and endothelin pathway.

The efficacy and safety of serelaxin were proved by a large, international, double-blinded, placebo-controlled Phase III trial: the RELAXin in Acute Heart Failure (RELAX-AHF) Trial 1161 patients presented with dyspnea, congestion, mild to moderate renal insufficiency were randomized to a 48 h infusion of either serelaxin (30 μg/kg/day) or placebo in addition to standard of care. Relax significantly improved VAS AUC (less dyspnea) over 5 days, but dyspnea which was evaluated by Likert scale, was not different for the first 24 h. The 60 day survival, death or readmission rates was no different with placebo, but 180 day mortality was lower in serelaxin group. The improvement in renal function in patients receiving serelaxin suggested potential benefits in cardiorenal syndrome (Teerlink et al. 2013; Ponikowski et al. 2014).

The RELAX-AHF trial exclude high-risk patients with low blood pressure, therefore further clinical trials with sufficient statistical power and a diverse, heterogeneous patient base are needed to evaluate outcome in heart failure treated with serelaxin.

Endothelin Receptor Antagonists

Endothelin receptor antagonists block the actions of endothelin-1 (ET-1), the most powerful endogenous vasoconstrictor that is produced by the vascular endothelial cells. It exerts its effects by binding to two receptors, ETA and ETB which are located on the vascular smooth muscle cells, resulting in significant systemic arterial vasoconstriction. Even though bearing the hope of improving AHF symptom, Tezosentan, a nonselective ETA-B antagonist, did not show significant difference in 24 h dyspnea and 7 day clinical end points between the tezosentan-treated and placebo-treated groups in a pivotal phase III clinical trial: The Value of Endothelin Receptor Inhibition with Tezosentan in Acute heart failure Study (VERITAS) (McMurray et al. 2007).

Soluble Guanylate Cyclase Activators

The mechanism of action of these compounds is similar to that of organic nitrates (and their end product nitric oxide [NO]), because both classes of drugs activate the soluble form of guanylate cyclase (sGC) in smooth muscle cells, thereby leading to the synthesis of cGMP and subsequent vasodilation. Cinaciguat has been shown to improve hemodynamics in patients with AHF; however, at high doses, it has been

associated with significant hypotension, which resulted in the termination of some recent clinical studies (Gheorghiade et al. 2012).

Cardiac Myosin Activators

Cardiac myosin activators represent a new mechanistic class of agents designed to increase myocardial contractility. Omecamtiv mecarbil (OM) is a selective small molecule activator of cardiac myosin that prolongs myocardial systole. ATOMIC-AHF was a prospective, phase II, randomized, double-blind, placebo-controlled, dose-escalation, sequential-cohort trial comparing OM with placebo in 606 patients hospitalized for AHF. Intravenous OM was well tolerated, and it increased systolic ejection time, but it did not meet the primary endpoint of dyspnea improvement, while in high-dose group it improves dyspnea in both healthy volunteers and patients with stable HfrEF (Teerlink et al. 2016).

Istaroxime

Istaroxime—(E, Z)—3—[(2-aminoethoxy)-imino] androstane-6,17-dione is a steroidal drug unrelated to cardiac glycosides that improves cellular calcium cycling by dual action: SERCA 2a stimulation causes rapid Ca2+ sequestration in sarcoplasmic reticulum (SR) during diastole (lusitropism); without enhancing spontaneous Ca2+ efflux from the SR. Secondly, Na+–K+ ATPase inhibition induces cytosolic calcium accumulation during systole (Micheletti et al. 2007). These unique mechanisms increased inotropic effects as well as enhance diastolic function (Khan et al. 2009). The efficacy of istaroxime was tested in HORIZON-HF study which proved that the addition of istaroxime to standard therapy lowered PCWP and heart rate and increased SBP in 120 patients admitted with AHF and decreased ejection fraction (Shah et al. 2009).

Stresscopin

Stresscopin, or urocortin 2, is a member of peptide hormones of the corticotropin-releasing factor (CRF) family. It strongly binds to the corticotropin-releasing hormone receptor type 2 (CRH-R2) which is highly expressed in myocardium and in the vascular endothelium. Urocortins exhibit potent systolic and diastolic effects on rat and sheep hearts, and also it activates “reperfusion injury salvage kinase” (RISK) pathway to protect heart. Brief intravenous infusions of stresscopin in patients produced dose-related increases in cardiac output, heart rate, and LV ejection fraction while decreasing systemic vascular resistance (Gheorghiade et al. 2013).

Nicorandil

Nicorandil is a balanced vasodilator that acts as both NO donor and arterial K(+) ATP channel opener. Nicorandil might also exhibit cardioprotective properties via mitochondrial ischemic preconditioning.

In a prospective, randomized controlled trial, 106 AHF patients were randomized within one hour of arrival to receive either standard therapy or standard therapy plus simultaneous intravenous nicorandil (0.2 mg/kg bolus followed by 0.2 mg/kg/h for 24 h; nicorandil group, n = 50). Patients in the nicorandil group exhibited greater improvement of dyspnea as measured by change in a five-point Likert scale compared to those in the control group, also improved left ventricular filling pressure measured by E/e′ but it did not reduce all-cause mortality and readmission rates at 60 days. Intravenous nicorandil therapy was safe and did not cause side effects such as excessive hypotension or reflex tachycardia (Harada et al. 2017).

Most of the large clinical trials of new therapies for acute heart failure (AHF) have yielded negative results in terms of long-term outcomes. In view of the diverse pathophysiology of AHF, it would be unrealistic to expect that a single drug would exert beneficial effects in all patients with AHF. There remain areas of significant unmet need including vasodilators with proven clinical benefits, agents that optimize myocardial performance without significant adverse effects, and agents that improve or protect renal function (Vaduganathan et al. 2013).

7.3.2 Prevention of Disease Progression

Drugs that reverse cardiac remodeling such as those interfere with the excessive activation of the renin-angiotensin-aldosterone system and the adrenergic nervous system can prevent heart failure progression. For clinicians, Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers/ARNI, Beta Blockers and Aldosterone Antagonists are must be used medicine to prolong patients' lives unless there are contraindications for use.

7.3.2.1 Angiotensin-Converting Enzyme Inhibitors

Key Evidence Supporting the Use of Angiotensing-Converting Enzyme Inhibitors

The effectiveness of ACE inhibitors has been consistently demonstrated in clinical trials in patients with asymptomatic and symptomatic LV dysfunction. Up to now, there are no evidences that which kinds of ACE inhibitors are better, but all of them are required to add up to target dosages unless there are intolerant side effects.

The major RCTs, Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) (Group 1987) and Studies of Left Ventricular Dysfunction

(SOLVD)-Treatment (Nauman and Greenberg 1993), proved that enalapril reduced mortality in 2,800 patients [relative risk reduction (RRR) 27% in CONSENSUS and 16% in SOLVD-Treatment]. In SOLVD-Treatment there was also an RRR of 26% in HF hospitalization.

ACE inhibitors also prevent the asymptomatic patients from symptomatic HF and hospitalization with HF. In the SOLVD-Prevention trial, enalapril reduced 20% RRR in death or HF hospitalization in 4228 asymptomatic LV systolic dysfunction patients. ACE inhibitor also reduced death or HF hospitalization in myocardial infarction trials, such as captopril [Survival and Ventricular Enlargement (SAVE)] (Pfeffer 1993), ramipril [Acute Infarction Ramipril Efficacy (AIRE)], and trandolapril [TRAndolapril Cardiac Evaluation (TRACE)] (Flather et al. 2000). The Vasodilator in Heart Failure II (V-HeFT-II) trial provided evidence that ACE inhibitors improved the natural history of HF through mechanisms other than vasodilation, as subjects treated with enalapril had significantly lower mortality than subjects treated with the vasodilatory combination of hydralazine plus isosorbide dinitrate (Cohn et al. 1991). Furthermore, the absolute benefit is greatest in patients with the most severe HF.

Taken together, these observations support the conclusion that the effects of ACE inhibitors on the change of natural history of HF. Even though patients with a low blood pressure (less than 90 mm Hg systolic) or impaired renal function (serum creatinine greater than 2.5 mg/dL) represented only a small proportion of patients who participated in these trials, some studies also showed these patients also benefited from ACE inhibitor.

Complications of Angiotensin-Converting Enzyme Inhibitor Use

The side effects of ACE inhibitors include worsening of renal function, hyperkalaemia, symptomatic hypotension, cough, and, rarely, angioedema. An ACE inhibitor should not be used in patients with creatinine $\geqslant$221 mmol/L or $\geqslant$2.5 mg/dL or eGFR $\leqslant$30 mL/min/1.73 m^2 or hyperkalaemia.

Angiotensin Receptor Blockers (ARBs) are recommended for patients who cannot tolerate ACE inhibitors because of cough or angioedema. While patients intolerant to ACE inhibitors are likely to have the same side effects with ARBs. In these situations, the combination of hydralazine and an oral nitrate should be considered.

7.3.2.2 Angiotensin Receptor Blockers

ARBs are well tolerated in patients who are intolerant of ACE inhibitors because of cough, skin rash, and angioedema and should therefore be used in symptomatic and asymptomatic patients with an EF below 40%. ACE inhibitors and ARBs inhibit the renin-angiotensin system by a different mechanism: ACE inhibitors block the enzyme responsible for converting angiotensin I to angiotensin II, ARBs block the effects of angiotensin II on the angiotensin type 1 receptor, the receptor subtype that is responsible for all of the adverse biologic effects. Multiple ARBs are approved for

the treatment of hypertension. Three of these—losartan, valsartan, and candesartan—have been extensively evaluated in HF.

7,600 patients with mild to severe symptomatic HF was assigned to receive a placebo or an ARB (valsartan and candesartan) in two key placebo-controlled RCTs (Val-HEFT and CHARM-Added), and the ARB treatment reduced the risk of hospital admission for worsening HF (RRR 24% in Val-HeFT and 17% in CHARM-Added) but not all-cause hospitalization. Candesartan reduced 16% RRR in the risk of death from a cardiovascular cause (McMurray et al. 2012).

In 2028 patients with LVEF <40% who were intolerant to an ACEI, candesartan treatment resulted in an RRR of death from a cardiovascular cause or hospital admission for worsening HF of 23% in CHARM-Alternative trial (McMurray et al. 2012; Cohn et al. 2001).

7.3.2.3 Angiotensin Receptor–Neprilysin Inhibitor (ARNI) (Valsartan/Sacubitril)

An ARNI is combined ARB with an inhibitor of neprilysin, an enzyme that degrades natriuretic peptides, bradykinin, adrenomedullin, and other vasoactive peptides. ARNI is recommended to patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB. PARADIGM-HF first proved that ARNI reduced the composit endpoint of cardiovscular death and HR hospitalization by 20%. In this trial, the ARNI, valsartan/sacubitril, was compared with enalapril in symptomatic patients with an ejection fraction of 40% or less. These patients received either valsartan/sacubitril (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended theraphy, the ARNI reduced the composite endpoint of cardiovascular death or HF hospitalization by 20% (McMurray et al. 2014). The use of ARNI is associated with the risk of hypotension and renal insufficiency and may lead to angioedema, as well (Yancy et al. 2017).

7.3.2.4 Beta Blockers

Beta blocker therapy represents a major advance in the treatment of patients with HFrEF. Beta blockers interfere with the harmful effects of sustained activation of the central nervous system by competitively antagonizing one or more adrenergic receptors (alpha1, beta1, and beta2), especially beta1 adrenergic receptor. Beta blockers can reverse the process of LV remodeling of HF patients, relief patient symptoms, prevent hospitalization, and prolong life. Therefore beta blockers are indicated for patients with EF below 40%.

Major Clinical Trails

Three key trials [Cardiac Insufficiency Bisoprolol Study II (CIBISII), Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS), and Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)] proved the efficacy of beta blockers. Nearly 9,000 patients with mild to severe symptomatic HF were randomized to receive a placebo or a beta blocker (bisoprolol, carvedilol, or metoprolol succinate CR/XL) (McMurray et al. 2012; The Cardiac Insufficiency Bisoprolol Study II 1999; Effect of metoprolol CR/XL in chronic heart failure 1999; Hjalmarson et al. 2000; Packer et al. 2001, 2002). More than 90% of the patients also took an ACE inhibitor or ARB as well.

All of the three beta blockers have been shown to be effective in reducing the risk of death in patients with chronic HF: bisoprolol and sustained-release metoprolol succinate both competitively block the beta1 receptor, and carvedilol competitively blocks the alpha1, beta1, and beta2 receptors.

Side Effects of Beta Blockers

Beta blocker therapy is well tolerated by the great majority of patients with HF (>85%), including those with diabetes mellitus, chronic obstructive lung disease, and peripheral vascular disease. Nonetheless, a subset of patients (10–15%) might be intolerant to beta blockers because of worsening fluid retention or symptomatic hypotension (McMurray et al. 2012).

