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2023 Guidelines of the Taiwan Society of Cardiology on the Diagnosis and Management of Chronic Coronary Syndrome

Kwo-Chang Ueng,[1] Chern-En Chiang,[2,3] Ting-Hsing Chao,[4] Yen-Wen Wu,[3,5] Wen-Lieng Lee,[3,6] Yi-Heng Li,[4] Ke-Hsin Ting,[7] Chun-Hung Su,[1] Hung-Ju Lin,[8] Ta-Chen Su,[8,9] Tsun-Jui Liu,[6] Tsung-Hsien Lin,[10] Po-Chao Hsu,[10] Yu-Chen Wang,[11] Zhih-Cherng Chen,[12] Hsu-Lung Jen,[13] Po-Lin Lin,[14] Feng-You Ko,[15] Hsueh-Wei Yen,[10] Wen-Jone Chen[16] and Charles Jia-Yin Hou[17]**

Coronary artery disease (CAD) covers a wide spectrum from persons who are asymptomatic to those presenting with acute coronary syndromes (ACS) and sudden cardiac death. Coronary atherosclerotic disease is a chronic, progressive process that leads to atherosclerotic plaque development and progression within the epicardial coronary arteries. Being a dynamic process, CAD generally presents with a prolonged stable phase, which may then suddenly become unstable and lead to an acute coronary event. Thus, the concept of "stable CAD" may be misleading, as the risk for acute events continues to exist, despite the use of pharmacological therapies and revascularization. Many advances in coronary care have been made, and guidelines from other international societies have been updated. The 2023 guidelines of the Taiwan Society of Cardiology for CAD introduce a new concept that categorizes the disease entity according to its clinical presentation into acute or chronic coronary syndromes (ACS and CCS, respectively). Previously defined as stable CAD, CCS include a heterogeneous population with or without chest pain, with or without prior ACS, and with or without previous coronary revascularization procedures. As cardiologists, we now face the complexity of CAD, which involves not only the epicardial but also the microcirculatory domains of the coronary circulation and the myocardium. New findings about the development and progression of coronary atherosclerosis have changed the clinical landscape. After a nearly 50-year ischemia-centric paradigm of coronary stenosis, growing evidence indicates that coronary atherosclerosis and its features are both diagnostic and therapeutic targets beyond obstructive CAD. Taken together, these factors have shifted the clinicians' focus from the functional evaluation of coronary ischemia to the anatomic burden of disease. Research over the past decades has strengthened the case for prevention and optimal medical therapy as central interventions in patients with CCS. Even though functional capacity has clear prognostic implications, it does not include the evaluation of non-obstructive lesions, plaque burden or additional risk-modifying factors beyond epicardial coronary stenosis-driven ischemia. The

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[1]Division of Cardiology, Department of Internal Medicine, Chung Shan Medical University Hospital; School of Medicine, Chung Shan Medical University, Taichung; [2]General Clinical Research Center and Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei; [3]School of Medicine, National Yang Ming Chiao Tung University, Taipei; [4]Department of Internal Medicine, National Cheng Kung University Hospital; College of Medicine, National Cheng Kung University, Tainan; [5]Division of Cardiology, Cardiovascular Medical Center, Far Eastern Memorial Hospital, New Taipei City; [6]Cardiovascular Center, Taichung Veterans General Hospital, Taichung; [7]Division of Cardiology, Department of Internal Medicine, Yunlin Christian Hospital, Yunlin; [8]Cardiovascular Center, Department of Internal Medicine, National Taiwan University Hospital; [9]Department of Environmental and Occupational Medicine, National Taiwan University College of Medicine, Taipei; [10]Division of Cardiology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung; [11]Division of Cardiology, Asia University Hospital, Department of Medical Laboratory Science and Biotechnology, Asia University, Taichung; [12]Division of Cardiology, Department of Internal Medicine, Chi-Mei Medical Center, Tainan; [13]Division of Cardiology, Cheng Hsin Rehabilitation Medical Center, Taipei; [14]Division of Cardiology, Hsinchu MacKay Memorial Hospital, Hsinchu; [15]Cardiovascular Center, Kaohsiung Veterans General Hospital, Kaohsiung; [16]Division of Cardiology, Department of Internal Medicine, Min Sheng General Hospital, Taoyuan; [17]Cardiovascular Center, Department of Internal Medicine, MacKay Memorial Hospital; Department of Medicine, Mackay Medical College, New Taipei City, Taiwan.
Corresponding author: Dr. Chern-En Chiang, MD, PhD, Division of Cardiology; Director, General Clinical Research Center, Department of Medical Research and Education, Taipei Veterans General Hospital; Professor of Medicine, National Yang-Ming University, No. 201, Shih-Pai Road, Section 2, Taipei, Taiwan. Tel: 886-2-2875-7774; Fax: 886-2-2872-3191; E-mail: cechiang@vghtpe.gov.tw
* Charles Jia-Yin Hou and Chern-En Chiang jointly supervised this work and serve as corresponding authors.

recommended first-line diagnostic tests for CCS now include coronary computed tomographic angiography, an increasingly used anatomic imaging modality capable of detecting not only obstructive but also non-obstructive coronary plaques that may be missed with stress testing. This non-invasive anatomical modality improves risk assessment and potentially allows for the appropriate allocation of preventive therapies. Initial invasive strategies cannot improve mortality or the risk of myocardial infarction. Emphasis should be placed on optimizing the control of risk factors through preventive measures, and invasive strategies should be reserved for highly selected patients with refractory symptoms, high ischemic burden, high-risk anatomies, and hemodynamically significant lesions. These guidelines provide current evidence-based diagnosis and treatment recommendations. However, the guidelines are not mandatory, and members of the Task Force fully realize that the treatment of CCS should be individualized to address each patient's circumstances. Ultimately, the decision of healthcare professionals is most important in clinical practice.

Key Words: Coronary • Diagnosis • Guidelines • Treatment

Abbreviations

ACC/AHA	American College of Cardiology/American Heart Association
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AMI	Acute myocardial infarction
ASCVD	Atherosclerotic cardiovascular disease
BARC	Bleeding Academic Research Consortium
BMS	Bare metal stent
BP	Blood pressure
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CAC	Coronary artery calcium (calcification)
CCS	Chronic coronary syndrome
CCTA	Coronary computed tomography angiography
CFR	Coronary flow reserve
CI	Confidence interval
CKD	Chronic kidney disease
CMD	Coronary microvascular dysfunction
CMR	Cardiac magnetic resonance imaging
COR	Class of recommendation
CT	Computed tomography
CV	Cardiovascular
CVD	Cardiovascular disease
CYP2C19	Cytochrome P450 family 2 subfamily C member 19
CZT	cadmium zinc telluride
DAPT	Dual antiplatelet therapy
DES	Drug-eluting stent
DPI	Dual pathway inhibition
DPP4	Dipeptidyl peptidase 4
ECG	Electrocardiography
EF	Ejection fraction
eGFR	Estimated Glomerular filtration rate
ESC	European Society of Cardiology
FFR	Fractional flow reserve
FFR-CT	Fractional flow reserve by computed tomography
FRS	Framingham Risk Score
GLP-1	Glucagon-like peptide-1
HDL-C	High-density lipoprotein cholesterol
HR	Hazard ratio
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
Hs-CRP	High sensitivity C-reactive protein
hs-TnI or hs-TnT	High-sensitive cardiac troponin
ICA	Invasive coronary angiography
IL	Interleukin
INOCA	Ischemia with no obstructive coronary artery disease
ISTH	International Society on Thrombosis and Hemostasis
iwFR	Instantaneous wave-free ratio
IVUS	Intravascular ultrasound
LAD	Left anterior descending artery
LBBB	Left bundle branch block
LDL-C	Low-density lipoprotein cholesterol
LOE	Level of evidence
LM	Left main
LSM	Lifestyle modification
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac event
MACCE	Major adverse cardiac and cerebrovascular event
MET	Metabolic equivalent
MI	Myocardial infarction
MPI	Myocardial perfusion imaging
MRI	Magnetic resonance imaging
MVA	Microvascular angina
MVD	Multiple vessel disease
NG-DES	New-generation drug eluting stents

