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Practice Guideline

A performance guide for major risk factors control in patients with atherosclerotic cardiovascular disease in Taiwan

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Atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease, cerebrovascular disease, and peripheral artery disease, carries a high morbidity and mortality. Risk factor control is especially important for patients with ASCVD to reduce recurrent cardiovascular events. Clinical guidelines have been developed by the Taiwan Society of Cardiology, Taiwan Society of Lipids and Atherosclerosis, and Diabetes Association of Republic of China (Taiwan) to assist health care professionals in Taiwan about the control of hypertension, hypercholesterolemia and diabetes mellitus. This article is to highlight the recommendations about blood pressure, cholesterol, and sugar control for ASCVD. Some medications that are beneficial for ASCVD were also reviewed. We hope the clinical outcomes of ASCVD can be improved in Taiwan through the implementation of these recommendations.

Introduction

Cardiovascular (CV) disease is the leading cause of death in the world and second leading cause of death in Taiwan.[1,2] Atherosclerotic cardiovascular disease (ASCVD) is caused by atherosclerotic plaque formation in arterial wall and results in: (1) coronary artery disease (CAD), such as acute coronary syndrome (ACS) or stable angina with significant coronary artery stenosis; (2) cerebrovascular disease, such as ischemic stroke, transient ischemic attack, or significant carotid artery stenosis; and (3) peripheral artery disease (PAD), such as claudication with significant peripheral arterial stenosis. The major goal of treatment for ASCVD is to reduce CV events and decrease mortality. ASCVD share many common risk factors, such as hypertension, hypercholesterolemia, diabetes mellitus, and smoking. Associated with abdominal obesity, diet, and sedentary lifestyle, these risk factors contribute to about 90% of the risk of myocardial infarction (MI) and stroke.[3,4] Treatment or correction of these risk factors not only primarily prevents the occurrence of ASCVD but also secondarily decreases the risk of recurrent CV events in patients with preexisting ASCVD. The Taiwan Society of Cardiology, Taiwan Society of Lipids and Atherosclerosis, and Diabetes Association

of Republic of China (Taiwan) have developed clinical practice guidelines to assist in the diagnosis and management of hypertension, hypercholesterolemia and diabetes mellitus.[5–9] Most of the recommendations provided in these guidelines are based on scientific evidences from literature review. The results from large scale randomized clinical trials are the most commonly used evidences. Other data from the small clinical trials, observational studies and expert opinions are also taken into consideration in the guidelines. Previous studies have demonstrated that adherence to clinical guidelines not only decreases morbidity and mortality of ASCVD but also saves medical cost through reduction of disability caused by ASCVD.[10,11] In 2018, meetings supported by the Health Promotion Administration, Ministry of Health and Welfare of Taiwan Government were held to review the recommendations in the local guidelines by the experts invited from different hospitals in Taiwan. The suggestions of major vascular risk factors control specifically for patients with ASCVD were discussed and a final consensus was achieved. The purposes of this article were: (1) to highlight the current recommendations from the local guidelines in Taiwan about blood pressure (BP), cholesterol and sugar control for patients with ASCVD; (2) to describe the final expert consensus about some modifications of the recommendation that can be more appropriately applied in Taiwan; and (3) to recommend anticoagulants that are beneficial for stroke prevention in atrial fibrillation (AF) and antiplatelets for PAD.

The evidence-based classification system, including class of recommendation (COR) and level of evidence (LOE), was used in this article. For COR, class I indicates the recommendations are beneficial and supported by multiple clinical trials. Class III indicates they are harmful. Class IIa indicates that evidences favor the recommendations; while class IIb indicates that the recommendations are less well established (Table 1). For LOE, LOE A indicates that there were multiple randomized trials supporting the recommendations. LOE B indicates that only one randomized trial or observation studies support the recommendations. LOE C indicates that only small studies or expert opinions suggest the recommendations (Table 2). Since there are various clinical conditions in different patients, the recommendations only provide general principles and the final treatment decisions still need clinical judgment of the physicians.