The dose titration of beta blockers should proceed no sooner than 2-week intervals, because the initiation and/or increased dosing of these agents may lead to worsening fluid retention. Therefore it is important to optimize the dose of diuretic and patients should be in their dry weight before starting beta blockers.

Patients might have feelings of general fatigue or weakness when starting a beta blocker treatment. In most instances, the increased fatigue spontaneously resolves within several weeks or months; however, sometimes it may be severe enough to limit the dose or withdrawal the treatment. Therapy with beta blockers can lead to bradycardia and/or exacerbate heart block. Therefore the dose of beta blockers should be decreased if the heart rate decreases to less than 50 beats/min and/or if second- or third-degree heart block or symptomatic hypotension develops, beta blockers are not recommended for patients with asthma with active bronchospasm (Mann et al. 2014).

7.3.2.5 Aldosterone Antagonists

Major Clinical Trials

The administration of an aldosterone antagonist is recommended for patients with NYHA class II or IV HF who have a depressed EF (<35%), and who are receiving

standard therapy including diuretics, ACE inhibitors, and beta blockers (Jessup et al. 2009).

Spironolactone is a synthetic steroid that competes for cytoplasmic aldosterone receptor. It does not produce hypokalemia because it inhibits aldosterone-sensitive sodium reabsorption, less potassium and hydrogen ion are exchanged for sodium by this transporter and therefore less potassium and hydrogen are lost to the urine. Spironolactone is generally relatively weak diuretics (Michael 2010).

The first evidence that aldosterone antagonists could produce a major clinical benefit in HF was demonstrated by the Randomized Aldactone Evaluation Study (RALES) trial (Uchida et al. 2005), which evaluated spironolactone (25 mg/day initially, titrated to 50 mg/day for signs of worsening HF) versus placebo in NYHA class III or IV HF patients with an LVEF below 35%. Administration of spironolactone led to a 30% reduction in total mortality when compared with placebo ($P = 0.001$). The frequency of hospitalization for worsening HF also was 35% lower in the spironolactone group than in the placebo group.

Eplerenone was developed by replacing the 17-alpha-thioacetyl group of spironolactone with a carbomethoxy group. The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial (Zannad et al. 2011), which was performed in patients with NYHA class II HF with an EF below 30% (or 35% if the QRS width was more than 130 ms), demonstrated that eplerenone (titrated to 50 mg/day) led to a significant 27% decrease in cardiovascular death or HF hospitalization (HR, 0.63 [95% CI, 0.54–0.74]; $P < 0.001$). Significant decreases were also observed in all-cause death (24%), cardiovascular death (24%), all-cause hospitalization (23%), and HF hospitalizations (43%). Of importance, the effect of eplerenone was consistent across all prespecified subgroups.

Spironolactone should be initiated at a dose of 12.5–25 mg daily and uptitrated to 25–50 mg daily, whereas eplerenone should be initiated at doses of 25 mg/day and increased to 50 mg/day.

Side Effects of Aldosterone Antagonists

The major side effects with the use of aldosterone antagonists are the development of life-threatening hyperkalemia, especially in patients who are receiving potassium supplements or with underlying renal insufficiency. Aldosterone antagonists are not recommended when the serum creatinine is greater than 2.5 mg/dL (or creatinine clearance is below 30 mL/min) or the serum potassium is greater than 5.5 mmol/l. Painful gynecomastia may develop in 10–15% of patients who use spironolactone, in which case eplerenone may be substituted (Mann et al. 2014).

7.3.2.6 Other Agents That Could Be Used in HF

Ivabradine

Ivabradine is a heart rate lowering agent that acts by selectively blocking the cardiac pacemaker If current that controls the spontaneous diastolic depolarization of the sinoatrial node. Ivabradine blocks If channels in a concentration-dependent manner by entering the channel pore from the intracellular side and thus can only block the channel when it is open. The magnitude of If inhibition is directly related to the frequency of channel opening and would therefore be expected to be most effective at higher heart rates.

Ivabradine also was shown to improve outcomes in the Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial (SHIFT) (Swedberg et al. 2012), which enrolled symptomatic patients with an LVEF of 35% or less who were in sinus rhythm with heart rate of 70 beats/min or higher and on standard medical therapy for HF (including beta blockers).

Cardiac Glycosides

Major Clinical Trials

Digoxin and digitoxin are the most frequently used cardiac glycosides. Digoxin acts through inhibition of the sarcolemmal Na–K ATPase pump thus leading to increased intracellular sodium that is then exchanged with calcium. The increase in intracellular calcium causes the inotropic effect of the drug. Digoxin rapidly improves hemodynamics without increasing heart rate or decreasing BP and may be considered in patients with a low BP resulting from a low cardiac output (Gheorghiade and Braunwald 2009). Digoxin should not be used in patients with moderate to severe renal impairment, ongoing ischemia, or advanced atrioventricular block.

Therapy with digoxin commonly is initiated and maintained at a dose of 0.125–0.25 mg daily. For the great majority of patients, the dose should be 0.125 mg daily and the serum digoxin level should be below 1.0 ng/mL, especially in elderly patients, patients with impaired renal function, and patients with a low body mass.

Digitalis Investigation Group (DIG) trial evaluated the influence of digoxin in 6,800 patients with an EF $\leqslant$45% and in NYHA functional class II–IV. Patients were randomized to placebo or digoxin (0.25 mg once daily) to standard treatment. Digoxin did not alter all-cause mortality but decrease hospitalization admission (Gheorghiade and Braunwald 2009).

Complications of Digoxin Use

The principal adverse effects of digoxin are (1) cardiac arrhythmias including heart block (especially in the elderly) and ectopic and reentrant cardiac rhythms; (2) neurologic complaints such as visual disturbances, disorientation, and confusion; and (3) gastrointestinal symptoms such as anorexia, nausea, and vomiting.

7.3.2.7 Traditional Chinese Medicine (TCM)

TCM has a history of more than 2,000 years with unique theories and rich experience, even though TCM is considered as an alternative medicine in most western countries, nearly 70% patients in China preferred the use of both western medicine and TCM (Hao et al. 2017). Recently TCM proved their effects in improving hard and/or surrogate endpoints in heart failure patients by a series of high quality random control trials. The efficacy and safety of Qiliqiangxin capsule were compared with placebo in a RCT enrolling 512 chronic heart failure for 12 weeks, the medicine significantly reduced N-terminal pro-B-type natriuretic peptide and improve LVEF and quality of life as well as composite cardiac events (Li et al. 2013). Nuanxin capsule and placebo were randomly assigned to 5150 chronic heart failure patients for 24 weeks, and the TCM reduced hospitalization rate and incidence of acute heart failure (Zuo et al. 2010). The ability to increase LVEF of Shencaotongmai was also proved in a multicenter RCT enrolling 280 patients (Hao et al. 2017). And all of these TCM show good safe profiles. Even though the effect of TCM medications on long-term outcomes is still unclear, they would play an active role in heart failure treatment.

7.3.3 Heart Failure with Preserved EF

It is well accepted that at least half of the HF population burden is accompanied by a preserved EF. Although commonly thought to involve abnormalities of relaxation, compliance, and filling of the left ventricle, the pathophysiology is much more complex so that numerous RCTs have failed to find an approach that affects the natural history of the syndrome (Ponikowski et al. 2016). Medications that improve outcomes in patients who have heart failure with a reduced ejection fraction have not been shown to be of benefit in those who have heart failure with a preserved ejection fraction. Treatment of heart failure with a preserved ejection fraction should include diuretics for volume overload, treatment for cardiovascular and noncardiovascular coexisting conditions, aerobic exercise training, and education regarding self-care, and disease management programs for patients with refractory symptoms or frequent hospitalizations for heart failure.

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Chapter 8
Drug Discovery for Coronary Artery Disease

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Abstract Cardiovascular disease is the number one cause of human morbidity and mortality worldwide. Although cholesterol-lowering drugs, including statins and recently approved PCSK9 inhibitors, together with antithrombotic drugs have been historically successful in reducing the occurrence of coronary artery disease (CAD), the high incidence of CAD remains imposing the largest disease burden on our healthcare systems. We reviewed cardiovascular drugs recently approved or under clinical development, with a particular focus on their pharmacology and limitations. New agents targeting cholesterol/triglyceride lowering bear promise of further cardiovascular risk reduction. Some new antidiabetic agents show cardiovascular benefit in patients with diabetes. Improved antithrombotic agents with diminished bleeding risk are in clinical development. The recent clinical success of the IL-1β antibody in reducing atherothrombosis opens a new era of therapeutic discovery that targets inflammation. Chinese traditional medicine and cardiac regeneration are also discussed. Human genetics studies of CAD and further delineation of key determinants/pathways underlying the residual risk of CAD under current standard therapy will continue to fuel the pipeline of cardiovascular drug discovery.

Keywords Coronary artery disease · Drug discovery · Therapy · Inflammation · Lipid

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Currently available therapeutics for patients with atherosclerotic cardiovascular disease is largely restricted to alleviating hyperlipidemia or preventing thrombotic complications. Discovery of cholesterol-lowering drugs and antithrombotic drugs has been historically successful in reducing the occurrence of coronary artery disease (CAD) and its complications. Despite these progress,cardiovascular disease remains the major cause of human death worldwide. Ischemic heart disease is the number one disease burden to the whole society (Murray et al. 2015). Understanding of new mechanisms of the disease will provide further opportunities to prevent and treat CAD. In this chapter,we mainly overview CAD drugs that are under clinical development or approved recentlywith particular focus on those of new mechanisms of action or being first of class. Their pharmacologyadvantages and limitations will be discussed. Traditional medicine and regenerative medicine for CAD will also be discussed.

8.1 Lipids Modulating Drugs

The discovery that statins reduce cholesterol levels and CAD has promoted searching for new targets to lower cholesterol. This has yielded new drugs, such as PCSK9 inhibitors and cholesterol-absorption blockers, as well as drug candidates.

8.1.1 Proprotein convertase subtilisin/kexin type 9 inhibition

Low-density lipoprotein (LDL) particles receptor (LDLR) binds and initiates the ingestion of LDL-particles, which contains lipid molecules (including cholesterol), from the circulation, thus reducing plasma cholesterol concentrations. Proprotein convertase subtilisin/kexin type 9 (PCSK9) interacts with LDLR and mediates its intracellular degradation. When PCSK9 is blocked, more LDLRs are recycled to remove LDL-particles from the circulation. Thus, PCSK9 inhibition promotes LDLR-mediated liver uptake of circulating LDL, lowering plasma cholesterol levels. A link between PCSK9 and hypercholesterolemia was initially published in 2003, and PCSK9 monoclonal antibodies were approved as a new therapeutic strategy to reduce LDL-C in 2015. The progress from PCSK9 discovery to targeted treatment is unprecedented in terms of scale and speed.

Monoclonal Antibodies

Treatment of patients at high risk for cardiovascular events with antibodies blocking PCSK9 allows further cholesterol lowering by ~60% on top of standard therapy, including statin (Sabatine et al. 2015; Robinson et al. 2015). The first two PCSK9 inhibitors, alirocumab (Praluent, Sanofi/Regeneron) and evolocumab (Repatha, Amgen), were approved as biweekly subcutaneous injections, by the U.S. Food and Drug Administration (FDA) for lowering LDL cholesterol when statins and

other drugs are not sufficiently effective or poorly tolerated. The GLAGOV (Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound) trial (Nicholls et al. 2016) showed that adding evolocumab to statin therapy produced significant atheroma regression and a continuous benefit with LDL-C levels down to as low as 20 mg/dL. The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial showed that in patients with atherosclerotic cardiovascular disease who were receiving statin therapy, subcutaneous injection of evolocumab (either 140 mg every 2 weeks or 420 mg monthly) reduced LDL cholesterol by 59%, from a median baseline value of 92 mg per deciliter (2.4 mmol/L) to 30 mg per deciliter (0.78 mmol/L), and decreased cardiovascular risk (the primary composite endpoint of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) by 15% (Sabatine et al. 2017). There was no significant difference between the study groups with regard to adverse events (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were more common with evolocumab. No difference in cognitive function was observed between evolocumab and placebo over a median of 19 months (Giugliano et al. 2017). Recent ODYSSEY OUTCOMES trial shows that among patients who had a previous acute coronary syndrome and who were receiving high-intensity statin therapy, alirocumab treatment with a target level of LDL cholesterol level of 25–50 mg per deciliter (0.6–1.3 mmol/L) reduces the risk of recurrent ischemic cardiovascular events (Schwartz et al. 2018).

Future use of these PCSK9 antibodies may rely on compliance with injection delivery, safety of prolonged exposure to very low levels of LDL cholesterol and on possibilities of developing anti-drug antibodies, which may curtail cholesterol-lowering efficacy. Cost-effectiveness analysis indicates limitations on the general use of PCSK9 antibody drugs (about $14,000 per year) (Hlatky and Kazi 2017). Their use may particularly be appropriate for those with genetic defects for whom statins are not sufficiently effective, or intolerable (Nissen et al. 2016).