NHI	National Health Insurance
NICE	National Institute for Health and Care Excellence
NOAC	Novel oral anticoagulants
NPV	Negative predictive value
NSTE-ACS	Non-ST elevationacute coronary syndrome
NT-proBNP	N terminal-pro B type natriuretic peptide
OCT	Optical coherence tomography
OMT	Optimal medical therapy
OR	Odds ratio
PAD	Peripheral artery disease
PCE	Pooled Cohort Equation risk calculator
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin-kexin type 9
PET	Positron emission tomography
PT INR	Prothrombin time-international normalized ratio
PTP	Pretest probability
P2Y12	Purinergic receptor type Y, subtype 12
QoL	Quality of life
RCT	Randomized controlled trial
RR	Relative risk; Risk ratio
SCD	Sudden cardiac death
SCORE	Systematic COronary Risk Evaluation
SPECT	Single photon emission tomography
SGLT2	Sodium-glucose cotransporter 2
SYNTAX	SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery
STEMI	ST-segment elevation myocardial infarction
TG	Triglyceride
TIMI	Thrombolysis in Myocardial Infarction
TSOC	Taiwan Society of Cardiology
TwCCCC	Taiwan Chin-Shan Community Cardiovascular Cohort
3P-MACE	3-point major adverse cardiovascular events

1. INTRODUCTION, EPIDEMIOLOGY, AND PROGNOSIS

Cardiovascular disease (CVD) remains the leading cause of mortality, and importantly coronary artery disease (CAD) is the most common cause of premature and avoidable death worldwide.[1,2] In 2019, CVDs accounted for 27.5% of all deaths in Taiwan, making it the second highest cause of death behind total cancer at 28.6%. In Taiwan, more than 17,000 people die of CAD each year.[3] As CAD is so multifaceted, its prevalence and incidence have been difficult to assess and numbers vary between studies depending on the definition that has been used. The prevalence of so-called "stable angina" increases with age, ranging from 4% to 7% in adults aged 40 to 79 years to greater than 10% in those older than 80 years.[4] The average annual risk of death or myocardial infarction (MI) among CAD patients receiving medical therapy is approximately 3% to 4% per year, with generally consistent findings from previous registries and randomized controlled trials (RCTs).[5-8] The CLARIFY registry, a multicentric study conducted between 2009 and 2010 in 45 countries, reported 32,703 CAD patients with 5-year nonfatal MI or cardiovascular (CV) death rate of around 8.0% under evidence-based secondary prevention.[9] Furthermore, patients with prior MI and more frequent or severe angina were more prone to developing the primary event (11.8%) compared to those without angina. The past decades have seen tremendous progress in elucidating mechanisms leading to acute coronary events and sudden cardiac death (SCD). Of note, a large proportion of patients with SCD or nonfatal MI do not experience prior symptoms of chest pain or exertional dyspnea, emphasizing the importance of early detection and treatment of underlying subclinical coronary atherosclerosis. Autopsy data have revealed that most culprit lesions in patients dying of SCD have angiographic lumen diameter stenosis of 40% to 69% which may not be detected by stress test prior to thrombotic occlusion.[10] Acute coronary events are commonly not caused by slow, progressive arterial lumen narrowing, but rather by sudden flow obstruction due to plaque disruption-associated coronary thrombosis, with culprit lesions being non-obstructive before the events. On the other hand, some patients even with advanced occlusive lesions may be asymptomatic, and thus early detection and treatment of both obstructive and non-obstructive lesions can reduce the risk of MI and/or death.

2. TERMINOLOGY AND DEFINITION OF CHRONIC CORONARY SYNDROME

CAD has many different facets and is a dynamic process of plaque accumulation and functional changes in coronary circulation that can be modified by medical intervention. To reflect the dynamic nature of the syndrome, the term "chronic coronary syndrome" (CCS) was introduced to replace the previous terms "stable coronary artery disease" or "stable angina" in these

guidelines. The change in nomenclature emphasizes the fact that CAD is a continuous and dynamic atherosclerotic process involving intravascular plaque accumulation, whether obstructive or non-obstructive. The natural pathogenesis of CAD gives us some insight into why this disease is never really "stable". The term "stable" is usually used to describe characteristics of plaque disease, however some patients with CAD do not have plaque disease, with the etiology of their CAD being epicardial coronary artery spasm or microvascular dysfunction. Moreover, the term "stable" implies that these patients are low risk and that there is less urgency to initiate optimal medical treatment (OMT) or lifestyle modification (LSM). This results in a disease process that can have long, stable periods, but can also become unstable, mainly due to an acute atherothrombotic event caused by plaque rupture or erosion, at any time. Specifically, CCS encompass clinical scenarios in subjects with suspected or established CCS (Figure 1), including the following 6 entities:

1. Patients with stable chest pain with/without dyspnea and suspected CAD.
2. New-onset heart failure (HF) with or without reduced ejection fraction (EF) in patients with suspected CAD.
3. Patients with stabilized symptoms after an initial acute coronary syndrome (ACS) diagnosis or revascularization procedure.
4. Patients with vasospastic angina (variant angina).
5. Patients with microvascular dysfunction.
6. Asymptomatic patients in whom screening detects CAD.

Hence, CCS can better reflect the heterogeneous pathophysiology of the coronary circulation. Using this new term, CAD can be categorized as either ACS or CCS. The scope of the present guidelines, therefore, spans from asymptomatic subjects to individuals after stabilization of an ACS. Indeed, patients who present with unstable angina symptoms would be classified into the ACS category and follow a different clinical assessment route. The main pathological process of CCS includes that of CAD characterized by obstructive or non-obstructive atherosclerotic plaque formation in the epicardial arteries. Specifically, the risk of CAD can change over time and, of course, decrease with the appropriate use of secondary prevention actions and revascularization. In addition, it also includes microvascular and/or vasospastic coronary disease without epicardial coronary disease.

3. GUIDELINE DEVELOPMENT PROCESS AND PURPOSE

In 2021, the Executive Board of Taiwan Society of Cardiology (TSOC) decided to develop the first clinical practice guidelines for CCS in Taiwan. The members of this writing group were selected by the chairperson of the Preventive Medicine Committee of TSOC. To prevent the risk of spreading coronavirus disease 2019 (COVID-19), three online meetings were held before starting to draft the guidelines in March 27, April 10 and April 24, 2021. Clinical evidence was reviewed and consensus about the diagnosis and treatment of CCS were achieved during the meetings. Since then, several sympo-

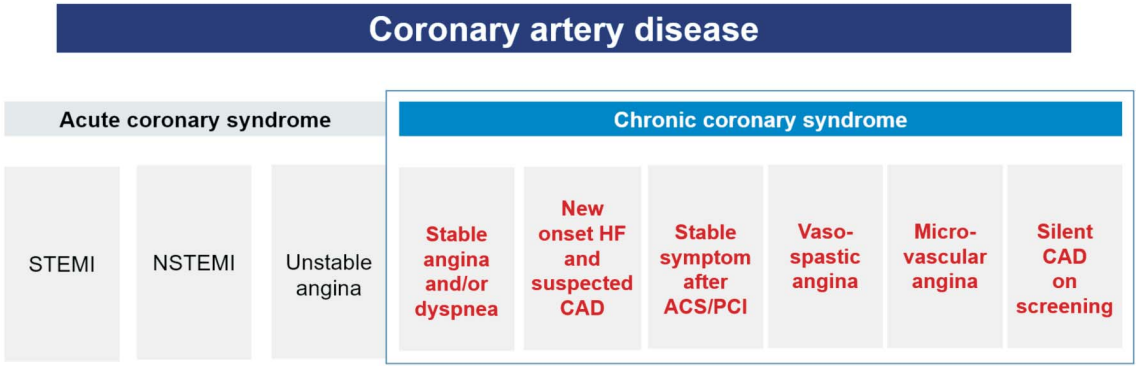


Figure 1. *Terminology and definition of chronic coronary syndrome. ACS, acute coronary syndrome; CAD, coronary artery disease; HF, heart failure; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.*

siums have been held throughout Taiwan to review the recommendations suggested in the draft guidelines. Modifications of the draft guidelines were performed according to the opinions raised in these symposiums. A total of 101 recommendations are presented in Table 1. The top 10 key messages and highlights from these guidelines are summarized in Table 2. These guidelines aim to assist decision-making in clinical practice, based on the best available evidence to assist healthcare professionals provide the best management for CCS in Taiwan. However, they are not intended to define a standard of care and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice.