Healthy lifestyle

The first step to reduce adverse CV events in patients with ASCVD is to have a healthy lifestyle. Table 3 summarizes the suggestions for a healthy lifestyle which include sodium restriction, alcohol limitation, body weight reduction, cigarette smoke cessation, diet adaptation, and regular exercise.[7] For sodium restriction, the optimal daily sodium consumption is 2.0—4.0 g/day. For alcohol limitation, the daily intake of alcohol should be limited to <30 g/day in men and <20 g/day in women. The ideal body mass index is 22.5—25.0 kg/m^2. Cigarette smoking should be stopped. Smoking cessation is especially important because smoking is one of the most preventable risk factors for MI.[3] Smoking cessation also reduces mortality rate of stroke in Taiwan.[12] The Dietary Approaches to Stop Hypertension (DASH) diet is recommended and includes high amount of vegetables, fruits, low-fat dairy products, whole grains, poultry, fish, and nuts and minimized intake of sweets, sugar-sweetened beverages, and red meats. Regular physical exercise at least 40 minutes/day and at least 3—4 days/week is also an integral part of the healthy lifestyle.

Recommendation

- A healthy lifestyle should be adopted in ASCVD patients. (COR I, LOE A)
- Smoking cessation is especially important for ASCVD. (COR I, LOE A)

Coronary artery disease

Hypertension

Hypertension is a major risk factor of CAD. Many studies have shown that BP reduction can prevent CV events in patients with CAD. The Heart Outcomes Prevention Evaluation (HOPE), the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA), and the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) studies are the major 3 randomized controlled trials comparing angiotensin-converting

Table 1 Class of recommendation.

Class of recommendation	Definition	Strength
Class I	Evidence or general agreement that a given treatment is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence or a divergence of opinion about the usefulness or efficacy of a treatment.	
Class IIa	Weight of evidence/opinion is in favor of usefulness or efficacy	Should be considered
Class IIb	Usefulness or efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment is not useful or effective and in some cases may be harmful.	Is not recommended

Adapted from reference [7].

Table 2 Level of evidence.

Level of evidence A	Data derived from multiple randomized clinical trials
Level of evidence B	Data derived from a single randomized clinical trial, meta-analyses, or large non-randomized studies
Level of evidence C	Subgroup analyses, post-hoc analyses, retrospective studies, cohort studies, registries, small studies, or expert opinion

Adapted from reference [7].

Table 3 Suggestions for a healthy lifestyle.

Lifestyle change	Recommendation
Sodium restriction	2.0—4.0 gm/d
Alcohol limitation	Men: < 30 gm/d ethanol Women: < 20 gm/d ethanol
Body weight reduction	BMI: 22.5—25.0
Cigarette smoking cessation	Complete abstinence
Diet adaptation	DASH diet: rich in fruits and vegetables (8—10 servings/d), rich in low-fat dairy products (2—3 servings/d), and reduced in saturated fat and cholesterol
Exercise adoption	Aerobic, at least 40 min/d, and at least 3—4 days/week

BMI: body mass index; DASH: Dietary Approaches to Stop Hypertension.
Adapted from reference [5].