Antisense Oligonucleotide

Suppression of PCSK9 expression by antisense oligonucleotide has been explored for functional inhibition of PCSK9. Inclisiran is a synthetic small interference RNA (siRNA) molecule, inhibits intracellular PCSK9 synthesis by suppressing mRNA translation in hepatocytes. In phase I and II clinical trials (Fitzgerald et al. 2017; Ray et al. 2017), subcutaneous injection of inclisiran results in a dose-dependent, long-term, sustained reduction in LDL-C, with a single or double doses of 300 mg (at a 90 days interval) achieved ~50% reduction at day 180. Inclisiran provides advantages over monoclonal antibodies with an infrequent dosing interval of twice a year to reduce LDL-C by over 50%, similar to that achieved with biweekly or monthly administered antibodies. Inclisiran has been well tolerated and safe, without severe adverse events so far. Serious adverse events (myalgia, headache, fatigue, nasopharyngitis, back pain, hypertension, diarrhea, and dizziness) occurred similarly between inclisiran group and placebo group (11% vs. 8%) (Ray et al. 2017). Ongoing studies will establish the long-term safety of inclisiran, which is also important to RNA based therapy in general.

Vaccination
A vaccine that targets PCSK9 has been developed to treat high LDL-particle concentrations. The vaccine uses a virus-like particle (VLP) as an immunogenic carrier of an antigenic PCSK9 peptide. VLP's are viruses that have had their DNA removed so that they retain their external structure for antigen display and can induce an immune response but are unable to cause infection. Mice and macaques vaccinated with bacteriophage VLPs displaying PCSK9-derived peptides developed high-titer IgG antibodies that bound to circulating PCSK9. Vaccination was associated with significant reductions in total cholesterol, free cholesterol, phospholipids, and triglycerides (Crossey et al. 2015).

Small Molecules
Development of small molecular inhibitor for PCSK9 is challenging. This may reflect general difficulty to use small molecules to directly block protein-protein interaction. The plant alkaloid berberine inhibits the transcription of the PCSK9 gene in immortalized human hepatocytes in vitro, and lowers serum PCSK9 in mice and hamsters in vivo (Dong et al. 2015). Given the low bioavailability of berberine, its action on intestinal microbiota has recently emerged as a new mechanism underlying its hypolipidemic effect (See also in the section of Traditional Chinese Medicine).
Cholesterol-lowering drugs with differential mechanisms of action may have complementary clinical applications. For example, PCSK9 inhibitors may be appropriate for patients with statin intolerance, such as those with statin-associated muscle symptoms.

8.1.2 Cholesterol absorption

Blocking the absorption of cholesterol from the small intestine decreases the amount of cholesterol normally available to liver cells, leading them to absorb more from circulation and thus lowering levels of circulating cholesterol. Ezetimibe targets the critical mediator of cholesterol absorption, the Niemann-Pick C1-like 1 (NPC1L1) protein on the gastrointestinal tract epithelial cells and in hepatocytes, thereby reducing the absorption of cholesterol from the intestine. The IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) (Cannon et al. 2015) reports that, in stable patients who had had an acute coronary syndrome within the preceding 10 days, Ezetimibe, when added to statin therapy, resulted in incremental lowering of LDL cholesterol levels (1.4 mM vs. 1.8 mM) and improved cardiovascular outcomes—32.7% versus 34.7% on composite rate of cardiovascular death, nonfatal MI, unstable angina requiring rehospitalization, coronary revascularization, or nonfatal stroke, over an median follow-up of 6 years.

8.1.3 Cholesteryl ester transfer protein inhibition

Cholesteryl ester transfer protein (CETP) mediates the transfer of HDL cholesteryl esters for triglyceride (TG) in VLDL/LDL (Millar et al. 2017; Krauss et al. 2015). CETP inhibition increases high-density lipoprotein (HDL) cholesterol (traditionally regarded as good cholesterol) levels and decreases low-density lipoprotein (LDL) cholesterol (traditionally regarded as bad cholesterol) levels. It once bears promise to reduce the risk of atherosclerosis and other cardiovascular diseases by improving blood lipid levels. However, four drugs of this class failed in clinical trials for high-risk patients. Torcetrapib failed due to excess deaths in Phase III clinical trials, likely owing to the off-target effects of the drug. Lacking clinical efficacy, Dalcetrapib, Evacetrapib, and Obicetrapib halted, respectively, in 2012, 2015, and 2017. REVEAL (Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification) trial evaluated Anacetrapib, a novel CETP inhibitor, in patients with atherosclerotic vascular disease who were receiving intensive statin therapy (Group et al. 2017). The mean level of HDL cholesterol was higher by 1.12 mM in the anacetrapib group than in the placebo group (a relative difference of 104%), and the mean level of non-HDL cholesterol was lower by 0.44 mM, a relative difference of −18%. The major coronary event occurred in 10.8% of patients in the anacetrapib group versus 11.8% of patients in the placebo group (9% relative risk difference), after 4.1 years of follow-up (Group et al. 2017). Anacetrapib treatment was associated with a slightly higher systolic blood pressure level (0.7 mm/Hg) and an elevated risk for a diminished estimated glomerular filtration rate, with no significant between-group differences in the risk of death, cancer, or other serious adverse events. It is unclear whether the reduction in cardiovascular risk is the consequence of effects on the HDL raising or on CETP inhibitor-mediated reductions in LDL cholesterol, which has been validated with statins. Anacetrapib accumulates in adipose tissue with prolonged administration, and only minimally decline 1 year after cessation of treatment. Merck halted the development of anacetrapib, likely due to relatively modest benefit and safety concerns. It remains unknown whether CETP inhibitors may work better as monotherapy (intensive statin use in the patients of REVEAL trial may actually attenuate the efficacy), and whether certain subgroups with certain genotype may respond better to CETP inhibition in terms of HDL particles taking up cholesterol from the vessel wall. It is necessary to gain insights into the relation between HDL-particle content and beneficial function and to identify alternative targets and drug candidates.

8.1.4 Targeting high-density lipoprotein cholesterol

High-density lipoprotein (HDL) mediates reverse transport of cholesterol from atherosclerotic plaque and thus HDL cholesterol is traditionally believed to be “good cholesterol”, as compared to LDL cholesterol, which increases cardiovascular risk.

However, this notion has been challenged. Niacin lowers the LDL cholesterol level and raises the HDL cholesterol level. Among participants with atherosclerotic vascular disease, the addition of extended-release niacin–laropiprant(a drug itself has no cholesterol-lowering effect, but reduces facial flushes induced by niacin) to statin-based LDL cholesterol-lowering therapy did not significantly reduce the risk of major vascular events but did increase the risk of serious adverse events (HPS2-THRIVE trial).

Artificial HDL-like apolipoprotein A1 complexes (apoA1-Milano) once held promise in mediating regression of atherosclerosis. The failure to show benefits with MDCO-216 in the MILANO-PILOT trial further challenges the idea of raising HDL for cardiovascular benefit. There are other forms of HDL that continue to undergo clinical trials, as these trials progress we will see how the HDL story ultimately plays out.

8.1.5 Triglyceride lowering drugs

There is compelling epidemiological and genetic evidence indicating that triglyceride lowering may lower cardiovascular risk. Different approaches to lowering triglyceride are being evaluated in cardiovascular outcome trials.

Peroxisome Proliferator-Activated Receptor Alpha Agonist

Peroxisome proliferator-activated receptor alpha (PPARα) is the main target of fibrate drugs, a class of amphipathic carboxylic acids (clofibrate, gemfibrozil, ciprofibrate, bezafibrate, and fenofibrate). They were originally indicated for cholesterol disorders and more recently for disorders of high triglycerides.

Pemafibrate (marketed as Parmodia) is a PPARα agonist. It is approved in July 2017 in Japan, indicated for the treatment of dyslipidaemia. Parmodia is available in 0.1 mg tablets and the recommended dose is 0.1 mg twice daily. In clinical trials (Camejo 2017), pemafibrate as a monotherapy remarkably promotes triglycerides (TG) catabolism by enhancing fatty acid oxidation and inducing lipoprotein lipase gene transcription in liver and muscle. It reduces plasma TG in VLDL and postprandial chylomicrons and also the levels of cholesterol-rich remnants from these two lipoproteins. Pemafibrate as an add-on to statin therapy for managing atherogenic dyslipidaemia reduces TG with a dose–response relationship, remnant cholesterol, Apo B48 and Apo C-III (Fruchart 2017; Arai et al. 2017). Activation of PPARα by pemafibrate has multiple metabolic effects, rendering it difficult to attribute its potential cardiovascular benefit to individual change. For example, pemafibrate elevated levels of FGF21 that can improve plasma lipids, plasma glucose, and insulin resistance, pemafibrate upregulates hepatic ApoA-I synthesis and HDL production, and enhances cholesterol transport to the liver through ApoA-I apolipoprotein (Hennuyer et al. 2016).

PROMINENT (Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes) trial is a phase-3 trial to determine whether

pemafibrate administered 0.2 mg tablet twice daily will delay the time to first occurrence of any component of the clinical composite endpoint of nonfatal MI, nonfatal ischemic stroke, hospitalization for unstable angina requiring unplanned coronary revascularization, or cardiovascular death, in patients with type 2 diabetes and dyslipidemia. This trial is estimated to complete in 2022.

Eicosapentaenoic Acid

Eicosapentaenoic acid (EPA) is the main component of fish oil. EPA belongs to the omega-3 series of polyunsaturated fatty acids (PUFA). It is an indispensable essential nutrient that cannot be synthesized by the human body. Therefore, it is called an essential fatty acid. Although linolenic acid can be converted into EPA in the human body, this reaction is very slow in the human body and the amount of conversion is very small, far from meeting the human body's need for EPA, and therefore must be supplemented directly from food. Clinical trials have demonstrated that omega-3 series fatty acids not only can lower cholesterol and triglyceride levels, but inhibit platelet aggregation and inflammatory responses. Its mechanism of action may be that omega-3 PUFA competes with the storage of arachidonic acid to replace it and block the production of pro-inflammatory eicosanoids (Davinelli et al. 2018). Extensive research shows marine-derived omega-3 fatty acids decrease triglycerides with a potential reduction in cardiovascular disease in certain populations.

AMR101 (icosapent ethyl) is ethyl eicosapentaenoic acid, an ethyl ester of eicosapentaenoic acid (EPA, an omega-3 fatty acid). AMR101 is a highly purified ethyl ester of EPA, and is approved by the FDA in 2012 for severe hypertriglyceridemia. REDUCE-IT (Bhatt et al. 2019) (Reduction of Cardiovascular Events With EPA—Intervention Trial) evaluated the cardiovascular effect of 2 g of icosapent ethyl twice daily in patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135–499 mg per deciliter (1.52–5.63 mmol/L) and a low-density lipoprotein cholesterol level of 41–100 mg per deciliter (1.06–2.59 mmol/L). Compared with placebo, 4 g/Day AMR101 reduced long-term cardiovascular events (Composite endpoint of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina) (17.2% vs. 22.0%, hazard ratio, 0.75; 95% [CI], 0.68–0.83; $P < 0.001$) in high-risk patients with elevated triglyceride levels despite the use of statins. A larger percentage of patients in the icosapent ethyl group than in the placebo group were hospitalized for atrial fibrillation or flutter (3.1% vs. 2.1%, $P = 0.004$).

The cardiovascular benefit of n–3 fatty acids appears to relate to disease condition and/or dose. In general, populations at usual risk (VITAL trial, a primary prevention trial among men 50 years of age or older and women 55 years of age or older), marine n–3 fatty acids (at a dose of 1 g per day) did not result in a lower incidence of major cardiovascular events (primary endpoint, a composite of myocardial infarction, stroke, or death from cardiovascular causes) (hazard ratio, 0.92; 95% confidence interval [CI], 0.80–1.06; $P = 0.24$), but reduced a key secondary endpoint, total myocardial infarction, 0.72 (95% CI, 0.59–0.90) (Manson et al. 2019). Among patients with diabetes without atherosclerotic cardiovascular disease (ASCEND trial)

(Group et al. 2018) 1 g n – 3 fatty acids daily did not reduce the risk of serious vascular events compared with placebo (olive oil).

Epanova (omega-3 carboxylic acids) is a concentrate of omega-3 free fatty acids, developed from fish oils. STRENGTH (STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia) trial is a long-term cardiovascular outcome study to assess Epanova, taken once daily on top of statin, in patients with hypertriglyceridemia and low HDL and high risk for CVD. This phase 3 trial is started in 2014 and estimated to complete in late 2019.