4. GRADE OF RECOMMENDATION AND LEVEL OF EVIDENCE

In these guidelines, the classes of recommendation (CORs) and levels of evidence (LOEs) (Table 3) are defined as follows. CORs are used to indicate whether a recommendation or suggestion is useful or harmful. Class I recommendations indicate they are useful and should be used. Class III recommendations indicate they are harmful and should not be done. Class IIa indicates that the evidence favors the recommendations; while class IIb indicates that the recommendations are less well established. LOEs are used to denote the strength of evidence supporting the recommendations. LOE A indicates that multiple randomized trials or meta-analyses of high-quality RCTs support the recommendations. LOE B indicates that only one RCT or large non-randomized studies, meta-analyses of moderate-quality RCTs or non-randomized studies support the recommendations. LOE C indicates that only small studies, post-hoc analyses, retrospective studies, cohort studies, registries, subgroup analyses, or consensus of expert opinion suggest the recommendations.

5. ASSESSMENT AND DIAGNOSIS

The diagnosis and assessment of CCS involves clinical evaluation and specific cardiac investigations such as stress testing or coronary imaging. These investigations may be used to confirm the diagnosis of ischemia and also for prognostic assessments in patients with suspected CCS, to identify or exclude associated clinical conditions, assist in stratifying risk, and evaluate the efficacy of treatment.

5.1 Assessment of risk and severity in symptomatic patients with suspected CCS

Appropriate risk stratification of patients presenting with stable chest pain or its equivalent (mainly dyspnea) is crucial not only for the individual but also for healthcare systems. The evaluation of CCS is complex, requiring a comprehensive clinical assessment of risk, stratification with pretest probability (PTP), and appropriate choice of non-invasive diagnostic testing. A focused examination is necessary to evaluate physical findings suggestive of non-atherosclerotic causes of chest pain and/or dyspnea such as aortic stenosis, hypertrophic cardiomyopathy, or pulmonary hypertension. Resting electrocardiography (ECG) should be performed to screen for prior infarction or left ventricular (LV) hypertrophy. A normal ECG does not exclude the diagnosis, but an abnormal resting ECG increases the probability and might influence the choice of diagnostic tests. A chest x-ray is helpful in cases of atypical symptoms, suspected HF or pulmonary disease, but does not provide specific information for the diagnosis of CCS or risk stratification.

5.1.1 Patients with chest pain and/or dyspnea suspected of having CCS

Angina or angina equivalent is the most common presentation in patients with suspected CCS. Chronic chest pain can arise from cardiac and noncardiac etiologies. While there are multiple potential noncardiac causes of chest pain such as costochondritis, arthritic or degenerative diseases, prior trauma, primary or metastatic tumors, pleural disease, or gastrointestinal causes, the scope of these guidelines is focused on evaluating chest pain when a cardiac etiology is the concern. A detailed history is of paramount importance. The four-level grading system from the Canadian Cardiovascular Society has been used for decades, with higher grades reflecting significantly more limitations due to angina. Angina is classified into three categories according to the clinical

Table 1. Summary of COR and LOE in the 2023 TSOC-CCS guidelines

Recommendations	COR	LOE
Cardiac biomarkers for CCS		
• Not all symptomatic patients with CCS maintain in the stable condition, troponin (especially high sensitivity assays) should be measured to detect the instability of CCS or ACS.	I	A
CAC for symptomatic patients with suspected CCS		
• CAC should be considered for a risk modifier in symptomatic patients with low-intermediate PTP of obstructive CAD.	IIa	B
• CAC is not recommended in patients with high-risk features to identify symptomatic individuals with obstructive CAD.	III	B
• CAC is not recommended for patients with previously documented CAD.	III	C
• CAC zero cannot exclude obstructive CAD in symptomatic patients with high PTP of CAD.	III	B
CCTA for symptomatic patients with suspected CCS		
• CCTA is recommended as the initial test to diagnose CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone.	I	B
• CCTA may be considered as an alternative to ICA if another non-invasive test is equivocal or non-diagnostic.	IIb	C
• CCTA may be considered as an alternative to ICA to screen CAD in patients with HFrEF.	IIb	B
• A reduction in coronary arterial luminal diameter of ≥ 50% on CCTA should require further non-invasive stress testing.	I	A
• Significant stenosis (≥ 50%) of the LM coronary artery, high-grade (≥ 80% stenosis) of the proximal LAD or three-vessel obstructive disease indicates high risk and should consider ICA.	IIa	B
• FFR-CT should be considered in the determination of hemodynamic relevance of coronary stenosis.	IIa	B
Physiology-guided PCI		
• OMT is recommended before considering ICAand ≥ 2 anti-anginal drugs should be used.	IIa	B
• Invasive strategy for CCS patients fulfilling the appropriate criteria for ICA is associated with a significant improvement in anginal symptoms and angina-related health status outcomes than OMT alone, especially in patients with more severe angina.	I	A
• Routine invasive strategy for CCS patients with advanced CKD is not recommended.	III	B
• Routine invasive strategy is not recommended in CCS patients for reducing total death, CV death, or MI.	III	A
• A FFR ≤ 0.8 or an iwFR ≤ 0.89 indicates a high-risk lesion.	I	A
• Invasive strategy should be considered in CCS patients with high-risk features related to LV dysfunction (LVEF < 35%), coronary anatomy (LM or MVD with proximal epicardial lesions), or functional ischemia assessment (high peak stress wall motion index score > 1.7 by stress echo or large ischemic myocardium by stress tests (> 10%).	IIa	B
Coronary revascularization for CCS		
• In CCS patients with undetermined ischemia, and angiographically intermediate stenoses, the use of FFR or iwFR is recommended to guide the decision to proceed to PCI.	I	A
• In CCS patients with LM stenosis or MVD with a SYNTAX score > 32 and LVEF < 35%, CABG should be considered for preferred revascularization option.	IIa	B
• CABG may be considered for the preferred option even in the presence of a lower SYNTAX score when multiple complex lesions are present, and PCI remains technically limited to achieve complete revascularization.	IIb	B
• In selected patients with CCS and 1- or 2-vessel disease involving the proximal LAD, isolated ostial or shaft LM disease, and MVD with simple lesions (a SYNTAX score < 23), PCI should be considered.	IIa	B
• For patients with significant LM disease and a SYNTAX score > 32, CABG is better than PCI to improve survival.	I	A
• PCI can be considered but tends to be inferior to CABG for a distal LM (bifurcation) lesion, especially in combination with MVD and a SYNTAX score of < 32.	IIa	B