enzyme inhibitor (ACEI) with placebo in patients with CAD.[13—15] The final achieved BPs were 136/76 mm Hg in the HOPE, 132/80 mm Hg in the EUROPA and 129/74 mm Hg in the PEACE trial, respectively. A combined analysis of the 3 trials showed that ACEIs reduced total mortality, non-fatal MI, and stroke in patients with CAD.[16] The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study is a randomized controlled trial to compare calcium channel blocker (CCB, amlodipine), ACEI (enalapril), or placebo in CAD patients. The study showed that amlodipine can reduce the primary endpoint by 31%.[17] The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial randomized CAD patients to either optimal medical treatment or optimal medical treatment plus percutaneous coronary intervention (PCI). The optimal medical treatment included beta-blockers, CCB, and ACEI or angiotensin receptor blocker (ARB). The COURAGE study demonstrated that the effects of optimal medical treatment, including BP control, was comparable to optimal medical treatment plus PCI in CAD patients.[18] In a meta-analysis including 15 randomized trials of CAD patients treated with either antihypertensive agent or placebo, intensive BP treatment (systolic BP $\leq$ 135 mmHg) could decrease heart failure (−15%) and stroke (−10%) compared with standard BP treatment (systolic BP $\leq$ 140 mmHg). More intensive BP reduction with systolic BP $\leq$ 130 mmHg further reduced MI and angina.[19] Another meta-analysis of 64,162 patients with CV disease enrolled in 25 studies also showed that antihypertensive drugs can reduce stroke, MI, heart failure, and CV death.[20] In another meta-analysis investigating the effects of antihypertensive drugs on CAD and stroke, a total of 464,000 patients in 147 clinical trials were analyzed and divided into 3 groups: patients without history of CV disease, patients with CAD, and patients with stroke. The study found that antihypertensive drugs can reduce the risk of CAD and stroke, regardless of the pre-treatment BP values or history of CV disease. The study also showed that all antihypertensive drugs had similar effects for CAD and stroke, except that beta-blockers had additional protective effect on MI; while CCBs had additional protective effect on stroke.[21] The BP Lowering Treatment Trialists' Collaboration (BPLTTC) included a total of 201,566 patients in 32 clinical trials and divided into systolic BP < 140, 140—159, 160—179, and $\geq$180 mmHg according to the pretreatment baseline BP before treatment. The study found that different antihypertensive drugs and different baseline BP groups did not affect the reduction of the primary endpoint.[22] The Systolic Blood Pressure Intervention Trial (SPRINT) trial investigated the effects of intensive BP treatment (systolic BP < 120 mmHg) and standard BP treatment (systolic BP < 140 mmHg) on patients with high CV risk but without diabetes. After an average follow-up time of 3.26 years, patients receiving intensive BP treatment had fewer primary endpoints, including CV events and overall mortality.[23] Currently, the Taiwan Hypertension Guideline suggests that BP in patients with CAD should be controlled to systolic BP < 130 mmHg and diastolic BP < 80 mmHg.[5]

Recommendation

- For CAD patients, the BP target is < 130/80 mmHg. (COR I, LOE B)

Hypercholesterolemia

Elevated serum cholesterol especially low-density lipoprotein cholesterol (LDL-C) is one of the most important risk factors of ASCVD.[24] Lipid-lowering drugs that reduce LDL-C significantly improve the clinical outcomes of ASCVD. However, the control rate of LDL-C is disappointing in Taiwan. In the recent Taiwanese Secondary Prevention for patients with AtheRosCLErotic disease (T-SPARCLE) registry study in Taiwan, only 54% of the ASCVD patients could achieve a serum LDL-C level < 100 mg/dL.[25] Recently, the 2017 Taiwan Lipid Guideline for High Risk Patients was published.[7] According to this guideline, LDL-C should be controlled to < 70 mg/dL in patients with ACS. The recommendation is based on several randomized clinical trials, including the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study,[26] the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT—TIMI 22) study,[27] the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study[28]

and several other smaller studies in Asia. The average achieved LDL-C level in patients with intensive treatment group was 72 mg/dL in the MIRACL study, 62 mg/dL in the PROVE IT-TIMI 22 study, and 53 mg/dL in the IMPROVE IT study. Based on these evidences, it is reasonable to suggest a LDL-C target of <70 mg/dL in ACS patients.