Apolipoprotein C-III Inhibition

Apolipoprotein C-III (APOC3) is a component of TG-rich lipoproteins, known to inhibit lipoprotein lipase-mediated hydrolysis of TG-rich lipoproteins and to negatively affect receptor-mediated hepatic uptake of remnants of TG-rich lipoproteins, thereby regulating plasma TG levels. Elevated APOC3 levels result in accumulation of atherogenic very-low-density lipoproteins (VLDL) and chylomicron remnants, as a consequence of impaired lipolysis and disturbed clearance of TG-rich lipoproteins. Elevated APOC3 levels, especially when present on apolipoprotein E-containing lipoproteins, are an independent risk factor for CVD. Rare mutations that disrupt APOC3 function were associated with lower levels of plasma triglycerides and APOC3 and with a reduced risk of CAD (Tg et al. 2014). People with homozygous loss of function of APOC3 show marked blunting of the usual postprandial rise in plasma triglycerides (Saleheen et al. 2017). Although fibrates, statins and omega-3 fatty acids modestly decrease triglyceride levels (and apoC-III concentrations), there are many patients who still have severe hypertriglyceridemia and are at increased risk for pancreatitis and potentially for CVD.

ISIS 304801 is an antisense oligonucleotide that specifically binds to *APOC3* mRNA and induces its degradation. It robustly decreases both, apoC-III production and triglyceride concentrations. In a phase 2 trial in patients with severe or uncontrolled hypertriglyceridaemia, weekly subcutaneous injections of 100, 200, or 300 mg of ISIS 304801 for 13 weeks ISIS 304801 as monotherapy produced a dose-dependent, prolonged reduction in TG levels (largest decrease with 300 mg: 70.9% vs. 20.1% increase on placebo) and increase in HDL levels (300 mg: 45.7% vs. 0.7% with placebo). A similar effect was observed when the drug was used as an add-on to stable doses of fibrate therapy (Gaudet et al. 2015). It is being currently evaluated in phase 3 trials (Schmitz and Gouni-Berthold 2018). An outcome trial is needed to establish clinical proof-of-concept with therapeutics that inhibit APOC3.

Angiopoietin-Like 3 Inhibition

Angiopoietin-like 3 (ANGPTL3) is a protein that inhibits lipoprotein lipase (LPL) and endothelial lipase (EL), thereby increasing plasma triglyceride, LDL cholesterol, and HDL cholesterol. LPL is a rate-limiting enzyme for the hydrolysis of circulating triglycerides (TG) into free fatty acids that are absorbed by peripheral tissues (Zhang 2016). ANGPTL3 is a novel target to reduce triglyceride-rich lipoproteins (Olkkonen et al. 2018). Evinacumab is an antibody from Regeneron, which blocks the actions of ANGPTL3. An antisense oligonucleotide from Ionis Pharmaceuticals also blocks ANGPTL3 activity. Animal studies, as well as early clinical studies, show that

they can lower triglycerides to unprecedented levels. Further cardiovascular outcome studies are needed before considering these drugs for clinical approval.

8.1.6 Other lipid modulators

ETC-1002 (bempedoic acid) is a small molecule with a unique mechanism of action shown in nonclinical studies to modulate pathways of cholesterol, fatty acid, and carbohydrate metabolism (Nikolic et al. 2014; Bilen and Ballantyne 2016). ETC-1002 lowers LDL cholesterol and other lipids and shows that high-sensitivity C-reactive protein is improved in patients with type 2 diabetes and hypercholesterolemia (Gutierrez et al. 2014). In phase 2 studies, ETC-1002 reduced LDL-C as monotherapy, combined with ezetimibe, and added to statin therapy, with LDL-C lowering most pronounced when ETC-1002 was combined with ezetimibe in patients who cannot tolerate statins (Thompson et al. 2016).

8.2 Targeting Inflammation

Historical success of statins, together with the recent approval of PCSK9 inhibitors, has firmly established the therapeutic principle of lowering LDL-C for treating CAD. However, residual cardiovascular risk following successful LDL-C lowering therapy remains substantial. Inflammation is thought of as an essential pathology for CAD and its acute manifestation, myocardial infarction (MI), which involves cytokines, such as interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α, and C-reactive protein (CRP, a marker of inflammation) production. In addition to innate immunity, adaptive immunity is also associated with atherosclerosis through antigen-presenting cells, T and B lymphocytes. Statin is known to have anti-inflammatory activity besides LDL-C lowering effects, which may also contribute to its cardiovascular efficacy. Indeed, aggressive lipid lowering by high-dose atorvastatin decreases high-sensitivity CRP (hsCRP) serum levels and entails regression of atheromas. The clinical benefit is extended to primary prevention in patients with LDL-C levels < 130 mg/dl but elevated hsCRP, where rosuvastatin significantly reduces major cardiovascular event rates, with reductions in both LDL-C and hsCRP. In acute coronary syndrome (ACS), aggressive statin therapy also lowered the incidence of primary endpoints including MI, with the most substantial benefit in patients with declines in both LDL-C and CRP. Recent FOURIER Trial reveals that LDL-C and hsCRP are independently associated with the cardiovascular outcome (Bohula et al. 2018). Nevertheless, teasing out the anti-inflammatory effect of statin from its LDL cholesterol-lowering effect in cardiovascular prevention appears practically impossible.

Previous trials exploring treatment that specifically targets inflammation failed to show clinical benefits in CAD patients. The targets involved include p38 MAP

kinase, CRP, secretory phospholipase A2 (sPLA2, an enzyme catalyzes the first step of the arachidonic acid pathway of inflammation), lipoprotein-associated phospholipase A2 (Lp-PLA2, a secreted acetylhydrolase that catalyzes the degradation of platelet-activating factor), IL-1R, the IL-6 receptor, CC2 chemokine receptor, and some immunomodulatory or immunosuppressive therapies, such as cyclosporine and colchicine, CD20 blocker. Recently, the CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) trial provides first clinical evidence that an IL-1β antibody that leads to marked reductions in IL-6 and CRP reduces cardiovascular risk.

- **IL-1β inhibition**

IL-1, a pro-inflammatory cytokine, promotes the development of atherosclerosis and contributes to adverse remodeling and left ventricular dysfunction after acute myocardial infarction (AMI). In phase II studies, IL-1 blockade suppressed the inflammatory response associated with ST-segment elevation AMI and prevented heart failure (HF). Other phase II studies show improved exercise capacity with IL-1 blockade in patients with HF. Several IL-1 blockers are available for clinical use, which differ in mechanism of action, and potentially also efficacy and safety.

Canakinumab (trade name Ilaris) is a human monoclonal antibody that specifically inhibits IL-1β function. IL-1β is synthesized as a precursor form protein only after stimulation, in contrast to IL-1α. Canakinumab was approved for the treatment of cryopyrin-associated periodic syndromes (CAPS) in 2009. CAPS is a spectrum of auto-inflammatory syndromes including familial cold autoinflammatory syndrome, Muckle–Wells syndrome, and neonatal-onset multisystem inflammatory disease. In September 2016, FDA approved the use of canakinumab on 3 additional rare and serious auto-inflammatory diseases: TNF receptor-associated periodic syndrome, hyper immunoglobulin D syndrome/mevalonate kinase deficiency and Familial Mediterranean fever.

CANTOS trial shows that, in patients with previous myocardial infarction and persistently elevated hsCRP (>= 2 mg/L), subcutaneous administration of canakinumab every 3 months at 150 mg led to a significantly lower rate of recurrent cardiovascular events (nonfatal MI, nonfatal stroke, or cardiovascular death) than placebo with a hazard ratio (HR) of 0.85 (95% CI, 0.74–0.98), independent of lipid-level lowering (Ridker et al. 2017). Baseline clinical characteristics did not define patient groups with greater or lesser cardiovascular benefits when treated with canakinumab. However, trial participants allocated to canakinumab who achieved hsCRP concentrations less than 2 mg/L had a 25% reduction in major adverse cardiovascular events (HR = 0.75, 95% CI 0.66–0.85), whereas no significant benefit was observed among those with on-treatment hsCRP concentrations of 2 mg/L or above (HR = 0.90, 0.79–1.02, p = 0.11). These data further suggest that lower is better for inflammation reduction with canakinumab (Ridker et al. 2018). This phase 3 trial provides the first clinical proof-of-principle for anti-inflammatory therapy for atherosclerosis. Interestingly, the CANTOS trial also showed a significant reduction in lung cancer incidence and mortality in the canakinumab treated group compared to the placebo. A higher incidence of fatal infection was observed in the canakinumab group than in

the placebo, which is likely due to a blunting of the inflammatory signs of infection leading to delayed presentation and diagnosis. IL-1 blockade was not associated with opportunistic infections and there was no difference in all-cause mortality with the canakinumab treatment. Cost-effectiveness and potential risk of immune suppression determine whether and who might benefit from the use of canakinumab for cardiovascular prevention.

- **Methotrexate and lessons learned**

Methotrexate inhibits dihydrofolate reductase that is essential for DNA synthesis and it also inhibits lymphocyte activation. It is on the World Health Organization's List of Essential Medicines being used as a chemotherapy agent and immune system suppressant. Low-dose methotrexate is an effective anti-inflammatory therapy widely used to treat rheumatoid arthritis. The CIRT (Cardiovascular Inflammation Reduction Trial) evaluates effects of low-dose (15–20 mg per week) methotrexate on rates of MI, stroke, and cardiovascular death among patients with previous MI or multivessel coronary disease who additionally had either type 2 diabetes or metabolic syndrome, conditions associated with an enhanced pro-inflammatory response. However, low-dose methotrexate did not reduce levels of IL-1β, IL-6, or CRP and did not result in fewer cardiovascular events than placebo in these patients with stable atherosclerosis (Ridker et al. 2018), raising questions on the dose and population selected.

Clinical data on inflammatory biomarkers, biological data and recent Mendelian randomization data suggest that inflammatory mediators of atherosclerosis may converge on the central IL-1, tumor necrosis factor (TNF-a), IL-6 signaling pathway. On this basis, emerging anti-inflammatory approaches to vascular protection can be categorized into two broad groups, those that target the central IL-6 inflammatory signaling pathway and those that do not. Both approaches have the potential to benefit patients and reduce vascular events, but may not concord each other. The inflammatory system is redundant, compensatory, and crucial for survival, evaluation of risks, as well as benefits, must drive the development of agents in this class.

8.3 Antiplatelet Drugs

Thrombosis that occludes blood vessels is the direct cause of acute manifestations of CAD. Antiplatelet drugs reduce thrombotic risk by inhibiting platelet activation and aggregation. Thromboxane and ADP activate their corresponding platelet receptors TP and P2Y12, respectively, and result in platelet inside-out signaling and integrin αIIbβ3 (glycoprotein IIb/IIIa) conformation change allowing its binding to fibrinogen to aggregate platelets. Drugs targeting the above pathways have been successfully used in the clinic. Aspirin suppresses thromboxane production and inhibits platelet aggregation. It is a cornerstone therapy for secondary cardiovascular prevention in ACS, a benefit further enhanced by additional P2Y12 antagonism through clopidogrel, or, more recently developed prasugrel or ticagrelor. Platelet integrin αIIbβ3 inhibitors are potent antithrombotic drugs that are used intravenously to treat

ACS, but they also have the life-threatening adverse effect of causing bleeding. Discovery of antiplatelet drugs that can effectively prevent thrombosis while sparing bleeding side effects remains an unmet medical need.

- **Proteinase-activated receptors**

Thrombin activates platelets by cleaving/activating a G–protein-coupled family of proteinase-activated receptors (PARs). The signaling mechanism involves the proteolytic unmasking of an N-terminal receptor sequence that acts as a tethered receptor-activating ligand. The recognized targets of thrombin cleavage and activation for signaling are PAR1 and PAR4, in which thrombin cleaves at a conserved target arginine to reveal a tethered ligand. Unlike anticoagulants, PAR1 inhibitors block downstream of PAR1 without directly impacting thrombin-induced fibrin polymerization. Vorapaxar (Zontivity), a competitive PAR1 antagonist, is effective in treating ACS, however, the severe bleeding associated with this drug has limited its use in the clinic. Due to the efficacy of thrombin acting via PAR1, strategies to selectively inhibit specific PAR1-mediated G protein signaling pathways or to target the second thrombin platelet receptor, PAR4, are being devised (Wong et al. 2017). The rationale behind these alternative approaches is to bias downstream thrombin activity via PARs to allow for inhibition of pro-thrombotic pathways but maintain other pathways that may preserve hemostatic balance and improve bleeding profiles for widespread clinical use.

- **Platelet integrin outside-in signaling**

Activated platelets facilitate coagulation (platelet procoagulant activity, PPA) mainly by exposing the procoagulant phospholipid phosphatidylserine (PS) on the outer membrane surfaces and releasing PS-expressed microvesicles (MVs). Recent studies indicate that selective targeting of integrin outside-in signaling as a new antithrombotic strategy that has the advantage of potently inhibiting occlusive platelet thrombus expansion without causing excessive bleeding (Shen et al. 2013). β3 integrins serve as a shear sensor activating the Gα13-dependent outside-in signaling pathway to facilitate platelet procoagulant function. An inhibitor of outside-in signaling that targets Gα13-integrin interaction was discovered to prevent occlusive thrombosis in vivo by inhibiting both coagulation and platelet thrombus formation (Pang et al. 2018). It is known that partial inhibition of platelet thrombus formation by platelet activation inhibitors or by integrin inhibitors are not effective in inhibiting fibrin clot formation, whereas complete inhibition of integrin ligand-binding function is likely to cause excessive bleeding. Thus, by targeting integrin outside-in signaling without blocking platelet adhesion and primary aggregation, it is possible to diminish platelet-dependent intravascular fibrin clot without causing excessive bleeding. Because the intravascular fibrin clot around the platelet thrombus is associated with thrombus expansion and stabilization, this novel effect of outside-in signaling inhibitors is likely to contribute to the potency and anticlotting effect of these new drugs, and is advantageous over the current antiplatelet drugs. Pharmacological targeting of Gα13-integrin interaction is under preclinical development.