Table 1. Continued

Screening for CCS in apparently healthy individuals without known ASCVD		
Screening for CCS in asymptomatic patients with diabetes above age 40		
• Routine screening for CAD is not recommended in asymptomatic patients with diabetes.	III	A
• Screening for silent CAD by noninvasive stress tests may be considered in selected high-risk diabetic patients with PAD, CKD with eGFR < 60 ml/min/1.73 m^2 or, proteinuria, or a high CAC score (i.e., ≥ 400).	IIb	C
Taiwan CAD risk calculator in the primary prevention		
• After the age of 40, it is reasonable to assess traditional CAD risk factors.	IIa	A
• For adults 40 to 75 years of age without established ASCVD, chronic inflammatory diseases, diabetes, CKD with eGFR < 60 ml/min/1.73 m^2), or a family history of premature MI, clinicians should consider assessment of traditional risk factors and calculate 10-year risk of CAD by using the TwCCCC risk charts.	IIa,	B
Exercise ECG for screening for CCS in asymptomatic adults		
• Exercise ECG is not recommended in low-risk, asymptomatic adults (10-year CAD risk < 3%), as determined by TwCCCC charts.	III	B
• Exercise ECG, if tolerated, should be considered for the preferred test in asymptomatic adults at intermediate-high risk (10-year CAD risk, > 7%), as determined by TwCCCC chart.	IIa	C
CAC for screening for CCS in asymptomatic adults		
• CAC score may be considered as risk modifier in the CV risk assessment of asymptomatic individuals at low-moderate risk.	IIb	B
• CAC score is not recommended for asymptomatic patients who are at high risk.	I	B
CAC-guided statin use		
• If the CAC score is zero, aspirin or statin therapy is not indicated in asymptomatic low-intermediate risk adults.	III	C
• If the CAC score is 1-99, statin therapy may be considered for primary prevention.	IIb	B
• If the CACscore is 1-99, aspirin therapy may be considered for primary prevention in those with low bleeding risk.	IIb	C
• For asymptomatic adults with CAC 100-399, statins use may be considered if they are above 75th centile for age and gender.	IIb	B
• For asymptomatic patients with CAC 100-399 and low bleeding risk, aspirin may be considered if they are above 75th percentile for age and gender.	IIb	B
• For asymptomatic subjects, if the CAC score is ≥ 400 or ≥ 75th percentile, statin therapy should be considered.	IIa	B
• For asymptomatic subjects, if the CAC score is ≥ 400 and low bleeding risk, aspirin therapy may be considered.	IIb	B
CCTA for screening for CCS in asymptomatic adults		
• In low-risk asymptomatic adults (TwCCCC 10-year CAD risk < 3%), CCTA is not indicated not indicated for CV risk assessment.	III	C
• In intermediate-high risk asymptomatic adults (TwCCCC 10-year CAD risk > 7%), CCTA may be considered for CV risk assessment.	IIb	C
• In high-risk asymptomatic adults (diabetes, strong family history of CAD, high risk of CAD in noninvasive tests, TwCCCC 10-year risk > 10%), CCTA should be considered for CV risk assessment.	IIa	C
CCTA for screening for CCS in asymptomatic diabetic adults		
• In high-risk asymptomatic adults with diabetes (e.g., with a strong family history of MI, multiple risk factors, PAD, CKD with eGFR < 60 ml/min/1.73 m^2, stress test for myocardial ischemia may be considered for CAD risk assessment.	IIa	B
CCTA-guided medical therapy in primary prevention		
• If the was no plaques in CCTA, aspirin or statin therapy is not indicated in asymptomatic low-intermediate risk adults.	III	B
• If non-obstructive plaques with SIS score > 4 in CCTA, aspirin therapy may be considered for primary prevention in asymptomatic adults with low bleeding risk.	IIb	B
• If non-obstructive plaques with SIS score > 4 in CCTA, statin therapy should be considered for primary prevention.	IIa	B

Table 1. Continued

Screening for CCS in apparently healthy individuals without known ASCVD		
LDL-C target for CCS patients		
• In general, the LDL-C target is < 70 mg/dl in CCS patients.	I	B
• In extreme-risk CCS patients, defined with recent MI (< 12 months), multiple prior MIs, MVD disease, post-ACS plus diabetes, or CAD with polyvascular disease (including extremity or carotid artery), a lower target of LDL-C < 50 mg/dl should be considered.	IIa	A
Upfront combination of statin and non-statin agents in CCS patients at extreme risks		
• Moderate-high intensity statin is the first-line treatment for CCS.	I	A
• Moderate-intensity statin plus ezetimibe can be used as the first-line treatment, especially if patient's general condition is not suitable for or cannot tolerate high-intensity statin.	IIa	B
• PCSK9 inhibitor is considered if LDL-C target is not achieved after combination therapy of high-intensity statin and ezetimibe, or statin intolerance occurs.	I	B
• Earlier initiation of PCSK9 inhibitor should be considered if LDL-C target is not achieved after statin plus ezetimibe therapy in CCS patients with extreme risk conditions.	IIa	B
• In extreme risk CCS patients, upfront combination treatment of high intensity statins first with ezetimibe and then a PCSK9 inhibitor to achieve the target < 50 mg/dl should be considered.	IIa	A
Pharmacological treatment of diabetes in CCS		
• For patients with CCS and diabetes, the target HbA1c is < 7.0%.	I	C
• GLP1 receptor agonists and SGLT2 inhibitors are preferred medications in patients with CCS and diabetes.	I	A
• Patients with CCS and a history of HF or CKD, SGLT2 inhibitors are preferred medications.	I	A
• Patients with CCS and a history of ischemic stroke, GLP-1 receptor agonists are more effective than SGLT2 inhibitors.	IIa	B
BP target for CCS patients		
• For CCS patients with hypertension, BP targets are < 130/80 mmHg, using the home BP monitoring [preferred].	I	A
Pharmacological treatment of hypertension in CCS		
• For hypertensive subjects with symptomatic angina, β-blockers and/or CCBs are recommended.	IIa	C
• For hypertensive CCS patients with previous MI or HFrEF, β-blockers, RAS inhibitors, and aldosterone receptor antagonists are preferred.	I	A
• For subjects with a requirement for multiple anti-hypertensive agents for BP control, the combination of a RAS inhibitor and a dihydropyridine CCB may be preferable to a RAS inhibitor and a thiazide/thiazide-like diuretic.	IIa	B
• The combination of a β-blocker and either of the non-dihydropyridine CCBs (diltiazem or verapamil) should be used with caution in patients with symptomatic CCS and hypertension because of the increased risk of significant bradyarrhythmia and HF.	IIb	C
• Short-acting dihydropyridine CCBs should not be used for long-term therapy because of their potential to increase mortality.	III	B
Anti-platelet drugs in CCS without PCI		
• Aspirin 75-100 mg daily is recommended in CCS patients with previous MI, stroke or PAD.	I	A
• Clopidogrel 75 mg daily may be considered in preference to aspirin in CCS patients with either PAD or a history of ischemic stroke.	IIb	B
• Routine DAPT therapy for CCS patients without PCI is not recommended.	III	B