For patients with stable CAD, the 2017 Taiwan Lipid Guideline for High Risk Patients suggests that the therapeutic goal of serum LDL-C is < 70 mg/dL. The recently published data from the T-SPARCLE registry demonstrated that, for patients with stable ASCVD (including CAD, cerebrovascular disease or PAD), the CV events were significantly reduced in patients who can achieve LDL-C < 100 mg/dL compared with those who had LDL-C ≥ 100 mg/dL. There were no differences in the incidence of future CV events between patients with LDL-C level <70 and ≥70 mg/dL.[29,30] These data in Taiwan carry a clinical implication that the therapeutic goal of LDL-C < 70 mg/dL probably should be given to high risk stable CAD patients. In the recently published 2018 American Heart Association/American College of Cardiology (AHA/ACC) Guideline on the Management of Blood Cholesterol, very high risk stable ASCVD patients whose LDL-C level remains > 70 mg/dL on maximally tolerated statin, addition of nonstatin therapy should be considered.[31] The very high risk condition is defined as a history of major ASCVD events or 1 major ASCVD event with high risk conditions. The high risk conditions indicate age ≥65 years, familial hypercholesterolemia, history of prior coronary artery bypass surgery (CABG) or PCI, diabetes mellitus, hypertension, chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, current smoking, persistently elevated LDL-C (LDL-C ≥ 100 mg/dL) despite maximally tolerated statin therapy and ezetimibe, and history of congestive heart failure. In Taiwan, expert consensus suggests that it is reasonable to recommend a LDL-C target <70 mg/dL in stable CAD patients who have either≧1 major ASCVD events or≧2 risk factors if there is no history of major ASCVD events (Table 4). Among lipid-lowering drugs, statin is the first-line and cornerstone therapy. Moderate to high intensity statins are suggested. Other LDL-lowering drugs include ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors should be considered if the LDL target cannot be achieved after maximally tolerated statin.

Recommendation

- For ACS patients, the LDL-C target is < 70 mg/dL (COR I, LOE A)
- For stable CAD patients who have either≧1 major ASCVD events or≧2 risk factors if there is no history of major ASCVD events (Table 4), the LDL-C target is < 70 mg/dL (COR I, LOE C)

Diabetes

The CV risk and total mortality has a linear relationship with the level of HbA1c. However, several randomized clinical trials that evaluated intensive versus conventional glucose control could not demonstrate further reduction of macrovascular events in the intensive treatment group. Intensively treated patients also had significantly higher major hypoglycemic events. According to the 2018 Taiwan Diabetes Care Guideline, the HbA1c target is <7%, the fasting glucose level is 80−130 mg/dL, and 2-hour postprandial glucose level is < 160 mg/dL.[8] The balance between the benefit and risk of hypoglycemia should be taken into consideration. Based on these evidences, it is reasonable to suggest the HbA1c target <7.0% for diabetic patients with CAD. In fragile patients and patients with limited life expectancy, less intensive control with the HbA1c target <8% is suggested. Sodium−glucose cotransporter 2 (SGLT2) inhibitors or glucagon-like peptide 1 (GLP-1) receptor agonists have been suggested to be used in patients with ASCVD in recent guidelines because clinical trials demonstrated that these drugs could improve CV outcomes and progression of renal disease in diabetic patients with established CV disease.[9,32] Metformin is still the first line therapy for patients with diabetes and CAD. SGLT2 inhibitors or GLP-1 receptor agonists with proven CV benefit are recommended as part of glycemic management.

Recommendation

- In patients with diabetes and CAD, the HbA1c target is <7.0%. In patents with frailty or limited life expectancy, the HbA1c target is <8.0% (Class I, LOE C)

Ischemic stroke/transient ischemic attack

Hypertension

There were several major CV outcome trials that recruited patients who had suffered from stroke.[13,33−36] Aggressive BP reduction lowers recurrent stroke and CV events, but the achieved BP was higher than 130 mmHg in these clinical trials. Therefore, the target BP level is set to be < 140/90 mmHg for patients with history of cerebrovascular disease according to current Taiwan Hypertension Guideline.[6] For long-term hypertension control in patients with a history of stroke, BP control to the target level is mandatory. Anti-hypertensive agents including CCB, ACEI/ARB, diuretic and beta-blocker have been proved to reduce stroke. However, a meta-analysis indicated that, in patients with uncomplicated hypertension, first-line therapy with beta-blocker was associated with an increased risk of stroke compared with the other antihypertensive agents, especially in the elderly patients.[37] The unfavorable data of beta-blocker were derived from studies using traditional non-vasodilating beta-blocker, especially atenolol. Vasodilatory beta-blockers, such as carvedilol and nebivolol reduce BP in large part through decreasing systemic vascular resistance and reduce the metabolic side effects of traditional beta-blocker.[38] Beta-blockers, except atenolol, still can be used as the first-line therapy for BP control and are especially important for patients with history of CAD, MI, and heart failure.

Table 4 High risk features of stable CAD.

Major ASCVD events
History of acute coronary syndrome
History of ischemic stroke or transient ischemic attack
History of symptomatic peripheral artery disease
History of coronary artery bypass surgery or percutaneous coronary intervention
History of premature CAD (CAD was diagnosed ≦45 years in male and ≦55 years in female)
Risk factors
Age ≧65 years
Hypertension
Diabetes mellitus
Current smoking
Chronic kidney disease (estimated glomerular filtration rate 15–59 mL/min/1.73 m^2)
Familial hypercholesterolemia
Heart failure

ASCVD: atherosclerotic cardiovascular disease; CAD: coronary artery disease.
Adapted and modified from reference [31].

Recommendation

- For patients with a history of stroke, the BP target is < 140/90 mmHg. (COR I, LOE A)

Hypercholesterolemia

Elevated LDL-C is a significant risk factor for developing atherothrombotic stroke.[39,40] The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study was the only trial designed to evaluate statin in secondary stroke prevention. The mean level of LDL-C during the study is 72.9 mg/dL in the intensive statin therapy group and 128.5 mg/dL in the placebo group. The result showed intensive statin therapy reduced the overall incidence of stroke in patients with a history of stroke or transient ischemic attack.[41] Other clinical trials in the high risk populations, such as patients with hypertension in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) trial and patients with diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS) trial, statins also lower the risk of stroke. The achieved LDL-C levels in the statin treatment group were around 80–90 mg/dL.[42,43] Meta-analysis also showed statin treatment can decrease the risk of stroke.[44,45]

Recommendation

- For patients with atherosclerotic ischemic stroke or transient ischemic attack, the LDL-C target is < 100 mg/dL (COR I, LOE B)

Diabetes

The risk of ischemic stroke is increased in patients with diabetes.[46–48] However, meta-analysis shows very intensive sugar-lowering therapy was not associated with a further reduction of stroke risk.[49,50] Therefore, the recommended HbA1c target is <7.0% for diabetic patients with a history of stroke. However, in patients with frailty or limited life expectancy, an HbA1c target <8% can be considered. There is no specific randomized control trial to test the efficacy of hypoglycemic agents in diabetic patients with previous stroke. Pioglitazone, a thiazolidinedione (TZD), was associated with a 47% relative risk reduction of recurrent stroke among diabetics with a history of stroke in the subgroup analysis of the PROspective pioglitAzone Clinical Trial In macrovascular Events (PROactive) trial. The baseline HbA1C was 8.1% and a 0.9% HbA1C decrease was noted in the pioglitazone group.[51] The Insulin Resistance Intervention after Stroke (IRIS) trial included patients without diabetes but had insulin resistance and a recent history of ischemic stroke or transient ischemic attack. The risk of stroke or MI was lower in the pioglitazone group than placebo.[52] Recent clinical trials of the new generation antidiabetic drugs, such as GLP-1 receptor agonist and SGLT2 inhibitor demonstrated benefits on major adverse CV events reduction in diabetic patients.[53,54] The Taiwan Society of Cardiology and the Diabetes Association of Republic of China (Taiwan) developed a consensus to provide specific recommendations for choosing diabetic drugs in patients with CV diseases.[9] For diabetic patients with a history of stroke, metformin is still the first line therapy if there is no contraindication. TZD, followed by GLP-1 receptor agonist, and then SGLT2 inhibitor can be considered as the second line therapy.

Recommendation

- The HbA1c target is <7.0% in diabetic patients with a history of stroke. In patents with frailty or limited life expectancy, the HbA1c target is <8.0% (Class I, LOE C).

Atrial fibrillation

Development and subsequent embolization of atrial thrombi can occur with paroxysmal, persistent, or permanent AF. Therefore, chronic oral anticoagulation treatment is recommended for most AF patients to prevent stroke. However, such therapy is associated with an increased risk of bleeding, therefore, recommendation for its use must take both benefit and risk into account. Currently, CHA_2DS_2-VASc score (Table 5) is used to identify low risk patients who do not need anticoagulants.[55] In AF patients with a history of ischemic stroke or transient ischemic attack, the CHA_2DS_2-VASc is ≥ 2 and anticoagulation treatment becomes necessary if there is an acceptable risk of bleeding. There is little role of antiplatelet agents in AF stroke prevention. Large scale randomized trials demonstrated that non-vitamin K antagonist oral anticoagulants (NOACs)

Table 5 The CHA_2DS_2-VASc score.

Risk Factor	Score
[a]Congestive heart failure/Left ventricular dysfunction	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke/Transient ischemic attack/Thromboembolsim	2
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65—74 years	1
Sex category (i.e. female gender)	1

[a] Documented moderate-to-severe systolic dysfunction [i.e. heart failure with reduced ejection fraction <40% (HF-REF)] or patients with recent decompensated heart failure requiring hospitalization, irrespective of ejection fraction [i.e. both HF-REF and heart failure with preserved ejection fraction (HF-PEF)].
Adapted from reference [55].

including dabigatran, rivaroxaban, apixaban, and edoxaban have similar or lower rates of ischemic stroke and major bleeding compared to warfarin in patients with nonvalvular AF.[56] The advantages of NOAC over warfarin include convenience with no requirement for routine monitoring and decreased susceptibility to dietary or drug interactions.

Recommendation

- For AF patients with a history of ischemic stroke or transient ischemic attack, NOACs should be considered as the first-line anticoagulation treatment if there is no contraindication. (Class I, LOE A)
- Warfarin is the drug of choice for AF patients with mechanical heart valve, moderate to severe rheumatic mitral valve stenosis, or advanced CKD with eGFR < 15 mL/min/1.73 m^2. (Class I, LOE B)

Peripheral artery disease

Hypertension

PAD is a manifestation of diffuse atherosclerotic change. These patients carry a very high CV risk, especially in those with multiple arterial beds involvement of atherosclerosis, such as PAD with coronary and/or carotid atherosclerosis.[57] BP control is important for CV risk reduction in these patients. In patients with PAD and hypertension, the BP control should follow the current Taiwan Hypertension Guideline that a target BP < 140/90 mmHg is generally recommended except in patients with diabetes, CAD and CKD with proteinuria, in whom the BP should be controlled to <130/80 mmHg.[5] For PAD, it would be better to keep a systolic BP > 120 mmHg because the post hoc analysis of the INternational VErapamil-SR/Trandolapril (INVEST) study reported a J curve phenomenon between systolic BP < 120 mmHg and increased CV events in hypertensive patients with PAD.[58] CCB or ACEI/ARB are suitable first line antihypertensive treatment, either as monotherapy or in combination for PAD patients. Because there are no prospective randomized clinical trials specifically designed for PAD, it is unknown whether significant benefit or risk exists for one class of antihypertensive drugs over the other. Previous clinical trials of ACEI and ARB have shown that these classes of drugs significantly improved CV outcome in PAD subgroup.[13,59] Concerns have been raised about using diuretics or beta-blockers in patients with PAD. Multiple studies have demonstrated that BP-lowering treatment, including the use of beta-blockers, does not worsen claudication symptoms or impair functional status in patients with PAD.[60—62] Beta-blockers, especially those with vasodilating property, are not contraindicated in patients with PAD. Beta blockers do not alter walking capacity in PAD patients and reduce coronary events in patients with PAD and prior MI.[63]

Recommendation

- In PAD with hypertension, the BP target is < 140/90 mmHg. PAD patients with diabetes, CAD and CKD with proteinuria, the BP target is < 130/80 mmHg. (Class I, LOE C)

Hypercholesterolemia

All PAD patients should receive LDL-C-lowering therapy. According to current Taiwan Lipid Guidelines for High Risk Patients, the target LDL-C level is < 100 mg/dL for PAD and LDL-C level should be < 70 mg/dL for patients with PAD and CAD.[7] A meta-analysis including 17 lipid-lowering trials revealed a 26% reduction CV events in patients with PAD treated with statins.[64] Although a number of lipid-lowering drugs were assessed, the most consistent benefits were from statin therapy. Usually, statins are the first-line therapy for PAD. To help PAD patients to reach the suggested target, moderate or high intensity statins are preferred, unless patients cannot tolerate. In recent years, clinical studies demonstrated that add on non-statin therapies including ezetimibe or PCSK9 inhibitor to statins could cause more LDL-C lowering and not only improve CV outcomes but also decrease the major adverse limb events in PAD patients.[65,66]

Recommendation

- The LDL-C target in PAD is < 100 mg/dL and <70 mg/dL if there is coexisting CAD. (Class I, LOE B)

Diabetes

Diabetes is a strong risk factor for the development of PAD and increases the risk of adverse outcomes of PAD, such as critical limb ischemia, amputation, and death. Strict glycemic control is recommended for PAD patients. According to the 2018 guideline from the Diabetes Association of Republic of China (Taiwan), the HbA1c should be controlled

to < 7%, the sugar before meal should be 80—130 mg/dL and the postprandial sugar should be < 160 mg/dL.[8] However, considering patients' age, comorbidities, fragility and life expectancy, less strict HbA1c target < 8% also can be considered. All means of sugar-lowering therapies, either in mono- or combination therapy can be considered for PAD patients to reach the HbA1c target. In recent years, many CV outcome trials of new generation anti-diabetic drugs have been published. The Taiwan Society of Cardiology and the Diabetes Association of Republic of China (Taiwan) developed a consensus to provide specific recommendations for choosing diabetic drugs in patients with CV diseases.[9] For diabetic patients with CAD, metformin should be the first-line therapy if there is no contraindication. TZD, SGLT2 inhibitor, and GLP-1 receptor agonist are the preferred second-line add on therapy because randomized clinical trials demonstrated CV outcome benefits of these anti-diabetic drugs for CAD. This recommendation could also be applied to PAD patient with concomitant CAD. However, amputation risk was reported in some SGLT2 inhibitor and should be used carefully in PAD patients.

Recommendation

- In PAD with diabetes, the HbA1c target is <7.0%. In patents with frailty or limited life expectancy, the HbA1c target is <8.0%. (Class I, LOE C)

Antiplatelet agents

Antiplatelet therapy is recommended in all patients with PAD if there is no contraindication. The commonly used antiplatelet agents in PAD include aspirin, clopidogrel and cilostazol.

Aspirin

Aspirin is usually the first line antiplatelet agent in PAD. A meta-analysis including 9214 patients with symptomatic PAD showed a 23% reduction in the risk of CV events.[67] In another meta-analysis comprising 5269 PAD patients, subjects treated with aspirin or aspirin plus dipyridamole were found to be associated with 12% risk reduction in non-fatal MI, non-fatal stroke, and CV death.[68] Therefore, antiplatelet therapy with aspirin (100 mg per day in Taiwan) is suggested for patients with symptomatic PAD. However, for asymptomatic PAD patients, the role of aspirin is less certain based on current limited evidences. In the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial, 1276 diabetic patients with asymptomatic PAD were recruited to study the efficacy of aspirin on CV outcomes. Aspirin was not associated with CV benefits after a median 6.7 years follow-up.[69] In the Aspirin for Prevention of Cardiovascular Events in a General Population Screened for a Low Ankle Brachial Index (AAA) trial, 3350 patients with reduced ABI value (≤0.95) and without other established CV diseases were randomized to aspirin or placebo. There was also no benefit of aspirin for both primary and secondary endpoints.[70] It is controversial whether antiplatelet agents should be given to asymptomatic PAD patients.

Clopidogrel

In the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, 19185 high risk patients (recent MI, recent ischemic stroke, or symptomatic PAD) were randomized to clopidogrel (75 mg/day) or aspirin (325 mg/day). After a mean of 1.9 years follow-up, clopidogrel was associated with 8.7% relative risk reduction (P = 0.043; 95% CI 0.3—16.5) in the composite endpoint of MI, stroke and vascular death. The subgroup analysis of PAD subjects showed a 23.8% relative risk reduction (P = 0.0028; 95% CI 8.9—36.2) in the clopidogrel group.[71] Therefore, clopidogrel is also recommended for symptomatic PAD. In clinical practice, aspirin should be the first line therapy, and clopidogrel is considered if aspirin is contraindicated or intolerable.

Cilostazol

Cilostazol is a phosphodiesterase III inhibitor, which reversibly inhibits platelet aggregation and possesses vasodilatory effects. It increases blood flow to the limbs and is an effective therapy to improve symptoms and walking distance for symptomatic PAD. Cilostazol has been widely studied in PAD. A meta-analysis including 8 randomized control trials for symptomatic PAD patients showed that cilostazol was associated with maximal and pain-free walking distances by 44% and 50% respectively.[72] In another Cochrane review including 15 double-blind randomized clinical trials with a total of 3718 participants, cilostazol was associated with improvement in claudication symptoms when compared with placebo.[73] Hence, cilostazol can be used to improve claudication symptoms and increase the walking distance in PAD patients.

Ticagrelor or dual antiplatelet therapy

Ticagrelor or dual antiplatelet therapy (DAPT) for PAD is not recommended routinely. In the Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor was shown to be superior to clopidogrel to reduce ischemic events in ACS patients. However, in the Examining Use of Ticagrelor in Peripheral Artery Disease (EUCLID) trial, ticagrelor and clopidogrel were shown to have similar CV and limb ischemic outcomes in PAD patients. The major bleeding risk was also similar. However, higher medication discontinuation rate was noted in the ticagrelor group due to the side effects of dyspnea and any bleeding event.[74] Therefore, ticagrelor is not routinely recommended for PAD patients unless patients have ACS or contraindications for all other antiplatelet agents. DAPT is also not routinely used in PAD. In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study, 15603 high risk or documented vascular diseases patients were randomized into either DAPT with aspirin plus clopidogrel or aspirin alone. DAPT did not further reduce the ischemic risk including MI, stroke, or CV death compared with aspirin monotherapy.[75] The PAD subgroup analysis also showed no significant benefit from DAPT strategy.[76] The effect of DAPT with aspirin plus ticagrelor versus aspirin monotherapy was studied in patients with prior MI in the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin—Thrombolysis In Myocardial Infarction 54 (PEGASUS-TIMI 54) trial.[77] In the

PAD subgroup analysis, DAPT with aspirin plus ticagrelor was found to have lower CV and adverse limb events comparing with aspirin alone.[78] However, due to the small patient numbers, further larger study is still needed to confirmed the beneficial effect of this DAPT strategy in PAD.

Recommendation

- For symptomatic PAD patients, antiplatelet therapy with aspirin or clopidogrel is recommended to reduce CV risk. (Class I, LOE A)
- In PAD patients with claudication symptoms, cilostazol should be considered to improve symptoms and walking distances. (Class I, LOE A)

Conflict of interest

The authors have no conflicts of interest relevant to this article.

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