- **Reactive oxygen species**

Reactive oxygen species is known to regulate thrombosis (Pietraforte et al. 2014; Forstermann 2008; Delaney et al. 2016). In a randomized, placebo-controlled clinical trial in patients with antiphospholipid syndrome, treatment with ubiquinol, the reduced equivalent of coenzyme Q10, improved endothelial function, and reduced thrombotic risk markers, likely through reduced platelet activation and endothelial inflammation related to oxidative stress (Perez-Sanchez et al. 2017).

8.4 Anticoagulation Drugs

Activation of coagulation is essential to thrombosis. The coagulation pathway is a protease activation cascade in the blood, leading to the formation of fibrin that stabilizes blood clot (Fig. 8.1). It is classified into the extrinsic pathway and intrinsic pathway, which are initiated by tissue factor and contact activation, respectively. Both pathways share the common pathway of coagulation that generates factor Xa and thrombin, which cleaves fibrinogen to form fibrin.

Heparin and vitamin K antagonists (VKAs) are the first used as anticoagulants in the middle of the twentieth century. Heparin is a naturally occurring anticoagulant produced in the body. It binds to and activates antithrombin III (AT), thus inactivating thrombin and factor Xa. VKAs, such as warfarin, inhibit vitamin K epoxide reductase and thus the formation of vitamin K that is required for the production of certain

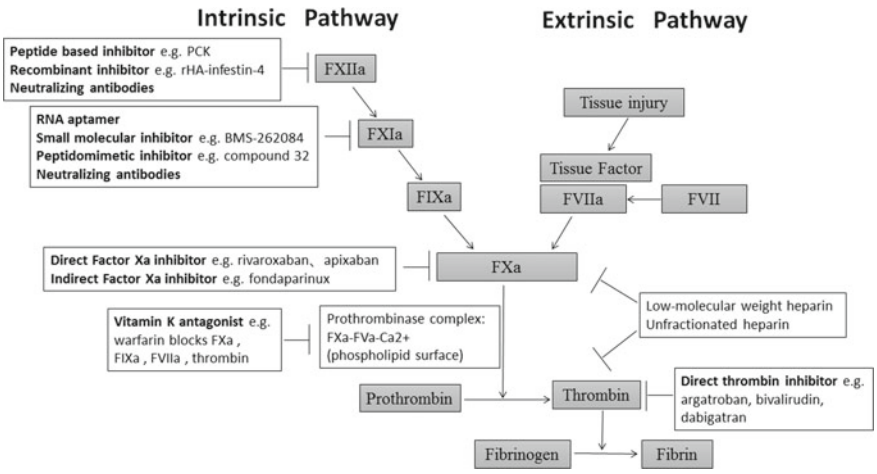

Fig. 8.1 Coagulation pathway and anticoagulant targets. Coagulation cascade is a series of sequential reactions in which zymogens are converted to active serine proteases ultimately resulting in the formation of covalently cross-linked fibrin. Blood coagulation can be triggered via the extrinsic pathway that is initiated by tissue factor following tissue trauma or via an intrinsic pathway that is driven by FXII activation. Anticoagulants targeting FXII, FXI and FIX are in development

clotting proteins, including the carboxylation of prothrombin to form active thrombin. VKAs and heparin have been the gold standard for the treatment and prevention of thromboembolic disease for many years. Unfortunately, they are accompanied by serious bleeding problems, it is necessary to monitor the therapeutic window, and there are various interactions with food and other drugs. A serious side-effect of heparin is heparin-induced thrombocytopenia, caused by an immunological reaction against platelets, resulting in platelet degradation. VKAs are very effective in the prevention and treatment of venous and arterial thrombosis. However, warfarin has many side effects of which bleeding is the most pronounced. It is estimated that, on a yearly basis, 0.5% of patients on VKAs suffer from major bleeding for which medical treatment is necessary, with a death rate of 0.25% due to bleeding. In 1985 and 2001, low-molecular-weight heparin (LMWH) and fondaparinux (chemically related to LMWH) were developed, respectively, which demonstrate better bioavailability after subcutaneous injection than heparin and more predictable anticoagulant responses. They do not need coagulation monitoring, thereby reducing healthcare costs and increasing patient satisfaction.

Coincident with these advances was the development of bivalirudin, a parenteral synthetic peptide inhibitor of thrombin that is derived from the naturally occurring drug hirudin found in the saliva of the medicinal leech. Bivalirudin is a synthetic peptide that directly inhibits thrombin and overcomes many of the limitations seen with indirect thrombin inhibitors. It inhibits both circulating and clot-bound thrombin, and also inhibits thrombin-mediated platelet activation. It does not bind to plasma proteins or to red blood cells and has a half-life of approximately 25 min in patients with normal renal function with a predictable antithrombotic response. It does not activate platelets and has been used in patients with, or at risk of, heparin-induced thrombocytopenia or heparin-induced thrombocytopenia and thrombosis syndrome. Following two large randomized controlled trials, HORIZONS-AMI and ACUITY, which showed a reduced rate of adverse clinical events (primarily driven by lower major bleeding events) with bivalirudin compared with unfractionated heparin (UFH) with glycoprotein IIb/IIIa inhibitors, bivalirudin rapidly gained favor in the United States, surpassing the use of UFH as the anticoagulant of choice during percutaneous coronary interventions (PCI) for NSTEMI and STEMI. Bivalirudin is widely used in place of heparin during PCI (Erlinge et al. 2017).

Efforts in seeking oral anticoagulants that are more convenient to administer than VKAs lead to the discovery of a new generation of drugs, which is known as direct oral anticoagulants (DOACs). DOACs include dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, edoxaban, and betrixaban, which inhibit factor Xa. These agents are at least as effective as VKAs but are associated with less bleeding, particularly less intracranial bleeding, and are easier to administer because they can be given in fixed doses without routine coagulation monitoring. Because of these attributes, current guidelines give preference to the DOACs over VKAs for stroke prevention in atrial fibrillation and for treatment of venous thromboembolism. Prescriptions for DOACs now surpass those for VKAs in several countries and are likely to increase as new indications are identified.

Currently available coagulants inhibit the common pathway of the coagulation cascade that is also required for hemostasis and, as such, bear an inherent risk for bleeding complications. Despite a similar or even superior effectiveness compared to VKAs, DOACs have different limitations: (1) bleeding is still an important problem; (2) there is no routine, widely available diagnostic test that can safely monitor the therapeutic window; (3) there is no reversal agent available for these anticoagulants, which is particularly undesirable in trauma patients. Therefore, the search for new anticoagulants continues. The goal of anticoagulant therapy is to attenuate thrombosis without compromising hemostasis. Drugs targeting the intrinsic pathway of coagulation (factor XIIa, factor XIa, and factor IXa) bear such potential. This pathway amplifies the clotting cascade but unlike the extrinsic (tissue factor and factor VIIa) and common pathways (factor Xa and thrombin) appears not essential for hemostasis.

- **Coagulation factor XI**

Growing evidence suggests that factor (F) XI plays an important role in thrombosis with a relatively limited contribution to hemostasis. Congenital FXI deficiency defined using an FXI activity assay is protective against venous thromboembolism (VTE), ischemic stroke, and myocardial infarction (Preis et al. 2017). Subjects with higher levels of FXI are more prone to ischemic stroke and VTE, Inhibitors targeting FXI/FXIa (the active form of FXI) have emerged as a new generation of anticoagulants to effectively curtail thromboembolic diseases without potential fatal bleeding. Available inhibitors of FXI/FXIa include polypeptides, active site peptidomimetic inhibitors, allosteric inhibitors, antibodies, aptamers, and antisense oligonucleotides (ASOs), which reduce FXI biosynthesis by blocking its expression. In animal studies, FXI antibodies attenuate platelet and fibrin deposition and FXI ASO reduces thrombosis in a concentration-dependent manner.

Proof-of-concept comes from a small phase 2 study of patients undergoing elective knee arthroplasty (Buller et al. 2015). Subcutaneous injection of an FXI ASO (IONIS-416858, 300 mg) starting 35 days before surgery reduced mean FXI levels to 28% of baseline values, at the time of surgery. Compared with 40-mg enoxaparin (low-molecular-weight heparin) once daily starting after surgery and continued for at least 10 days, IONIS-416858 reduced venous thromboembolism events (asymptomatic or symptomatic deep-vein thrombosis, symptomatic pulmonary embolism, and VTE-related mortality) 4% (3 of 71 patients) versus 30% (21 of 69 patients). The rates of the composite of major and clinically relevant nonmajor bleeding were 3% in the IONIS-416858 group and 8% in the enoxaparin groups. Nevertheless, this encouraging observation needs confirmation in larger trials to show the relative advantage of lowering FXI levels in reducing VTE risk but without increasing bleeding risk, compared with enoxaparin. The addition of low doses of rivaroxaban (FXa inhibitor) to patients with recent ACS reduces the rates of death from cardiovascular causes without increasing fatal bleeding, but increases intracranial hemorrhage. In light of this, reducing FXI levels or inhibition of FXI in patients with a recent ACS might also reduce death rates in a similar manner to treatment with rivaroxaban but without an increase in intracranial hemorrhage. It is likely that inhibition of FXI

prevents the propagation of coagulation by suppressing both intrinsic pathway and its amplification of extrinsic activation. Thus, FXI-directed strategies may be further explored for additional clinical indications. Initial findings have also demonstrated the potential of FXI/FXIa inhibitors in sepsis, listeriosis, and arterial hypertension.

- **Coagulation factor XII**

FXII is a plasma protease that is activated by binding to negatively charged surfaces. The active form of FXII (FXIIa) initiates the intrinsic coagulation pathway. Although there is a lack of human data supporting the relationship between factor XII and thrombosis, FXII deficiency is not associated with bleeding (Key 2014). Preclinical evidence consistently shows that pharmacological inhibition of FXII/FXIIa may be a promising therapeutic anticoagulation treatment strategy with less bleeding risk (Nickel et al. 2017). FXIIa also contributes to inflammation through the activation of the bradykinin-producing kallikrein–kinin system. FXII(a) inhibitors have been developed, including recombinant proteins, synthetic peptides, small molecular inhibitors, antibodies, and ASO. Most of these inhibitors showed antithrombotic effects with additional anti-inflammatory properties.

FXII monoclonal antibody 15H8 inhibited thrombosis formation in baboons (Matafonov et al. 2014). 3F7 is a recombinant fully human FXIIa-neutralizing antibody, which blocked experimental thrombosis in mice and rabbits (Larsson et al. 2014) and inhibited thrombosis as efficiently as heparin in a rabbit model of cardiopulmonary bypass, without the increased bleeding risk seen with heparin. 3F7 was also reported to abolish bradykinin generation in hereditary angioedema (HAE) type III patient plasma and to blunt edema in a mouse model (Bjorkqvist et al. 2015). Suppressing FXII expression with ASO reduced arterial and venous thrombosis in mice (Revenko et al. 2011) and attenuated catheter-induced thrombosis in rabbits (Yau et al. 2014) without increasing bleeding risk. Targeting FXII by ASO has a slow onset of action and requires multiple parenteral ASO administration. Small-molecule inhibitors of FXIIa are still under development.

The FXII-driven coagulation mediates not only thrombosis but also inflammatory life-threatening diseases. These include edema, experimental autoimmune encephalomyelitis, hereditary angioedema and settings where the blood comes in contact with nonphysiological surfaces such as catheters, extracorporeal membrane oxygenation, dialysis membranes, and ventricular assist devices. Although pharmacological inhibition of FXII has been identified as a potent strategy to limit thrombosis in animal models, without increased bleeding tendency, and to treat edema formation and hypotension in mice with possible implications for patients, these promises await confirmation in clinical trials.