Table 1. Continued

Screening for CCS in apparently healthy individuals without known ASCVD		
Anti-platelet drugs in CCS after PCI		
• Life-long aspirin use is recommended unless contraindicated in patients with CCS undergoing PCI.	I	A
• Monotherapy with P2Y12 receptor inhibitor should be considered when aspirin is contraindicated in patients with CCS undergoing PCI.	IIa	B
• In patients with CCS treated with PCI with NG-DES implantation, 1-3 months' DAPT with P2Y12 receptor inhibitor in addition to aspirin is recommended.	I	A
• Shortening of DAPT to 1-3 months should be considered for patients with HBR in patients with CCS undergoing PCI.	IIa	B
• Monotherapy with P2Y12 receptor inhibitor should be considered in CCS patients with low thrombotic risk and HBR following 1-3 months' DAPT after PCI.	IIa	A
• In patients with previous MI who are at low bleeding and high thrombotic risk, extended DAPT with ticagrelor 60 mg twice daily in addition to aspirin for > 12 months and < 36 months should be considered.	IIa	B
Oral anticoagulant		
• Adding rivaroxaban 2.5 mg twice per day to aspirin 100 mg once daily may be considered in CCS (without AF) patients with high ischemic risk and without HBR for long-term secondary prevention.	IIb	B
• Routine use of warfarin as an alternative or add-on therapy to aspirin in CCS patients is not recommended.	III	A
Diet modification		
• A diet highlighting intake of plant-based and high in fruit, nuts, vegetable, legume, fiber and lean vegetable or animal protein (preferably fish) consumption is recommended to decrease CAD risk.	I	B
• Minimizing intake of processed meats, and replacement of saturated fat with dietary monounsaturated and polyunsaturated fats can be beneficial to reduce CAD risk.	IIa	B
• A diet containing reduced amounts of sodium can be beneficial to decrease CAD risk.	IIa	B
• As a part of a healthy diet, the intake of trans fats should be avoided to reduce CAD risk.	III	B
Alcohol consumption		
• Individuals who do not have a habit of alcohol consumption should avoid starting drinking for any reason.	I	C
• Alcohol drinking 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 or AAFS. (One drink = 14 g pure alcohol)	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 or AAFS.	IIa	B
Physical activity		
• Asymptomatic patients should have accumulated moderate-intensity of physical activity of at least 150 minutes per week or vigorous-intensity physical activity 75 minutes per weeks.	I	B
• Physical activity counseling is considered beneficial for those with pervious sedentary life and high-risk patients. Cardiac rehabilitation program is indicated to improve the compliance and persistence.	I	B
• Education for symptoms management during physical activity should be considered.	IIa	C
Sexual activity		
• Sexual activity is acceptable for those who can perform physical activities more than 3 to 5 METs without symptoms, such as angina, excessive dyspnea, hypotension or arrhythmia.	IIa	B

Table 1. Continued

Screening for CCS in apparently healthy individuals without known ASCVD		
Psychological interventions		
• Acute and chronic stress are risk factors for the development and progression of coronary atherosclerosis.	IIa	B
• For patients with CCS, the stress management training should be considered as a part of routine cardiac rehabilitation.	IIb	B
Smoking cessation		
• As a recommendation to reduce the risk of ASCVD, smoking cessation should be indicated to individuals with CCS.	I	A
• To reduce the risk of ASCVD, all subjects with CCS are advised to avoid exposure to secondhand smoke.	III	A
• As a method of smoking cessation, E-cigarette should not be recommended.	I	B
• Varenicline over a nicotine patch and bupropion for nicotine-dependent adults in whom treatment is being initiated.	I	A
Pneumococcal vaccination		
• Annual influenza vaccination is recommended for patients with CCS, especially in the elderly.	I	B
• In adults ≥ 65 years of age who have not previously received a pneumococcal vaccine, the administration of PCV13 followed by PPV23 one year or later is recommended.	I	B
• In adults who have been vaccinated PPV23 after the age of 65, the administration of PCV13 is recommended at least one year following the PPV23 dose.	I	B
• In adults who received PPV23 before age 65 years who are now ≥ 65 years of age at the time of their visit should receive a dose of PCV13 at least one year after their last PPV23, followed by a dose of PPV23 at least one year after the PCV13 dose and at least five years following the previous PPV23 dose.	I	B
• For adults over 19 years of age and under 65 years of age with CCS, the administration of PCV13 followed by PPV23 eight weeks or later is recommended.	I	B
Dietary supplements and nutraceuticals		
• For high-risk population (i.e., patients with ASCVD, or diabetes with additional risk factor) under statin treatment, high-dose EPA should be considered if TG level (> 150 mg/dl).	IIa	B
• Red yeast could be considered for secondary prevention without background statin treatment.	IIb	B
• CoQ10, vitamin C, D, E and multivitamin are not recommended for CAD prevention.	III	A
Ambient fine particulate matter exposure		
• Both Long-term and short-term ambient $PM_{2.5}$ exposure increase the risk of CAD.	I	A
• Reducing ambient $PM_{2.5}$ exposure may benefit human health with longer life expectancy in patients with CAD.	IIa	B
Recommendation classes		
Class I	**Class IIa**	**Class IIb**	**Class III**

AAFS, Asian alcohol flushing syndrome; ACS, acute coronary syndrome; AF, atrial fibrillation; ALDH2, aldehyde dehydrogenase 2 family member; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CABG, coronary artery bypass graft surgery; CAC, coronary artery calcium; CAD, coronary artery disease; CCB, calcium channel blocker; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CKD, chronic kidney disease; COR, classes of recommendation; CT, computed tomography; CV, cardiovascular; DAPT, dual antiplatelet therapy; ECG, electrocardiography; eGFR; estimated glomerular filtration rate; EPA, eicosapentaenoic acid; FFR, fractional flow reserve; GLP-1,glucagon-like peptide-1; HbA1c, glycated hemoglobin; HBR, high bleeding risk; HFrEF, heart failure with reduced ejection fraction; ICA, invasive coronary angiography; iwFR, instantaneous wave-free ratio; LAD, left anterior descending; LDL-C, low-density lipoprotein cholesterol; LM, left main; LOE, levels of evidence; LV, left ventricular; LVEF, left ventricular ejection fraction; MET, metabolic equivalent; MI, myocardial infarction; MVD, multiple vessel disease; NG-DES, new-generation drug eluting stents; OMT, optimal medical therapy; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin-kexin type 9; PCV13, 13-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine; $PM_{2.5}$, particulate matter of 2.5 μm; PTP, pretest probability; P2Y12, purinergic receptor type Y, subtype 12; RAS, renin-angiotensin system; SGLT2, sodium-glucose cotransporter 2; SIS, segment involvement score; SYNTAX, SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery; TSOC, Taiwan Society of Cardiology; TG, triglyceride; TwCCCC, Taiwan Chin-Shan Community Cardiovascular Cohort; TZD, thiazolidinedione.

Table 2. The top-10 key messages/highlights from the 2023 TSOC CCS guidelines

1. The most important aspect of 2023 TSOC guidelines is the adoption of a "new" classification of CAD, categorizing the entity as either ACS or CCS. The new terminology of CCS was introduced to replace the previous "stable coronary artery disease" or "stable angina" to highlight the dynamic nature of the CAD process. CCS have been classified into 6 separate entities, each of which have an impact on further studies and management.
2. That the majority of MIs occur in patients without ischemia or stenosis – along with the observed outcomes benefit for patients undergoing CCTA stemming from improved preventive treatment – emphasizes a new approach beyond the "stenosis" "ischemia" paradigm to incorporate all measures of atherosclerosis, and to leverage CCTA unique ability to noninvasively perform all-round assessment of whole heart. CCTA can be selected an effective first-line test in patients with suspected CCS. The CCTA-first strategy may aid in early diagnosis, provides evidence of presence and extent of plaque, guides intensification of preventive measures, and eventfully improve outcomes.
3. Initial invasive strategy for CCS cannot improve mortality or risk of MI. Emphasis should be placed on optimizing risk factors control by preventive measures. Invasive strategy be only considered in CCS patients with persistent symptoms despite OMT, high ischemic territories ≥ 10% of the LV myocardium on stress test, high-risk anatomy features (LM stenosis ≥ 50% stenosis, proximal-LAD ≥ 80% stenosis or significant MVD on CCTA), and/or clinically HFrEF with suspicion of ischemic cardiomyopathy.
4. Lumen stenosis should not be the sole method for defining CAD severity and risk. Invasive functional testing is state of the art for evaluation of CAD with borderline stenosis. A FFR ≤ 0.8 or an iwFR ≤ 0.89 indicates a high-risk lesion. Revascularization decisions in high-risk patients with diabetes, LM disease, and complex MVD are optimized using a heart team approach with consideration of LV function, disease complexity and technical feasibility of treatment and patient preferences.
5. For primary prevention, the TSOC guidelines recommend use of the TwCCCC risk calculator to estimate the 10-year CAD risk in Taiwan. To facilitate routine clinical practice, this risk calculator is available at website (http://140.112.117.151/klchien/).
6. The guidelines emphasizes the paramount importance of comprehensive LSM plus OMT interventions for all CCS patients, summarized as "ABCDE-PS2": Antiplatelet therapy, BP target < 130 mmHg, LDL-Cholesterol control to target, Diet adaptation, Exercise adoption, less PM2.5 exposure, Smoking cessation, and less Stress.
7. In general, the LDL-C target is < 70 mg/dl in CCS all patients. In particular, new LDL-C target < 50 mg/dl is recommended for CCS patients at extreme risk, defined as clinical settings with a history of recent ACS, multiple prior MIs, MVD, post-ACS plus diabetes, or polyvascular disease with concomitant PAD. In such patients, upfront combination treatment of high intensity statins first with ezetimibe and then a PCSK9 inhibitor to achieve the target should be considered.
8. New to the guidelines is the continued use of long-term antithrombotic therapy in those considered to be very high ischemic and low bleeding risk with prolonged DAPT in the form of aspirin and a P2Y12 inhibitor or DPI with aspirin plus very low dose rivaroxaban. A one-size-fits-all approach is not suited to antithrombotic therapies for East Asian patients with CCS. A careful and individualized assessment of ischemic and bleeding risks is always recommended to determine the antithrombotic strategy for all CCS.
9. The aims of pharmacological therapy for CCS should include symptom relief, improved QoL and CV outcomes. As a novelty, the guidelines propose a tailored 3-step approach beyond the angina paradigm for the medical treatment of patients taking into consideration the comorbidities of patients as well as the pathophysiology of myocardial ischemia. Such approach would have additional cardiac benefits beyond angina relief.
10. In the absence of obstructive CAD, abnormality of stress tests in patients with CCS may indicate INOCA. INOCA is associated with a higher risk of adverse outcome, it has been often misdiagnosed as noncardiac because of limited understanding of disease entity and diagnostic challenges. The application of suggested invasive diagnostic methods is recommended.

ACS, acute coronary syndrome; BP, blood pressure; CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CV, cardiovascular; DAPT, dual antiplatelet therapy; DPI, dual pathway inhibition; FFR, fractional flow reserve; HFrEF, heart failure with reduced ejection fraction; INOCA, Ischemia and no obstructive coronary artery disease; iwFR, instantaneous wave-free ratio; LAD, left anterior descending; LDL-C, Low-density lipoprotein cholesterol; LM, left main; LSM, lifestyle modification; LV, left ventricular; MVD, multiple vessel disease; OMT, optimal medical therapy; PAD, peripheral artery disease; PCSK9, proprotein convertase subtilisin-kexin type 9; P2Y12, purinergic receptor type Y, subtype 12; QoL, quality of life; TSOC, Taiwan Society of Cardiology; TwCCCC, Taiwan Chin-Shan Community Cardiovascular Cohort.

features regarding the location, characteristic, relationship with exertion, and precipitating/alleviating factors. Although occurring in only 10-15% of CAD patients,[11] typical angina has the three following characteristics: tightness/discomfort over the precordial area, or in the neck, jaw, shoulder, or arm; precipitated by exertion;

Table 3. The TSOC classes of recommendation and levels of evidence

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 • Is indicated • 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 • Should be considered • Can be performed
Class IIb (Benefit ≥ Risk)	Usefulness/efficacy is less well established by evidence/ opinion	• May/might be considered • May/might be reasonable • 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 • Is not indicated • 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.

and relieved by rest or nitrates within 5 minutes.[12] Of these three features, the presence of any two is defined as atypical angina, while the presence of any one or none is defined as non-anginal chest pain. However, nonclassical symptoms are more likely in women, older, and diabetic patients. As for the severity of angina, the Canadian Cardiovascular Society established a grading classification system to define the threshold of physical activities inducing angina. In this grading system, "grade 1" angina indicates that angina develops with strenuous exertion; "grade 2" with moderate exertion; "grade 3" with mild exertion; and "grade 4" even at rest. Patients with suspected CCS should be first evaluated to rule out the diagnosis of ACS before proceeding with non-invasive examinations. Resting ECG can be crucial to detect myocardial ischemia if dynamic ST-segment changes or new-onset left bundle branch block (LBBB) are recorded during ongoing chest pain. Notably, a normal or unchanged ECG is reasonably useful but not sufficient to rule out ACS. The progression of symptoms merits attention, particularly when chest pain occurs more frequently, is unprovoked, is more severe, or lasts longer. This may reflect progression of underlying coronary lesions; if severe rest symptoms are noted, ACS should be suspected and evaluated immediately. ACS should be suspected if any one of following is present: i) grade 4 angina for a prolonged period (> 20 minutes); ii) new-onset grade 2 or 3 angina over the past 2 months; iii) crescendo angina, i.e., increasing severity and frequency, and lower threshold of angina on exertion.

5.1.2 Patients with dyspnea suspected of having CCS

For symptomatic patients, dyspnea is considered an angina equivalent on the basis of the increased prevalence and severity of myocardial ischemia and heightened mortality risk compared to asymptomatic patients or symptomatic patients with non-cardiac or atypical angina.[13,14] While dyspnea is associated with an even worse prognosis than typical angina for patients referred for non-invasive imaging tests, the presence of LV dysfunction carries greater prognostic importance than the severity of CAD or ischemia.[15] Assessment of LV function (mostly by transthoracic echocardiography) is important in all patients for risk stratification and should therefore be performed in all symptomatic patients with suspected CAD. In the presence of depressed LV function, it is im-

portant to determine if this is due to infarcted dead tissue or viable but stunned or hibernating ischemic myocardium. This can be done by stress imaging techniques. Many patients with dilated cardiomyopathy presenting with only dyspnea have a hidden ischemic etiology. All patients with heart failure with reduced ejection fraction (HFrEF) < 40% should undergo stress testing or invasive coronary angiography (ICA) to rule out an ischemic etiology even when angina is absent. A large proportion of dilated cardiomyopathy patients (up to 20%) may have significant obstructive CAD, which can be considerably improved by timely interventions with revascularization based on coronary anatomical and functional testing.[16] Myocardial revascularization should be considered in patients with HFrEF based on their symptoms, coronary anatomy, and risk profile. Successful revascularization in patients with HFrEF due to ischemic cardiomyopathy may improve LV dysfunction and prognosis by reducing ischemia to viable, hibernating myocardium.

5.2 Estimating pretest probability and clinical likelihood of obstructive CAD

Estimating the PTP of obstructive CAD is a crucial step in the clinical assessment of patients with suspected CAD. Before diagnostic tests for CAD are selected, PTP should be determined to achieve optimal performance and clinical benefit of the diagnostic tests. This determination directly influences the subsequent work-up, choice of test, and interpretation of the results. The lower the PTP, the higher the false positive results of diagnostic tests for obstructive CAD.[17] The overestimation of PTP could expose patients to unnecessary downstream procedures and costs, while underestimation could preclude appropriate treatment of the disease. The previous 2013 European Society of Cardiology (ESC)-PTP model was based only on age, sex, and symptom typicality, derived from the Diamond-Forrester prediction model, and it substantially overestimated the prevalence of obstructive CAD in patients with suspected CCS.[18] Based on contemporary data from low CVD risk countries, a new PTP assessment model of the risk was developed and classified into three categories, low (< 5%), intermediate (5-15%), or high (> 15%) (Table 4), to guide decisions for further evaluations with non-invasive stress testing to detect obstructive CAD.[17,19] Based on this model, we suggest withholding further testing for patients with PTP < 5%, and that symptomatic patients with high PTP > 15% will benefit most from further diagnostic tests. A new concept of the clinical likelihood of obstructive CAD has been introduced to consider risk modifiers of PTP beyond age, sex, and nature of symptoms. This is particularly helpful in refining the clinical likelihood of CAD in patients with a PTP of 5-15%. Intermediate PTP could be further reclassified according to the presence of risk factors (dyslipidemia, diabetes, hypertension, smoking, family history of CVD), abnormal findings of resting ECG (Q-wave or ST-T changes), LV dysfunction by echocardiography (regional wall motion abnormalities/impaired LV systolic contractility), abnormal exercise ECG, or high coronary artery calcium (CAC) by computed tomography (CT).[19] Using this approach, the optimal range of PTP can be estimated for each test, and the patients can be reclassified from intermediate to either low or high risk of CAD. The overall schematic flow of risk and severity

Table 4. The pretest probabilities of obstructive coronary artery disease based on age, sex, and symptom typicality

Age	Typical*		Atypical#		Non-anginal†		Dyspnea	
	Men	Women	Men	Women	Men	Women	Men	Women
30-39	Low	Low	Low	Low	Low	Low	Low	Low
40-49	High	Medium	Medium	Medium	Low	Low	Medium	Low
50-59	High	Medium	High	Medium	Medium	Low	High	Medium
60-69	High	High	High	Medium	High	Medium	High	Medium
≥ 70	High	High	High	High	High	Medium	High	Medium

"High" denotes pre-test probabilities > 15%; "Medium" denotes pre-test probabilities around 5-15%; "Low" denotes pre-test probabilities < 5%.

* Typical angina meets the following three characteristics: (i) Constricting discomfort in the front of the chest or in the neck, jaw, shoulder, or arm; (ii) Precipitated by physical exertion; (iii) Relieved by rest or nitrates within 5 minutes. # Of these three features, presence of any two is defined as atypical angina, † While presence of any one or none is as non-anginal chest pain.

assessment and management in patients with suspected CCS is presented in Figure 2.

5.3 Biochemical tests and cardiac biomarkers for CCS

Routine biochemical tests can identify important comorbidities including kidney impairment, diabetes, dyslipidemia, and may identify anemia, which can lower the anginal threshold. During recent years, several circulating biomarkers have been found to carry prognostic information and have been proposed as potential tools for risk stratification in CCS setting. Higher levels of cardiac biomarkers, such as N terminal-pro B type natriuretic peptide (NT-proBNP) and cardiac troponins, measured with high-sensitivity assays, are associated with a higher risk of CV events in CCS patients.

5.3.1 High sensitivity troponin

Troponin is a necessary biomarker to diagnose myocardial injury or infarction. Although cardiac biomarkers such as troponin play an important role in ACS, the role of cardiac biomarkers for CCS still needs further evaluation. Because not all patients with CCS maintain a stable condition, troponin (especially with high sensitivity assays) should be measured to detect the instability of CCS.[19-21] If ACS is diagnosed, further management should follow the current guidelines for ACS. In addition, elevated troponin levels are also associated with adverse prognosis and have potential diagnostic value for suspected CCS.[22]

5.3.2 B-type natriuretic peptide and NT-proBNP

Natriuretic peptides have been widely used in patients with HF, ACS, pulmonary embolism, and so on. However, less is known about patients with CCS. NT-proBNP has been reported to be a potential biomarker for risk stratification and therapeutic decision-making in patients with three-vessel disease.[23] A higher NT-proBNP level has also been associated with a higher risk of

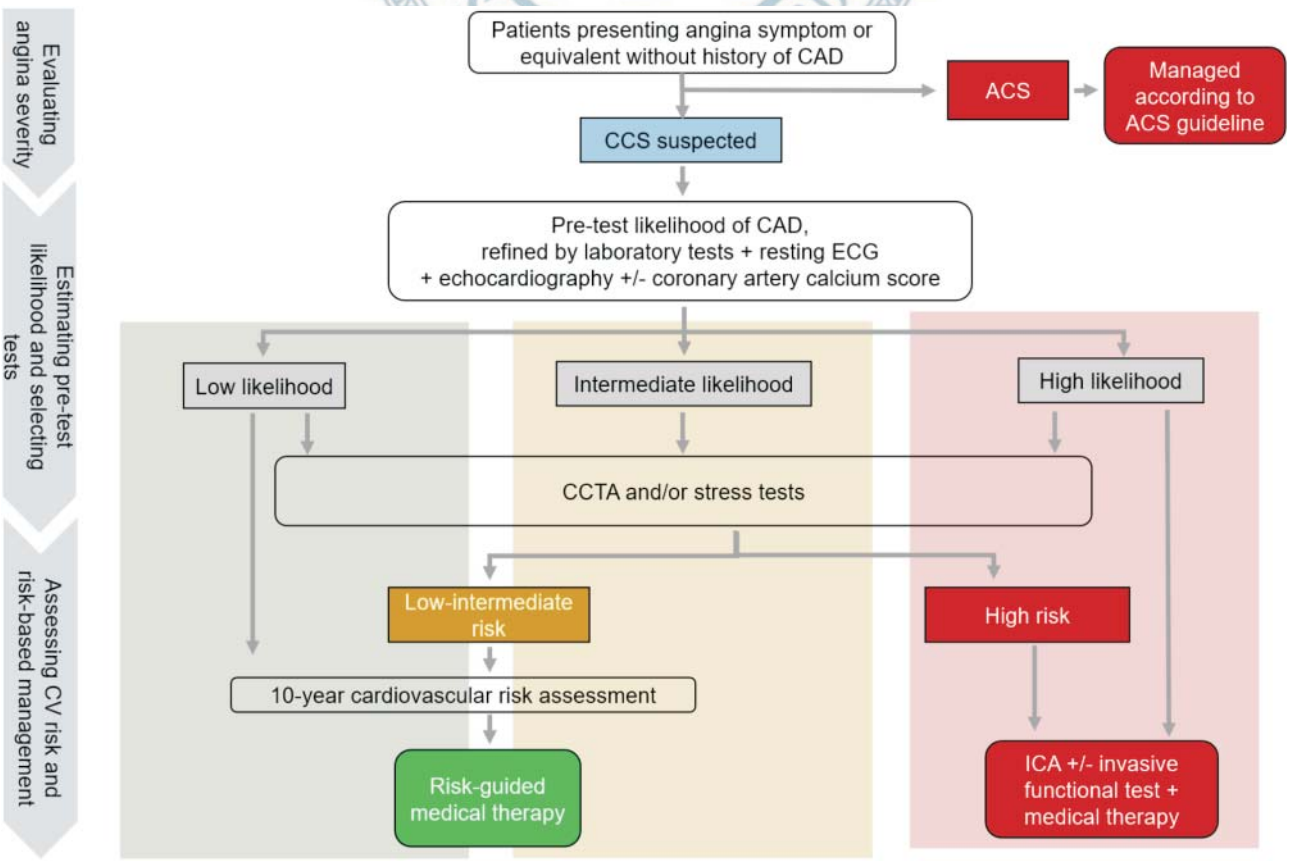


Figure 2. *Schematic flow of risk/severity assessment and management in patients with suspected CCS. ACS, acute coronary syndrome; CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; ECG, electrocardiogram; ICA, invasive coronary angiography.*

CV events in patients with CCS.[24,25]

5.3.3 Inflammatory-related biomarkers

Several inflammatory-related biomarkers such as high sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) have also been shown to carry predictive and prognostic information in CCS.[26-28] Hs-CRP has shown prognostic value in predicting adverse outcomes in a number of studies, however, its routine use was not recommended in a systemic analysis of 83 studies, which raised uncertainty about its association with CCS.[29] IL-6 levels have been correlated with severe stenosis of the left anterior descending artery (LAD) and higher angiographic Gensini score in CCS patients.[27]

5.3.4 Homocysteine

Hyperhomocysteinemia has been associated with CV risk in several studies and considered to be an independent risk factor for atherosclerosis.[30,31] It has also been associated with the severity of CAD[32] and higher thromboembolic events.[30,33] Although the initial studies suggested that homocysteine-lowering therapy may induce plaque regression, this finding was not confirmed in subsequent clinical studies.[34,35]

5.3.5 Lipoprotein(a)

Lipoprotein(a) has also been considered as an emerging biomarker for atherosclerotic cardiovascular disease (ASCVD) in epidemiological, genomewide association, and Mendelian randomization studies.[36-40] It is an apoB-containing lipoprotein bound to a hydrophilic highly glycosylated protein. However, its concentration has been weakly correlated with several known risk factors such as total cholesterol, non-high-density lipoprotein (HDL) cholesterol, and apolipoprotein B100.[37] In addition, statins only marginally affect plasma lipoprotein(a) levels,[41] but PCSK9 inhibitors may play a role in lowering lipoprotein(a) and CV risk reduction.[42] Currently, there are ongoing RCTs using RNA-based therapies such as antisense oligonucleotides and small interfering RNAs to evaluate whether reducing lipoprotein(a) can improve CV outcomes.[43]

5.3.6 Incorporating multiple biomarkers and clinical variables

Patients with CCS are heterogeneous in their risk of future CV events and may benefit from different intensities and durations of preventive treatments. Correctly identifying CCS patients at an increased risk of major adverse cardiac events (MACEs) is crucial when assessing such patients. To appropriately tailor the intensity of secondary preventive treatments, there is a need for improved risk stratification tools for patients with CCS. Recently, experts developed a biomarker-based "ABC-CCS" prediction model containing age (A); the biomarkers (B) NT-proBNP, high-sensitive cardiac troponin (hs-TnI or hs-TnT), and low-density lipoprotein cholesterol (LDL-C); and the clinical variables (C) smoking, diabetes, and prior peripheral artery disease (PAD) and reported high discriminatory power for CV death and other CV outcomes (C-index 0.78 in the validation cohort).[44] The ABC-CCS risk score might serve as a clinically useful decision support tool in CCS patients.

Key Recommendation:

- Not all symptomatic patients with CCS maintain a stable condition, troponin (especially with high sensitivity assays) should be measured to detect the instability of CCS or ACS (COR I, LOE A).

6. CHOICE OF APPROPRIATE NON-INVASIVE TESTING: STRESS TEST VERSUS ANATOMIC TEST

In patients in whom obstructive CAD cannot be excluded by clinical assessment alone, non-invasive diagnostic tests are recommended to establish the diagnosis and assess the event risk. Appropriate utilization of non-invasive diagnostic testing is important to ensure that patients with CAD are referred to angiography for the diagnosis, and that patients who do not have CAD can avoid unnecessary invasive testing. In patients with high PTP, ongoing symptoms unresponsive to medical therapy or typical angina at a low level of exercise, and an initial clinical evaluation that indicates a high event risk, proceeding directly to ICA without further diagnostic testing is a reasonable option. In other patients in whom CCS cannot be excluded by clinical assessment alone, non-invasive diagnostic tests are recommended to establish the diagnosis and assess the event risk. While ICA remains the gold standard for the diagnosis of obstructive CAD, non-invasive testing serves an important

gatekeeping role to ensure the catheterization laboratory remains an interventional tool rather than a diagnostic one. Noninvasive testing modalities can be categorized into stress testing, such as exercise ECG, stress echocardiography, myocardial perfusion imaging (MPI) with single photon emission tomography (SPECT) or positron emission tomography (PET), and anatomic testing, such as coronary computed tomography angiography (CCTA). For decades, the use of stress testing has remained a pivotal component of algorithms designed to evaluate anginal pain. Over the past several years, however, mounting evidence from large RCTs supports anatomic imaging, with special attention given to CCTA as the more diagnostically and prognostically accurate non-invasive testing modality. The results derived from these large RCTs, as well as their subsequent post hoc analyses, have led to the escalation of CCTA as the first-line test in international guidelines for the evaluation of CCS in symptomatic patients with intermediate-high PTP of CAD. These results must be taken into consideration when choosing the initial test for the evaluation of patients with suspected CAD. However, the choice of non-invasive test should be based on a combination of PTP, ability to perform adequate exercise to an adequate workload, resting ECG abnormalities, local expertise, availability, the presence or absence of contraindications, and patient preferences. Stress tests for the diagnosis of obstructive CAD are designed to detect myocardial ischemia through ECG changes, wall motion abnormalities by stress echo or stress SPECT, PET, or cardiac magnetic resonance imaging (CMR). Ischemia can be provoked by exercise or pharmacological stressors. Pharmacologic stress testing, usually using a vasodilator (adenosine; dipyridamole) or inotropes and/or chronotropes (dobutamine) is typically performed when a patient is unable to exercise, but it is also frequently used in patients with LBBB or ventricular paced rhythm. A summary of the performance of diagnostic tests for the detection of CAD based on recent meta-analyses is shown in Table 5.[45,46] The diagnostic work-up according to risk assessment in patients with suspected CCS is shown in Figure 3.

6.1 Exercise ECG in the evaluation of symptomatic patients with suspected CCS

Exercise ECG (treadmill exercise test) has been considered historically as an initial tool for patients with suspected CCS who can exercise and achieve an adequate cardiac workload and heart rate, and who have an interpretable ECG. Symptom-limited exercise is the preferred form of stress test for patients who can attain an adequate level of exercise because it provides the most information concerning symptoms and the hemodynamic response during exercise. The patient's maximal exercise capacity, maximal heart rate, heart rate at symptoms, blood pressure (BP) response, and symptoms are all valuable findings to predict cardiac events from an exercise test. Patients who exercise at > 10 metabolic equivalents (METs), the unit used to estimate the amount of oxygen used by the body during physical activity, during stress testing have been shown to have a very low prevalence of significant ischemia and very low rates of cardiac events during follow-up.[47] The advantages of this test include its non-invasiveness, lack of exposure to pharmacological stressors or ionizing radiation, and ability to assess the patient's functional and rhythmic status during exercise stimulation. Exercise ECG is the lowest cost diagnostic procedure compared with other stress imaging or anatomic procedures. However, submaximal exercise decreases the sensitivity for the detection of ischemia and prevents accurate assessment of the extent of ischemia, and it is important to achieve ≥ 85% of the maximum heart rate. Abnormal findings of exercise ECG can be a useful modifier to refine intermediate PTP in patients with suspected CCS, including threshold of exercise-induced angina/ST-segment changes, exercise tolerance, presence of arrhythmia, and BP/heart rate response. The Duke treadmill score was developed to provide diagnostic and prognostic information to help evaluate patients with suspected obstructive lesions. The Duke treadmill score stratifies patients into low risk (score ≥ +5), intermediate risk (score +4 to -10), or high risk (score < -10) categories based on exercise duration, symptoms, and ECG changes.[48,49] However, exercise ECG has limited power to rule in or rule out obstructive CAD. Compared with exercise ECG, noninvasive stress imaging tests have the advantage of indicating the location of ischemia, and also of superior diagnostic performance for the detection of obstructive CAD, partially because the diagnostic power of exercise ECG can be limited by the presence of LBBB, paced rhythm, Wolff-Parkinson-White syndrome, and 0.1 mV ST-segment depression of

Table 5. Noninvasive diagnostic tests for suspected obstructive coronary artery disease

Test	Stress ECG	SPECT MPI	Stress echo	Stress PET	Stress CMR	CCTA
Requirements and considerations	• Exercise tolerated • