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# 2024 Guidelines of the Taiwan Society of Cardiology on the Primary Prevention of Atherosclerotic Cardiovascular Disease --- Part I

*Ting-Hsing Chao,[1,2]* Tsung-Hsien Lin,[3,4] Cheng-I Cheng,[5] Yen-Wen Wu,[6,7,8] Kwo-Chang Ueng,[2] Yih-Jer Wu,[9,10] Wei-Wen Lin,[11] Hsing-Ban Leu,[7,12,13,14] Hao-Min Cheng,[15] Chin-Chou Huang,[7,14,16] Chih-Cheng Wu,[17] Chao-Feng Lin,[18] Wei-Ting Chang,[19] Wen-Han Pan,[20] Pey-Rong Chen,[21] Ke-Hsin Ting,[22] Chun-Hung Su,[2] Chih-Sheng Chu,[23] Kuo-Liong Chien,[24] Hsueh-Wei Yen,[3] Yu-Chen Wang,[25] Ta-Chen Su,[26,27] Pang-Yen Liu,[28] Hsien-Yuan Chang,[1] Po-Wei Chen,[1] Jyh-Ming Jimmy Juang,[29] Ya-Wen Lu,[11,12,30] Po-Lin Lin,[31] Chao-Ping Wang,[32] Yu-Shien Ko,[33] Chern-En Chiang,[34] Charles Jia-Yin Hou,[10] Tzung-Dau Wang,[35] Yen-Hung Lin,[36] Po-Hsun Huang[12,14] and Wen-Jone Chen[37]*

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[1]Division of Cardiology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan; [2]Division of Cardiology, Department of Internal Medicine, Chung-Shan Medical University Hospital; School of Medicine, Chung Shan Medical University, Taichung; [3]Division of Cardiology, Department of Internal Medicine Kaohsiung Medical University Hospital; [4]Faculty of Medicine and Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University; [5]Division of Cardiology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung; School of Medicine, College of Medicine, Chang Gung University, Taoyuan; [6]Division of Cardiology, Cardiovascular Medical Center, Far Eastern Memorial Hospital, New Taipei City; [7]School of Medicine, National Yang Ming Chiao Tung University, Taipei; [8]Graduate Institute of Medicine, Yuan Ze University, Taoyuan; [9]Department of Medicine and Institute of Biomedical Sciences, MacKay Medical College, New Taipei City; [10]Cardiovascular Center, Department of Internal Medicine, MacKay Memorial Hospital, Taipei; [11]Cardiovascular Center, Taichung Veterans General Hospital, Taichung; [12]Cardiovascular Research Center, National Yang Ming Chiao Tung University; [13]Healthcare and Management Center; [14]Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital; [15]Ph.D. Program of Interdisciplinary Medicine (PIM), National Yang Ming Chiao Tung University College of Medicine; Division of Faculty Development; Center for Evidence-based Medicine, Taipei Veterans General Hospital; Institute of Public Health; Institute of Health and Welfare Policy, National Yang Ming Chiao Tung University College of Medicine; [16]Institute of Pharmacology, National Yang Ming Chiao Tung University, Taipei. [17]Center of Quality Management, National Taiwan University Hospital Hsinchu Branch, Hsinchu; College of Medicine, National Taiwan University, Taipei; Institute of Biomedical Engineering, National Tsing-Hua University, Hsinchu; Institute of Cellular and System Medicine, National Health Research Institutes, Zhunan; [18]Department of Medicine, MacKay Medical College, New Taipei City; Department of Cardiology, MacKay Memorial Hospital, Taipei; [19]School of Medicine and Doctoral Program of Clinical and Experimental Medicine, College of Medicine and Center of Excellence for Metabolic Associated Fatty Liver Disease, National Sun Yat-sen University, Kaohsiung; Division of Cardiology, Department of Internal Medicine, Chi Mei Medical Center, Tainan; [20]Institute of Biomedical Sciences, Academia Sinica, Taipei; Institute of Population Health Sciences, National Health Research Institutes, Miaoli; and Institute of Biochemistry and Biotechnology, National Taiwan University; [21]Department of Dietetics, National Taiwan University Hospital, Taipei; [22]Division of Cardiology, Department of Internal Medicine, Yunlin Christian Hospital, Yunlin; [23]Division of Cardiology, Department of Internal Medicine, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University, Kaohsiung; [24]Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University; Department of Internal Medicine, National Taiwan University Hospital and College of Medicine; Population Health Research Center, National Taiwan University, Taipei; [25]Division of Cardiology, Asia University Hospital; Department of Medical Laboratory Science and Biotechnology, Asia University; Division of Cardiology, China Medical University College of Medicine and Hospital, Taichung; [26]Cardiovascular Center, Department of Internal Medicine, National Taiwan University Hospital; [27]Department of Environmental and Occupational Medicine, National Taiwan University College of Medicine; [28]Division of Cardiology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center; [29]Heart Failure Center and Division of Cardiology, Department of Internal Medicine, National Taiwan University College of Medicine, and National Taiwan University Hospital; [30]Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei; [31]Division of Cardiology, Department of Internal Medicine, Hsinchu MacKay Memorial Hospital, Hsinchu; [32]Division of Cardiology, E-Da Hospital; School of Medicine for International Students, College of Medicine, I-Shou University, Kaohsiung; [33]Cardiovascular Division, Chang Gung Memorial Hospital; College of Medicine, Chang Gung University, Taoyuan; [34]General Clinical Research Center and Division of Cardiology, Taipei Veterans General Hospital and National Yang Ming Chiao Tung University; [35]Cardiovascular Center and Divisions of Hospital Medicine and Cardiology, Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine; [36]Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei; [37]Department of Internal Medicine, Min-Sheng General Hospital, Taoyuan; Department of Internal Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan.
Corresponding author: Dr. Ting-Hsing Chao, Division of Cardiology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan 704302; Division of Cardiology, Department of Internal Medicine, Chung-Shan Medical University Hospital; School of Medicine, Chung Shan Medical University, Taichung, Taiwan. Tel: 886-6-235-3535 ext. 2389; Fax: 886-6-275-3834; E-mail: chaoth@mail.ncku.edu.tw, chaotinghsing@gmai.com
* Wen-Jone Chen and Ting-Hsing Chao jointly supervised this work and serve as corresponding authors.

Atherosclerotic cardiovascular disease (ASCVD) is one of the leading causes of death worldwide and in Taiwan. It is highly prevalent and has a tremendous impact on global health. Therefore, the Taiwan Society of Cardiology developed these best-evidence preventive guidelines for decision-making in clinical practice involving aspects of primordial prevention including national policies, promotion of health education, primary prevention of clinical risk factors, and management and control of clinical risk factors. These guidelines cover the full spectrum of ASCVD, including chronic coronary syndrome, acute coronary syndrome, cerebrovascular disease, peripheral artery disease, and aortic aneurysm. In order to enhance medical education and health promotion not only for physicians but also for the general public, we propose a slogan **(2H2L)** for the primary prevention of ASCVD on the basis of the essential role of healthy dietary pattern and lifestyles: "**Healthy Diet and Healthy Lifestyles to Help Your Life and Save Your Lives**". We also propose an acronym of the modifiable risk factors/enhancers and relevant strategies to facilitate memory: "**$ABC_2D_2EFG$-I'$M_2$ ACE":** Adiposity, Blood pressure, Cholesterol and Cigarette smoking, Diabetes mellitus and Dietary pattern, Exercise, Frailty, Gout/hyperuricemia, Inflammation/infection, Metabolic syndrome and Metabolic dysfunction-associated fatty liver disease, Atmosphere (environment), Chronic kidney disease, and Easy life (sleep well and no stress). Some imaging studies can be risk enhancers. Some risk factors/clinical conditions are deemed to be preventable, and healthy dietary pattern, physical activity, and body weight control remain the cornerstone of the preventive strategy.

**Key Words:** Atherosclerotic cardiovascular disease • Guidelines • Primary prevention

**Abbreviations**

| | |
|---|---|
| ABI | Ankle-brachial index |
| ACC | American College of Cardiology |
| ACS | Acute coronary syndrome |
| ADH | Alcohol dehydrogenase |
| AHA | American Heart Association |
| ALDH | Aldehyde dehydrogenase |
| AMI | Acute myocardial infarction |
| apoB | Apolipoprotein B |
| ArtS | Arterial stiffness |
| ASCVD | Atherosclerotic cardiovascular disease |
| baPWV | Brachial-ankle pulse wave velocity |
| BMI | Body mass index |
| BP | Blood pressure |
| CAC | Coronary artery calcium |
| CAD | Coronary artery disease |
| CCS | Chronic coronary syndrome |
| CCTA | Coronary computed tomographic angiography |
| cfPWV | Carotid-femoral pulse wave velocity |
| CI | Confidence interval |
| CIMT | Carotid intima-media thickness |
| CKD | Chronic kidney disease |
| COPD | Chronic obstructive pulmonary disease |
| COR | Class of recommendation |
| CVD | Cardiovascular disease |
| DASH | Dietary Approaches to Stop Hypertension |
| DBP | Diastolic blood pressure |
| DHA | Docosahexaenoic acid |
| DM | Diabetes mellitus |
| eGFR | Estimated glomerular filtration rate |
| EPA | Eicosapentaenoic acid |
| ESC | European Society of Cardiology |
| FH | Familial hypercholesterolemia |
| HbA1C | Hemoglobin A1C |
| HDL-C | High-density lipoprotein cholesterol |
| HR | Hazard ratio |
| hsCRP | High-sensitivity C-reactive protein |
| LDL-C | Low-density lipoprotein cholesterol |
| LOE | Level of evidence |
| Lp(a) | Lipoprotein (a) |
| MAFLD | Metabolic dysfunction-associated fatty liver disease |
| MeDiet | Mediterranean diet |
| MetS | Metabolic syndrome |
| MI | Myocardial infarction |
| NRT | Nicotine replacement therapy |
| OSA | Obstructive sleep apnea |
| PAD | Peripheral artery disease |
| PCE | Pooled Cohort Equation |
| PCSK9 | Proprotein convertase subtilisin/kexin 9 |
| PM | Particulate matter |
| RCT | Randomized controlled trial |
| SBP | Systolic blood pressure |
| SCORE | Systemic COronary Risk Evaluation |
| SGLT2 | Sodium-dependent glucose cotransporter-2 |
| TC | Total cholesterol |
| TEA | Taiwanese Eating Approaches |
| TG | Triglyceride |
| TNHIRD | Taiwan National Health Insurance Research Database |
| TSOC | Taiwan Society of Cardiology |
| TwCCCC | Taiwan Chin-Shan Community Cardiovascular Cohort |
| UACR | Urine albumin clearance ratio |

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## 1. INTRODUCTION

This guideline is divided into 2 parts. Part I (section 1.1-3.4) includes introduction, impact of risk factors and clinical conditions, preventive strategies, and surrogate markers. Part II (section 4.1-5.13) includes other concomitant disorders and interventions.

### 1.1. Scope of the guidelines

#### *1.1.1. Definition of atherosclerotic cardiovascular disease (ASCVD)*

The initiation and progression of atherosclerosis involve complex mechanisms, including atherogenic lipid deposition and oxidation, pro-inflammation, vascular endothelial dysfunction, smooth muscle cell proliferation and migration, extracellular matrix degradation, and immune cell recruitment, thereby leading to plaque formation and growth.[1] Clinically manifested ASCVD occurs when atherosclerotic plaque obstructs vascular lumen due to blood flow limitation or thrombosis formation from rupture of vulnerable plaque.[1] The initiation of atherosclerosis usually occurs early in life.[2] Some studies have demonstrated that fatty streak, an early pathological sign of atherosclerosis, can be found in relatively younger individuals.[2-4] The scope of the current primary prevention guidelines focus on the prevention of ASCVD involving aspects of primordial prevention.[5] The definition of ASCVD in these guidelinesis in line with the recently published Taiwan lipid guidelines for primary prevention[6] and chronic coronary syndrome (CCS),[7] and includes:

1. CCS, such as stable angina with positive stress test and/or major coronary artery diameter stenosis ≥ 50% by imaging studies, stable symptoms after acute coronary syndrome (ACS)/percutaneous coronary intervention, vasospastic angina, micro-vascular angina, and silent coronary artery disease (CAD) on screening.
2. ACS, such as unstable angina and acute myocardial infarction (AMI).
3. Cerebrovascular disease, such as transient ischemic attack, ischemic stroke, and carotid artery stenosis ≥ 50% by imaging studies.
4. Peripheral artery disease (PAD), such as symptoms suggestive of PAD with ankle-brachial index (ABI) < 0.9 or ≥ 1.3, and major extremity artery diameter stenosis ≥ 50% by imaging studies.
5. Aortic atherosclerotic disease, such as thoracic or abdominal aortic aneurysm by imaging studies.

The full spectrum of ASCVD is covered in these guidelines (Figure 1), and the scope is demonstrated (blue area) in the hierarchy of ASCVD prevention shown in Figure 2.

### *1.1.2. Epidemiology and prognosis*

ASCVD is one of the leading causes of death worldwide and in Taiwan.[8,9] In 2022, cardiovascular disease (CVD) accounted for approximately 24,000 deaths in Taiwan.[9] More than 17,000 people die of CAD annually in Taiwan.[7]

According to analyses of the Taiwan National Health

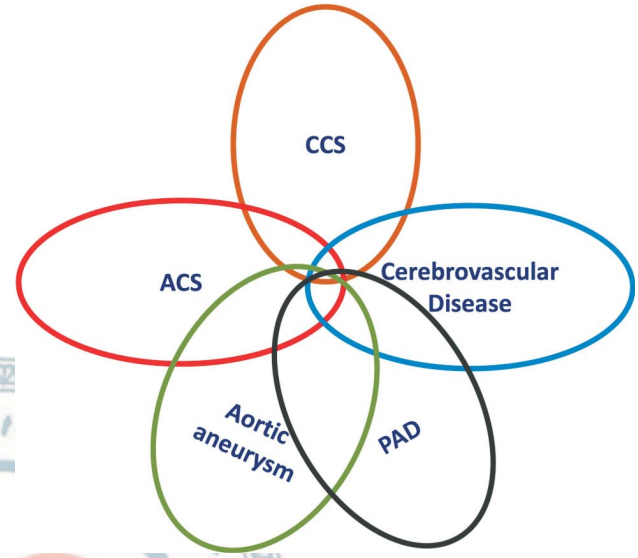


***Figure 1.*** *Full spectrum of ASCVD. ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CCS, chronic coronary syndrome; PAD, peripheral artery disease.*

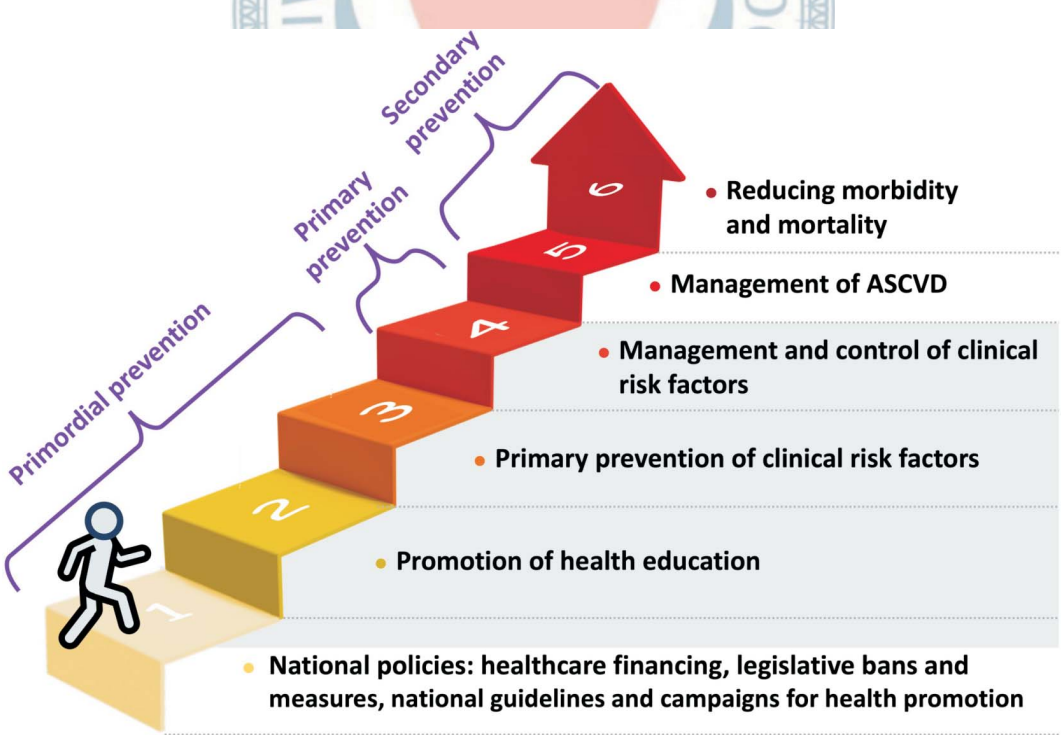


***Figure 2.*** *The scope of the guidelines: ASCVD prevention hierarchy. The scope of these guidelines is demonstrated in blue area. ASCVD, atherosclerotic cardiovascular disease.*

Insurance Research Database (TNHIRD), the incidence rate of AMI gradually increased from 1997-2011, mainly driven by an increase in non-ST segment elevation myocardial infarction (MI),[10-12] and the in-hospital mortality rate of AMI was 6.5% in 2011.[11] The incidence rate of ischemic stroke has declined worldwide, whereas the mean global life-time risk of stroke has increased.[8,13] In agreement with global data, the incidence rate of ischemic stroke declined from 2000-2011 in Taiwan, and the 30-day in-hospital mortality rate was 1.9% from 2008-2011.[14] The reported prevalence rate of aortic aneurysm in Western countries is around 1.3% to 8%.[15] A population-based nationwide analysis showed an increasing trend in the incidence and prevalence of aortic aneurysm from 2005 to 2011, with average annual incidence and prevalence rates of 7.35 per 100,000 persons and 29.04 per 100,000 persons, respectively.[15] In addition, the mortality rate increased from 1.41 per 100,000 persons to 4.70 per 100,000 persons during this period.[15] Owing to discrepancies in the definitions and study populations of CCS and PAD in the literature, it is difficult to clearly identify the prevalence and incidence of both diseases. A systematic review estimated that the global prevalence of PAD was 5.6% in 2015.[16,17] Taken together, ASCVD is highly prevalent and has a tremendous impact on global health, and this was the rationale for developing these primary prevention guidelines.

*1.1.3. Guideline development process*

In October 2022, the development of guidelines for the primary prevention of ASCVD was proposed by the Preventive Medicine Committee of the Taiwan Society of Cardiology (TSOC) and approved by the Executive Board of the TSOC thereafter. The members of the writing group were selected by the chairperson of the Preventive Medicine Committee of the TSOC and some of them were also recommended by the Hypertension Committee of the TSOC, the Taiwan Hypertension Society, and the Taiwan Society of Lipid and Atherosclerosis. To establish consensus among the writers by reviewing clinical evidence, three virtual meetings were held on February 11, 12 and 13 in 2023. Some issues were further discussed and clarified during subsequent symposiums held by the TSOC to reach final consensus. All recommendations are listed in Table 1, and the top ten features/key messages/highlights are summarized in Table 2.

*1.1.4. The purpose and thinking map of the guidelines*

The purpose of the guidelines is to provide best-evidence guidance for decision-making in clinical practice rather than exclusive regulation. Healthcare providers are at full discretion in clinical practice, owing to the diversity of individuals and practice, and the availability of resources and facilities.

A review of the evidence with respect to risk factors and concomitant diseases was arranged in the following order if appropriate:

1. Epidemiology of this risk factor or concomitant disease.
2. Clinical impact of this risk factor or concomitant disease on the development of ASCVD.
3. Potential role of this risk factor or concomitant disease for risk assessment.
4. Strategies to prevent this risk factor or concomitant disease.
5. Strategies to prevent ASCVD by modifying this risk factor or concomitant disease.

*1.1.5. Class of recommendation (COR) and level of evidence (LOE)*

We adopted COR and LOE for each recommendation in these guidelines for a better understanding of how strong our recommendations are with the available evidence. The definitions of COR and LOE, in line with previous TSOC guidelines,[7,18] are shown as follows and listed in Table 3. CORs are used to denote whether a recommendation is beneficial/useful/effective or not useful/effective and may be harmful in some cases.[7,18] Class I recommendations indicate that they are beneficial/useful/effective and should be performed. Class II recommendations indicate that there is conflicting evidence and/or divergent opinions about the benefit/usefulness/efficacy and should be weighed with benefit and risk if they are applied in clinical practice.[7,18] Class IIa indicates that the weight of benefit and risk is in favor of the recommendations, whereas class IIb indicates that the recommendations are less well established by evidence/opinions.[7,18] Class III recommendations indicate that they are not useful/effective and may be harmful in some cases, and should not be performed.[7,18] LOEs are used to denote the strength of evidence supporting the recommendations.[7,18] LOE A indicates that the recommendations are based on multiple randomized controlled

**Table 1.** Recommendations

| Recommendations | COR | LOE |
|---|---|---|
| Risk assessment | | |
| • After the age of 35 years, it is reasonable to assess traditional ASCVD risk factors. | IIa | A |
| • For adults aged 35 to 75 without established ASCVD, clinicians should consider assessing traditional risk factors and calculate the 10-year or 15-year risk of CAD or stroke by using the TwCCCC risk chart or the coefficient-based risk prediction model constructed by Chang et al.[†] | IIa | B |
| DM | | |
| • Regular monitoring for the development of type 2 DM in those with prediabetes annually is recommended. | I | C |
| • Lifestyle modifications to prevent or delay the onset of type 2 DM is recommended. | I | A |
| • With respect to the primary prevention of ASCVD by pharmacological glucose-lowering treatment, a GLP-1 RA proven to be effective in RCTs is recommended. | I | A |
| • For primary prevention of ASCVD by pharmacological glucose-lowering treatment, metformin can be used, and an SGLT2 inhibitor should be considered in patients with CKD. | IIa | B |
| • A target HbA1C < 7% is recommended in glucose control for the primary prevention of ASCVD. | I | B |
| Hypertension | | |
| • Individuals with high BP, hypertension, or who are currently on medication to lower BP, as well as those who are 40 years old or older, should consider using a validated BP monitor at home to measure their BP. | IIa | B |
| • People with high BP should live a healthier lifestyle to reduce their lifetime BP burden. | I | A |
| • In low-risk hypertensive patients (those without hypertension-mediated organ damage and with fewer than three ASCVD risk indicators), the starting point for pharmacological treatment should be a BP of 140/90 mmHg. | I | A |
| • For other hypertension patients, a BP of 130/80 mmHg is recommended as the starting point for pharmacological treatment. | I | A |
| • Based on home BP monitoring, a universal BP target of 130/80 mmHg is suggested for all hypertensive individuals. | I | A |
| • If it is manageable, the SBP target for patients at high ASCVD risk can be 120 mmHg. | IIa | B |
| Dyslipidemia | | |
| • For the primary prevention of ASCVD in individuals with dyslipidemia, risk stratification according to comorbidities and other risk factors is necessary. | I | B |
| • ApoB and non-HDL-C can be used to predict the risk of ASCVD. | IIa | B |
| • For the primary prevention of ASCVD, persistently elevated TG ≥ 175 mg/dL, Lp(a) ≥ 50 mg/dL, apoB ≥ 130 mg/dL, and non-HDL-C 190-219 mg/dL are respectively recognized as risk-enhancing factors, and the initiation of specific lipid-lowering therapy should be considered. | IIa | B |
| • For the primary prevention of ASCVD, subjects with DM, non-dialysis CKD, or LDL-C ≥ 190 mg/dL are at high risk of ASCVD, and immediate lipid-lowering therapy is necessary (COE I, LOE A); the LDL-C target is < 100 mg/dL. | I | B |
| • For the primary prevention of ASCVD, in patients with 2 (moderate risk), 1 (low risk), and 0 (minimal risk) risk factors without a high-risk profile (DM, non-dialysis CKD, or LDL-C ≥ 190 mg/dL), the LDL-C targets should be < 115, < 130, and < 160 mg/dL, respectively. | IIa | C |
| • For the primary prevention of ASCVD, statins are the first-line therapy. It is reasonable to initiate moderate-intensity statins first, and then titrate to high intensity if the treatment goal is not reached. | I | A |
| • For the primary prevention of ASCVD, ezetimibe may be considered in patients who are indicated for lipid-lowering treatment but cannot reach the LDL-C target with statin therapy or cannot tolerate statins. | IIb | B |
| • PCSK9 inhibitors are reasonable for primary prevention in patients at high risk who cannot achieve the LDL-C target with high-intensity or maximal tolerated statins and ezetimibe. | IIa | A |
| • Non-HDL-C can be used a secondary target, and the target of non-HDL-C is 30 mg/dL above the recommended LDL-C treatment target. | IIa | B |
| Cigarette smoking | | |
| • All adults are recommended to be assessed at every healthcare visit for tobacco use and their tobacco use status should be recorded as a vital sign for ASCVD risk assessment and facilitating smoking cessation. | I | A |
| • To reduce the risk of ASCVD, all adults and adolescents are advised to avoid exposure to secondhand smoke. | III | B |

**Table 1.** Continued

| Recommendations | COR | LOE |
|---|---|---|
| Cigarette smoking | | |
| • Legislative bans and measures to avoid cigarette smoking and secondhand smoke exposure are recommended to enhance the prohibition/restriction power via government authorities. | I | B |
| • To reduce the risk of ASCVD, smoking cessation is recommended in all individuals who have a habit of tobacco smoking. | I | A |
| • With regards to the method of smoking cessation, electronic nicotine delivery systems or heat-not-burn tobacco should not be recommended. | IIb | B |
| • Seven drugs are recommended for smoking cessation, including five NRT products, varenicline, and bupropion. | I | A |
| • Varenicline can be more effective in smoking cessation than nicotine patches and bupropion for nicotine-dependent adults in whom treatment is being initiated. | I | B |
| • For pregnant women who smoke, behavioral interventions for smoking cessation to improve perinatal outcomes and promote smoking abstinence are recommended. | I | A |
| Obesity | | |
| • Early detection and interventions to effectively mitigate the risks associated with ASCVD and obesity-related co-morbidities are needed. | I | A |
| • It is recommended to calculate BMI at least annually, or even more frequently, in individuals who are overweight or obese. Additionally, measuring waist circumference is considered a reasonable approach to identify individuals with MetS, a cluster of risk factors for ASCVD. | I | C |
| • To reduce body weight and mitigate the risk of ASCVD, it is recommended to establish a comprehensive weight loss plan that incorporates exercise training and diet control. These interventions aim to promote healthy habits and encourage individuals to lose approximately 5-10% of their body weight. | I | A |
| • To attain the desired weight loss, a low carbohydrate diet ranging from 1200-1600 kcal/day should be generally preferred over a very low carbohydrate diet (< 800 kcal/day) when considering long-term calorie restriction. | IIa | B |
| • A ketogenic diet or a very low-calorie diet may be considered in terms of short-term benefits and rapid initial weight loss under the supervision of medical professionals but might not be utilized as a long-term dietary nutritional intervention due to various considerations. | IIb | B |
| • The recommended approach for patients initiating moderate intensity exercise training is to start with 5-7 sessions per week, with each session lasting more than 30 minutes. The exercise intensity should be set within the range of 40-59% of the heart rate reserve. As individuals progress, it is recommended to gradually increase both the duration and intensity of the exercise training. | I | B |
| • Pharmacotherapy is recommended as a treatment option for obese patients with a BMI $\geq$ 30 kg/m$^2$ (or $\geq$ 27 kg/m$^2$ who also have at least one ASCVD risk factor or obesity-related comorbidity). | I | A |
| • GLP-1 RA (Liraglutide and semaglutide), orlistat, or naltrexone/bupropion ER is recommended to assist in weight management for these individuals. | I | A |
| • Bariatric surgery is recommended for obese patients who have a BMI $\geq$ 37.5 kg/m$^2$ or $\geq$ 32.5 kg/m$^2$ in the presence of related comorbidities such as type 2 DM. | I | A |
| Hyperuricemia | | |
| • Measuring serum uric acid levels can serve as a valuable means of identifying individuals who may be at an elevated risk of developing ASCVD. | I | C |
| • Weight control and increased physical activity remain cornerstones among lifestyle modifications for the prevention of hyperuricemia. | I | C |
| • For the primary prevention of ASCVD, the routine use of urate-lowering therapy in subjects with hyperuricemia or gout is not recommended. | III | B |
| MetS | | |
| • MetS is considered to be a risk enhancer and should be included in the risk assessment of ASCVD. | IIa | C |
| • Healthy lifestyle factors such as physical activity and healthy dietary pattern are recommended to prevent MetS. | I | C |
| Gender | | |
| • In women with a history of preeclampsia and/or pregnancy-induced hypertension, periodic screening for hypertension and DM should be considered. | IIa | B |
| • In women with a history of polycystic ovary syndrome or gestational DM, periodic screening for DM should be considered. | IIa | B |
| • In women with a history of pregnancy-associated conditions and adverse pregnancy outcomes, periodic screening for cardiovascular risk factors may be considered. | IIb | B |

**Table 1.** Continued

| Recommendations | COR | LOE |
|---|---|---|
| Genetics and family history | | |
| • The routine use of genetic testing in patients with ASCVD or in healthy individuals is not recommended. | III | B |
| • Genetic testing may be considered in selected patients with a high risk of ASCVD or with a family history of premature CAD or ACS. | IIb | B |
| • A family history of CAD or premature CAD may be included in the risk assessment of ASCVD. | IIa | B |
| CKD | | |
| • Renal function should be evaluated annually in individuals with DM, hypertension, older age (> 65 years old), obesity, hypercholesterolemia or tobacco smoking. | I | B |
| • Lifestyle modifications, especially higher diet quality (low salt, high potassium, energy-reduced, and high vegetable diet intake), should be considered in the primary prevention of CKD. | IIa | B |
| • BP control may be beneficial in the context of the primary prevention of CKD in patients with hypertension. | IIb | C |
| • Blood sugar control is recommended for the primary prevention of CKD in patients with DM. The HbA1c control target for patients with multiple risk factors should be < 7%. | I | A |
| • Weight loss is beneficial for the preservation of renal function in individuals with overweight/obesity. | IIa | B |
| • For the primary prevention of ASCVD in patients with non-dialysis CKD, the home BP target is < 130/80 mmHg. | I | A |
| • For the primary prevention of ASCVD in patients with non-dialysis CKD, the HbA1C control target should be < 7.0%. | IIa | B |
| • For the primary prevention of ASCVD in patients with non-dialysis CKD, the target LDL-C level should be < 100 mg/dL. | IIa | C |
| • Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, SGLT2 inhibitors, GLP-1 RAs, and finerenone have renoprotective effects. | I | A |
| • Finerenone or a GLP-1 RA is recommended in patients with type 2 DM and CKD, while an angiotensin-converting enzyme inhibitor, an angiotensin receptor blocker, or an SGLT2 inhibitorcan be used in CKD patients with or without type 2 DM for better renal outcomes. | I | A |
| • For the primary prevention of ASCVD, an angiotensin-converting enzyme inhibitor and an SGLT2 inhibitor should be used in diabetic patients with CKD. | IIa | B |
| • For the primary prevention of ASCVD, a GLP-1 RA is recommended in diabetic patients with CKD. | I | A |
| • For the primary prevention of ASCVD, finerenone can be used in diabetic patients with CKD. | I | A |
| Sleep disorders/OSA | | |
| • 7 to 9 hours of sleep per night is recommended for good health. | I | C |
| • In patients with obesity, hypertension, MetS, atrial fibrillation or heart failure, screening for sleep problems, especially OSA, is indicated. | I | C |
| Inflammation/infection | | |
| • Routine measurement of hsCRP for ASCVD risk assessment is not recommended. | III | A |
| • Periodontitis patients with other ASCVD risk factors who have not seen a physician within the last year should be referred to a specialist. | IIa | C |
| • For patients with rheumatoid arthritis, psoriasis, or psoriatic arthritis without pre-existing ASCVD, a comprehensive cardiovascular risk evaluation for primary prevention should be performed at the diagnosis. | IIa | C |
| • The frequency of repeat screening of laboratory data for ASCVD risk assessment in patients with periodontitis, rheumatoid arthritis, psoriasis, or psoriatic arthritis should follow the Health Promotion Administration recommendations for adult preventative health screening (every 3 years for adults aged 40-64 years or annually for adults aged 65 years or older). | IIa | C |
| • Lifestyle modifications, especially a healthy diet, regular exercise and smoking cessation, and management of ASCVD risk factors are recommended for all patients with periodontitis, rheumatoid arthritis, psoriasis, or psoriatic arthritis. | I | C |
| • Annual influenza vaccination is recommended, especially for individuals with older age, ASCVD risk factors, or concomitant disease. | I | B |
| Mental disorders and socioeconomic stress | | |
| • Physicians should be aware of the emerging and strengthening evidence of the association of mental disorders or socioeconomic stress with the development and worse outcomes of ASCVD. | IIa | B |
| • Physicians may advise patients to implement healthy lifestyles for the primary prevention of this factor. | IIb | C |
| • For the primary prevention of ASCVD, a healthy lifestyle, such as smoking cessation, physical exercise, and healthy dietary pattern, and appropriate medications should be considered in patients with mental disorders. | IIa | B |

**Table 1.** Continued

| Recommendations | COR | LOE |
|---|---|---|
| Frailty | | |
| • Frailty is a complex geriatric syndrome characterized by functional decline and inability to withstand acute stressors, and it is an emerging ASCVD risk factor in the increasingly aged society. | IIa | C |
| • Lifestyle interventions, such as dietary quality, micronutrient supplementation, and exercise training, may be considered to prevent and attenuate frailty. | IIb | C |
| Environmental exposure | | |
| • Both long-term and short-term ambient $PM_{2.5}$ exposure increase the risk of ASCVD. | I | B |
| • Reducing ambient air pollution exposure can be beneficial for cardio-pulmonary health. | IIa | B |
| • Reducing ambient air pollution exposure may be helpful in the primary prevention of ASCVD. | IIa | C |
| • Climate change with inappropriate increases in temperature elevates the risk of ASCVD. | I | B |
| • Reducing the use of fossil fuels and limiting carbon dioxide emissions may be reasonable for the primary prevention of ASCVD. | IIb | C |
| • Higher heavy metals exposure to lead, cadmium, mercury, and arsenic increases the risk of ASCVD. | I | B |
| • Reducing exposure to heavy metals, including lead, cadmium, mercury, and arsenic, may be reasonable to prevent ASCVD in the general population. | IIb | C |
| Imaging (CAC score/CCTA) | | |
| • CAC score may be considered as a risk modifier in the cardiovascular risk assessment of asymptomatic individuals at low-moderate risk of ASCVD. | IIb | B |
| • Use of the CAC score is not recommended for asymptomatic individuals who are at high risk of ASCVD. | III | B |
| • It is reasonable to use the CAC score when making the decision to withhold, postpone, or initiate statin therapy in asymptomatic adults with a borderline to intermediate risk of ASCVD, if the decision about statin use remains uncertain. | IIa | B |
| • For the primary prevention of ASCVD, whether CCTA improves risk classification or adds prognostic value over CAC score in asymptomatic individuals is unknown, and may not currently be recommended. | IIb | B |
| Carotid ultrasound | | |
| • Using carotid ultrasound to evaluate the carotid plaque burden should be considered to enhance cardiovascular risk classification in selected patients. | IIa | B |
| • End-diastolic velocity in the common carotid artery (< 15 cm/s) emeasured by carotid ultrasound may be used to improve the risk prediction of cardiovascular events. | IIb | B |
| • Routine CIMT screening by ultrasound to improve cardiovascular risk stratification is not recommended. | III | B |
| Arterial stiffness | | |
| • The cutoff value for the risk assessment should be 10 m/s for cfPWV or 1800 cm/s for baPWV, indicating a subclinical organ damage in primary prevention. | IIa | B |
| • PWV, as a risk enhancer, should be helpful for clinical decision-making to guide intensification of lifestyle and pharmacological interventions or to choose further testing in people at borderline to intermediate risk. | IIa | A |
| • PWV should be considered for clinical decision-making to guide clinician-patient risk discussions in those with DM, hypertension, and CKD, in whom the cardiovascular risk is higher. | IIa | B |
| • PWV may be considered for clinical decision-making in those with stage 1 hypertension (SBP 130-139 mmHg) or those in whom the need to initiate pharmacologic anti-hypertensive therapy is uncertain. | IIb | B |
| ABI | | |
| • ABI should be considered as a risk enhancer for the primary prevention of ASCVD in individuals classified as having a borderline or intermediate risk of ASCVD. | IIa | B |
| • ABI might be considered for cardiovascular outcome assessment in specific populations at a high risk of ASCVD, such as patients with DM or undergoing hemodialysis. | IIb | C |
| COPD | | |
| • Physicians should be aware of the emerging and strengthening evidence that COPD and CVD are common concomitant diseases and should advise patients about the risk if COPD is present. | IIa | B |
| • The identification and tight control of shared risk factors, such as cigarette smoking, hypertension and DM, and intensification of lifestyle modifications for the primary prevention of ASCVD are recommended in patients with COPD. | I | C |
| • For individuals with COPD, long-acting β2-agonists and long-acting muscarinic antagonists can be safely used in consideration of cardiovascular safety. | IIa | A |

**Table 1.** Continued

| Recommendations | COR | LOE |
|---|---|---|
| MAFLD | | |
| • MAFLD increases the risk of hepatic-related and cardiovascular events, and it should be considered a risk enhancer of ASCVD. | IIa | B |
| • In patients with MAFLD, cardiovascular risk screening and management are recommended. | I | B |
| • Lifestyle modifications constitute the basic and important approach to modify MAFLD. Body weight reduction is the cornerstone of the nonpharmacological management of MAFLD. | I | A |
| • Regressing hepatic steatosis/fibrosis and improving cardiovascular/metabolic outcomes are the optimal goals of pharmacological interventions for MAFLD. | IIa | C |
| Nephrolithiasis | | |
| • The evaluation of cardiometabolic risk factors and MetS should be routinely performed in the assessment of patients with nephrolithiasis. | IIb | C |
| • Weight reduction, regular exercise and cardiovascular risk management should be considered to prevent cardiovascular complications in patients with nephrolithiasis. | IIb | C |
| Erectile dysfunction | | |
| • Assessment of CVD risk should be considered in men with erectile dysfunction. | IIb | C |
| Dietary pattern | | |
| • Assess personal energy requirement. Eat a balanced and diverse diet composed of recommended amounts of six food groups: grains/tubers/roots, vegetables, fruits, protein foods, nuts/seeds/oil, and dairy at personalized energy level as recommended by the Taiwanese food guide. | I | A |
| • Eat at least three servings of vegetables and two servings of fruits a day and more if your caloric level is higher than average. For those who have a high genetic susceptibility to hypertension or dyslipidemia, individuals are recommended to eat more vegetables than recommended for the general public. | I | B |
| • Choose healthy protein foods preferably in the following order: high protein containing legumes, fish and other aquatic or sea foods, eggs, lean poultry, pork, and beef. Drink a glass of low-fat or non-fat milk or equivalent a day for those without lactose intolerance. | I | A |
| • Calcium-enriched plant-based protein-rich beverages is reasonable. | IIa | B |
| • Eat whole grains, roots, and tubers as at least one-third, and preferably half, of staple foods. | I | B |
| • Use liquid plant oils or nuts and seeds in cooking rather than tropical oils, animal fats and partially hydrogenated fats. | I | A |
| • Minimize fatty or organ meats, deep-fried foods, and ultra-processed foods. | I | B |
| • Drink water or tea as the main beverage. Minimize intake of sweetened or sugar-containing beverages. | I | B |
| • Avoid salty foods and minimize salt in cooking and seasoning. | I | A |
| • Adopt the above principles early in life and make adequate adjustments in certain life stages (such as adolescence, childbearing age, pregnancy and lactation) whenever needed. | IIa | B |
| • Those who have hyperglycemia, hypertension, hyperlipidemia and hyperuricemia should follow at least the Taiwanese food guide and preferentially the MeDiet or DASH diet. It is highly recommended to refer these high-risk individuals to registered dietitians for individualized nutrition plans. | I | A |
| Fatty acid and fish oil supplements | | |
| • For the primary prevention of ASCVD, patients with elevated TG levels (≥ 150 mg/dL) who are at high ASCVD risk and have not achieved their lipid-lowering goals with statin therapy alone, the addition of icosapent ethyl, a highly purified form of EPA, at a dose of 2-4 g per day might be considered. | IIb | B |
| • Patients who have very high TG levels (≥ 500 mg/dL) with pancreatic risk may benefit from prescription-strength omega-3 fatty acid supplements, including EPA and/or DHA. | IIa | B |
| • The routine use of fish oil or omega-3 supplements for the primary prevention of ASCVD in patients with normal TG levels is not recommended. | III | A |
| Alcohol beverages | | |
| • It is not recommended for people who do not have a habit of alcohol consumption to start drinking for any reason. | III | C |
| • Alcohol consumption should be limited to < 100 g/week (14 g/day or 1 drink†/day) in men and < 50 g/week (7 g/day or 0.5 drink†/day) in women without the ALDH2*2 dysfunctional allele for better BP control and lower risk of all-cause mortality. | I | A |
| • Alcohol consumption should be limited to < 64 g/week (9 g/day or 4 drinks†/week) in men and < 28 g/week (4 g/day or 2 drinks†/week) in women with the ALDH2*2 dysfunctional allele for better BP control and lower risk of all-cause mortality. | IIa | C |
| • Binge drinking# should be strictly avoided to reduce BP, the risk of stroke and sudden death. | III | C |

**Table 1.** Continued

| Recommendations | COR | LOE |
|---|---|---|
| Coffee and tea | | |
| • Moderate coffee consumption (3 cups[##]/day) reduces the risk of ASCVD and related death in people without severe hypertension. | IIa | B |
| • Moderate coffee consumption (≥ 2 cups[##]/day) is not recommended in people with severe hypertension. | III | B |
| • Habitual tea drinking (≥ 3 times/week) reduces the risk of ASCVD and all-cause mortality. | IIa | B |
| Physical activity and exercise | | |
| • Adults should accumulate at least 150 minutes of moderate-intensity physical activity per week or 75 minutes of vigorous-intensity physical activity per week to reduce ASCVD risk. | I | B |
| • Physical activity counseling is considered benefit to optimize a physically active life. | I | B |
| • Strategies to reduce sedentary time and achieve the recommended amount of physical activity may be beneficial to reduce ASCVD risk. | IIa | B |
| Hormone replacement therapy | | |
| • Avoidance of combined hormonal contraceptives may be considered in women with migraine with aura. | IIb | B |
| • Post-menopausal hormone replacement therapy is not recommended for the primary prevention of ASCVD. | III | C |
| Anti-platelet therapy | | |
| • Routine antiplatelet therapy for the primary prevention of ASCVD among adults of any age is not recommended. | III | A |
| • Aspirin 75-100 mg orally daily might be used for the primary prevention of ASCVD among diabetic adults aged above 50 years who are at high ASCVD risk and low bleeding risk. | IIb | A |
| • Antiplatelet therapy is not recommended for the primary prevention of ASCVD among adults with a CAC score of 0. | III | B |
| • Aspirin 75-100 mg orally daily might be considered for the primary prevention of ASCVD among adults with a CAC score ≥ 100 Agatston units and low bleeding risk. | IIb | B |

[†] Chang HY, et al.[29] [‡] One standard drink = 14 g of pure alcohol. [#] Binge drinking is defined as 5 or more and 4 or more drinks for the typical adult male and female, respectively, in about 2 hours. [##] One cup of coffee = 150 ml.
ABI, ankle-brachial index; ACS, acute coronary syndrome; *ALDH*, aldehyde dehydrogenase gene; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BP, blood pressure; CAC, coronary artery calcification; CAD, coronary artery disease; CCTA, coronary computed tomographic angiography; cfPWV, carotid-femoral pulse wave velocity; CIMT, carotid intima-media thickness; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; DHA, docosahexaenoic acid; DM, diabetes mellitus; EPA, eicosapentaenoic acid; ER, extended release; GLP1-RA, glucagon-like peptide-1 receptor agonist; HbA1C, hemoglobin A1C; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); MAFLD, metabolic dysfunction-associated fatty liver disease; MeDiet, Mediterranean diet; MetS, metabolic syndrome; NRT, nicotine replacement therapy; OSA, obstructive sleep apnea; PCSK9, proprotein convertase subtilisin/kexin 9; PM, particulate matter; RA, receptor agonist; RCT, randomized controlled trial; SBP, systolic blood pressure; SGLT2, sodium-dependent glucose cotransporter-2; TG, triglyceride; TwCCCC, Taiwan Chin-Shan Community Cardiovascular Cohort.

trials (RCTs) or meta-analyses of high-quality RCTs.[7,18] LOE B indicates that the recommendations are derived from one RCT only or large non-randomized studies, meta-analyses of moderate-quality RCTs or non-randomized studies.[7,18] LOE C indicates that the recommendations are established by only small studies, expert consensus, or observational studies, that is, subgroup analyses, post-hoc analyses, retrospective studies, cohort studies, and registries.[7,18]

### *1.1.6. The TSOC slogan for the primordial and primary prevention of ASCVD and the acronym of the modifiable risk factors/enhancers and strategies*

In order to enhance medical education and health promotion not only for physicians but also for all people in the world, we propose a slogan (**2H2L**) for the primordial and primary prevention of ASCVD on the basis of the essential role of healthy dietary pattern and lifestyles: "**Healthy Diet and Healthy Lifestyles to Help Your Life and Save Your Lives**" (Figure 3). Furthermore, we propose an acronym of the modifiable risk factors/enhancers and relevant strategies to facilitate memory: "**ABC$_2$D$_2$EFG-I'M$_2$ ACE**" (Figure 4). **A** denotes adiposity, **B** indicates blood pressure (BP), **C$_2$** denotes cholesterol and cigarette smoking, **D$_2$** represents diabetes mellitus (DM) and dietary pattern, **E** indicates exercise, **F** denotes frailty, **G** denotes gout/hyperuricemia, **I** represents inflammation/infection, **M** indicates metabolic syndrome (MetS) and metabolic dysfunction-associated fatty liver disease (MAFLD), **A** denotes atmosphere (en-

**Table 2.** Top 10 features/key messages/highlights of the recommendations

1. We clearly define the definitions of ASCVD and cover the full spectrum of ASCVD, not only MI or stroke, elsewhere appropriate in this guideline.
2. The scope of the current primary prevention guideline focuses on primary prevention of ASCVD involving parts of primordial prevention, including national policies, promotion of health education, primary prevention of clinical risk factors, management and control of clinical risk factors.
3. In order to enhance medical education and health promotion not only for physicians but also for the general public, we propose a slogan for primary prevention of ASCVD on the basis of the essential role of healthy dietary pattern and lifestyles: "**Healthy Diet and Healthy Lifestyles to Help Your Life and Save Your Lives**".
4. In addition to the TwCCCC point-based risk chart, we also recommend the coefficient-based risk prediction model constructed by Chang et al. for risk assessment.
5. We design an acronym of the modifiable risk factors/enhancers and relevant strategies to facilitate memories: "**ABC$_2$D$_2$EFG-I'M$_2$ ACE**": Adiposity, BP, Cholesterol and Cigarette smoking, DM and Dietary pattern, Exercise, Frailty, Gout/hyperuricemia, Inflammation/infection, MetS and MAFLD, Atmosphere (environment), CKD, and Easy life (sleep well and no stress).
6. Among common concomitant disorders, we particularly focus on the MAFLD, sleep disorders and psoriasis arthritis based on the consensus statement jointly published by the TSOC and other relevant Societies/Associations in Taiwan.
7. For primary prevention of ASCVD, the treatment target for each modifiable risk factor is shown as below: reducing body weight by 5-10%; BP < 130/80 mmHg (SBP < 120 mmHg in high risk); LDL-C < 100 mg/dL in high risk, LDL-C < 115 mg/dL in moderate risk, LDL-C < 130 mg/dL in low risk, and LDL-C < 160 mg/dL in minimal risk; complete and persistent abstinence from cigarette smoking; HbA1C < 7.0%; fulfilling recommended amounts of six food groups by the Taiwan food guide; and moderate-intensity physical activity 150 min/wk or vigorous physical activity 75 min/wk.
8. With regard to the role of images on ASCVD risk assessment, a CAC score might be useful in low-to-intermediate risk; carotid plaque burden evaluated by carotid ultrasound should be considered and measurement of end-diastolic velocity in the common carotid artery may be used to enhance cardiovascular risk classification; cfPWV (> 10 m/s) or baPWV (> 1800 cm/s) should be helpful to make the clinical decision making in selected individuals; ABI should be considered as a risk enhancer in borderline or intermediate risk.
9. Some risk factors/clinical conditions, such as hypertension, DM, cigarette smoking, obesity, MetS, CKD, and mental disorders, are deemed to be preventable. Healthy dietary pattern, physical activity, and body weight control remain the cornerstone of the preventive strategy.
10. For primary prevention of ASCVD, pharmacological approach for management of risk factors/clinical conditions includes: Statin is the first-line therapy for reducing LDL-C levels and ezetimibe may be considered if LDL-C not on target under statin therapy or statin intolerance. A PCSK9 inhibitor is reasonable in high risk in the context of high-intensity statin or maximally tolerated statin + ezetimibe therapy; a GLP-1 RA is recommended and metformin can be used in patients with type 2 DM and an SGLT2 inhibitor should be considered in patients with type 2 DM and CKD; GLP-1 RAs (liraglutide or semaglutide), orlistat, or naltrexone/bupropion ER is recommended to assist in weight management for obese patients with a BMI $\geq$ 30 Kg/m$^2$ (or 27 kg/m$^2$ who also have at least one ASCVD risk factor or obesity-related comorbidity) despite no RCT in terms of primary prevention of ASCVD; an angiotensin converting enzyme inhibitor should be and finerenone can be used in diabetic patients with CKD for primary prevention of ASCVD; aspirin 75-100 mg orally daily might be used for primary prevention of ASCVD among adults who are at high ASCVD risk or with a CAC score $\geq$ 100 and low bleeding risk.

ABI, ankle-brachial index; ASCVD, atherosclerotic cardiovascular disease; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BP, blood pressure; CAC, coronary artery calcium; cfPWV, carotid-femoral pulse wave velocity; CKD, chronic kidney disease; DM, diabetes mellitus; ER, extended release; GLP-1 RA, Glucagon-like peptide-1 receptor agonist; HbA1C, hemoglobin A1C; LDL-C, low-density lipoprotein cholesterol; MAFLD, metabolic dysfunction-associated fatty liver disease; MetS, metabolic syndrome; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin 9; RCT, randomized controlled trial; SGLT2, sodium-dependent glucose cotransporter-2; TSOC, Taiwan Society of Cardiology; TwCCCC, Taiwan Chin-Shan Community Cardiovascular Cohort.

vironment), **C** denotes chronic kidney disease (CKD), and the last **E** represents easy life (sleep well and no stress).

## 1.2. Risk assessment

### *1.2.1. Introduction of risk assessment*

ASCVD causes a great disease burden in Taiwan and globally. Risk assessment for primary prevention in the general population is helpful to identify individuals at risk of ASCVD and further consultation and treatment of high-risk groups. The purpose of risk assessment is to identify individuals who are at high risk for ASCVD and to implement preventive strategies to reduce their risk. Risk assessment involves collecting and analyzing data

**Table 3.** The definitions of the class of recommendation and level of evidence in the TSOC guidelines (Adapted from Ueng KC, et al.[7] with permission)

| Classes of recommendations | Definition | Suggested phrases |
|---|---|---|
| Class I (Benefit>>>Risk) | Evidence and/or general agreement that a given treatment of procedure is beneficial, useful, and effective | • Is recommended<br>• Is indicated<br>• Should be performed |
| Class II | Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure | |
| Class IIa (Benefit>/>>Risk) | Weight of evidence/opinion is in favor of usefulness/efficacy | • Is probably recommended<br>• Should be considered<br>• Can be performed |
| Class IIb (Benefit ≥ Risk) | Usefulness/efficacy is less well established by evidence/opinion | • May/might be considered<br>• May/might be reasonable<br>• May/might be performed |
| Class III (Benefit ≤ Risk) | Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful | • Is not recommended<br>• Is not indicated<br>• Should not be performed |

Level A: Data derived from multiple (≥ 2) RCTs, or meta-analyses of high-quality RCTs. Level B: Data derived from a single RCT, large non-randomized studies, meta-analyses of moderate-quality RCTs or non-randomized studies. Level C: Subgroup analyses, post-hoc analyses, retrospective studies, cohort studies, registries, small studies, or consensus of expert opinion.
RCT, randomized controlled trial; TSOC, Taiwan Society of Cardiology.


***Figure 3.*** *A slogan for the primordial and primary prevention of ASCVD. ASCVD, atherosclerotic cardiovascular disease.*

on various risk factors such as demographic information, lifestyle factors, clinical disease status, and biological markers, and the collected information is then used to construct a prediction model for the absolute risk for ASCVD.

*1.2.2. Steps for constructing the prediction model and evaluation of the prediction model performance*

A score chart can be applied to calculate a person's overall risk score, summarizing the weight of specific risk factors. First, a researcher applied a multivariate Cox proportional hazards model to establish a parsimonious model to predict the risk of ASCVD. This model was comprised of several significant predictors, including age, gender and significant lifestyle factors and clinical disease status. The researcher then constructed a categorization point system according to the concise model,[19] and the predictive performance of the model was evaluated against available models in the literature.

*1.2.3. Major risk assessment models for ASCVD globally and in Taiwan*

The Pooled Cohort Equation (PCE) model,[20] Systemic COronary Risk Evaluation (SCORE) algorithm,[21] and Framingham Heart Study Risk Score[22] have been applied to assess the risk of ASCVD in the USA, Europe, and globally. The PCE modelis currently recommended by the 2019 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on the primary prevention of CVD.[23] The SCORE 2 algorithm was adopted in the 2021 European Society of Cardiology (ESC) guidelines on CVD prevention in clinical practice.[24] However, due to ethnic differences in ASCVD risk, the risk assessment models developed and adopted in Caucasians can-

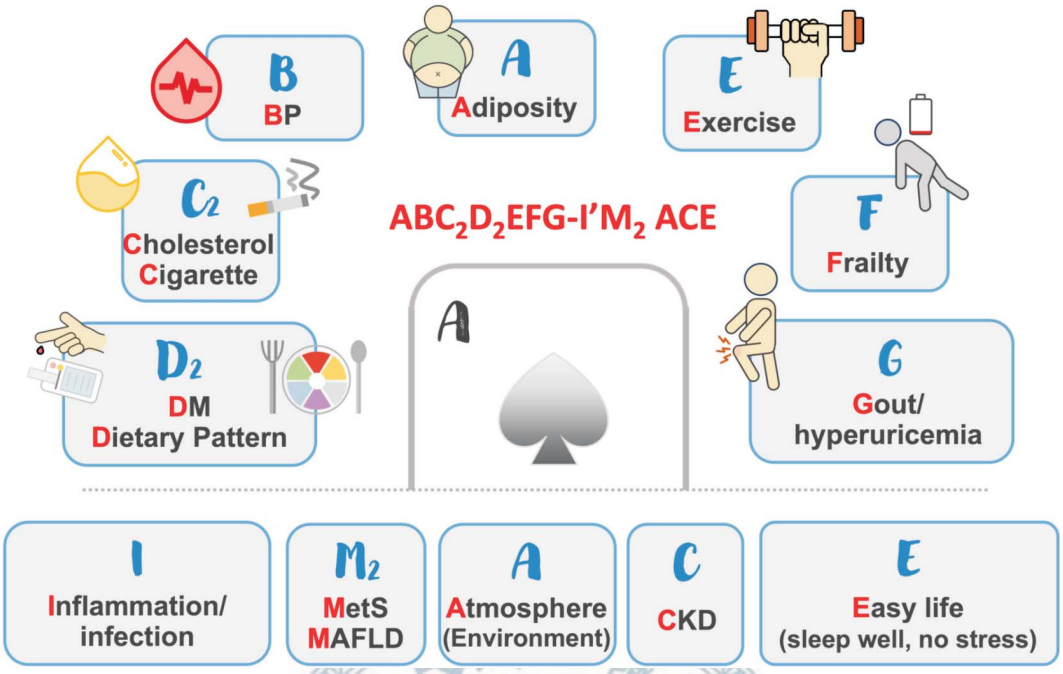


***Figure 4.*** *An acronym of the modifiable risk factors/enhancers and strategies. BP, blood pressure; CKD, chronic kidney disease; DM, diabetes mellitus; MAFLD, metabolic dysfunction-associated fatty liver disease; MetS, metabolic syndrome.*

not precisely predict the overall ASCVD risks in Asians[25] and Chinese,[26] although validation of the Framingham General Cardiovascular Risk Score and PCE showed good calibration and modest discrimination in a recent prospective cohort study in Taiwan, except for PCE in females.[27] Therefore, various prediction models have been developed in specific countries. In Taiwan, there are two major risk assessment models: 1) a point-based Taiwan Chin-Shan Community Cardiovascular Cohort (TwCCCC) prediction model for CAD (Table 4)[26] and stroke,[28] and 2) a coefficient-based major cardiovascular event (CAD and stroke) prediction model derived from national survey data linked with national insurance records for validation (Table 5).[29]

The risk estimators in the TwCCCC prediction model were derived from a community based TwCCCC cohort study, comprising 3,430 adults aged 35 years old and above without pre-existing ASCVD, conducted in Northern Taiwan in the 1990s. The risk estimators for predicting CAD risk include age, sex, body mass index (BMI), systolic blood pressure (SBP), serum levels of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). However, the risk estimators for predicting stroke risk include age, sex, SBP, diastolic blood pressure (DBP), family history of stroke, atrial fibrillation, and DM. The TwCCCC risk prediction models for CAD and stroke were externally validated.[26,28] Based on this model, a 10-year risk of future CAD is calculated and categorized into those at low (1-14 points; < 3%/10 years), borderline (15-17 points; 3-7%/10 years), intermediate (18-19 points; > 7%-10%/10 years), and high (20-24 points; > 10%/10 years) risk.[26] A web-based calculator has been established and is available at http://140.112.117.151/klchien/.[26] Furthermore, a 15-year risk of future stroke is categorized into those at lowest (1-3 points; < 1%/15 years), low (4-8 points; 1-4.9%/15 years), medium (9-12 points; 5-20%/15 years), and high (≥ 13 points; > 20%/15 years) risk. Therefore, the 2023 TSOC CCS guidelines recommended the TwCCCC prediction model for risk assessment in the primary prevention of CCS.[7]

The coefficient-based prediction model constructed by Chang et al.[29] was derived from a nationwide survey, the 1993-1996 Nutrition and Health Survey in Taiwan, comprising 3,310 adults (1,658 men and 1,652 women) aged between 35-70 years without disease at baseline. The model was externally validated using Taiwanese Survey on Hypertension, Hyperglycemia, and Hyperlipidemia data linked to TNHIRD.[29] The risk estimators include age, SBP, plasma or serum levels of glucose, triglyceride (TG), HDL-C, LDL-C, uric acid, total cholesterol

**Table 4.** The point-based TwCCCC risk prediction model for CAD (adapted from Chien KL, et al.[26] and Ueng KC, et al.[7] with permission)

| Risk factor | Category | Points |
|---|---|---|
| Age | 35-39 | 0 |
| | 40-44 | 1 |
| | 45-49 | 2 |
| | 50-54 | 3 |
| | 55-59 | 4 |
| | 60-64 | 5 |
| | 65-69 | 6 |
| | 70-74 | 7 |
| | ≥ 75 | 8 |
| Sex | Men | 3 |
| | Women | 0 |
| BMI | < 22 | 0 |
| | 22-25.9 | 1 |
| | ≥ 26 | 2 |
| SBP | < 110 | 0 |
| | 110-129 | 1 |
| | 130-149 | 2 |
| | 150-159 | 3 |
| | ≥ 160 | 4 |
| LDL | < 90 | 0 |
| | 90-149 | 1 |
| | ≥ 150 | 2 |
| HDL | < 30 | 5 |
| | 30-39 | 4 |
| | 40-59 | 3 |
| | 60-69 | 2 |
| | 70-79 | 1 |
| | ≥ 80 | 0 |

| Total point | Estimated risk |
|---|---|
| 3 | 0.001 |
| 4 | 0.001 |
| 5 | 0.002 |
| 6 | 0.003 |
| 7 | 0.003 |
| 8 | 0.005 |
| 9 | 0.006 |
| 10 | 0.008 |
| 11 | 0.011 |
| 12 | 0.014 |
| 13 | 0.019 |
| 14 | 0.025 |
| 15 | 0.033 |
| 16 | 0.044 |
| 17 | 0.058 |
| 18 | 0.076 |
| 19 | 0.099 |
| 20 | 0.129 |
| 21 | 0.168 |
| 22 | 0.216 |
| 23 | 0.276 |
| 24 | 0.349 |

An on-line TwCCCC risk calculator is available at website (http://140.112.117.151/klchien/).
BMI, body mass index; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TwCCCC, Taiwan Chin-Shan Community Cardiovascular Cohort.

(TC)/HDL-C ratio, waist-hip ratio, waist circumference, and duration of tobacco smoking, DM or hypertension. The variables included are different in the models for each disease by sex.[29] The predictive performance has been shown to be good compared to previous prediction models.[26,28] In addition, the samples in this model were selected using a probability sampling scheme and covered the entire population of Taiwan, implying that it is more representative.[29] Furthermore, a web-based calculator for this model is currently available (https://cdrc.hpa.gov.tw/index.jsp).

*1.2.4. Some issues in further developments*

Novel biomarkers, such as genomic information using the polygenic risk score,[30] and subclinical disease status such as coronary artery calcification,[31] can be incorporated into the risk assessment tools to improve risk stratification. In addition, some artificial intelligence-based technologies using machine learning and deep learning have been implemented in risk assessment from big data.[32] In addition to clinically related information, geographic area, air pollutants, neighborhood, socioeconomic status and psychosocial factors have also been implemented in risk assessment.[33] Besides, risk assessment is not a one-time event, but rather a continuous process that should be revisited periodically to monitor changes in risk and adjust preventive strategies accordingly. Moreover, in Taiwan, the Aboriginal population and new incomers have a high ASCVD burden. Therefore, specific populations should be taken into consideration for risk assessment. However, evidence regarding these issues is not strong enough to make recommendations for clinical practice and incorporate these factors into current guidelines.

**Table 5.** The Chang's et al. risk prediction model (from Chang HY, et al.)[29]

| | | Disease | |
|---|---|---|---|
| Men | MACE | CHD | Stroke |
| Incidence | 13.77/1000 | 7.14/1000 | 9.53/1000 |
| Variable | Coefficient | Coefficient | Coefficient |
| Age (years) | 7.2782 | 8.3007 | 8.9606 |
| SBP (mmHg) | 0.0257 | - | 0.0231 |
| Glucose (mg/dL) | | - | 0.0050 |
| Triglycerides (mg/dL) | | - | 0.0013 |
| HDL | -0.0039 | - | |
| LDL | | -0.0081 | |
| Uric acid (mg/dL) | 0.0214 | - | 0.0603 |
| Cholesterol/HDL | | - | |
| Waist-hip ratio | | - | |
| Waist (cm) | | 0.0163 | |
| Smoke (yes) | | - | |
| Diabetes (yes) | | - | |
| Hypertension (yes) | | 0.6715 | |
| C statistic | 0.76 | 0.73 | 0.80 |
| Women | MACE | CHD | Stroke |
| Incidence | 7.76/1000 | 4.63/1000 | 6.98/1000 |
| Variable | Coefficient | Coefficient | Coefficient |
| Age (years) | 6.8833 | 9.3891 | 4.3538 |
| SBP (mmHg) | 0.0128 | 0.0015 | 0.0138 |
| Glucose (mg/dL) | | | |
| Triglycerides (mg/dL) | | 0.0001 | |
| HDL | | | |
| LDL | | | |
| Uric acid (mg/dL) | | | |
| CHOL/HDL | 0.3054 | 0.3581 | |
| Waist-hip ratio | | | 3.9712 |
| Waist (cm) | 0.0257 | 0.0425 | |
| Smoke (yes) | 0.1923 | | 0.7821 |
| Diabetes (yes) | | | 0.5348 |
| Hypertension (yes) | | | 0.5572 |
| C statistic | 0.7 | 0.8 | 0.7529 |

An on-line risk calculator is available at website (https://cdrc.hpa.gov.tw/index.jsp).
CHD, coronary heart disease; CHOL, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MACE, major adverse cardiovascular events; SBP, systolic blood pressure.

In conclusion, the results of a risk assessment can inform the development of personalized preventive strategies, such as lifestyle changes, medical treatments, and monitoring for early signs of ASCVD.

**Key Recommendations**

- After the age of 35 years, it is reasonable to assess traditional ASCVD risk factors (COR IIa, LOE A).
- For adults aged 35 to 75 years without established ASCVD, clinicians should consider assessing traditional risk factors and calculate the 10-year or 15-year risk of CAD or stroke by using the TwCCCC risk chartor the coefficient-based risk prediction model constructed by Chang et al. (COR IIa, LOE B).

## 2. IMPACT OF RISK FACTORS/CLINICAL CONDITIONS AND PREVENTIVE STRATEGIES FOR MODIFIABLE RISK FACTORS/CLINICAL CONDITIONS

Currently, the well-documented risk factors for ASCVD include hypertension, DM, hypercholesterolemia, cigarette smoking, obesity, age, family history, and gender.

### 2.1. DM

*2.1.1. Prevalence and incidence of DM*

The prevalence of DM in Taiwan continues to increase. From 2005 to 2014, the total population with DM increased by 66%, and the age-standardized prevalence in adults aged 20-79 years increased by 41%.[34] The prevalence of DM was generally higher in men; however, the prevalence was higher in women aged ≥ 65 years.[34] The prevalence of DM was approximately 50% in those aged > 80 years.[34] In the 10th edition of the International Diabetes Federation Diabetes Atlas, the age-adjusted comparative prevalence of DM, impaired glucose tolerance and impaired fasting glucose were 9.7%, 11.5%, and 4.5%, respectively, in Taiwanese aged 20-79 years in 2021.[35] The age-adjusted prevalence of DM is expected to increase to 11.5% in 2030 and 12.6% in 2045 in Taiwan.[35] The incidence also increased by 19% from 0.621% to 0.741% between 2005 and 2014, and this increase was most obvious in patients aged 20-39 years.[34] The higher incidence of DM in men is consistent with the pandemic of overweight and obesity in men in Taiwan.[34]

*2.1.2. Impact of diabetes on the development of ASCVD*

Patients with type 2 DM and impaired glucose tolerance tend to have advanced CAD and systemic atherosclerosis. The pathophysiology of hyperglycemic vascular disease is complex, and includes endothelial dysfunc-

tion, inflammation and thrombosis.[36] Studies have also suggested that type 2 DM and impaired glucose tolerance are significant causes of coronary plaque progression and affect plaque vulnerability.[37] Furthermore, patients with hyperglycemia also have additional risk factors which can promote atherosclerosis including obesity, dyslipidemia, hypertension, and insulin resistance.

*2.1.3. Role of diabetes in cardiovascular risk*

There is a close relationship between abnormal glucose tolerance/type 2 DM and CVD. An updated meta-analysis of 10,069,955 individuals showed that prediabetes was associated with an increased 13% risk of all-cause mortality, 15% risk of composite CVD, 16% risk of CAD, and 14% risk of stroke in a median follow-up duration of 9.8 years.[38] Patients with DM are at a 2-fold increased risk of CVD compared to non-diabetic individuals.[39,40] Diabetic patients without any history of MI have an equivalent risk of a future acute coronary event as non-diabetic individuals with a prior history of MI, i.e., a "coronary risk equivalent".[41] In the Multiple Risk Factor Intervention Trial, men who reported taking medications for diabetes were three times as likely to develop a stroke.[42] Epidemiological studies have also identified a 2- to 4-fold higher incidence of PAD in patients with diabetes.[36] Although DM is a major cardiovascular risk factor, most epidemiological studies have revealed a paradoxically inverse relationship between DM and the incidence, growth rate, and rupture risk of an aortic aneurysm.[43] Mechanisms of action underlying the negative relationship have been reported, involving a number of biological pathways and glucose-lowering agents.[44] Nevertheless, clinicians should always keep in mind that the surgical risk of an aortic aneurysm remains higher in patients with DM than in those without.[43]

*2.1.4. Strategies to prevent the occurrence of DM*

Screening and appropriate management of prediabetes might contribute to primary and secondary prevention of CVD.[45] It is suggested to monitor for the development of type 2 DM in those with prediabetes at least annually.[45] Several major RCTs, including the Da Qing Diabetes Prevention Study, the Diabetes Prevention Program trial and the Finnish Diabetes Prevention Study, have shown that lifestyle modifications and behavioral interventions can prevent or delay the onset of type 2 DM.[46-48] Based on findings from the Diabetes Prevention Program trial, metformin can be recommended as a diabetes prevention medication option for high-risk individuals, such as those with a BMI $\geq$ 35 kg/m$^2$, in younger participants aged 25-44 years, or individuals with a history of gestational diabetes.[45,46] However, official labeling of metformin in Taiwan is not indicated for the prevention of DM. Glucagon-like peptide-1 receptor agonists, $\alpha$-glucosidase inhibitors, thiazolidinediones, insulin, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have also been shown to lower the incidence of diabetes in specific populations, however long-term data are lacking and the cost-effectiveness is unclear.[45]

**Key Recommendations**

- Regular monitoring for the development of type 2 DM in those with prediabetes annually is recommended (COR I, LOE C).
- Lifestyle modifications to prevent or delay the onset of type 2 DM is recommended (COR I, LOE A).

## 2.2. Hypertension

*2.2.1. Prevalence and incidence of hypertension*

The prevalence and incidence of hypertension vary according to the definition of hypertension. According to analysis of national statistics in Taiwan in 2018 using 140/90 mmHg as the cutoff for hypertension, the prevalence, awareness and treatment rates of hypertension were 24.1%, 72.8%, and 57.2%, respectively.[49] However, the age- and sex-standardized median of the relative increase in the rate of hypertension with a change in thresholds from $\geq$ 140/$\geq$ 90 to $\geq$ 130/$\geq$ 80 mmHg was reported to be 72.3% globally.[50] When 130/80 mmHg was used as the threshold, 52% of females and 60.7% of males were classified as having hypertension according to an international registry, the May Measurement Month initiative conducted by the International Society of Hypertension between 2017-2019.[50] The lifetime risk of having hypertension is approximately 90%.[51,52]

*2.2.2. Impact of hypertension on the development of ASCVD and cardiovascular risk*

High BP is the most important risk factor for global disease burden, especially ASCVD.[52-54] In 2017, high BP

was the leading risk factor globally, accounting for 10.4 million deaths.[53] The largest numbers of SBP-related deaths are caused by CAD (4.9 million), hemorrhagic stroke (2.0 million), and ischemic stroke (1.5 million),[54] and approximately 47% of cases of CAD and 54% of stroke are attributable to high BP worldwide.[52,55] In addition, every 10 mmHg increase in SBP has been associated with a 45% higher risk of CAD and approximately 65% higher risk of stroke in individuals aged 55-64 years.[56-58] Large-scale epidemiological studies have demonstrated a strong connection between eventual cardiovascular events and BP levels even as low as 90/60 mmHg.[59,60] Many epidemiological studies and pharmacological intervention trials have shown that lowering BP can lower the risk of cardiovascular events and mortality.[59,61] Hypertension is one of the major risk factors for PAD[16] and abdominal aortic aneurysm.[62] Taken together, hypertension is always included in the risk assessment of ASCVD.

*2.2.3. Strategies to prevent the occurrence of hypertension*

A healthy lifestyle and diet pattern is strongly advised for the general population since it can effectively modify and avoid cardiovascular risk factors such as hypertension.[63-65] Healthy diet pattern and exercise are especially effective in the prevention of hypertension in prehypertensive individuals.[66,67] Furthermore, the risk of elevated BP has been strongly associated with pediatric obesity in elementary and high school students both in Taiwan and Japan.[68,69] Therefore, it is essential to educate young people to be aware of their health status and learn about healthy lifestyles beginning in childhood to modify this factor for the lifetime prevention of hypertension.[69]

Furthermore, it may be advisable to have a validated BP monitor at home for measuring BP, not only for individuals with high BP, hypertension, or who are taking medication, but also for those who are over the age of 40.

**Key Recommendations**

- Individuals with high BP, hypertension, or who are currently on medication to lower BP, as well as those who are 40 years old or older, should consider using a validated BP monitor at home to measure their BP (COR IIa, LOE B).
- People with high BP should live a healthier lifestyle to reduce their lifetime BP burden (COR I, LOE A).

## 2.3. Dyslipidemia

*2.3.1. Prevalence and incidence of dyslipidemia*

According to a report of the Nutrition and Health Surveys 2017-2020 in Taiwan, the prevalence rate of dyslipidemia was 34.4% in male and 25.5% in female adults (≥ 19 years old), which were higher than that (22.9% and 18.0%, respectively) in the first surveys conducted between 1993-1996.[70] The definition of dyslipidemia used in these surveys was TC ≥ 240 mg/dL, TG ≥ 200 mg/dL, LDL-C ≥ 160 mg/dL, or receiving lipid-lowering treatment.

*2.3.2. Impact of dyslipidemia on the development of ASCVD*

LDL-C and other apolipoprotein B (apoB)-rich lipoproteins, including very low-density lipoprotein, their remnants, and lipoprotein(a) (Lp(a)), efficiently enter and accumulate in the arterial intima at sites of predilection for plaque formation to initiate the development and progression of ASCVD.[71] When the plasma LDL-C concentration is above the physiological level (20-40 mg/dL), the probability of intimal retention of LDL leading to the initiation and progression of atherosclerotic plaque increases in a dose-dependent manner.[71,72]

*2.3.3. Role of dyslipidemia in cardiovascular risk*

Evidence regarding the association of LDL-C levels and ASCVD risk is strongly based on observations from inherited disorders of lipid metabolism, prospective epidemiologic studies, Mendelian randomization studies, and RCTs of interventions.[71] Therefore, LDL-C is considered as a causal factor for ASCVD and is traditionally included in risk assessment.

The effect of accumulative exposure to LDL-C has attracted increasing attention recently. This effect refers to the association of the cumulative amount of LDL-C exposure over time and the development of atherosclerosis.[71] A recent study proposed a statistical model estimating the effect of accumulative exposure to LDL-C by calculating the area under the curve derived from the product of an individual's LDL-C levels and time.[73] The results from this study highlighted that cumulative LDL-

C exposure before the age of 40, as assessed by the area under the curve for the 18- to 40-year-old period, was significantly associated with the future risk of ASCVD. In addition, the same area accumulated earlier in life, compared with later in life, conferred a higher risk of ASCVD. Similar outcomes were also observed in Japanese patients with familial hypercholesterolemia (FH),[74] in which the effect of accumulative exposure to LDL-C was significantly associated with ASCVD events independently of other traditional risk factors, including age, male sex, hypertension, diabetes, smoking, and serum LDL-C levels.

Severe hypercholesterolemia, defined as serum LDL-C ≥ 190 mg/dL, is a complex disorder that may result from a combination of genetic and environmental factors. Severe hypercholesterolemia has been associated with a 5-fold higher risk of developing ASCVD and a 10-20-year acceleration in ASCVD progression in males and 20-30 years in females when compared to the general population with normal LDL-C levels.[75] It is worth noting that about 7.2% of patients with LDL-C ≥ 190 mg/dL meet the diagnosis of FH,[76] which is an inherited genetic disorder caused by mutations in genes encoding the LDL receptor, apoB, or proprotein convertase subtilisin/kexin type 9.[77]

The association and causal effects of serum TG levels and the risk of ASCVD are supported by observation from epidemiological and Mendelian randomization studies;[78] however, the relationships are further complicated by interindividual heterogeneity in the fate of TG-rich lipoproteins due to variability in the function of key enzymes.[79] Furthermore, few RCTs have clearly demonstrated a specific effect of TG-targeting therapy on ASCVD risk, especially when statins have already been used.[79] Finally, the correlation of TG levels and ASCVD risk in epidemiological studies has been attenuated or even lost after adjusting for non-HDL-C or apoB.[78] Therefore, ASCVD risk is probably determined by the atherogenic component of TG-rich lipoproteins, such as apoB, rather than TG per se.[78,79] Collectively, the current ACC/AHA guidelines have recommended that persistently elevated TG ≥ 175 mg/dL is considered as a risk-enhancing factor.[80]

Although an inverse relationship between serum HDL-C concentrations and ASCVD risk has been found in population studies,[81,82] evidence from genetic studies and Mendelian randomized trials has questioned whether the inverse association is causal.[82] HDL-C can be atherogenic.[81] Furthermore, RCTs regarding HDL-elevating therapy have mostly failed to demonstrate the expected outcome.[81,82] With regards to the effect of HDL-C on ASCVD, the focus of recent research has shifted to the function of HDL particles, especially in the context of macrophage cholesterol efflux, from serum HDL-C levels alone.[81] Nevertheless, the concentration of HDL-C remains a useful tool in the risk stratification of ASCVD.

In the context of primary prevention, other emerging lipoprotein biomarkers have been proposed when assessing an individual's risk of ASCVD, including Lp(a), apoB, and remnant cholesterol. Lp(a) is a lipoprotein subclass which contains an additional protein called apolipoprotein(a), and it is of emerging importance in atherosclerosis formation. Multiple studies have confirmed the association between elevated levels of Lp(a) and the risk of ASCVD.[83-85] There may be a myriad of mechanisms by which Lp(a) contributes to ASCVD, including proatherogenic, proinflammatory, and prothrombotic pathways.[85] In addition, Lp(a) also potentiates vascular inflammation through its content of oxidized phospholipids, and interrupts antifibrinolytic effects by inhibiting plasminogen. The current ACC/AHA guidelines have identified that Lp(a) ≥ 50 mg/dL is a risk-enhancing factor for ASCVD.[80]

ApoB is the primary protein constituent of atherogenic lipoproteins, including chylomicrons, LDL, intermediate-density lipoprotein, and very low-density lipoprotein particles. Its unique one-to-one ratio with each lipoprotein particle makes it a direct biomarker of the amount of circulating atherogenic lipoproteins. Furthermore, a robust correlation has been observed between apoB and non-HDL-C, suggesting that apoB and non-HDL-C are potentially better predictors of ASCVD than LDL-C.[86-88] Currently, the serum levels of apoB ≥ 130 mg/dL and non-HDL-C 190-219 mg/dL are both considered as risk-enhancing factors of ASCVD by the ACC/AHA guidelines.[80]

Remnant cholesterol, which can be simply calculated as TC minus HDL-C and LDL-C, is an emerging biomarker for assessing the risk of ASCVD. It represents cholesterol in chylomicrons, very low-density lipoprotein, and intermediate-density lipoprotein, and is formed during the process of TG-rich lipoprotein metabolism.[89] In a post-hoc analysis of a large RCT, it was found that remnant cholesterol levels were an independent risk factor for

ASCVD in high-risk patients, with a better predictive power than LDL-C levels.[90] These findings suggest that measuring remnant cholesterol levels in addition to LDL-C and HDL-C may provide additional value to the evaluation of ASCVD risk. However, current evidence focusing on this topic and the optimal serum levels of remnant cholesterol are still limited, and further research is required before it can be used clinically.

*2.3.4. Strategies to prevent the occurrence of dyslipidemia*

Genetic variants partially account for the occurrence of dyslipidemia. Secondary causes of hypertriglyceridemia include diet with high positive energy-intake balance and high fat or high glycemic index, increased alcohol consumption, obesity, MetS, insulin resistance, type 2 DM, hypothyroidism, renal disease, and some medications, etc.[78] Various clinical conditions such as obesity,[91] DM,[92] and CKD[93] are frequently associated with variable types of dyslipidemia, and strategies to modify relevant risk factors and avoid the occurrence of these clinical conditions can also reduce the risk of dyslipidemia.

Patients with genetically confirmed FH have a significantly higher risk of ASCVD compared to individuals with LDL-C $\geq$ 190 mg/dL but no identified genetic mutation.[94] Therefore, it is advisable to raise clinical suspicion and conduct comprehensive family screening with genetic testing among patients with LDL-C $\geq$ 190 mg/dL, especially in those who have typical characteristics of tendinous xanthoma, corneal arcus, and family history of premature ASCVD.

**Key Recommendations**

- For the primary prevention of ASCVD in individuals with dyslipidemia, risk stratification according to comorbidities and other risk factors is necessary (COR I, LOE B).
- ApoB and non-HDL-C can be used to predict the risk of ASCVD (COR IIa, LOE B).
- For the primary prevention of ASCVD, persistently elevated TG $\geq$ 175 mg/dL, Lp(a) $\geq$ 50 mg/dL, apoB $\geq$ 130 mg/dL, and non-HDL-C 190-219 mg/dL are respectively recognized as risk-enhancing factors, and the initiation of specific lipid-lowering therapy should be considered (COR IIa, LOE B).

## 2.4. Tobacco smoking

*2.4.1. Prevalence and incidence of tobacco smoking*

According to the Adult Smoking Behavior Survey reported by the Taiwan Health Promotion Administration in 2023, the prevalence of smoking among people aged over 18 years was 21.9% in 2008 but it decreased to 14.0% in 2022. Of these people, 24.4% were male and 3.7% were female with a peak age ranging from 40-49 years.[95] However, the prevalence of secondhand smoke exposure at home increased from 27.2% in 2008 to 28.9% in 2022. Of note, the prevalence of e-cigarette smoking among people aged over 18 years was 0.6% in 2018 but it increased to 1.4% in 2022. The main age of people consuming e-cigarettes was younger than 40 years.

*2.4.2. Impact of tobacco smoking on the development of ASCVD*

Smoking induces ASCVD via endothelial dysfunction, atherosclerosis, stimulation of inflammatory cytokines and activated prothrombotic state. These factors are mediated through three principal constituents: nicotine, carbon monoxide, and oxidant gases.[96] In the brain, nicotine binds to $\alpha 4\beta 2$ nicotinic cholinergic receptors and acts as a sympathomimetic agent. This stimulates the release of catecholamines, resulting in tachycardia, hypertension and myocardial stress, which induce the imbalance of myocardial work and oxygen demand.[97] Carbon monoxide can cause relative hypoxemia that precipitates ischemic events. The high levels of nitrogen oxides and free radicals in cigarette smoke induce inflammation, decrease the cellular production of nitric oxide, cause dysfunction of the endothelial system, and activate prothrombotic state and lipid oxidation, which are associated with the pathogenesis of ASCVD.

Even though e-cigarettes have previously been considered to be less harmful than smoking combustible tobacco products in the short term, their long-term safety is uncertain due to other constituent chemicals, that is, nicotine, propylene glycol, and glycerin.[98] Electronic cigarette or vaping product use-associated lung injury is a described organizing pneumonia in patients with the past 90 days of vaping history.[99] Su et al. found that vegetable glycerin enhances neutrophil chemotaxis and fibrosis and amplifies the inflammatory response associated with lipopolysaccharide-induced lung injury by en-

hancing p38 MAPK activity.[100]

Secondhand smoke is the combination of smoke from the burning end of a cigarette and smoke breathed out by smokers. Secondhand smoke contains more than 7,000 chemicals and causes almost 34,000 premature deaths from heart disease every year in the United States.[101]

*2.4.3. Role of tobacco smoking in cardiovascular risk*

Based on the previous epidemiology, tobacco use is a major health concern worldwide, and it is responsible for over 6 million deaths annually — almost 12% of all deaths.[102] Tobacco-attributable mortality accounts for 10% to 30% of all deaths from ASCVD based on the Global Report of the World Health Organization.[101] In the United States, almost a third of all deaths associated with smoking are related to ASCVD.[103] According to the 2019 report of the Taiwan Health Promotion Administration, nearly 25,000 people die of smoking-related heart disease every year in Taiwan, with 1 person dying of smoking-induced harm every 20 min.[104] Smoking has been shown to increase the risk of CAD [hazard ratio (HR): 3.2-3.5], CVD (HR: 1.7-3.2), PAD, and abdominal aortic aneurysm.[105] The sex-specific relative risk of smoking mortality in Taiwan is the same as that in international reports. Mortality from all causes and CVD is significantly higher in women than in men.[106] Observational epidemiological research and clinical studies have provided evidence of a non-linear dose effect of exposure to cigarette smoke on ASCVD.[107,108] In the INTERHEART study,[109] the odds of MI were 9-fold higher in those who smoked over 40 cigarettes per day [HR: 9.16, 95% confidence interval (CI): 6.79-12.36] than in never smokers, and the risk increased by 5.6% for every additional cigarette smoked. The influence of smoking on younger individuals (HR: 3.53, 95% CI: 3.23-3.86) was higher when compared to older individuals (HR: 2.55, 95% CI: 2.35-2.76; $p < 0.0001$ for interaction).

The INTERHEART study found that secondhand smoke was associated with a graded increase in exposure-related AMI risk; the HR was 1.24 (1.17-1.32) in individuals with a lower exposure (1-7 h per week) and 1.62 (1.45-1.81) in those with higher exposure (> 21 h per week).[109] A systematic review and meta-analysis[110] reported that pooled relative risks for never smokers exposed to secondhand smoke compared with those unexposed were 1.23 (95% CI: 1.16-1.31) for CVD and 1.18 (95% CI: 1.10-1.27) for all-cause mortality.

In the American Health eHeart Study regarding cigarette and e-cigarette users,[111] dual users had a higher risk of CAD than single cigarette users due to the two different sources of poison. In the National Health Interview Surveys of 2014 (n = 36,697) and 2016 (n = 33,028),[112] daily e-cigarette use was independently associated with an increased odds of MI (HR: 1.79, 95% CI: 1.20-2.66), as was daily conventional cigarette smoking (HR: 2.72, 95% CI: 2.29-3.24).

Heat-not-burn tobacco is heated with an electric blade at 350 °C, lower than a conventional cigarette (684 °C). Volatile organic compounds, polycyclic aromatic hydrocarbons, and carbon monoxide are present in heat-not-burn tobacco. Additionally, heat-not-burn tobacco has 84% of the nicotine found in conventional cigarette smoke.[113] In a systematic review,[114] heat-not-burn tobacco exposed users and bystanders to potentially harmful toxicants, although at substantially lower levels than cigarettes.

Waterpipe smoking or hookah is an emerging trend in the United States, especially among youths.[115] Waterpipe smoking affects heart rate, BP regulation, baroreflex sensitivity, tissue oxygenation, and vascular function over the short term. Long-term water pipe use is associated with an increased risk of CAD due to several harmful or potentially harmful substances.[116]

*2.4.4. Strategies to avoid cigarette smoking in non-smokers and secondhand smoke exposure*

Several guidelines state that all patients should avoid secondhand smoke exposure to reduce ASCVD risk as primary prevention.[7,23] Laws regarding tobacco hazard prevention including avoiding cigarette smoke and secondhand smoke for non-smokers based on national administration policy would be useful. Robust evidence supports many measures to avoid cigarette smoking and secondhand smoke exposure, and they can be included in such laws to enhance the prohibition/restriction power via government authorities. This can include standardized packs with larger health warnings,[117] targeted mass media interventions promoting healthy behaviors,[118] legislative smoking bans to reduce harm from secondhand smoke exposure and smoking prevalence,[119] and tobacco taxation to reduce the initiation of tobacco smoking.[120]

The recently updated Taiwan Tobacco Hazards Prevention Act has implemented a complete ban on e-cigarette and strict control of heat-not-burn tobacco products.[104,121] After the introduction of the first version of the Taiwan Tobacco Hazards Prevention Act in 1997 and following revisions, the prevalence of smoking among people aged over 18 years declined from 29.2% in 1996 to 14.0% in 2022.[95]

**Key Recommendations**

- All adults are recommended to be assessed at every healthcare visit for tobacco use, and their tobacco use status should be recorded as a vital sign for ASCVD risk assessment and facilitating smoking cessation (COR I, LOE A).
- To reduce the risk of ASCVD, all adults and adolescents are advised to avoid exposure to secondhand smoke (COR III, LOE B).
- Legislative bans and measures to avoid cigarette smoking and secondhand smoke exposure are recommended to enhance the prohibition/restriction power via government authorities (COR I, LOE B).

## 2.5. Obesity

The National Health Promotion Administration of Taiwan has been utilizing specific diagnostic cut points for overweight and obesity since 2013, considering the degree of comorbidity, overall mortality rate, and public health epidemic screening. These cut points are based on BMI measurements, with a BMI of ≥ 24 kg/m$^2$ being considered overweight, and a BMI of ≥ 27 kg/m$^2$ indicating obesity.[122] This approach ensures a standardized and consistent method for identifying individuals who fall within these weight categories, allowing for effective monitoring and intervention strategies to promote better health outcomes. In addition, the Ministry of Health and Welfare has recommended using waist circumference measurements as another indicator for obesity and as one of the diagnostic criteria for MetS. According to these guidelines, a waist circumference above 90 cm for men and 80 cm for women is considered indicative of obesity. However, there is currently no definitive consensus on whether to employ waist-hip ratio or percentage of body fat as alternative diagnostic criteria. Table 6 presents the established cutoff point standards for overweight and obesity.

### *2.5.1. Prevalence and incidence of obesity*

Over the past 3 decades, the prevalence of obesity has steadily increased throughout the world.[123] Based on data provided by the World Health Organization, it is estimated that the global prevalence of overweight, defined as a BMI of ≥ 25 kg/m$^2$, was approximately 1.9 billion people in 2014. This accounted for approximately 39% of the total population, with 39% of females and 38% of males falling into this category. Among the individuals classified as overweight or obese, around 13% had a BMI of ≥ 30 kg/m$^2$, indicating obesity. The prevalence of obesity was higher in women, with 15% classified as obese, compared to 11% of men. Furthermore, the statistics revealed that severe obesity, defined as a BMI of ≥ 40 kg/m$^2$, affected approximately 1.6% of women and 0.64% of men. These figures highlight the significant global burden of overweight and obesity, emphasizing the need for effective strategies to address this public health issue.[124] According to the World Obesity Federation, the global adult population affected by overweight or obesity is projected to increase from 2 billion in 2014 to 2.7 billion by 2025. In Taiwan, data from the three waves of the Taiwan National Nutrition and Health Change Survey (conducted during the periods of 1993-1996, 2005-2008, and 2013-2016) indicate notable trends in weight categories. The proportion of individuals with a normal BMI (18.5 ≤ BMI < 24 kg/m$^2$) gradually declined over time, from 58.1% in the first wave to 51.5% in the second wave, and further decreasing to 49.2% in the third wave. On the other hand, the prevalence of overweight and obesity (defined as a BMI of ≥ 24 kg/m$^2$) steadily increased, rising from 33.2% in the first wave to 43.4% in the second wave, and further reaching 45.9% in the third wave. Within this category, the prevalence of overweight (defined as a BMI ranging

**Table 6.** Classification of body weight according to BMI

| | BMI | Waist circumference |
|---|---|---|
| Underweight | BMI < 18.5 kg/m$^2$ | |
| Normal | 18.5 ≤ BMI < 24 kg/m$^2$ | |
| Overweight | 24 ≤ BMI < 27 kg/m$^2$ | |
| Mild obesity | 27 ≤ BMI < 30 kg/m$^2$ | Men ≥ 90 cm |
| Moderate obesity | 30 ≤ BMI < 35 kg/m$^2$ | Women ≥ 80 cm |
| Severe obesity | BMI ≥ 35 kg/m$^2$ | |

BMI, body mass index.

from 24 to < 27 kg/m$^2$) decreased slightly from 21.5% in the first wave to 25.5% in the second wave, and then stabilized at 22.8% in the third wave. In contrast, the prevalence of obesity (BMI ≥ 27 kg/m$^2$) showed a significant rise, increasing from 11.8% in the first wave to 17.9% in the second wave, and further to 23.0% in the third wave. Of particular concern is the substantial increase in severe obesity (BMI ≥ 35 kg/m$^2$) over a 20-year period. The prevalence of severe obesity more than tripled, escalating from 0.4% in the first wave to 0.6% in the second wave, and ultimately reaching 1.3% in the third wave. These findings underscore the growing prevalence of overweight and obesity, particularly severe obesity, and highlight the urgent need for effective measures to address this escalating public health issue.[125,126]

*2.5.2. Impact of obesity on the development of ASCVD*

Obesity is strongly linked to an increased risk of various CVDs, including hypertension, diabetes, dyslipidemia, MetS, and sleep apnea. It is recognized as a major risk factor for the development of ASCVD, and associated with other specific cardiovascular conditions such as atrial fibrillation and heart failure.[127] Findings from the 2013-2016 National Nutrition and Health Survey in Taiwan highlighted the association between obesity, central obesity in particular, and the development of isolated systolic hypertension, and a strong association between higher levels of the atherogenic index of plasma (log TG/HDL-C) and the presence of obesity, indicating the importance of managing weight and addressing obesity-related factors in the prevention and treatment of ASCVD.[128,129] Furthermore, the Taiwanese Survey on Hypertension, Hyperglycemia, and Hyperlipidemia study revealed that the metabolically healthy obesity group (BMI ≥ 24 kg/m$^2$) had a significantly higher risk of CVD (adjusted HR: 1.74, 95% CI: 1.02-2.99) when compared to the normal weight group.[130] These findings indicate that even in the absence of metabolic abnormalities, obesity itself remains a significant risk factor for CVD. Based on data of the National Health Interview Survey collected in 2013, it has been estimated that an 18% reduction in ASCVD could be achieved if obesity/overweight can be prevented.[131]

*2.5.3. Role of obesity in CVD risk assessment*

The 2019 ACC/AHA Guidelines on the Primary Prevention of Cardiovascular Disease recommends calculating BMI on an annual basis or even more frequently for individuals identified as obese.[23] This emphasizes the importance of ongoing monitoring of weight status in order to assess and manage CVD risk. Additionally, the guidelines suggest that measuring waist circumference is a reasonable approach to identify individuals who may be at higher risk of cardiometabolic complications.[23] By incorporating these measurements into routine clinical practice, healthcare professionals can effectively identify individuals who may require closer monitoring and appropriate interventions to mitigate their cardiovascular risk.[23] It is recommended to conduct screening for other concomitant risks of ASCVD, including non-alcoholic fatty liver disease and obstructive sleep apnea (OSA).[132,133] In obese patients with hypertension and those with clinically evident CVD, it is recommended to perform an electrocardiogram to detect left ventricular hypertrophy. Furthermore, it is crucial to screen for the occurrence of atrial fibrillation in individuals suspected of having this condition. In cases where sleep apnea is suspected, it is recommended to conduct nocturnal polysomnography. By incorporating these screening measures, healthcare providers can effectively identify and address underlying cardiovascular conditions and associated risks in obese patients. This enables appropriate interventions and management strategies to reduce the burden of CVD in this population.[134]

*2.5.4. Strategies to prevent obesity*

The pathogenesis of obesity is complex and multifactorial, involving energy imbalance, hormone disorders, genetic diseases, gut microbiota and medications.[135,136] While adopting a population health approach within an obesogenic environment is crucial to tackle the complexity of obesity, it is equally important to expand the scope of health services beyond medical treatment to encompass obesity prevention.[137,138] It is of utmost importance to initiate obesity prevention efforts early, beginning within the settings of early care and education as well as schools. Research has shown that interventions targeting obesity prevention in these settings yield significant benefits, with particularly noteworthy effects observed in children between the ages of 6 and 12 years.[139] Meta-analyses have consistently demonstrated the positive impact of school-based interventions and worksite he-

alth promotion programs on improving physical activity and/or nutrition, leading to reductions in body weight and BMI.[140,141] Favorable outcomes regarding reducing weight have still been found in adults at risk of obesity.[142]

**Key Recommendations**

- Early detection and interventions to effectively mitigate the risks associated with ASCVD and obesity-related co-morbidities are needed (COR I, LOE A).
- It is recommended to calculate BMI at least annually, or even more frequently, in individuals who are overweight or obese. Additionally, measuring waist circumference is considered a reasonable approach to identify individuals with MetS, a cluster of risk factors for ASCVD (COR I, LOE C).

## 2.6. Hyperuricemia

Hyperuricemia can be defined as: (1) serum uric acid levels 7.0 mg/dL or higher in males and 6.0 mg/dL or higher in females; (2) uric acid levels 7.7 mg/dL or higher in males, 6.6 mg/dL or higher in females; or (3) those already taking uric acid lowering agents.[70]

### *2.6.1. Prevalence and incidence of hyperuricemia*

Hyperuricemia is a common condition with a prevalence of 17.4% to 21.2% worldwide.[143,144] According to the first wave of the Taiwan National Nutrition and Health Change Survey (conducted from 1993-1996), the prevalence rate of hyperuricemia was approximately 26.1% in male adults and 17.0% in female adults (≥ 19 years old) by using definition 2 in Taiwan.[145] According to the report of the Nutrition and Health Surveys 2017-2020 in Taiwan, the prevalence rate of hyperuricemia was 17.9% in male and 9.9% in female adults (≥ 19 years old),[70] both of which were lower than the first survey conducted between 1993-1996. The definition of hyperuricemia used in the Nutrition and Health Surveys 2017-2020 was a combination of definitions 2 and 3.

### *2.6.2. Impact of hyperuricemia on the development of ASCVD*

Hyperuricemia is associated with an increased risk of developing ASCVD, including mortality (HR: 1.209), CAD (HR: 1.206),[146] and stroke (HR: 1.47).[147] An analysis of a health check-up database from Taiwan showed that hyperuricemia, defined as definition 1, was associated with an increased risk of CAD (HR: 1.25, 95% CI: 1.11-1.40 in males and HR: 1.19, 95% CI: 1.02-1.38 in females, respectively),[148] and it was also associated with an increased risk of total mortality (HR: 1.16) and ischemic stroke (HR: 1.35).[149] An analysis of the TNHIRD further demonstrated that gout was associated with an increased risk of CAD and stroke 3 years after diagnosis.[150] The underlying mechanisms may include endothelial dysfunction, oxidative stress, and inflammation, among others. Furthermore, hyperuricemia can also contribute to the development of cardiovascular risk factors including hypertension,[151] MetS,[152] and CKD,[153] thereby further increasing the risk of ASCVD.

### *2.6.3. Role of hyperuricemia in ASCVD risk assessment*

Hyperuricemia has been associated with the occurrence of traditional cardiovascular risk factors such as hypertension, dyslipidemia, DM, and MetS.[154,155] Furthermore, it was significantly associated with the clustering of cardiovascular risk factors, and a higher 10-year ASCVD risk score in those with higher quintiles of serum uric acid levels.[154] In addition, hyperuricemia has been independently associated with a higher risk of ASCVD after adjusting for traditional risk factors.[148,149] Therefore, measuring serum uric acid levels can serve as a valuable means of identifying individuals who may be at an elevated risk of developing ASCVD.

### *2.6.4. Strategies to prevent hyperuricemia*

In addition to genetic factors and tumor lysis, causes of hyperuricemia include obesity, increased purine consumption from meat, alcohol, and high fructose corn syrup, as well as medications such as cyclosporine, low-dose aspirin, and diuretics.[156,157] While diet may contribute to hyperuricemia, the direct effect of diet on hyperuricemia is weak,[158] and genetic contributions and obesity itself appear to be larger drivers of hyperuricemia in the general population.[157] Therefore, weight control and increased physical activity remain cornerstones among lifestyle modifications for the prevention of hyperuricemia,[158] whereas limited evidence suggests that avoidance of certain foods and beverages may decrease the frequency of gout flares.[157]

**Key Recommendations**

- Measuring serum uric acid levels can serve as a valu-

able means of identifying individuals who may be at an elevated risk of developing ASCVD (COR I, LOE C).
- Weight control and increased physical activity remain cornerstones among lifestyle modifications for the prevention of hyperuricemia (COR I, LOE C).

## 2.7. MetS

The Asian-modified definition of MetS is widely used in Taiwan and is shown as follows: ≥ 3 of the following: waist size ≥ 90 cm in men or ≥ 80 cm in women; TG ≥ 150 mg/dL or taking a TG-lowering agent; HDL-C < 40 mg/dL in men or < 50 mg/dL in women; SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or taking a BP-lowering agent; fasting plasma glucose ≥ 100 mg/dL or taking a glucose-lowering agent.[70,159,160]

### *2.7.1. Prevalence and incidence of MetS*

According to the report of the Nutrition and Health Surveys 2017-2020 in Taiwan, the prevalence rate of MetS was 39.3% in male and 30.3% in female adults (≥ 19 years old), which were higher than 9.8% and 13.9%, respectively, reported in the first surveys conducted between 1993-1996.[70] The prevalence rate reached a peak of 59.2% at 65-74 years of age in males, whereas it increased sharply after 45-64 years and reached up to 67.0% in female adults aged ≥ 75 years old.[70]

### *2.7.2. Impact of MetS on the development of ASCVD*

Individuals with MetS have 6-, 4- and 3-fold higher risks of developing DM, hypertension, and hyperlipidemia, respectively.[160] MetS has been found to be more prevalent in non-diabetic patients with CAD than in those without CAD.[161] An analysis of TwCCCC showed that as the number of MetS components increased, the HR increased significantly, up to 5.5 (95% CI: 2.2-13.7) for CAD and 3.5 (95% CI: 1.9-6.5) for stroke.[162] Another cohort study in Taiwan revealed that the HR for the risk of stroke of subjects with 1 to 2 and ≥ 3 MetS components were 3.16 and 5.15, respectively, according to the 2005 definition from the National Cholesterol Education Program Adult Treatment Panel III.[163] A follow-up study of a Chinese cohort involving 10,292 individuals in Taiwan showed that MetS with hypertension as a component was associated with an increased risk of ischemic and hemorrhagic stroke [adjusted HR: 2.96 (95% CI: 1.94-4.50) and 2.93 (95% CI: 1.25-6.90), respectively] compared with those who had neither hypertension nor MetS.[164]

### *2.7.3. Role of MetS in ASCVD risk assessment*

Debate on the definition of the diagnosis of MetS has continued since its introduction.[165,166] Areas of debate include whether 1) insulin resistance, obesity, or inflammation is the core mechanism of action; 2) only the cutoff values of each component should be present rather than continuous values or the degree of the severity of the syndrome with multiple cutoff values; 3) to incorporate all the risk factors known for CVD, such as physical activity; 4) MetS should be considered a cluster of risk factors or an additional independent risk factor to assess CVD risk; and 5) MetS is a better predictor than obesity to prevent CVD.[165,166] Nevertheless, there is no doubt that MetS is associated with a higher risk of developing traditional metabolic risk factors as well as ASCVD.[160-164] In addition, it is considered to be a risk enhancer and is often included in the risk assessment of ASCVD in lipid guidelines.[6,167]

### *2.7.4. Strategies to prevent MetS*

Healthy lifestyle factors such as physical activity and healthy dietary pattern are associated with a lower risk of MetS and are recommended as the best strategy to prevent MetS.[166,168,169] Physical fitness training among 1,720 soldiers was shown to improve the components of MetS, with running performance proving to be most relevant to MetS, in Taiwan.[170] In addition, an RCT involving 136 metabolically abnormal obese individuals in Taiwan showed that a 6-month community-based exercise intervention program, including providing exercise environments, exercise skills and reminding from volunteers, could significantly improve the components of MetS including HDL-C, BMI, waist circumference, BP and fasting blood glucose levels.[171] The Health Promotion Administration in Taiwan provides free checks for the components of MetS every 3 years for individuals aged ≥ 40 and < 65 years and every year for those aged ≥ 65 years.[172]

**Key Recommendations**
- MetS is considered to be a risk enhancer and should be included in the risk assessment of ASCVD (COR IIa, LOE C).
- Healthy lifestyle factors such as physical activity and healthy dietary pattern are recommended to prevent MetS (COR I, LOE C).

## 2.8. Gender

### *2.8.1. Sex and gender and their impact on the development of ASCVD*

CVD is the leading cause of death among both men and women in Taiwan, while the burden is greater for women than for men, especially with the aging population. Compared with men, women are less likely to be diagnosed appropriately, receive preventive care, or be treated aggressively for CVD. The current prevention guidelines recognize the importance of integrating sex, gender, and gender identity considerations into the risk assessment and clinical management of individuals and populations. With these differing risk profiles, risk assessment, risk stratification, and primary preventive measures for ASCVD are different in women and men.[173] Evidence exists for the risk modifying effects of sex or sex-specific clinical conditions on socioeconomic status, determinants of health access, healthcare utilization, clinical management strategies, and even therapeutic responses in the field of CVD and ASCVD prevention.[174-176] Research is ongoing, however gaps in the evidence remain. Sex differences between men and women have allowed for the identification of CVD risk factors and risk markers that are unique to women, including pregnancy-related cardiovascular health (cardio-obstetrics), premenopausal vs. postmenopausal status, sex hormone-related issues, cancer-related therapies (cardio-oncology), all of which can facilitate appropriate prevention strategies and might improve long-term outcomes.

### *2.8.2. Role of sex and gender in risk assessment*

For the primary prevention of ASCVD, risk scores and models have been developed to improve the ability to detect atherosclerosis at an earlier stage. In Taiwan, the TwCCCC risk model revealed that the risk of CVD/sudden death was higher for men than for women during follow-up (HR: 1.9, 95% CI: 1.3-2.9).[177] Another model built using data from the Nutrition and Health Survey in Taiwan from 1993-1996 and linked with 10-year events from the TNHIRD showed that the incidence rates of major adverse cardiovascular events per 1000 person-years were 13.77 for men and 7.76 for women.[28] Furthermore, the incidence rates of major adverse cardiovascular events in the Taiwanese Survey on Hypertension, Hyperglycemia, and Hyperlipidemia conducted in 2002 were 7.27 for men and 3.58 for women.[28]

Recent US population estimates from the National Health and Nutrition Examination Survey found that significantly fewer women had high-risk (< 1% vs. 5%) and intermediate-risk (4% vs. 29%) scores than men, respectively, and that the lifetime risk of developing CVD for men was higher than for women (approximately 1 in 2 for men and 1 in 3 for women).[25,178-183] Similar trends have also been noted in Chinese populations.[7,184,185] A study in Sweden comprising a large, random sample of the general population aged 50 to 64 years (50.6% women) without established disease using coronary computed tomography angiography (CCTA), found that silent coronary atherosclerosis was not uncommon (42.1%), and that the onset of atherosclerosis was delayed on average by 10 years in women.[183] Some reports have suggested that women are more likely to develop plaque erosions with non-calcified plaques, more diffuse lesions and multivessel disease, resulting in higher mortality.[186]

Some cardiovascular risk factors are unique to women,[173,187-189] including pregnancy-related conditions (eclampsia, pre-eclampsia, gestational hypertension or/diabetes), polycystic ovary syndrome, early menopause, premature ovarian insufficiency, functional hypothalamic amenorrhea, failure of fertility therapy, infertility, exogenic hormone use, etc. Early and late onset of menarche is also associated with an increased risk of CVD, while breast-feeding has been demonstrated to have a cardioprotective effect. A history of inflammatory diseases, especially rheumatoid arthritis and psoriasis,[190] enhances the risk of ASCVD, and their prevalence is higher in women. Furthermore, clinical cardio-oncology considerations specific to women span many areas and are particularly relevant for the management of patients with sex-specific cancers, such as breast cancer.[191,192] These factors, if present, would favor more intensified lifestyle interventions and consideration of initiating or intensifying statin therapy for primary prevention to mitigate the increased risk. In patients receiving cardio-toxic agents, it is recommended to periodically monitor cardiac function and screen for CVD risk factors.

#### *2.8.2.1. Obstetric and adverse pregnancy outcome-related conditions*

Pre-eclampsia, defined as pregnancy-related hyper-

tension accompanied by proteinuria, occurs in 1-2% of all pregnancies and is associated with a 1.5-2.7-fold increased risk of CVD compared with all women,[193,194] while the relative risk of developing hypertension is 3-fold and DM is 2-fold.[193] A retrospective longitudinal study using the TNHIRD from 1996 to 2010 revealed that women with a history of pre-eclampsia/eclampsia were at increased risks of a subsequent diagnosis of DM, dyslipidemia, hypertension, congestive heart failure and cerebrovascular disease (HR: 3.84 and 5.42, HR: 2.75 and 3.40, HR: 6.52 and 7.31, HR: 9.07 and 7.39, and HR: 10.71 and 3.47, all $p < 0.05$).[195]

Pregnancy-related hypertension affects 10-15% of all pregnancies. The associated risk of later CVD is lower than for preeclampsia, but is still elevated (HR: 1.7-2.5).[196,197] The risks of sustained or future hypertension (HR from 2.0 to 7.2 or even higher)[198,199] and developing DM (HR: 1.6-2.0) are also elevated in these women.[200] Both preterm (HR: 1.6) and still-birth (HR: 1.5) have been associated with a moderate increase in the risk of CVD.[196]

Gestational diabetes confers a sharply elevated risk of future DM, with up to 50% of affected women developing DM within 5 years after pregnancy, and up to a 2-fold increased risk of future CVD.[201] Screening by fasting glucose or HbA1c may be preferable to oral glucose tolerance testing.[202]

Adverse pregnancy outcomes such as hypertensive disorders of pregnancy, preterm delivery, gestational diabetes, small-for-gestational-age delivery, placental abruption, and pregnancy loss increase a woman's risk of developing CVD risk factors and of developing subsequent CVD (including fatal and nonfatal CAD, stroke, PAD, and heart failure).[203,204] This is particularly relevant for younger women in whom global risk scores are in a low-risk range. Black and Asian women have a higher proportion of adverse pregnancy outcomes, with more severe clinical presentations and worse outcomes than Caucasian women. This highlights the importance of recognizing adverse pregnancy outcomes when evaluating the CVD risk in women, especially in Asia.

We stress the importance of eliciting a thorough obstetrical and gynecological history during cardiovascular risk assessment and providing a health care system framework for how to initiate appropriate preventive measures, periodic screening for hypertension, DM, and common cardiovascular risk factors. This can facilitate the transition of care for women with adverse pregnancy outcomes, and the implementation of strategies to reduce their long-term CVD risk when sex-specific risk factors are present.[205]

*2.8.2.2. Non-obstetric conditions*

The presence of components of MetS should prompt clinicians to look for polycystic ovarian syndrome, hormone contraceptive use, and gestational DM.

Polycystic ovary syndrome affects 5% of all women in their fertile years,[206,207] and it is associated with a 2- to 4-fold increase in the risk of developing DM. The risk of developing hypertension may also be increased, however conflicting data exist.[208] It has been associated with an increased risk of CVD, probably through common risk factors, suggesting that periodic screening for cardiovascular risk factors is appropriate.

Premature menopause occurs in approximately 1% of women under 40 years of age. Up to 10% of women experience an early menopause, defined as that occurring by 45 years of age.[209] Early menopause is associated with an increased risk of CVD (HR: 1.5).[210-212] A linear inverse relationship between earlier menopause and CAD risk has been found, whereby each 1-year decrease in age at menopause is associated with a 2% increased risk of CAD.[213]

**Key Recommendations**

- In women with a history of preeclampsia and/or pregnancy-induced hypertension, periodic screening for hypertension and DM should be considered (Class IIa, LOE B).
- In women with a history of polycystic ovary syndrome or gestational DM, periodic screening for DM should be considered (Class IIa, LOE B).
- In women with a history of pregnancy-associated conditions and adverse pregnancy outcomes, periodic screening for CV risk factors may be considered (Class IIb, LOE B).

### 2.9. Genetics and family history

Several previous studies have shown that the etiology and mechanisms of ASCVD have a genetic component, but these findings are complex,[214] and it is not currently used in personal and clinical preventive man-

agement. In the past few years, polygenic risk scoring has shown some potential to improve ASCVD risk prediction for primary prevention.[215-217] In addition, improving reporting standards and reproducibility of polygenic risk scores for risk stratification could open a window for clinical utility in ASCVD, and may increase the use of genetics in the primary prevention of ASCVD.[218-220] However, there are some limitations. First, the incremental prediction accuracy is relatively modest and needs further evaluation.[221,222] Second, consensus regarding which genes and corresponding single nucleotide polymorphisms should be included is currently lacking. Third, whether to use risk factor-specific or outcome-specific polygenic risk scores is under debate.[223] Fourth, most of these studies were mainly conducted in Caucasian populations with a large number of individuals. In East Asians, only one large-scale prospective Chinese cohort study using 41,271 individuals as a validation cohort showed that polygenic risk scores could stratify individuals into different trajectories of CAD risk, and further refine risk stratification for CAD within each clinical risk strata.[224] In South Asians, a validation study with 7,244 individuals in the UK Biobank also showed that compared to the middle quintile, the risk of CAD was most pronounced in those in the top 5% of the polygenic risk score distribution with odds ratios of 4.16, 2.46, and 3.22 in the South Asian UK Biobank, Bangladeshi, and Indian studies, respectively. On the other hand, more evidence is also needed to assess the clinical utility of polygenic risk scores in other clinical settings, such as in patients with pre-existing ASCVD.[225] Taken together, the routine use of genetic testing in patients with ASCVD or in healthy individuals is not recommended, although it could be considered in select patients with a high risk of CAD or with a family history of premature CAD or ACS.

A family history of premature CAD is a simple and traditional risk indicator of ASCVD, with an interplay of genetic and environmental effects.[24,226] There are varying definitions of family history.[24] A family history of CAD is usually defined as the onset of CAD [in males ≤ (or <) 55 years of age and females ≤ (or <) 65 years of age] in first degree relatives,[6,227] and a family history of premature CAD is usually defined as the onset of CAD in first degree relatives aged < 50 years.[18,227] The predicted value of family history varies. Some studies have shown incremental risk prediction of CAD or CAD death in addition to traditional risk factors,[226,228-230] whereas others have shown marginal incremental predicted value and risk reclassification effect on the basis of conventional and novel CAD risk factors.[231,232] This discrepancy may be due to the varying definitions of family history applied,[233] and because conventional ASCVD risk factors largely explain the impact of family history.[24]

**Key Recommendations**

- The routine use of genetic testing in patients with ASCVD or in healthy individuals is not recommended (Class III, LOE B).
- Genetic testing may be considered in select patients with a high risk of ASCVD or with a family history of premature CAD or ACS (Class IIb, LOE B).
- A family history of CAD or premature CAD may be included in the risk assessment of ASCVD (Class IIa, LOE B).

## 2.10. CKD

### *2.10.1. Prevalence and incidence of CKD*

The current prevalence of CKD worldwide is 11-13%.[234] Reasons for the high prevalence include population aging, DM, and high BP. Because the management of other chronic diseases such as malignant tumors, stroke and MI has improved, the mortality rate of these patients has been reduced. Therefore, in these patients, the chance of kidney failure has increased. An analysis of data from the TNHIRD estimated that the national prevalence of CKD was 11.9%.[235] About 6.9% of people over the age of 20 years have stage 3-5 CKD, and the prevalence and incidence of end-stage renal disease in Taiwan have been the highest globally for years.[236]

### *2.10.2. Impact of CKD on the development of ASCVD*

The relationship between CKD and ASCVD is complex and multifactorial. In general, two main mechanisms are thought to contribute to the development of ASCVD in patients with CKD.[234,237] First, CKD is associated with several traditional risk factors for ASCVD, including hypertension, DM, dyslipidemia, and obesity. Second, CKD is also associated with non-traditional risk factors for ASCVD, including chronic inflammation, oxidative stress, endothelial dysfunction, and mineral disorders. In addition to traditional and non-traditional risk factors, the kidneys can release hormones, enzymes and

cytokines in response to kidney injury, resulting in characteristic changes in the vasculature.[238] On the other hand, CKD-related mediators and hemodynamic changes contribute to heart damage. Patients with CKD are at an increased risk of developing ASCVD, and the risk increases as kidney function declines.

*2.10.3. Role of CKD in ASCVD risk assessment*

Individuals with CKD are at an increased risk of developing ASCVD and having poor ASCVD outcomes, including CAD,[239] stroke,[240,241] PAD,[242,243] and aortic aneurysm.[244,245] Assessing the risk of ASCVD in patients with CKD is important for identifying those who may benefit from early interventions to prevent or delay the onset of ASCVD.[246] Several factors should be taken into account when assessing the ASCVD risk in patients with CKD, including age, gender, BP, lipid levels, smoking status, and presence of DM.[247] In addition, kidney function itself can be used as a marker for CVD risk.[239,242,248] A decrease in estimated glomerular filtration rate (eGFR) and an increase in urine albumin clearance ratio (UACR) are associated with an increased risk of ASCVD events. Therefore, CKD is considered to be a high-risk factor for ASCVD, and modification of relevant risk factors should be more aggressive in the context of CKD, even in the primary prevention of ASCVD.[6,167] The Taiwan Society of Nephrology recommend that eGFR and UACR should be checked annually to identify CKD in individuals with type 2 DM, hypertension, older age (> 65 years), and obesity, while UACR should be checked every year in individuals with hypercholesterolemia or tobacco smoking.[249]

*2.10.4. Strategies to prevent the occurrence of CKD*

Several strategies can be applied for the primary prevention of CKD, including lifestyle modifications and the control of risk factors modulating both CKD and ASCVD. Several modifiable lifestyle factors have been identified for the primary prevention of CKD. A large meta-analysis[250] involving 104 studies of 2,755,719 participants with generally a low risk of bias showed that higher dietary potassium intake (HR: 0.78, 95% CI: 0.65-0.94), higher vegetable intake (HR: 0.79, 95% CI: 0.70-0.90), physically active versus sedentary (HR: 0.82, 95% CI: 0.69-0.98), and moderate consumption of alcohol versus no consumption (HR: 0.86, 95% CI: 0.79-0.93) were associated with a lower risk of CKD, whereas higher salt intake (HR: 1.21, 95% CI: 1.06-1.38), and current and former smokers were associated with a higher risk of CKD. These associations were consistent, but evidence was predominantly of low to very low certainty.[250] Higher diet quality was most important among these factors in the Framingham Heart Study.[251] Alcohol consumption can be a "double-edged sword" for CKD patients.[252] Drinking alcohol can cause adverse events, and non-drinkers do not need to start drinking, but moderate drinking may be beneficial for CKD. The definition of moderate consumption of alcohol here equal to less than 2 drinks/day (28 g/day alcohol) for men and less than 1 drink/day (14 g/day alcohol) for women. However, concerns about alcohol consumption are fully discussed in the Part II of the current guidelines (section 5.1.4). The following risk factors which modulate both CKD and ASCVD should be well controlled for the primary prevention of CKD. First, BP control: high BP can damage the kidneys and increase the risk of CKD and ASCVD.[253] BP control for the primary prevention of ASCVD is evident and recommended by guidelines.[18] Population-based cohort studies have shown that the primary prevention of CKD can be achieved with BP control.[254] Optimal BP control according to guidelines is essential. Second, blood sugar control: high blood sugar levels can damage the blood vessels and increase the risk of CKD and ASCVD.[36,255] Keeping blood sugar levels and HbA1C under control is crucial for preventing CKD and ASCVD.[256,257] Third, LDL-lowering treatment: high cholesterol levels lead to the initiation and progression of atherosclerosis, which remain the major causes of morbidity and mortality in patients with CKD and ASCVD.[258] A post hoc analysis of six RCTs regarding intensive LDL-lowering treatment with high-dose atorvastatin showed that atorvastatin improved kidney function over time in a dose-dependent manner, and that kidney function improvement was strongly associated with lower cardiovascular risk in patients at risk of or with CVD but no baseline kidney disease.[259] Fourth, weight loss: potential factors underlying the increased risks of CKD and end-stage renal disease include obesity-mediated hypertension, insulin resistance, obesity-related glomerulonephropathy, renin–angiotensin–aldosterone system activation, inflammation, and dysregulated adipocytokine production.[260] An RCT including 6,719 overweight/obese adults without ASCVD who were randomized to receive an intensive weight-loss lifestyle in-

tervention with an energy-reduced Mediterranean diet, physical activity promotion, and behavioral support (intervention group) or usual care advice to adhere to an energy-unrestricted Mediterranean diet (control group), showed that an intensive weight-loss lifestyle intervention approach may preserve renal function and delay CKD progression in overweight/obese adults.[260] A recently published RCT, the SELECT study, involving 17,604 participants (aged ≥ 45 years and BMI ≥ 27 kg/m$^2$) who were overweight or obese with established ASCVD and no history of DM demonstrated that weekly semaglutide injections (2.4 mg) provided a significant reduction in the risk of composite renal events accompanied with body weight reduction, although it was not an ASCVD primary prevention trial.[261] A cohort study in Taiwan showed that weight loss with bariatric surgery was associated with eGFR preservation even in individuals with baseline eGFR ≥ 90 mL/min/1.73 m$^2$ and UACR < 30 mg/g.[262]

**Key Recommendations**

- Renal function should be evaluated annually in individuals with DM, hypertension, older age (> 65 years), obesity, hypercholesterolemia or tobacco smoking (COR I, LOE B).
- Lifestyle modifications, especially higher diet quality (low salt, high potassium, energy-reduced, and high vegetable intake), should be considered for the primary prevention of CKD (COR IIa, LOE B).
- BP control may be beneficial in the context of the primary prevention of CKD in patients with hypertension (COR IIb, LOE C).
- Blood sugar control is recommended for the primary prevention of CKD in patients with DM. The HbA1c control target for patients with multiple risk factors should be < 7% (COR I, LOE A).
- Weight loss is beneficial for the preservation of renal function in individuals with overweight/obesity (COR IIa, LOE B).

## 2.11. Sleep disorders/OSA

*2.11.1. Prevalence and incidence of sleep disorders/OSA*

Sleep disturbances are common and underdiagnosed among middle-aged and older adults, and the prevalence varies by race/ethnicity, sex, and obesity status. In the general population, the prevalence of general sleep disturbances is around 32.1%, and 7.1% for sleep-related breathing disorders such as OSA.[263]

Approximately 34% and 17% of middle-aged men and women, respectively, meet the diagnostic criteria for OSA. The prevalence is as high as 40% to 80% in patients with hypertension, heart failure, CAD, pulmonary hypertension, atrial fibrillation, and stroke.[264-267] It is highly prevalent and associated with adverse outcomes in patients with heart failure.[264-267] The prevalence of sleep-disordered breathing among patients with symptomatic heart failure ranges from 40% to 60%, with OSA accounting for approximately one-third of cases.[264-267]

*2.11.2. Impact of sleep disorders/OSA on the development of ASCVD*

Sleep disturbance or abnormal sleep duration is associated with increased MI and severe CAD risks in Taiwan,[268] and optimal sleep duration (7 to 8 h) is associated with a lower risk of CVD.[269,270] A higher wakeup frequency has been associated with atherogenic dyslipidemia in Taiwanese adults, particularly in women.[271] OSA is considered as a risk factor for the development of arterial hypertension, DM, MetS,[272,273] CAD, MI, stroke,[274] PAD,[275] and progression of aortic aneurysm.[276,277] Longitudinal observational studies in clinical and community cohorts[278,279] have demonstrated that compared with mild and moderate OSA, untreated severe OSA was associated with a 2- to 3-fold higher rate of all-cause mortality and major adverse cardiac and cerebrovascular events during 5-10 years of follow-up. OSA may be linked to CVD in a bidirectional manner. In addition to shared risk factors, all sleep disturbances are strongly associated with mental disorders and share hyperarousal as an underlying mechanism.[280,281] The mechanisms of action underlying OSA-associated CVD include elevated sympathetic activity, cardiovascular variability, intrathoracic pressure changes, inflammation, oxidative stress, endothelial dysfunction, insulin resistance and thrombosis provoked by OSA.[274]

Well-established risk factors for OSA include older age, male sex, obesity, ethnicity, anomalies of craniofacial features, and menopause in women. Chinese patients have more craniofacial bony restrictions. Less well-established risk factors include smoking and family history, while alcohol and drug use may aggravate pre-

existing OSA but not cause it.[282-284]

*2.11.3. Role of sleep disorders/OSA in risk assessment*

Screening for OSA is important for ASCVD risk assessment in individuals at high risk of OSA. It is characterized by repeated partial or total collapse of the upper airway during sleep resulting in airflow cessation or reduction, and is associated with either desaturation or cortical arousal.[264,265,285,286] Symptoms suggestive of OSA include habitual snoring, witnessed breathing pause, choking or gasping during sleep, frequent awakening, nocturia, nocturnal gastroesophageal reflux, unrefreshed sleep, morning headache, fatigue, tiredness, and excessive daytime sleepiness. The assessment of OSA includes sleep history taking, physical examination, and questionnaires. Diagnostic testing, including in-lab or home polysomnography, or home sleep apnea testing, should be performed in conjunction with a comprehensive sleep evaluation and follow-up.

*2.11.4. Strategies to prevent sleep disorders/OSA*

There is no evidence regarding strategies to prevent OSA. Healthy sleeping habits is a complex balance between behavior, environment and circadian rhythm.[287] Appropriate behavior may be beneficial for the quality of sleep, such as eating tryptophan- and carbohydrate-rich foods, physical exercise in the afternoon, a cold shower just before going to bed, and thermoneutrality during sleep.[287] Caffeine intake 30 to 60 minutes before sleeping shortens total sleep time, and alcohol intake can also lead to night-time awakening due to sympathetic activation despite better initiation of sleep.[287] Therefore, both should be avoided before sleeping.

**Key Recommendations**

- 7 to 9 hours of sleep per night is recommended for good health (Class I, LOE C).
- In patients with obesity, hypertension, MetS, atrial fibrillation or heart failure, screening for sleep problems, especially OSA, is indicated (Class I, LOE C).

## 2.12. Inflammation/infection

*2.12.1. Prevalence and incidence of inflammation/infection*

Chronic low-grade inflammation/infection plays an important role in the pathogenesis of atherosclerosis and provocation of acute vascular events.[1,288] An analysis of the Atherosclerosis Risk in Communities Study, a large multicenter cohort study, involving 8,947 participants without CAD revealed that elevation of high-sensitivity C-reactive protein (hsCRP) level (≥ 2 mg/L) was observed in 5,018 participants (56.1%).[289] Furthermore, the Framingham Heart Study, a prospective community cohort study involving 4,446 participants without ASCVD, revealed that 2,831 participants (63.7%) had a higher CRP level (≥ 1 mg/L) and that 1,706 participants (38.4%) had a CRP level ≥ 3 mg/L.[290] Taken together, these findings imply that the prevalence of chronic low-grade inflammation/infection in relatively healthy populations is high.

*2.12.2. Impact of inflammation/infection on the development of ASCVD*

Inflammation is a critical driver in the multistep process of ASCVD development.[1,288] Inflammatory cascade also plays a key role in the architectural stability of fibrous caps. Destabilization of collagen in fibrous caps leads to plaque rupture and overlying thrombus formation, resulting in ACS.[291] Patients with ACS have a higher hsCRP level than those without.

*2.12.2.1. The role of periodontitis*

The relationship between inflammation/infection and the development of ASCVD has been reported in several association studies. The role of periodontitis has received more attention, and it probably plays a causative role rather than a coincidental association.[292] Periodontitis has been shown to contribute to elevated CRP levels in many studies.[292-295] CRP levels progressively increase from periodontal health to disease.[294] Non-surgical periodontal therapy can effectively reduce serum CRP levels either in individuals without or with ASCVD.[294-297] Relapse of periodontitis after surgery is reflected by changes in proinflammatory biomarkers, including hsCRP, during follow-up.[298] A genome-wide association study revealed a novel shared risk locus for CAD and periodontitis.[299] Associations between periodontitis and CAD,[300-304] ACS,[304,305] ischemic stroke,[303,304,306] PAD,[307,308] the development and progression of aortic aneurysm,[309] cardiovascular death,[304] and total mortality[304] have been reported in both cross-sectional and longitudinal follow-up studies. Furthermore, an analysis of the TNHIRD showed

that dental prophylaxis and periodontal treatment in patients with periodontitis was associated with a lower risk of ischemic stroke than in those without periodontitis (HR: 0.78, 95% CI: 0.75-0.81, and 0.95, 95% CI: 0.91-0.99, respectively) after adjusting for confounders, whereas those with periodontitis but no treatment had a significantly higher HR for ischemic stroke (1.15, 95% CI: 1.07-1.24).[310] The same study group further demonstrated that dental prophylaxis was associated with a lower risk of AMI (HR: 0.90, 95% CI: 0.86-0.95).[311] A nationwide database analysis from South Korea showed that performing one more tooth brushing a day was associated with a 9% significantly lower risk of cardiovascular events after multivariable adjustment, and that regular dental visits (once a year or more) for professional cleaning also reduced cardiovascular risk by 14%.[312] However, no well-designed RCT has evaluated the effects of dental prophylaxis/periodontal treatment on the primary prevention of ASCVD.[24,313]

*2.12.2.2. Hepatitis C*

Associations of hepatitis C infection and the occurrence of CAD,[314] ACS,[315,316] ischemic stroke,[316] PAD,[317] major arterial events (ACS, acute ischemic stroke, and PAD),[316] and all-cause mortality[316] have been reported. However, hepatitis B is not associated with ASCVD[316] or ASCVD-related death.[318] Furthermore, an analysis of the TNHIRD showed that antiviral treatment for hepatitis C infection resulted in a lower risk of ischemic stroke (HR: 0.53, 95% CI: 0.30-0.93) and a trend of a lower risk of ACS (HR: 0.64, 95% CI: 0.39-1.06).[319]

*2.12.2.3. Helicobacter pylori*

Associations of Helicobacter pylori infection and the occurrence of CAD,[320] ACS,[321] ischemic stroke,[322,323] and PAD[324] have been reported. However, no observational study or prospective RCT has evaluated the effect of eradicating this micro-organism infection on the occurrence of ASCVD.

*2.12.2.4. Mycoplasma pneumoniae*

Some observational studies have demonstrated an association between *Mycoplasma pneumoniae* infection and the occurrence of ASCVD.[325-328] However, clarithromycin treatment was shown to increase cardiovascular risks in several population-based studies,[329,330] and did not show outcome benefits in an ACS RCT.[331]

*2.12.2.5. Rheumatoid arthritis*

Rheumatoid arthritis has been reported to be associated with ASCVD.[332-334] A recently published study revealed that genetic liability to rheumatoid arthritis was associated with an increased risk of CAD, probably being mediated by CRP.[335] Patients with rheumatoid arthritis treated with disease-modifying anti-rheumatic drugs have been shown to have an improved cardiovascular profile.[336] Treatment with disease-modifying anti-rheumatic drugs as well as Chinese herbal medicine for rheumatoid arthritis has been associated with a lower risk of CVD,[337-340] whereas an inadequate response to disease-modifying anti-rheumatic drug therapy has been associated with a higher risk of ACS in Taiwan.[341] However, no RCT has evaluated the effects of anti-rheumatic treatment on the primary prevention of ASCVD in individuals with rheumatoid arthritis.

*2.12.2.6. Other inflammation/infections*

Other inflammation/infection-related diseases including systemic lupus erythematosus,[342,343] systemic sclerosis,[344] psoriasis,[345,346] inflammatory bowel disease,[347-349] human immunodeficiency virus infection,[350] gall stone disease,[351,352] influenza infection,[353] and tuberculosis infection,[354-356] have been reported to be associated with the occurrence of ASCVD. An analysis of the TNHIRD showed that long-term hydroxychloroquine treatment for systemic lupus erythematosus was associated with a lower risk of vascular events,[357] while patients with gall stone disease undergoing cholecystectomy were associated with a lower risk of ischemic stroke.[358] Taken together, chronic low-grade inflammation plays an important role in the pathogenesis of ASCVD.

*2.12.3. Role of inflammation/infection in risk assessment*

There are two approaches in terms of the role of inflammation/infection in ASCVD risk assessment. The first is a biomarker-oriented approach, and the second is a concomitant disease-oriented approach.

*2.12.3.1. Biomarker-oriented approach*

The role of hsCRP, a canonical biomarker of inflammation/infection, has been thoroughly investigated in ASCVD risk assessment. Its predicted value has been re-

ported to be independent from, and even superior to, traditional ASCVD risk factors.[359,360] Therefore, hsCRP was included in a risk-prediction model, which was deemed superior to other risk scoring models.[361,362] However, its role in ASCVD risk assessment is arguable,[363,364] and thus routine measurement of hsCRP is not recommended in the guidelines.[7,24]

*2.12.3.2. Concomitant disease-oriented approach*

In 2013, the European Federation of Periodontology and the American Academy of Periodontology recommended that[313] practitioners should be aware of the emerging and strengthening evidence that periodontitis is a risk factor for developing ASCVD and periodontitis patients with other risk factors for ASCVD who have not seen a physician within the last year, should be referred to a specialist.

In 2022, the Taiwanese Dermatological Association, the Taiwanese Association for Psoriasis and Skin Immunology, and the TSOC jointly published a consensus on the management of psoriatic disease with attention to cardiovascular comorbidities and recommended cardiovascular risk assessment and management.[365] Of note, for patients without pre-existing CVD, a comprehensive cardiovascular risk evaluation for primary prevention should be performed at the diagnosis of psoriasis. In addition, patients with severe psoriasis or at moderate or high CVD risk, or those who exhibit cardiovascular signs and symptoms should be referred to a cardiologist for further evaluation and management.

In 2017, the European League Against Rheumatism Task Force published update recommendations for CVD risk assessment and management in patients with rheumatoid arthritis and other inflammatory joint disorders, including ankylosing spondylitis and psoriatic arthritis.[366] CVD risk assessment is recommended for all patients with rheumatoid arthritis, ankylosing spondylitis or psoriatic arthritis at least once every 5 years and should be reconsidered following major changes in antirheumatic therapy, and lifestyle recommendations should emphasize the benefits of a healthy diet, regular exercise and smoking cessation for all patients.

The CV risk assessment and management in patients with systemic lupus erythematosus, gout, and other vasculitis were also discussed by the European League Against Rheumatism Task Force in 2022.[367]

*2.12.4. Strategies to prevent inflammation/infection*

Some ASCVD-relevant inflammatory and infectious diseases are preventable. Hyperuricemia with gouty arthritis, periodontitis, hepatitis C and human immunodeficiency virus infections should be prevented and managed according to the guidelines from related societies.

Influenza virus infection can be effectively prevented by vaccination. Most influenza vaccines can protect against three (trivalent) or four (quadrivalent) different influenza viruses.[7,368]

**Key Recommendations**

- Routine measurement of hsCRP for ASCVD risk assessment is not recommended (Class III, LOE A).
- Periodontitis patients with other ASCVD risk factors who have not seen a physician within the last year should be referred to a specialist (Class IIa, LOE C).
- For patients with rheumatoid arthritis, psoriasis, or psoriatic arthritis without pre-existing ASCVD, a comprehensive cardiovascular risk evaluation for primary prevention should be performed at the diagnosis (Class IIa, LOE C).
- The frequency of repeat screening of laboratory data for ASCVD risk assessment in patients with periodontitis, rheumatoid arthritis, psoriasis, or psoriatic arthritis should follow the Health Promotion Administration recommendations for adult preventative health screening (every 3 years for adults aged 40-64 years or annually for adults aged 65 years or older) (Class IIa, LOE C).
- Lifestyle modifications, especially a healthy diet, regular exercise and smoking cessation, and management of ASCVD risk factors are recommended for all patients with periodontitis, rheumatoid arthritis, psoriasis, or psoriatic arthritis (Class I, LOE C).
- Annual influenza vaccination is recommended, especially for individuals with older age, ASCVD risk factors, or concomitant disease (COR I, LOE B).

## 2.13. Mental disorders and socioeconomic stress

*2.13.1. The prevalence and incidence of mental disorders*

The prevalence of probable common mental disorders in Taiwan doubled from 11.5% in 1990 to 23.8% in 2010.[369] These increases paralleled rises in national rates of unemployment, divorce, and suicide.[369] According to a report from the Taiwan National Health Insurance Ad-

ministration, approximately 2.8 million patients with psychological disorders sought medical aid in 2019.[370] Therefore, it is an important issue in the current era.

*2.13.2. Impact of mental disorders and socioeconomic stress on the development of ASCVD*

Mental disorders (e.g. anxiety, mood, psychotic, personality, eating, sleep, sexuality-related or other disorders) mainly develop due to psychosocial stress, and are directly associated with socioeconomic and behavior risk factors.[371,372] The impact of mental disorders is independent of traditional CVD risk factors, and is associated with an increased risk of the development and progression of CVD and worse CV outcomes.[373,374] Severe mental illness (schizophrenia, bipolar disorder, and major depressive disorder) is associated with an increased risk of developing CAD (adjusted HR: 1.54, 95% CI: 1.30-1.82).[373] Anxiety symptoms/disorders (HR: 1.41, 95% CI: 1.23-1.61) as well as experiences of persistent or intense stress or posttraumatic stress disorder (adjusted HR: 1.27, 95% CI: 1.08-1.49) are also associated with a higher risk of CAD.[373] On the other hand, ASCVD patients are at an approximately 2- to 3-fold increased risk of mental disorders compared to healthy general populations.[375,376] A cross-sectional study involving 11,956 permanent residents in China aged ≥ 35 years revealed that depressive symptoms were associated with 10-year ASCVD risk after adjusting for confounding risk factors.[377]

Psychosocial, biological, and behavioral risk factors are prevalent in disadvantaged individuals, accentuating the link between socioeconomic status and ASCVD. Socioeconomic status has a measurable and significant effect on cardiovascular health. Considering the impact of socioeconomic stress, the INTERHEART study,[378] a large-scale case-control study in 52 countries, showed that all four psychosocial stressors (stress at work and at home, financial stress, major life events in the past year and locus of control and presence of depression) were associated with an increased risk of AMI events. Income level, educational attainment, employment status, and environmental factors are four dominant markers of socioeconomic status. An association of socioeconomic status with ASCVD in high income countries has been demonstrated.[379-383] A prospective observational cohort study in the United States showed that participants with both depressive symptoms and stress had the greatest elevation in the risk of developing total CVD (HR: 1.48, 95% CI: 1.21-1.81) and all-cause mortality (HR: 1.33, 95% CI: 1.13-1.56), but only in those with a low income.[384] Studies in Taiwan have shown that hospitalized AMI patients with low individual socioeconomic status had lower rates of diagnostic angiography and subsequent percutaneous coronary interventions and a higher mortality rate,[385] and that low-income patients undergoing coronary artery bypass grafting received lower-quality care and had higher mortality than high-income patients.[386]

*2.13.3. Role of mental disorders and socioeconomic stress in risk assessment*

Preliminary evidence suggests that taking mental disorders and low socioeconomic status into account improves classical ASCVD risk models and is thus recommended.[387,388] A cohort study reported that CVD risk assessment tools which did not include severe mental illness as a predictor underestimated CVD risk by about one-third in men and two-thirds in women.[387]

*2.13.4. Strategies to prevent mental disorders and socioeconomic stress*

Strategies which have been shown to be beneficial, and some of them cost-effective, in the primary prevention of common mental disorders include selective primary preventive interventions (interventions in the offspring of patients with severe mental disorders) and indicated primary preventive interventions (interventions in people at clinical high risk of mental disorders or psychosis).[389] Clinical and social preventive measures both seem to be important in the prevention of mental disorders by reducing socioeconomic stress.[369] It would be an important issue to survey and refer patients with low socioeconomic status to mental health services. Some lifestyle factors, such as exercise, physical activity, yoga, and qigong, may be effective in the primary prevention of common mental disorders.[390-391]

**Key Recommendations**

- Physicians should be aware of the emerging and strengthening evidence of the association of mental disorders or socioeconomic stress with the development and worse outcomes of ASCVD (Class IIa, LOE B). In addition, physicians may advise patients to implement

healthy lifestyles for the primary prevention of this factor (Class IIb, LOE C).

## 2.14. Frailty

*2.14.1. Prevalence and incidence of frailty*

Frailty is the health status of decreased resistance to stressors characterized by increased vulnerability and decline in multidirectional physiologic reserve. According to extensive cohort studies, the prevalence of frailty is varied, ranging from 5.0% to 6.4%, in residents over 50 years of age in Taiwan.[392,393] The discrepancy between both studies is due to different assessment tools of frailty and the various timing and areas of study enrollment.

*2.14.2. Impact of frailty on the development of ASCVD*

Taiwan became an aged society in 2018 due to a decline in fertility rate and increased life expectancy. The accelerating pace of aging is expected to make Taiwan a super-aged community in 2026. The prevalence of frailty and CVD increase with age, with shared common risk factors including activated inflammation.

The association between CVD and frailty is strong and bidirectional. Lifestyle risk factors such as smoking, low physical activity, economic stress, and aging link pathways between CVD and frailty.[394] A meta-analysis study found that frail individuals had an increased CVD risk compared to pre-frail or robust individuals.[395] Pre-frail status, defined as the presence of one or two Fried criteria, is also an independent risk factor for the development of CVD,[396] and frail individuals without previous CAD have significantly higher risks of major adverse cardiovascular events, AMI, stroke, PAD, and CAD.[397,398]

*2.14.3. Role of frailty in ASCVD risk assessment*

There are currently various definitions of frailty owing to a lack of consensus agreement.[399] The most commonly used approaches are to define phenotypic frailty and deficit accumulation index. Other domains including cognitive dysfunction and psychological and social frailty form the conceptual frailty framework.[400] A single tool is needed to define a comprehensive model of frailty, and some domains are less applicable in the clinical practice of CVD.

Various instruments have been developed to provide deficit scores based on at least 30 variables. The frailty index is based on comprehensive geriatric assessments, and scores the number of deficits in the domains of impairment, disability, and comorbidity burden.[401,402] The Canadian Study of Health and Aging clinical frailty score encompasses ten standard territories and 70 deficits from clinical assessments.[403]

The Fried frailty phenotype, developed using data from the Cardiovascular Health Study, is the most frequently cited instrument in previous studies.[404] The Fried frailty phenotype encompasses five measurable components, namely slow walking speed, weakness of grip strength, low physical activity, self-reported exhaustion, and unintentional weight loss. Participants who meet three or more of these criteria are defined as being frail, and those who meet one or two criteria as prefrail. Other single-item measures of frailty, such as questionnaires, gait speed, handgrip strength, or Short Physical Performance Battery[405,406] are used as surrogates for predictability because of the time-consuming and effort required for comprehensive assessments. To conclude, further research is required to develop a globally accepted tool to assess frailty and its specific application for CVD prevention. In addition, the ability of frailty measures to improve CVD risk prediction should be further evaluated.[407]

*2.14.4. Strategies to prevent frailty*

Lifestyle interventions such as dietary quality, micronutrient supplementation, and exercise training have been shown to be effective to prevent and attenuate frailty in observational studies and small-scale interventional trials.[24,408-410]

**Key Recommendations**

- Frailty is a complex geriatric syndrome characterized by functional decline and inability to withstand acute stressors, and it is an emerging ASCVD risk factor in the increasingly aged society (COR IIa, LOE C).
- Lifestyle interventions such as dietary quality, micronutrient supplementation, and exercise training may be considered to prevent and attenuate frailty (COR IIb, LOE C).

## 2.15. Environmental exposure

*2.15.1. Environmental exposure and CVD*

The rapid development of current civilization has

brought enormous improvements in our daily lives. However, these improvements have also resulted in byproducts that affect our health and the environment. The effects of environmental pollutants can have serious impacts on human health, particularly on populations living in industrialized societies. Diseases of civilization, such as CVD, asthma, and DM, are tightly linked to environmental pollutants. These pollutants, which come from sources such as industrial and agricultural activities, vehicle emissions, and waste disposal, can cause inflammation, atherothrombosis, endothelial dysfunction, and oxidative stress, leading to a range of adverse health outcomes.[411] Among them, air pollutants, and especially particulate matter (PM) with variable size, can penetrate the respiratory system via inhalation, causing respiratory disease and CVD, central nervous system dysfunction, reproductive abnormalities, and even an increase in cancer incidence.[412]

There are some emergent environmental exposures, such as air pollution, climate change, and heavy metal pollution that have been established closely related to ASCVD and mitigation measures should be taken in action for ASCVD prevention.

### *2.15.2. Ambient air pollution*

#### *2.15.2.1. Exposure to fine PM ($PM_{2.5}$) and gaseous pollutants increases the risk of CVD*

Numerous scientific studies have demonstrated the detrimental effects of ambient $PM_{2.5}$ exposure and gaseous pollutants on cardiovascular health and an increased risk of CVD.[413] $PM_{2.5}$ refers to fine particulate matter with a diameter of 2.5 micrometers or less, which can easily penetrate deep into the respiratory system and subsequently enter the blood circulation leading to systemic health effects.[411-414] Exposure to $PM_{2.5}$ has been consistently associated with adverse cardiovascular outcomes, including increased risks of heart attack, stroke, and heart failure.[415,416] Gaseous pollutants such as nitrogen dioxide, sulfur dioxide, and ozone have also been linked to increased inflammation, thrombosis, and autonomic imbalance,[417] and the incidence of CVD.[418,419] These pollutants can induce oxidative stress, inflammation, and endothelial dysfunction, contributing to the development and progression of cardiovascular pathologies.[420] One study of adolescents and young adults in Taiwan suggested that traffic and industrial sources of $PM_{2.5}$ and elements were associated with higher carotid intima-media thickness (CIMT).[421] Recent evidence indicates that even at low pollution levels below the current European and North American standards and World Health Organization guideline values, outdoor air pollution is associated with mortality.[422] These findings are supported by high-quality scientific evidence, including systematic reviews, cohort studies, and experimental studies.[411-414,423,424]

#### *2.15.2.2. Strategies to reduce ambient air pollution for the primary prevention of CVD in the general population*

Mounting evidence suggests that reducing ambient air pollution has the potential to prevent CVD in the general population. Epidemiological studies have consistently demonstrated an association between higher levels of air pollution and increased cardiovascular morbidity and mortality.[411-414] Implementing interventions to decrease air pollution levels, such as reducing the use of fossil fuels, adopting cleaner energy sources, and implementing stricter emission standards, has been shown to have positive impacts on cardiovascular health.[411,425] A previous study reported that a decrease of 10 $\mu g/m^3$ in $PM_{2.5}$ across 51 U.S. metropolitan areas with matching data for the late 1970s and early 1980s versus the late 1990s and early 2000s was associated with an estimated increase in mean life expectancy of $0.61 \pm 0.20$ years.[426] These findings are supported by a systematic review and meta-analysis of observational studies and intervention trials.[427-429] Therefore, reducing ambient air pollution has emerged as an important strategy for preventing CVD and promoting public health.

**Key Recommendations**

- Both long-term and short-term ambient $PM_{2.5}$ exposure increase the risk of ASCVD (COR I, LOE B).
- Reducing ambient air pollution exposure can be beneficial for cardio-pulmonary health (COR IIa, LOE B).
- Reducing ambient air pollution exposure may be helpful in the primary prevention of ASCVD (COR IIa, LOE C).

### *2.15.3. Climate change*

Scientific research indicates that climate change, and

particularly inappropriate temperature increases, can elevate the risk of CVD. Rising temperatures, heatwaves, and extreme weather events associated with climate change have been linked to adverse cardiovascular outcomes.[430,431] The physiological stress imposed by high temperatures can lead to increased cardiovascular strain, exacerbation of pre-existing conditions, and higher rates of hospitalizations and deaths due to cardiovascular events.[432,433] Moreover, climate change-related factors such as air pollution, changes in infectious disease patterns, and alterations in food availability and quality can further contribute to the burden of CVD.[430,434,435] Rajagopalan et al. supported the assertion that inappropriate temperature increases associated with climate change can elevate the risk of CVD.[436] Extreme temperature plays a crucial role in increasing the effects of air pollution and exacerbating cardiovascular risks.[437,438] A higher temperatures can intensify the harmful effects of air pollution on the cardiovascular system, leading to an increased incidence of heart attack, stroke, and other cardiovascular events.[436-438] Thus, climate warming can exacerbate the hazardous effects of other pre-existing environmental toxicants on the cardiovascular system, leading to adverse cardiovascular outcomes.

To reduce CVD morbidity and mortality, it is recommended to mitigate climate change by reducing the use of fossil fuels and limiting carbon dioxide emissions.[436,439] These measures can help to mitigate temperature increases and associated health risks, thereby safeguarding cardiovascular health. This recommendation is supported by scientific studies and expert consensus.[440-442] Implementing sustainable practices and transitioning to cleaner energy sources are crucial steps towards protecting cardiovascular health in the face of climate change.

**Key Recommendations**

- Climate change with inappropriate increases in temperature elevates the risk of ASCVD (COR I, LOE B).
- Reducing the use of fossil fuels and limiting carbon dioxide emissions may be reasonable for the primary prevention of ASCVD (COR IIb, LOE C).

*2.15.4. Heavy metals*

Previous studies have consistently demonstrated that higher exposure to heavy metals, including lead, cadmium, mercury, and arsenic, increases the risk of CVD.[443,444] Heavy metals, which can be found in various environmental sources such as air, water, soil, and food, have been implicated in the development and progression of ASCVD. These metals can induce oxidative stress, inflammation, endothelial dysfunction, DNA methylation, and disruption of vascular homeostasis, ultimately contributing to the pathogenesis of cardiovascular disorders.[436,445-448] Epidemiological studies have shown associations between heavy metal exposure and an increased incidence of CVDs, including CAD, hypertension, MetS, and heart failure.[436,443,444,448-450] To prevent CVD in the general population, reducing exposure to heavy metals is recommended. Strategies such as minimizing occupational and environmental exposure, implementing regulations on industrial emissions, and ensuring safe drinking water sources can help mitigate the risk of heavy metal-related cardiovascular health effects.[436,444,445] This recommendation is supported by scientific evidence, including epidemiological studies, experimental research, and systematic reviews.[451-456] Considering the widespread exposure of heavy metals, even modest contributions to CVD risk can have a substantial effect on the general population. Evidence-based clinical and public-health strategies aimed at reducing environmental exposure and mitigating the toxic effects could substantially lower the disease burden of CVD worldwide.[436,448,457] Arsenic is a naturally occurring element that an individual typically encounters every day in daily life, including food, water, soil, and air. In some areas of the world, high levels of arsenic are naturally present in the groundwater in some areas of the world, including Argentina, Bangladesh, Cambodia, Chile, China, Taiwan, India, Mexico, Pakistan, the United States of America and Vietnam, and are a toxicological concern.[458] The relative risks were found with dose-response relationship for those who had a cumulative arsenic exposure compared with those without the arsenic exposure after covariates adjustment from the earlier studies in Taiwan.[459,460] Reducing arsenic exposure may contribute to a lower risk of ASCVD.[461] Taking measures to reduce heavy metals exposure, particularly lead, cadmium, mercury, and arsenic, are essential for promoting cardiovascular health and preventing associated diseases.

**Key Recommendations**

- Higher heavy metal exposure to lead, cadmium, mer-

cury, and arsenic increases the risk of ASCVD (COR I, LOE B).

- Reducing exposure to heavy metals, including lead, cadmium, mercury, and arsenic, may be reasonable to prevent ASCVD in the general population (COR IIb, LOE C).

## 3. SURROGATE MARKERS AS RISK ENHANCERS

### 3.1. Imaging

*3.1.1. Coronary artery calcium (CAC)*

Vascular calcification is a hallmark of atherosclerosis. Factors including inflammatory processes and metabolic risks such as hyperlipidemia and DM all influence the process of coronary calcification.[462] The coronary calcium area is highly correlated with coronary plaque area both in individual arteries and the heart, indicating that CAC quantification can be used as an index of disease severity.[463,464] The current prognostic value of CAC in clinical practice is mainly derived from major prospective cohort studies which enrolled subjects aged between 45 and 75 years.[465-468] The population-based Rotterdam Study enrolled 1,795 asymptomatic participants with a mean follow-up of 3.3 years, and showed that the risk of CAD was highest in participants with a CAC score > 1000, followed by those with a score from 401 to 1000 and then 101 to 400 compared to those with a score < 100 (adjusted HR: 8.3, 4.6, and 3.1, respectively).[469] An analysis of pooled US population-based studies (the Framingham Heart Study, the Multi-Ethnic Study of Atherosclerosis, and the Cardiovascular Health Study) involving 4,778 participants over 11 years of follow-up revealed that CAC scores had a greater association with the occurrence of CAD and stroke than age.[470] In addition, adding CAC score to risk prediction models with traditional risk factors and only age being removed improved the discrimination for incident CAD but not for stroke.[470] Compared with other serum biomarkers, CAC score appears to be superior in the risk prediction of future ASCVD events, suggesting that CAC may be useful in the risk assessment and primary prevention of ASCVD.[471,472]

Considering cost-effectiveness, the primary prevention strategies for CAD mainly focus on eligibility for statin therapy. CAC is useful in asymptomatic people for planning primary prevention intervention strategies such as the use of statins and aspirin. Use of the CAC score in primary prevention is recommended by the ACC/AHA guidelines[23,80] for adults at intermediate risk or selected adults at borderline risk. If the decision on the use of statins remains uncertain, it is reasonable to use the CAC score in the decision to withhold, postpone, or initiate statin therapy (Class IIa, LOE B), and the CAC score may be considered as a risk modifier in the cardiovascular risk assessment of asymptomatic individuals at low or moderate risk. Therefore, after the assessment of future cardiovascular risk based on risk score analysis, the addition of CAC distribution measures can improve the discriminatory capacity of models for major CAD events. No prospective cohort study has investigated the use of CAC score in Taiwan. The TSOC recently published CCS guidelines recommending the use of CAC score to improve risk assessment in those with a borderline (10-year CAD risk 3-7%) or intermediate (10-year CAD risk 7-10%) risk.[7] CAC can reclassify the risk of CVD upwards or downwards in addition to conventional risk factors to guide the initiation or intensification of preventive pharmacotherapies (Figure 5).[7] In addition to statin use, CAC may also have value in the decision to recommend prophylactic daily aspirin. The Multi-Ethnic Study of Atherosclerosis cohort included 4,229 subjects without diabetes, and reported net harm with the use of aspirin in those with a CAC score of 0, and a net benefit in those with a CAC score > 100.[473] Therefore, the Society of Cardiovascular Computed Tomography recommend considering aspirin therapy for all patients with a CAC score > 100.[474]

Although the coronary calcification identified in the chest computed tomography is nongated, it predicts mortality in a manner similar to ECG-gated CAC scoring.[475-477] Therefore, notification of patients and their clinicians about the presence of significant CAC will result in risk category re-evaluation and initiation of statin therapy along with additional preventive interventions to reduce the risk of ASCVD.

CAC score has emerged as the most predictive single cardiovascular risk marker in asymptomatic people, capable of adding predictive information beyond the traditional cardiovascular risk factors. However, the CAC score does not provide direct information on total plaque burden or stenosis severity, and it can be low or even zero in middle-aged patients with soft non-calcified plaque.[24] Further-

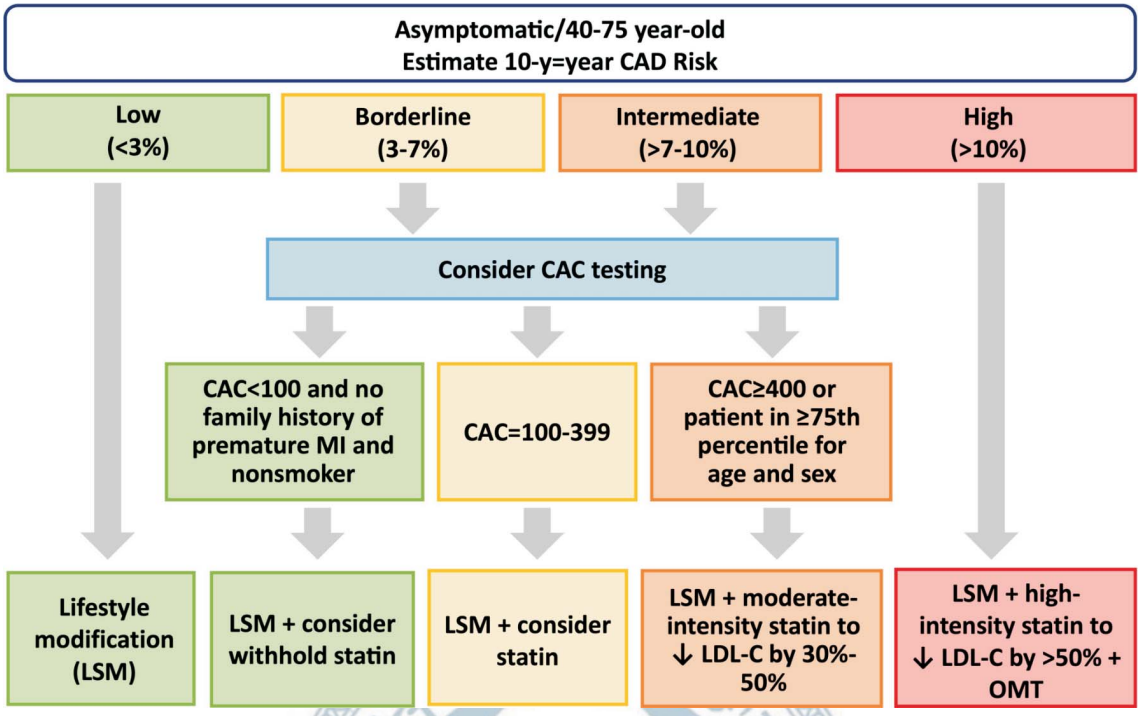


***Figure 5.*** *The role of CAC scoring in ASCVD risk stratification and management (Adapted from Ueng KC, et al. with permission).[7] Risk stratification is based on the TwCCCC risk prediction model.[26] ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcification; CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol; LSM, life-style modification; MI, myocardial infarction; OMT, optimal medical treatment; TwCCCC, Taiwan Chin-Shan Community Cardiovascular Cohort.*

more, although CAC measurements are considered to be useful for enhancing risk assessment in primary prevention, trial evidence is limited in younger and older adults, and there is currently no clinical trial evidence showing that better outcomes are achieved merely with a CAC testing approach.[478] The results of future clinical trials and observations are needed before recommendations for the use of CAC in young and elderly populations can be made.

*3.1.2. CCTA*

CCTA provides a comprehensive assessment of the entire coronary tree, including the presence of plaque, its morphology, and its extent.[479] In patients without significant epicardial obstruction, CCTA can rule out atherosclerosis or detect subclinical plaque that should be monitored for progression/regression following preventive therapy and provide risk classification.[480] In patients with significant epicardial obstruction, CCTA can assist in planning revascularization by determining the disease complexity, vessel size, lesion length and tissue composition of the atherosclerotic plaque, as well as the best fluoroscopic viewing angle. It may also help in selecting adjunctive percutaneous devices and in determining the best landing zone for stents or bypass grafts.[480]

Silent coronary atherosclerosis in the general population is common and is correlated with CAC. The Swedish Cardiopulmonary Bioimage Study recruited 30,154 randomly invited individuals aged 50 to 64 years who were not known to have CAD and had high-quality CCTA data, and the results showed that silent coronary atherosclerosis was common (42.1%), significant stenosis (≥ 50%) was less common (5.2%), and more severe forms such as left main, proximal left anterior descending artery or 3-vessel disease, were rare (1.9%) in the middle-aged population.[481] In addition, CCTA-detected atherosclerosis was found to increase in those with a higher CAC score, and all of the participants with a CAC score > 400 had atherosclerosis, of whom 45.7% had significant stenosis. In addition, 5.5% of those with a CAC score of 0 had atherosclerosis, of whom 0.4% had significant stenosis, with an increasing prevalence at higher baseline risk.[481] High CAC scores convey a significant probability of substantial stenosis, and a CAC score of 0 does not exclude atherosclerosis, particularly in those at higher ba-

seline risk.[481] Among 23,759 symptomatic patients from the Western Denmark Heart Registry who underwent diagnostic CCTA, the event rate increased stepwise with CAC scores, and patients with a comparable calcified atherosclerosis burden generally had a similar risk of CVD events regardless of whether they had nonobstructive or obstructive CAD.[482] This indicates that plaque burden, not stenosis per se, is the main predictor of the risk of CVD events and death.[482]

Although CCTA can be used to identify subclinical atherosclerosis and severity/stability of the atheroma, whether it can improve risk classification or add prognostic value for the purpose of primary prevention over CAC score is unknown.[483] In addition, increased cost, radiation exposure, and the use of downstream invasive coronary angiography and preventive treatment are other concerns. The CONFIRM study investigated statin or aspirin use in examining the risk of mortality associated with nonobstructive CAD by CCTA and evaluated the impact of baseline statin and aspirin use on mortality.[484] After analyzing 10,418 patients (5,712 with normal CCTA and 4,706 with nonobstructive CAD), a relationship between increasing burden of nonobstructive CAD and higher mortality rates was identified and a reduction in mortality risk associated with baseline statin therapy but not aspirin was observed. Like CAC score used in risk reclassification in intermediate risk group, baseline statin use is significantly beneficial in patients with the presence of nonobstructive coronary plaque. In CONFIRM study, there is no comparison investigating different impacts of CAC score or nonobsctructive plaque identified by CCTA on long term mortality associated with baseline statin use. Furthermore, it is only an observational study. An RCT involving 900 people with type 1 or type 2 DM without symptoms of CAD with a mean follow-up time of 4.0 years demonstrated that CCTA-directed treatment versus standard treatment did not result in a lower composite rate of all-cause mortality, nonfatal MI, and unstable angina requiring hospitalization.[485] An ongoing RCT planning to enroll at least 6,000 middle-aged participants at risk of CVD but without CAD at baseline to test the prognostic role of CCTA will provide more conclusive answers in terms of the role of CCTA in the primary prevention of ASCVD.[486] In the 2019 ESC guidelines for the diagnosis and management of CCS, CCTA with non-invasive functional imaging was recommended as the initial test to diagnose CAD in symptomatic patients in whom obstructive CAD could not be excluded by clinical assessments alone.[483]

**Key Recommendations**

- CAC score may be considered as a risk modifier in the cardiovascular risk assessment of asymptomatic individuals at low-moderate risk of ASCVD (COR IIb, LOE B).
- Use of the CAC score is not recommended for asymptomatic individuals who are at high risk of ASCVD (COR III, LOE B).
- It is reasonable to use the CAC score when making the decision to withhold, postpone, or initiate statin therapy in asymptomatic adults with a borderline to intermediate risk of ASCVD, if the decision about statin use remains uncertain (Class IIa, LOE B).
- For the primary prevention of ASCVD, whether CCTA improves risk classification or adds prognostic value over CAC score in asymptomatic individuals is unknown, and may not currently be recommended (Class IIb, LOE B).

*3.1.3. Carotid ultrasound*

Carotid ultrasound serves as a non-invasive technique for the early detection of subclinical or clinical atherosclerosis. This procedure primarily measures CIMT and checks for the presence of carotid plaques. However, the routine use of carotid ultrasound for screening in the general population is subject to debate and controversy.

CIMT is assessed at the far wall of the carotid arteries using ultrasound imaging. This measure is taken between the lumen-intima interface and the media-adventitia interface, clearly marked by a distinct double-line sign on ultrasound images. However, discrepancies across various studies have been noted and can be attributed to five primary factors: (1) the specific sites where CIMT is measured; (2) the specific CIMT parameters selected for statistical analysis; (3) the defined endpoints for each study; (4) the inclusion or exclusion of carotid plaques in the analysis; and (5) the predetermined cutoff values utilized to predict the CVD risk.[487] A meta-analysis of individual patient-level data which involved 16 prospective studies demonstrated a direct correlation between the mean CIMT and a 16% increase in cardiovascular risk.[488] However, no link was found between CIMT pro-

gression and cardiovascular event occurrence.[488] In another meta-analysis,[489] the added value of CIMT was questioned. This study revealed a minimal net reclassification improvement of only 0.8% when CIMT was incorporated into the 10-year Framingham risk score-based predictive model for cardiovascular risk.[489] The questionable predictive ability of CIMT progression along with the debatable additional value of integrating CIMT into traditional risk prediction models, diminishes the priority of including CIMT measurements in cardiovascular risk evaluations.[24,64,490]

Conversely, accumulating evidence from prospective studies has identified the presence of carotid plaques as a robust independent ASCVD risk factor, with significant additive value for risk prediction models.[491,492] A meta-analysis of 11 population-based studies with 54,336 patients showed that the presence of carotid plaque assessed by carotid ultrasound, compared with CIMT, had a higher diagnostic accuracy for the prediction of future CAD events.[492] Carotid plaques are characterized as having a local thickness that exceeds the surrounding wall thickness by at least 50%, or a distinct local thickness exceeding 1.5 mm, often protruding into the lumen, particularly at carotid bulbs.[493] According to the most recent guidelines from the American Society of Echocardiography[494] for evaluating carotid arterial plaques via ultrasound, carotid plaques can be divided into three categories. Grade I refers to protruding plaques with a CIMT of less than 1.5 mm. Grade II comprises either protruding or diffuse plaques with a CIMT of at least 1.5 mm but less than 2.5 mm. Grade III includes either protruding or diffuse plaques with a CIMT of 2.5 mm or more.[494] Overall, the presence of carotid plaques has been shown to be more potent than CIMT for predicting cardiovascular risks.

In addition to CIMT and the presence of carotid plaque, a low end-diastolic velocity in the common carotid artery has been independently associated with future cerebro-cardiovascular events in Taiwanese and Korean populations.[495,496] Moreover, the Two-Township Study in Taiwan demonstrated that end-diastolic velocity (< 15 cm/s) improved the prognostic power of future vascular events (combined ischemic heart disease and stroke) when added to traditional risk prediction models.[497] Therefore, end-diastolic velocity measured by carotid ultrasound may provide additional predictive value for cardiovascular events in selected patients.

**Key Recommendations**

- Using carotid ultrasound to evaluate the carotid plaque burden should be considered to enhance cardiovascular risk classification in selected patients (COR IIa, LOE B).
- End-diastolic velocity in the common carotid artery (< 15 cm/s) measured by carotid ultrasound may be used to improve the risk prediction of cardiovascular events (COR IIb, LOE B).
- Routine CIMT screening by ultrasound to improve cardiovascular risk stratification is not recommended (COR III, LOE B).

### 3.2. Arterial stiffness (ArtS)

#### *3.2.1. ArtS and ASCVD*

ArtS results mainly from arteriosclerosis of central arteries (principally a disease of the media) rather than from atherosclerosis of peripheral arteries (mainly a disease of the intima). ArtS largely reflects gradual fragmentation and loss of elastin fibers and the accumulation of stiffer collagen fibers in elastic arterial walls.[498] Elastic-type large arteries such as the aorta, carotid, and iliac arteries are primarily affected, as opposed to large muscular arteries such as the brachial, radial, and femoral arteries.[499] A large number of studies have reported that various physiological and pathophysiological conditions are associated with increased ArtS.[500] In a longitudinal study involving 1,518 community-dwelling persons in Taiwan, MetS affected the progression to ArtS in 3 years follow-up.[501] In this study, ArtS progressed as the number of MetS components increased.[501] Apart from the dominant effects of BP and aging, other important factors affecting ArtS include genetic background, cardiovascular risk factors, end-stage renal disease[502] and also chronic inflammatory diseases such as inflammatory bowel disease.[503]

#### *3.2.2. ArtS as a risk enhancer*

ArtS can be present even in the absence of traditional cardiovascular risk factors, and the loss of arterial elasticity has been linked to the full spectrum of ASCVD. Research indicates that ArtS precedes the typical and overt symptoms of diseases by many years. The predictive value of ArtS has been largely demonstrated. Recently, numerous studies in patients with uncomplicated essen-

tial hypertension[504,505] and the general population[506] have prospectively validated the predictive value of ArtS. Of note, central BP has been shown to be better than conventional brachial BP to assess target organ damage and long-term cardiovascular outcomes.[507,508] The major determinant of central BP is increased ArtS, which is also the dominant hemodynamic manifestation of arterial aging. Furthermore, ArtS is a robust predictor of all-cause and cardiovascular mortality, fatal and non-fatal coronary events and fatal strokes,[509] and thus it can serve as a surrogate marker for ASCVD events. Risk scores are used in clinical decision-making but can under- or over-estimate the risk. Of note, ArtS has been shown to be a predictor of ASCVD events and mortality independently of traditional risk factors. In addition, ArtS has been shown to retain its predictive value for cardiovascular events after adjusting for the Framingham Risk Score[510] or SCORE,[511] supporting that it can add value to a combination of traditional risk factors. Recent studies and an individual data meta-analysis showed that patients at intermediate risk could be reclassified into a different risk category when ArtS was measured.[506,511,512] In another recently published individual data meta-analysis (n = 17,635 participants), the improvements in the 5-year overall net reclassification for CAD and stroke that have some clinical relevance, especially for those at intermediate risk.[509] These studies indicate that ArtS, an early biomarker for ASCVD, is associated with the full spectrum of ASCVD, and that it can serve as a valuable risk modifier/enhancer in the setting of primary prevention. In terms of risk reclassification and risk stratification, ArtS has been even reported to be superior to carotid ultrasound or ABI.[500] In the setting of primary prevention, ArtS reflects early morphological changes well before overt disease manifests. This identification of subclinical disease may open a window of opportunity to prevent the occurrence of clinical ASCVD disease with timely interventions.

### *3.2.3. Methodology and standardization of ArtS measurements*

Many non-invasive methods to measure ArtS have been reported.[513] The most widely used and validated techniques involve the assessment of pulse waves as they travel over a significant portion of the arterial tree, including carotid-femoral pulse wave velocity (cfPWV) and brachial-ankle PWV (baPWV). The main differences between methods are the arterial measurement sites that vary from the central elastic aorta (cfPWV) to the aorta and peripheral muscular arteries (baPWV). Europeans favor cfPWV, whereas baPWV is favored in Asia. In 3,034 Atherosclerosis Risk in Communities study participants without CVD, cfPWV showed the strongest association with CVD among different PWV measures over a median follow-up of 4.4 years.[514] cfPWV is usually obtained using surface tonometry probes at the right common carotid artery and the right femoral artery, and the time delay (transit time) is measured between the two waveforms. By directly reflecting central ArtS and having the best predictive value for cardiovascular outcomes, cfPWV is now considered the gold standard for assessment in daily practice.[498] Reference values for cfPWV have been established in 1,455 healthy subjects and a larger population of 11,092 subjects with cardiovascular risk factors.[515] Due to the fact that age and BP are major determinants of PWV, a nomogram describing the correlation of the variables is needed.[516] For ease of use in daily practice, a threshold of 12 m/s was initially suggested as a conservative estimate of significant alterations in aortic function in middle-aged hypertensives,[517] however this value was subsequently revised in a recent consensus document to 10 m/s.[518] An increase in cfPWV by 1 m/s has been associated with age-, sex-, and risk factor-adjusted risk increases of 15% in cardiovascular mortality and all-cause mortality, respectively.[498] In Taiwan, baPWV, a composite of central and peripheral ArtS, is primarily used to measure a longer arterial length. The measurement of baPWV is easier than cfPWV, as it only involves wrapping a pressure cuff around each of the four exposed extremities without exposing the groin region. baPWV was shown to be a useful predictor of ASCVD in 4,881 Taiwanese subjects during voluntary health examinations.[519] In addition, the J-BAVEL trial, which included a total of 14,673 Japanese participants without a history of ASCVD, reported that a higher baPWV was significantly associated with a higher risk of CVD and mortality, even after adjustments for conventional risk factors.[520] Furthermore, the addition of baPWV to a model incorporating the clinical risk score significantly improved the accuracy of the risk assessment for ASCVD.[520] Considering the results of published prospective studies, a baPWV value of 1800 cm/s is used as a cutoff value in

the assessment of the ASCVD risk.[521] It has been reported that each 100 cm/s increase in baPWV is associated with a 13% increase in lethal cardiovascular events.[522] Of note, the standardization of PWV measures must consider how these procedures should be recorded in clinical practice. Most importantly, we recommend that the measurements are taken in a quiet and stable temperature environment after 10 min of rest, avoiding smoking, caffeine, alcohol, and eating in the hours preceding the measurement, and not speaking during the measurement.[523] Of note, each technique may have specific contraindications (e.g., significant carotid stenosis for cfPWV and PAD for baPWV).

*3.2.4. Strategies to improve ArtS*

Lifestyle modifications, and in particular weight reduction,[524] smoking cessation,[525] aerobic exercise[526] and sodium restriction,[527] appear to be clinically efficacious therapeutic interventions for preventing and treating ArtS. Pharmacological studies have shown that it is feasible to improve ArtS or to slow its progression with a few medications. Recent studies and a meta-analysis of RCTs have shown that statins can reduce ArtS by multiple mechanisms.[528,529] In a Chinese cohort study involving 5,105 participants, statin use was associated with slower progression of baPWV (-23.3 cm/s per year) compared with non-statin using adults with high ASCVD risk.[530] As such, statin therapy should be considered as a pharmacological strategy to improve arterial elasticity. ArtS is closely and bidirectionally related to BP, and is considered to be both a cause and a consequence of hypertension. Importantly, different antihypertensive drug classes may have different effects on ArtS. Despite the decrease in BP, substantial studies with diuretics and non-selective beta-blockers did not show a decrease in ArtS.[531,532] A recent meta-analysis of RCTs explored the effects of antihypertensive agents on both central and peripheral systolic BP and central augmentation index, and the results showed that compared with older agents (diuretics, beta-blockers, or $\alpha$-blockers), the newer agents (renin-angiotensin system inhibitors and calcium channel blockers) more efficaciously reduced both central SBP and augmentation index.[533] An angiotensin-converting enzyme inhibitor tended to be the most effective anti-hypertensive agent in a comparative study, suggesting a direct BP independent effect of this drug class on arterial wall remodeling.[534] Similar anti-stiffening effects have been reported after long-term treatment with olmesartan, suggesting that renin-angiotensin system blockade exerts beneficial effects on ArtS.[535,536] Selected antihypertensive drugs (renin-angiotensin system inhibitors and calcium channel blockers) can reduce PWV beyond the BP-lowering effect, and have pleiotropic beneficial effects on ArtS.[537]

*3.2.5. ArtS: from surrogate marker to therapeutic target?*

Given the evidence supporting ArtS as an independent risk factor for ASCVD and total mortality, some studies including RCTs have assessed the potential of PWV as a target for therapy and whether such a strategy would result in better clinical outcomes. One study of end-stage renal disease patients showed a better outcome in those with decreased ArtS.[538] Recently, a multicenter open-label RCT demonstrated that PWV-driven treatment for hypertension enabled better BP control and could prevent vascular aging in patients with hypertension at medium to very high risk, compared with the strict application of guidelines.[539] However, this study lacked sufficient statistical power to demonstrate its primary outcome. More evidence is needed to determine whether a PWV-guided therapeutic approach will be beneficial to the prevention of ASCVD beyond current strategies.

*3.2.6. Clinical applications of ArtS in primary prevention*

In 2013, the European Society of Hypertension and ESC Guidelines for the Management of Hypertension included cfPWV as an indicator of subclinical organ damage.[540] The last published 2021 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice recognized that ArtS can predict future ASCVD risk and improve risk classification, but that its systematic use in the general population is not recommended.[24] Asian hypertension guidelines include recommendations about the use of PWV for assessing ArtS. The 2018 Korean Society Hypertension Guidelines recommend that PWV can be a useful test at diagnosis, and that a cfPWV > 10 m/s or a baPWV > 1800 cm/s can be considered as a subclinical marker of organ damage.[541] Moreover, the 2019 Japanese Society of Hypertension Guidelines for the Management of Hypertension state that cfPWV > 10 m/s is an indicator of organ damage, and that it could also be used as needed for further evaluation of risk assessment.[542]

In summary, as ArtS predicts ASCVD risk independently of traditional risk factors, it has a significant impact on decision-making in various clinical scenarios. As such, PWV could be used effectively to improve referral decisions to more centralized cardiac evaluations. This proposed scenario is even more pertinent to patients with DM, hypertension, and kidney dysfunction, in whom the cardiovascular risk is higher.

**Key Recommendations**

- The cutoff value for risk assessment might be 10 m/s for cfPWV or 1800 cm/s for baPWV, indicating subclinical organ damage in primary prevention (COR IIa, LOE B).
- PWV, as a risk enhancer, should be helpful for clinical decision-making to guide intensification of lifestyle and pharmacological interventions or to choose further testing in people at borderline to intermediate risk (COR IIa, LOE A).
- PWV should be considered for clinical decision-making to guide clinician-patient risk discussions in those with DM, hypertension, and CKD, in whom the cardiovascular risk is higher (COR IIa, LOE B).
- PWV may be considered for clinical decision-making in those with stage 1 hypertension (SBP 130-139 mmHg) or those in whom the need to initiate pharmacologic anti-hypertensive therapy is uncertain (COR IIb, LOE B).

### 3.3. ABI

ABI is a quick, simple and non-invasive test that measures the ratio of SBP at the ankle and the brachial artery in both arms and legs. A value of < 0.9 or ≥ 1.3 is indicative of PAD, which is caused by the narrowing or blockage of the arteries that supply blood to the legs and feet.[543] While ABI is primarily used for diagnosing PAD, it has also been studied as a potential marker and tool for screening and risk assessment of ASCVD.[544]

Several studies have demonstrated that a low ABI is related to an increased risk of total and cardiovascular mortality, MI, and stroke. It is well established that PAD is a risk factor for other ASCVDs, and that the risk is greater with more advanced PAD. From a systematic review perspective, the specificity of a low ABI to predict future cardiovascular outcomes is high, but its sensitivity is low. ABI should be part of the vascular risk assessment strategy in select individuals.[545,546]

While ABI is categorized as having insufficient evidence for screening and risk stratification of suspected PAD without symptoms, numerous studies in diverse populations have demonstrated an association between low ABI and increased cardiovascular risk.[547] An analysis of data from the 1999-2004 National Health and Nutrition Examination Survey using the PCE for risk estimation, two-thirds of the participants with a low ABI had an intermediate or high risk of ASCVD.[548] In addition, a low ABI was linked to higher all-cause mortality in the overall cohort, and specifically among those with a borderline/intermediate or high risk of ASCVD but not in those with a low risk of ASCVD.[548] These studies suggest that ABI should be considered as a risk enhancer in the primary prevention of ASCVD in individuals classified as having a borderline or intermediate risk of ASCVD.[80,548] Recent studies have shown that the incorporation of ABI into the Framingham Risk Score is a cost-effective strategy, particularly for women classified as having a low or intermediate risk based on Framingham Risk Score alone.[549]

A wealth of local data support the use of ABI for ASCVD risk assessment, with many studies demonstrating its predictive power across different specific groups. For instance, one study found that either ABI alone or a combination of ABI < 0.9 and ABI difference (calculated as right ABI-left ABI) ≥ 0.17 was a significant predictor of overall and cardiovascular mortality.[550] The use of mean arterial pressure instead of SBP in ABI calculations has also been suggested to potentially enhance the accuracy of mortality prediction.[551] In another study of type 2 DM patients mostly without ASCVD, the use of the percentage of mean arterial pressure in combination with ABI was shown to significantly improve the prediction of all-cause mortality.[552] In addition, calculating ABI using DBP and mean arterial pressure may provide additional benefits in predicting survival in patients without known ASCVD undergoing hemodialysis, especially those with normal ABI by SBP.[553] In summary, local data support the usefulness of ABI measurements in predicting ASCVD risk and mortality in specific populations. The combination of ABI with other measures, such as mean arterial pressure, may enhance its predictive power and provide additional benefits in risk assessment. These findings highlight the importance of ABI screening as a tool for ASCVD risk assessment and the need for continued research to explore its potential benefits in different patient populations.

**Key Recommendations**

- ABI should be considered as a risk enhancer for the primary prevention of ASCVD in individuals classified as having a borderline or intermediate risk of ASCVD (COR IIa, LOE B).
- ABI might be considered for cardiovascular outcome assessment in specific populations at a high risk of ASCVD, such as patients with DM or undergoing hemodialysis (COR IIb, LOE C).

### 3.4. Biomarkers

*3.4.1. Inflammatory biomarkers*

Although elevated hsCRP levels are strongly associated with CVD events, the US Preventive Services Task Force suggested that the available evidence is not sufficient to evaluate the overall benefits and risks of incorporating hsCRP testing into the conventional assessment of ASCVD in asymptomatic adults for preventing further events.[364]

Several inflammatory biomarkers have been investigated. GlycA, a quantitative measurement of glycan N-acetylglucosamine residues on enzymatically glycosylated acute-phase proteins using nuclear magnetic resonance, has been correlated with inflammation markers including hsCRP and interleukin-6.[554] It exhibits better precision than hsCRP in predicting ASCVD risk.[554] Large-scale studies have shown that GlycA could independently predict future CVD events,[555-557] and that it was associated with subclinical atherosclerosis.[558,559] However, further investigations are needed before recommending it clinically, including establishing reference ranges.[554] In addition, the accessibility of GlycA is limited compared to CRP. The interpretation of dynamic inflammatory biomarkers should consider the context and serial measurements for identifying concerning trends.[554] Furthermore, myeloperoxidase, lipoprotein-associated phospholipase A2, myeloid-related protein, lectin-like oxidized low-density lipoprotein receptor-1, growth differentiation factor-15, osteoprotegerin and osteopontin have been studied as other potential inflammatory biomarkers.[560,561] Currently, there is insufficient evidence to include these inflammation-relevant biomarkers as risk enhancers in the primary prevention of ASCVD,[560] even though they may be helpful in identifying those at increased ASCVD risk warranting greater efforts for risk reduction using existing therapies.[560]

*3.4.2. Metabolic biomarkers*

Several metabolic biomarkers have been studied. Adiponectin is reduced in obesity, and it improves insulin sensitivity and reduces inflammation. In contrast, resistin is elevated in obesity, and it promotes dysfunction and inflammation. Adipokine dysregulation is linked to DM and ASCVD independently of BMI.[562] Homocysteine, ceramides, dimethylglycine, and choline have also been investigated as other potential metabolic biomarkers.[561] However, measuring these biomarkers is mainly done in research, not clinical practice. Further studies are needed to understand their role in ASCVD risk prediction and treatment monitoring, considering their interplay with lifestyle modifications and other factors.

*3.4.3. Biomarkers of myocardial injury and wall stress*

Previous studies have demonstrated the strong predictive ability of B-type natriuretic peptide level for CVD outcomes. The Framingham Heart Study revealed a significant association between plasma B-type natriuretic peptide levels and first major CVD events.[563] Furthermore, a meta-analysis of 40 long-term prospective studies involving over 87,000 patients indicated that individuals in the highest B-type natriuretic peptide tertile had a 2.8-fold greater risk of CVD events compared to those in the lowest tertile.[564] Similar results have been observed in the general population.[565] However, the improvement in risk discrimination was only modest.[564]

Cardiac troponin level has emerged as a critical component of risk stratification for ACS. With the advent of high-sensitivity assays, precise measurement of cardiac troponin levels in healthy individuals has become possible.[566] Several recent studies have demonstrated a growing association between cardiovascular risk and elevated cardiac troponin concentrations even within the normal range.[567-569] However, the role of cardiac troponins in assessing cardiovascular risk in asymptomatic populations remains a topic of active discussion among experts.[24] There is an urgent need to improve cardiovascular risk assessment in the general population by using cardiac troponins, validate the threshold of these biomarkers in those at high risk, and prove the utility of targeting these high-risk individuals for primary preventive strategies.[567]

*3.4.4. Renal-related biomarkers*

The presence of albuminuria has been linked to long-term all-cause mortality, regardless of Framingham risk.[570] While the addition of a panel of renal biomarkers has been explored for predicting risk, the benefits appear to be limited when compared to using the Framingham Risk Score alone.[570] Furthermore, in patients with CKD, high levels of albuminuria, serum cystatin C, and fibroblast growth factor-23, as well as low eGFR, have been shown to increase CAC progression. These novel risk factors have been shown to be independent of traditional CVD risk factors.[571]

*3.4.5. Novel biomarkers*

Novel biomarkers, including exosomes, microRNAs, and genetic risk scores, have been investigated in the primary prevention of ASCVD.[572,573] By integrating our current understanding of the molecular signatures in high-dimensional molecular data acquisition platforms (such as genome sequencing, epigenomic profiling, transcriptomic analysis, proteomic studies, metabolomic investigations, and gut microbiome characterization), it has become possible to capture snapshots of every phase in the development of ASCVD.[574,575] The future of cardiovascular medicine envisions precision medicine as a promising approach that has the potential to revolutionize the management of CVD.

Numerous biomarkers have been proposed to enhance risk stratification, each with its own potential benefits. Promising advancements have been made in the field of cardiac biomarkers, yet further research is required to fully evaluate their efficacy.

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## DECLARATION OF CONFLICT OF INTEREST

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