8.5 Antidiabetic Agents

Epidemiologic studies show a clear correlation between lower blood sugars and better health outcomes in patients with diabetes mellitus. Every 1% increase in the

hemoglobin A1c was associated with an 18% increase in the risk of cardiovascular (CV) events, 12–14% increase risk of death and a 37% increased risk of eye disease or kidney disease. Most diabetic patients die of cardiovascular disease (CVD). Hyperglycaemia itself contributes to the pathogenesis of atherosclerosis and heart failure (HF) in these patients. Treating blood glucose to current guidelines is safe and very important for reducing microvascular complications like nerve, kidney and eye disease. However, most glucose-lowering drugs studied, as in trials of ADVANCE, ACCORD, VADT, etc., failed to reduce cardiovascular adverse events despite the proven ability to lower blood glucose, especially in patients with a long duration of type 2 diabetes mellitus (T2D) and prevalent CVD. Such drugs include metformin, sulfonylureas, PPAR agonists thiazolidinediones and dipeptidyl peptidase-4 (DPP-4) inhibitors. No significant long-term efficacy of insulin on any clinical outcome in T2D was observed. Actually, some diabetes drugs, in particular, rosiglitazone, even increase adverse cardiovascular events. As such, regulatory guidance specifies the need to establish cardiovascular safety of new diabetes therapies in patients with T2D in order to rule out excess cardiovascular risk. There is evidence suggesting that earlier treatment in prediabetic patients before disease onset may be effective although its effects are delayed (UKPDS trial). Recent trials show that diabetes drugs targeting SGLT2 or GLP1 may improve cardiovascular outcome in patients with established T2D.

- **Sodium-glucose linked transporter 2 inhibition**

Sodium-glucose linked transporter (SGLT) is a family of glucose transporter, with SGLT1 and SGLT2 being the two most well-known members. SGLT1 is found in the enterocytes of the small intestine and in the proximal straight tubule. SGLT2 is mainly expressed in the proximal convoluted tubule of the nephron. They contribute to renal glucose reabsorption. In a healthy nephron, the filtered glucose in the glomerulus is all reabsorbed along the nephron (at least 90% in the proximal convoluted tubule, via SGLT2). In hyperglycemic condition, glucose is excreted in urine because SGLT is saturated with the filtered glucose. SGLT2 inhibitors increase urinary glucose excretion, thus improving glycemic control independent of insulin.

Empagliflozin (trade name Jardiance) is an SGLT2 inhibitor, approved for the treatment of T2D in adults in 2014. EMPA-REG OUTCOME trial (Zinman et al. 2015) reports that in a population of patients with T2D and established cardiovascular disease on a background of standard care, empagliflozin reduces the combined CV endpoint of CV death, nonfatal MI, and nonfatal stroke compared to placebo (10.5% vs. 12.1%, HR = 0.86). Empagliflozin also significantly and robustly reduced the individual endpoints of CV death (3.7%, vs. 5.9%; 38% relative risk reduction), any cause mortality (5.7% and 8.3%, respectively; 32% relative risk reduction), and hospitalization for HF (2.7% and 4.1%, respectively; 35% relative risk reduction) in this high-risk population. These cardiovascular beneficial effects of empagliflozin may result from an interplay of various factors beyond glucose control such as weight loss, blood pressure lowering and sodium depletion, renal hemodynamic effects, effects on myocardial energetics, and/or neurohormonal effects, etc. Future studies are warranted to clarify the underlying mechanisms, and importantly to assess whether such

beneficial effects are evident across the SGLT2-inhibitor class of medications or unique to empagliflozin. An increased rate of genital infection was observed among patients receiving empagliflozin (Zinman et al. 2015). Empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care (Wanner et al. 2016). The risk of developing diabetic ketoacidosis (DKA) among T2D patients initiating an SGLT2 inhibitor is about double that seen among patients starting a DPP-4 inhibitor, but the overall risk is still low (Fralick et al. 2017). Patients are advised to be monitored for signs of DKA after starting on SGLT2 inhibitors.

Canagliflozin is another SGLT2 inhibitor that reduces glycemia as well as blood pressure, body weight, and albuminuria in people with diabetes. Patients with T2D and prior cardiovascular events had higher rates of cardiovascular outcomes compared with the primary prevention patients. Canagliflozin reduced cardiovascular and renal outcomes similarly among both primary and secondary prevention participants (Mahaffey et al. 2018). In two CANVAS trials involving patients with T2D and an elevated risk of cardiovascular disease, patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo but a greater risk of amputation, primarily at the level of the toe or metatarsal (Neal et al. 2017). Canagliflozin was also associated with a lower rate of progression of albuminuria, however, amputation occurred more frequently. The benefit of canagliflozin may be greater among those with a prior history of heart failure, and did not appear to be modified by baseline renal function (Neuen et al. 2018; Radholm et al. 2018).

- **Glucagon-like peptide-1**

Glucagon-like peptide-1 (GLP-1) is an incretin and has the ability to decrease blood sugar levels in a glucose-dependent manner by enhancing the secretion of insulin. GLP-1 is a 30 amino acid long peptide hormone derived from posttranslational processing of the proglucagon peptide. It is produced and secreted by intestinal enteroendocrine L-cells and certain neurons in the brainstem upon food consumption. Endogenous GLP-1 is rapidly degraded primarily by DPP-4, but also neutral endopeptidase 24.11 and renal clearance, resulting in a half-life of approximately 2 min. Consequently, only 10–15% of GLP-1 reaches circulation intact, leading to fasting plasma levels of only 0–15 pmol/L. To overcome this, GLP-1 receptor agonists and DPP-4 inhibitors have been developed to increase GLP-1 activity. As opposed to common treatment agents such as insulin and sulphonylurea, GLP-1-based treatment has been associated with weight loss and a lower risk of hypoglycemia, two important considerations for patients with T2D.

Liraglutide (Victoza, Novo Nordisk) is a once-daily injectable derivative of the human incretin GLP-1, for the treatment of T2D or obesity. It binds to the same receptors as does the endogenous metabolic hormone GLP-1 that stimulates insulin secretion. Liraglutide reduces meal-related hyperglycemia by increasing insulin secretion when required by increasing glucose levels, delaying gastric emptying, and suppressing prandial glucagon secretion. In patients with T2D and high cardiovascular risk(LEADER Trial), liraglutide, when added to standard care, reduces the rate of the first occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal

stroke (13.0% vs. 14.9%, HR, 0.87; 95% CI, 0.78–0.97). The rate of death from cardiovascular cause (4.7% vs. 6.0%, HR, 0.78, 95% CI, 0.66–0.93) and from any cause (8.2% vs. 9.6%, HR, 0.85; 95% CI, 0.74–0.97) was lower in the liraglutide group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events (Alvarez-Villalobos et al. 2016).

Semaglutide (Ozempic, Novo Nordisk) is a GLP-1 analogue with an extended half-life of approximately 1 week. In a trial (SUSTAIN-6) of 3297 patients with T2D who were at high cardiovascular risk, semaglutide treatment significantly lowered the combined risk for CV death, nonfatal MI or nonfatal stroke compared to placebo (6.6% vs. 8.9%, HR, 0.74). The rates of nonfatal MI and nonfatal stroke, for the semaglutide group as compared to placebo group, were 2.9% versus 3.9% (HR, 0.74; $P = 0.12$) and 1.6% versus 2.7% (HR, 0.61; $P = 0.04$), respectively. Rates of death from cardiovascular causes were similar in the two groups. Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications were significantly higher (HR, 1.76; 95% CI, 1.11–2.78; $P = 0.02$). Fewer serious adverse events occurred in the semaglutide group, although more patients discontinued treatment because of adverse events, mainly gastrointestinal (Marso et al. 2016).

The cardiovascular beneficial effects of empagliflozin and liraglutide may attribute to effects other than their glucose-lowering effect, since both drugs only modestly reduced blood glucose (0.4% in HbA1c). Understanding the underlying mechanism may provide new therapeutic targets for patients with atherosclerotic disease or at risk.

8.6 Emerging Therapeutic Targets from GWAS

The exceptionally rapid development of the new class of cholesterol-lowering drugs targeting PCSK9 exemplifies how the genetic discovery of human diseases may expedite the development of new drugs. In this regard, genome-wide association studies (GWAS) of CAD provide tremendous opportunities for elucidating novel disease mechanisms and potential therapeutic targets (Consortium et al. 2013; Roberts 2014; Yao et al. 2018). Candidate genes of potential mechanistic relevance, such as CDKN2A/B, CXCL12, and LIPA, are under intensive research. Genetic loci of CXCL12, and plasma levels of its chemokine product, also known as SDF1, are associated with CAD. Recent studies of its secondarily discovered receptor, CXCR7, indicate that activation of CXCR7 promotes endothelial repair and angiogenesis, thus restrains injury-induced adverse vascular remodeling, and promotes hear functional recovery after an attack of MI (Hao et al. 2017).

8.7 Traditional Chinese Medicine

Coronary artery disease (CAD), also known as coronary heart diseases or ischemic heart disease, refers to a series of diseases such as stable angina, unstable angina, myocardial infarction and sudden cardiac death that are mainly attributable to coronary artery stenosis due to atherosclerotic plaque. The development of atherosclerosis leads to a decrease or even cessation (in the case of atherothrombosis) of the coronary artery flow, resulting in cardiomyocyte damage and functional loss. Some traditional Chinese medicine (TCM) has been used for CAD, to relieve symptoms. However, there is a lack of clinical outcome trials for most if not all TCM that are already in practice for CAD treatment. Because TCM is an impure natural product, potential multiple active ingredients and their interactions make it challenging to precisely delineate their molecular pharmacology or therapeutic target. Nevertheless, with a modern pharmacological approach, researchers have identified some bioactive components in TCM extractions. Further studies may lead to the discovery of new drugs that demonstrate clear pharmacology, clinical efficacy as well as toxic profile. Listed below are some bioactive ingredients derived from TCM extractions that have published evidence on their potential mechanism of action. It's worth to note that purified ingredients from TCM do not necessarily have a similar profile of efficacy or safety compared with the TCM from which they are isolated.

- **Berberine**

Berberine is a quaternary ammonium salt from the protoberberine group of benzylisoquinoline alkaloids found in such plants as Berberis. This first recorded use of berberine is described in the ancient Chinese medical book *The Divine Farmer's Herb-Root Classic*. Berberine is considered an antibiotic and has been used to treat gastroenteritis, bacillary dysentery, ocular conjunctivitis, suppurative otitis media. Whether berberine may be used for treating diabetes, hyperlipidemia is under investigation. Berberine might also possess antiaging (gero-suppressive) properties. The bioavailability of berberine is low (Liu et al. 2016). Berberine is reported to inhibit the intestinal absorption of cholesterol and promote the excretion of cholesterol from the liver to the bile in hyperlipidemic hamsters (Li et al. 2015). Berberine may influence microbiota in the intestine, which contributes to the reduced plasma cholesterol levels, a novel mechanism different from statin (Zhu et al. 2018; Feng et al. 2018). Phase II clinical trial of berberine is ongoing.

- **Danshensu**

Radix Salviae miltiorrhizae, danshen root (danshen), is one of the widely used Chinese herbal medicines in clinics, containing rich phenolic compounds. Danshensu (DSS) is the main active compound responsible for the pharmacologic effects of danshen. DSS has various various cardiovascular protective effects, which include coronary artery dilation, platelet inhibition, microcirculation improvement, cardiomyocyte protection from myocardial ischemia-reperfusion injury (Yu et al. 2017). DSS appears to act on mTOR signaling (Fan et al. 2016) and involve in ROS scavenging and boosting endogenous antioxidants, including SOD, CAT, MDA, GSH-PX

and HO-1, via activating nuclear factor erythroid-2-related factor 2 (Nrf2) signaling pathway (Yu et al. 2015).

Dantonic® (T89-07-CAESA) is a botanical drug that consists of extracts of danshen (Radix Salviae Miltiorrhizae) and sanqi (Radix Notoginseng) with borneol in a capsule form. The drug is currently approved in 26 countries outside the USA for the treatment and prevention of chronic stable angina pectoris and other cardiovascular disease related conditions. A Phase III clinical trial (https://clinicaltrials.gov/ct2/show/NCT01659580) is to confirm the efficacy and safety of the drug at 150 and 225 mg doses in the prevention and treatment of angina pectoris in patients with Chronic Stable Angina. The trial was completed in late 2016, with no results published.

- **Tanshione IIA**

Lipid-soluble extractions of Danshen consist of tanshinone I, IIA, B, cryptotanshinone, dihydrotanshinone I, methylenetanshinone, and isotanshinone IIA. Among the tanshinone, tanshinone IIA is widely used in treatment of various cardiovascular diseases. Tanshinone IIA decreases expression of TLR4, NF-Kb-p65, MyD88, IL-2, IL-6, IL-8, PICP, and PIINP, as well as alleviates macrophage infiltration, cardiomyocyte apoptosis, which might result from inhibition of TLR4/MyD88/NF-KB signaling pathway (Wu et al. 2018). In addition, the cardioprotective effect of tanshinone IIA may also partially mediated via blocking alternative complement pathway (Wang et al. 2011) and by repressing miR-1 level in ischemic and hypoxic cardiomyocytes, which subsequently restored its target Cx43 protein (Zhang et al. 2010).

- **Ligustrazine**

Ligustrazine (4-methyl-pyrazine[tetramethylpyrazine]), a crude herbal drug isolated from the dried root or rhizome of Rhizoma Chuanxiong, has been long used in China to treat CVDs including coronary heart disease, hypertension, arrhythmia, heart failure, dilated cardiomyopathy, dyslipidemia, and myocarditis (Lv et al. 2012; Kwan et al. 1990). Ligustrazine suppresses the development of atherosclerosis and hepatic lipid accumulation via the alleviation of oxidative stress and dyslipidemia (Jiang et al. 2011). Ligustrazine has a protective function on the endothelium via inhibition of immunological reactions, underscores its role in atherosclerotic prevention (Wu et al. 2012).

- **Ginkgolide B**

Ginkgolide B (GB) is the major terpenoid component extracted from G. Biloba leaves. GB exerts an antagonistic activity against the platelet-activating factor (PAF) and thus inhibits PAF-induced inflammatory reactions (Yang et al. 2004; Mahmoud et al. 2000). PAF antagonist GB has a protective effect against IR-induced myocardial dysfunction likely via protecting membrane phospholipids (Pei et al. 2015).

- **Astragaloside**

Astragalus membranaceus is a commonly used traditional Chinese herb that contains flavonoids, saponins, and other active ingredients that have wide pharmacological

actions, including antidiabetic, antihypertensive, anti-inflammatory, and cardioprotective effects as well as the prevention of heart failure. Astragaloside is one of the main components of Astragalus membranaceus, which could modulate the RAAS and inhibit cardiomyocyte hypertrophy and apoptosis to protect the heart (Huang et al. 2016; Li et al. 2017; Zhang et al. 2015). It is also noteworthy that Astragaloside alleviates heart failure via activating PPARα to switch glycolysis to fatty acidβ-oxidation. In this regard, recent research shown that Astragaloside significantly reduced anaerobic glycolysis and increased oxygen consumption ratio that was illustrated in the switch glycolysis to fatty acid β-oxidation in failure heart model. Furthermore, in vitro, Astragaloside increased the level of ATP production, enhanced mitochondrial function to regulate metabolism that attributes to increased oxygen consumption and slightly augmented mitochondrial Ca^{2+}uptake (Dong et al. 2017).

- **Ginsenoside Rg1**

Ginsenoside Rg1, one of the major medicines to treat Qi-deficiency related diseases in traditional Chinese medicine, is an active component derived from herbal medicine Radix ginseng (Renshen). Rg1 is shown to decrease myocardial infarction area (Wang et al. 2010), enhance the myocardial perfusion and preserve left ventricle (LV) function, as well as ameliorate ventricular remodeling in acute or chronic myocardial infarction animal model (Wei et al. 2007; Yin et al. 2011). These cardioprotective effects of Rg1 may reflect the improvement in myocardocyte apoptosis, myocardial blood flow, and restoration of ATP production in the myocardium after I/R (Li 2018).

- **Hydroxy safflower yellow A**

Hydroxy safflower yellow A (HSYA) is the active ingredient and is extracted from the flower of the safflower plant, *Carthamus tinctorius L.* HSYA inhibits platelet-activating factor receptor and is used to treat several ischemic diseases, including coronary heart disease and cerebral thrombosis. Additionally, HSYA may activate PPAR-γ which is a key regulator of lipid metabolism, and insulin sensitivity and endothelial inflammation. HSYA decreased the elevated ST segment and infarct size by augmenting the level of Bcl-2 positive cells in acute myocardial infarction in rat (Zhou et al. 2015).

- **Ginsenoside Rb1**

Ginseng as an important herbal drug has been worldwide used in oriental countries for thousands of years and is also one of the most extensively used botanical products in other areas in the world. Ginsenosides, the triterpene saponins, is one of the major components of ginseng. To date, more than 30 kinds of ginsenosides have been identified. Ginsenoside Rb1 (G-Rb1) possesses a variety of biological activities in the cardiovascular systems including anti-oxidation, anti-inflammation, and antiapoptosis, pro-angiogenesis, antiarrhythmic, suppression of ventricular remodeling after acute MI, and inhibition of hypertrophy and ventricular hypertrophy (Kwok et al. 2015; Lu et al. 2009; Zheng et al. 2017). G-Rb1 binds RhoA and inhibits activation

of the RhoA signaling pathway, and restores the production of ATP during cardiac I/R (Cui 2017).

Use of TCM mainly relies on empirical experience. Confirming the efficacy of TCM with placebo-controlled and randomized clinical trial, and clarification of their molecular pharmacology, will allow identification of new therapy/targets for treating CAD. In this regard, TCM is an enriched resource for new drug discovery.

8.8 Cardiac Regeneration

Coronary artery disease is a leading cause of death worldwide. Heart ischemia, mainly resulted from atherosclerosis, thrombosis, vasospasm or coronary microvascular dysfunction, or oxygen supply/demand imbalance alone, is followed by loss of the damaged cardiomyocytes, which are replaced with fibrotic scar tissue. Loss of normal cardiomyocytes results in decreased cardiac contraction, further pathological cardiac dilatation, and additional cardiomyocyte loss, culminating in heart failure. Many therapies have focused on preventing heart failure. However, after patients have developed end-stage heart failure, intervention is limited to heart transplantation, cardiac assistance device, or even artificial heart. Regenerating an injured heart holds promise for patients suffering from heart diseases. Reparative tools have been engineered to restore damaged heart tissue and function using the body's natural ability to regenerate. The mammalian heart appears to have the capacity to regenerate only for a brief period (~7 days) after birth (Porrello et al. 2011). Adult cardiomyocytes in mammals are terminally differentiated, with only limited regeneration capability (Bergmann et al. 2009, 2015). Substantial progress has been made toward understanding the cellular and molecular mechanisms regulating heart regeneration, offering the potential to control cardiac remodeling and redirect the adult heart to a regenerative state.

$Scar^+$ cardiac progenitor cells mainly differentiate into cardiac endothelial cells and fibroblasts but not cardiomyocytes during cardiac homeostasis and after injuries and non-cardiomyocyte does not differentiate to cardiomyocyte under physiology or post-MI injury (Tang et al. 2018). In adult mammals, new cardiomyocytes are more likely to be derived from preexisting cardiomyocytes that undergo proliferation to minimally regenerate rather than differentiation of cardiac stem cells or progenitor cells (Senyo et al. 2013; Kimura et al. 2015; van Berlo et al. 2014).

Generation of new coronary vasculature during cardiac homeostasis and after injury(such as ischemia) is fundamental in cardiac regeneration in CAD. Cardiac fibroblasts expand substantially after injury, but they do not contribute to the formation of new coronary blood vessels. Essentially all new coronary vessels in the injured heart are derived from preexisting endothelial cells, but not from other cell lineages. Targeting lineage transdifferentiation such as mesenchymal-to-endothelial transition may not be a viable approach to for therapeutic induction of neovascularization. Instead, preexisting endothelial cells appear more likely to be the therapeutic

target for promoting neovascularization and driving heart regeneration after injury (MI) (He et al. 2017).

In the past 2 decades, several strategies to repair the injured heart and improve heart function have been pursued, including cellular and noncellular therapies. Cell therapy is a central issue of regenerative medicine and is raising a growing interest in the scientific community, but its full therapeutic potential in CAD has not been reached yet. Different strategies for the production of cardiomyocytes from human embryonic stem cells or human-induced pluripotent stem cells, by direct reprogramming and induction of cardiomyocyte proliferation have been tried. Transplantation of induced pluripotent stem cell-derived cardiomyocytes for cardiac repair has encountered problems related to safety and low engraftment rates. Cell-free-based approaches for heart repair and regeneration involve cardioprotective secretory factors or direct reprogramming of resident cardiac fibroblasts to cardiomyocyte-like cells. Endogenous cardiomyocyte proliferation can be evoked by modulating cell cycle regulators, the Hippo signaling pathway, and the cardiac microenvironment. Hippo-Yap signaling pathway controls heart regeneration and size in adult mice. Agrin, a component of the extracellular matrix, has been identified to promote cardiomyocyte regeneration by interrupting the interaction between dystrophin glycoprotein complex and YAP (Bassat et al. 2017; Morikawa et al. 2017). In particular, treatment with Agrin after MI promoted cardiac regeneration in adult mice, raising a possibility of its clinical use of Agrin with a novel promising approach. Genome editing can correct underlying mutations causing heart disease in animals and offers a state-of-the-art therapeutic approach for cardiac repair. The therapeutic potential of cardiac regeneration approaches can be improved by optimizing the delivery method of therapeutic factors. Significant clinical efforts have been put forward following the explosion of preclinical research showing the efficacy of stem/progenitor cell therapy in failing heart. However, preclinical outcomes of cardiac regenerative therapy approaches have not translated effectively to clinical trials. A reproducible cell-based therapy or regenerative medicine remains to come.

8.9 Cardiovascular Drugs Under Clinical Development

A brief summary of cardiovascular drugs under clinical development is listed in Table 8.1. Also included are their indication, mechanism of action, development stage, and sponsor.

8.10 Conclusions and Perspectives

The high incidence of CAD imposes an enormous burden on healthcare systems. Atherosclerosis is the main cause of CAD, however, the pathological mechanism is complex. The key determinants/pathways underlying the residual risk of CAD under

Table 8.1 Cardiovascular drugs under clinical development

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
CER-001	Atherosclerosis and ACS and Familial Primary Hypo-Alphalipoproteinemia	An engineered complex of recombinant human apolipoprotein A-1 to increase apoA-I and the number of HDL particles	Phase 2	Cerenis Therapeutics
CER-209	Atherosclerois and of NASH	Oral P2Y13 receptor agonists that acts on the last step of the Reverse Lipid Transport pathway, increasing HDL recognition by the liver and facilitating the elimination of lipids in the feces, leading to a regression of atherosclerotic plaque	Phase 1	Cerenis Therapeutics
Metoprolol Succinate/Bisoprolol	AMI and Non-STEMI and STEMI	Evaluation of Decreased Usage of Beta-blockers After MI in the SWEDEHEART Registry (REDUCE-SWEDEHEART)	Phase 4	Karolinska Institutet
Dutogliptin Tartrate/Filgrastim	AMI and Acute Myocardial Ischemia and STEMI	Study of Dutogliptin in Combination With Filgrastim in Post-MI	Phase 2	Recardio, Inc.
Tocilizumab	MI and CAD	ASSessing the Effect of Anti-IL-6 Treatment in MI: The ASSAIL-MI Trial (ASSAIL-MI)	Phase 2	Oslo University Hospital
Paroxetine	MI and Cardiac Remodeling	Paroxetine-mediated GRK2 Inhibition to Reduce Cardiac Remodeling After AMI	Phase 2	University Hospital Inselspital, Berne

(continued)

Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
Beta-Blockers Carvedilol Phosphate	MI	Effect of Beta-blocker on Cardioprotective Effect of Remote Ischemic Conditioning	Phase 4	Seoul National University Hospital
SAR407899	Microvascular CAD	A Dose Titration Study to Assess the Effects of SAR407899 in Patients With MVA and/or Persistent Stable Angina Despite Angiographically Successful PCI	Phase 2	Sanofi
Nicardipine	CAD	Prevention of Coronary Microvascular Dysfunction Post-PCI by Intracoronary Nicardipine	Early Phase 1	Thomas Jefferson University
Hydroxychloroquine Sulfate	CAD	Hydroxychloroquine (Plaquenil) blocks toll-like receptor signaling and reduces the activation of dendritic cells and the inflammatory process. It is a disease-modifying antirheumatic drug (DMARD)	Phase 4	First Affiliated Hospital Xi'an Jiaotong University
AZD5718	CAD	AZD5718 Phase IIa Study to Evaluate Efficacy, Safety and Tolerability of Oral AZD5718 in Patients With Coronary Artery Disease (CAD)	Phase 2	AstraZeneca
PF-06282999	ACS	Irreversible inactivator of myeloperoxidase	Phase 1	Pfizer

(continued)

Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
AZD5718 oral suspension	CAD	A Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AZD5718 After Single and Multiple Ascending Dose Administration to Healthy Japanese Men	Phase 1	AstraZeneca
AZD5718 tablets	CAD	A Study to Assess the Bioavailability of Different Formulations of AZD5718 and the Food Effect on the Selected Formulation of AZD5718 in Healthy Volunteers	Phase 1	AstraZeneca
Sodium Thiosulfate Pentahydrate	ACS	Safety and Tolerability of Sodium Thiosulfate in Patients With an ACS Undergoing CAG Via Trans-radial Approach (SAFE-ACS)	Phase 2	University Medical Center Groningen
ACT-246475	Stable CAD	A Medical Research Study to Evaluate the Effects of ACT-246475 in Adults With CAD	Phase 2	Idorsia Pharmaceuticals Ltd.
Proleukin	IHD	Low-Dose IL-2 in Patients With Stable IHD and ACS (LILACS)	Phase 1	Cambridge University Hospitals NHS Foundation Trust

(continued)

Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
Sitagliptin/Saxagliptin	Platelet Aggregation During AMI	DPP-4 Inhibitors and AMI: Effects on Platelet Function	Phase 3	University of Sao Paulo General Hospital
Yangxinshi pill	CHD	A study to evaluate the effects of Yangxinshi pill in improving exercise tolerance of patients with CHD and quality of life or restore social function and mental health	Phase 2	Affiliated Hospital of Changchun University of Chinese Medicine
Danlou Tablets/Tongmai Yangxin Pills	CHD	A study to evaluate the relation between syndrome and disease of Turbid Phlegm and blood stasis for CHD and its biological basis	Not Applicable	Tianjin University of Traditional Chinese Medicine
68 Ga-NODAGA-E[c(RGDyK)]2	Chronic IHD	A study to examine the expression of αvβ3 integrin and investigate if it is a suitable tool for predicting myocardial recovery and thus prognosis after intervention	Phase 2	Rigshospitalet, Denmark
Varenicline	CHD	A study to determine if varenicline for smoking cessation is more effective than the standard nicotine replacement therapy aide currently used, “the patch” among smokers hospitalized with coronary heart disease	Phase 4	Ottawa Heart Institute Research Corporation, Heart and Stroke Foundation of Ontario

(continued)

Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
Proleukin	IHD	IL-2 supplementation appears to be an attractive therapeutic option playing a key role in Treg cell development, expansion, survival and suppressive function of post-ischemic immune responses and the promotion of myocardial healing	Phase 1	Cambridge University Hospitals NHS Foundation Trust
Amiloride	CHD	A study to evaluate the pharmacological effects of Amiloride on RBC K-uptake and transport and its impact on reversion of angina, electrocardiographic changes of myocardial ischemia and electrical regeneration of the heart in subjects with coronary artery diseases	Phase 2	University of Carabobo
BI10773 (empagliflozin)	HF	A small molecule that inhibits SGLT 2	Phase 3	Eli Lilly and Boehringer Ingelheim
AMG 986	HF	A small-molecule agonist of the Apelin receptor (APJ)	Phase 1	AMGEN
Omecamtiv mecarbil	Chronic HF	A small-molecule activator of cardiac myosin.	Phase 3	AMGEN

(continued)

Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
Anakinra	HF in Patients With Advanced Chronic Kidney Disease (E-HART)	A recombinant human IL-1 receptor antagonist	Phase 2	Virginia Commonwealth University
Vericiguat (MK-1242)	HF	A novel activator of cardiac myosin, the motor protein that powers cardiac muscle contraction	Phase 3	AMGEN and Cytokinetics
Pirfenidone	Cardiac Failure	The Efficacy and Safety of Pirfenidone in Patients With HFpEF	Phase 2	Manchester University NHS Foundation Trust
Metolazone Oral Tablet	HF	Prospective Comparison of Metolazone Versus Chlorothiazide for Acute Decompensated HF With Diuretic Resistance	Phase 4	University of Virginia
Macitentan	HFpEF	A Study to Evaluate Whether Macitentan is an Effective and Safe Treatment for Patients With HFpEF and Pulmonary Vascular Disease	Phase 2	Actelion
Bisoprolol	HF	Efficacy of Oral Bisoprolol on Heart Rate Reduction in Chinese Chronic Heart Failure Subjects	Phase 4	Merck KGaA
Tolvaptan	Pediatric Congestive HF Patients With Volume Overload	Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics Study of Tolvaptan in Pediatric Congestive HF Patients With Volume Overload	Phase 3	Otsuka Pharmaceutical Co., Ltd.

(continued)

Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
OPC-61815	Congestive HF	Phase I Study of OPC-61815	Phase 1	Otsuka Pharmaceutical Co., Ltd.
rhNRG-1	Chronic HF	Study of the Survival of Recombinant Human Neuregulin-1β in Chronic HF Patients	Phase 3	Zensun Sci. & Tech. Co., Ltd.
BMS-986224	HF	A Study of BMS-986224 in Healthy Subjects and HFrEF	Phase 1	Bristol-Myers Squibb
Omecamtiv Mecarbil/AMG423	HF	Registrational Study With Omecamtiv Mecarbil/AMG 423 to Treat Chronic HFrEF	Phase 3	AMGEN
HNO Donor	HF	Evaluate the Safety and Efficacy of 48 h Infusions of HNO (Nitroxyl) Donor in Hospitalized Patients With HF	Phase 2	Bristol-Myers Squibb
AZD8601	HF	AZD8601 Study in CABG Patients	Phase 2	AstraZeneca
Vericiguat (BAY1021189)	Chronic HFpEF	Patient-reported Outcomes in Vericiguat-treated Patients With HFpEF	Phase 2	Bayer

(continued)

Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
Dapagliflozin	Chronic HFrEF	Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening HF or Cardiovascular Death in Patients With Chronic HF	Phase 3	AstraZeneca
Empagliflozin	HF	EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced)	Phase 3	Boehringer Ingelheim
Sotagliflozin (SAR439954)	Cardiac Failure Aggravated	Safety, Tolerability and Pharmacodynamic Activity of Sotagliflozin in Hemodynamically Stable Patients With Worsening HF	Phase 2	Sanofi
Sacubitril/Valsartan	HFpEF	A Randomized, Double-blind Controlled Study Comparing LCZ696 to Medical Therapy for Comorbidities in HFpEF Patients (PARALLAX)	Phase 3	Novartis Pharmaceuticals
Valsartan/Sacubitril	HF	Differential Vascular and Endocrine Effects of Valsartan/Sacubitril in HFrEF	Phase 4	University of Zurich
Levosimendan	HF	Levosimendan for Cardiac Patients Undergoing Major Abdominal Cancer Surgeries	Phase 2	National Cancer Institute, Egypt
IW-1973	HFpEF	A Study of the Effect of IW-1973 on the Exercise Capacity of Patients With HFpEF (CAPACITY-HFpEF)	Phase 2	Ironwood Pharmaceuticals, Inc.

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Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
Ivabradine	HF, Cardiogenic Shock and Tachycardia	Effect of Ivabradine in Stage D HF/Cardiogenic Shock Patients on Dobutamine	Phase 4	Loyola University
Neladenoson bialanate (BAY1067197)	HF	A Trial to Study Neladenoson Bialanate Over 20 Weeks in Patients With Chronic HFrEF	Phase 2	Bayer
AMG 986	HF	AMG 986 20150186 Renal Impairment Study	Phase 1	AMGEN
Rilonacept	CVD and Chronic Kidney Disease	An antagonist of the cytokine IL-1	Phase 2	VA Office of Research and Development
AMG 598	CVD and obesity	A human monoclonal antibody being investigated as a treatment for obesity	Phase 1	AMGEN
OPC-269	CVD	NA	Phase 1	Ligand Pharmarceuticals, Inc.
Nitroxyl Donor	CVD	A small molecule inhibits inflammatory by reducing cytokine production and activating the cGMP/PKG/ATP-sensitive K+ channel	Phase 2	Bristol-Myers Squibb
CS-3150/Esaxerenone	CVD	A novel nonsteroidal mineralocorticoid receptor antagonist	Phase 3	Ligand Pharmarceuticals, Inc.
CXL-1427	CVD	A nitric oxide donor and prodrug of CXL-1020	Phase 2	Ligand Pharmarceuticals, Inc.

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Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
XL652/BMS-779788	CVD	A molecule is potent partial LXR agonist with LXRβ selectivity	Preclinical	Ligand
APJ Agonist	CVD	A small molecule could selective against the AT1 receptor and cell active	Phase 1	Bristol-Myers Squibb
FPR-2 Agonist	CVD	A small molecule could activate formyl peptide receptor 2 (a Gi-protein-coupled receptors that are expressed mainly by mammalian phagocytic leukocytes)	Phase 1	Bristol-Myers Squibb
OPC-108459	CVD	NA	Phase 1	Ligand and Otsuka
GNR-008	CVD	Selexis SURE technology	Phase 1	Ligand and IBC Generium
BMS986231	CVD	A second-generation prodrug that chemically breaks down to produce nitroxyl (HNO) and an inactive byproduct	Phase 2	Ligand and BMS
Sparsentan	Cardiovascular/Kidney disease	Dual mechanism of action combines angiotensin receptor blockade with endothelin receptor blockade	Phase 3	Ligand and Retrophin

(continued)

Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
hCDR1	CVD/Systematic Lupus Erythematosus	A new drug ameliorates autoimmune process by specific upstream immunomodulation through the generation of regulatory T cells	Phase 2	Ligand and XTL Bio
Edoxaban	Cardiac Disease	Edoxaban is an oral anticoagulant drug which acts as a direct factor Xa inhibitor. Edoxaban for Prevention of Blood Vessels Being Blocked by Clots (Thrombotic Events) in Children at Risk Because of Cardiac Disease	Phase 3	Daiichi Sankyo, Inc.
Ralinepag (APD811)	PAH	Prostacyclin receptor agonist	Phase 2	Arena
MRA/RG1569 (RO4877533, tocilizumab, Actemra®)	Large-vessel vasculitis, Giant cell arteritis and Systemic sclerosis	Humanized antihuman IL-6 receptor monoclonal antibody	Phase 3	Chugai Pharma USA, Inc.
DP9	Pectoris	DP9 provides transdermal skin cream progesterone in unit-dose packages that allow reliable achievement of effective exposure levels with optimized pharmacokinetics; DP9 provides transdermal skin cream progesterone in unit-dose packages that allow reliable achievement of effective exposure levels with optimized pharmacokinetics	Phase 2	Dimera

(continued)

Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
PF-06427878	Hyperlipidemia	NA	Phase 1	Pfizer
PF-05221304	NASH and Cardiovascular Risks	Acetyl CoA-Carboxylase (ACC) Inhibitor	Phase 1	Pfizer
PF-06835919	NASH and Cardiovascular Risks	Ketohexokinase (KHK) Inhibitor	Phase 1	Pfizer
PF-06865571	NASH and Cardiovascular Risks	Diacylglycerol O-Acyltransferase 2 (DGAT2) Inhibitor	Phase 1	Pfizer

CAD coronary artery disease; *ACS* acute coronary syndrome; *AMI* acute myocardial infarction; *STEMI* ST elevation myocardial infarction; *IHD* ischaemic heart disease; *HF* heart failure; *HFpEF* HF with preserved ejection fraction; *HFrEF* HF with reduced ejection fraction; *CABG* coronary artery bypass grafting; *NA* nonavailable; *CVD* cardiovascular disease; *NASH* nonalcoholic steatohepatitis; *PAH* pulmonary arterial hypertension

current standard therapy remain largely unknown. The atherogenic process as a consequence of hypercholesterolemia, and inflammation has been considerably refined by the appreciation of endothelial injury, the role of myeloid cells, T/B lymphocytes, and dendritic cells in innate and acquired immunity, subendothelial apoB-lipoprotein retention, and the identification of signals, such as chemotactic cytokines, regulating the lesional recruitment and homeostasis of inflammatory cells. Further understanding the mechanistic links among lipid metabolism disorder, inflammation, hypertension, and thrombosis continue to emerge as the pathogenic interface that fuels the therapeutic options for CAD.

Just like the Scandinavian Simvastatin Survival Study in 1994 marked the beginning of the statin era, the Canakinumab Anti-inflammatory Thrombosis Outcome Study in 2017 opens a new era for atherosclerosis prevention focused on inflammation inhibition. Canakinumab is currently the only agent specifically targeting inflammation that is proven to reduce cardiovascular event rates at clinical levels. Inhibition of IL-6 and modulation of upstream determinants of IL-1 activation, such as NLRP3 inflammasome, might be an alternative therapeutic option that is under investigation. Inhibition of other inflammatory pathways might also benefit from vascular disease patients. Future studies are needed for an in-depth understanding of cardiovascular inflammation, delineation of candidate target from the perspective of systems biology, appropriate selection of patients or timing of intervention that allows maximal benefit. New agents with improved safety profiles and favored cost-effectiveness are still in need.

Antihypertensive beta-blockers lower mortality from MI and delay atheroprogression (IVUS trials) (Sipahi et al. 2007). Intensive blood pressure lowering (Group et al. 2015; Chobanian et al. 2003) reduces major adverse cardiovascular events in patient population at high risk. In a population of intermediate-risk (HOPE-3 trial), cholesterol lowering (Yusuf et al. 2016), or combination of cholesterol lowering and blood pressure lowering (Yusuf et al. 2016), but not blood pressure lowering alone (Lonn et al. 2016), reduced the risk of cardiovascular events. Interference with the renin–angiotensin system improves endothelial function and reduces coronary event rates disproportionately to lower blood pressure, supporting direct atheroprotective effects (Investigators et al. 2008). Dyslipidemia and hypertension might contribute to the occurrence of cardiovascular events at different stages of atherosclerosis. Elucidation of the underlying mechanisms may allow new therapeutic intervention.

Human genome-wide association study, transcriptional, proteomic and metabolic profiling of CAD, complemented with animal studies of established and unstable atherosclerosis that faithfully recapitulate human biology, will further delineate molecular mechanism of CAD and pave the way toward discovery of new therapeutic targets and drugs. New strategies are emerging, such as anti-inflammation, triglyceride lowering, chemokine signaling modulation and vaccination against oxidized/pro-inflammatory phospholipids (Que et al. 2018). These strategies will have to overcome translational challenges before further reducing CAD, the main disease burden to mankind.

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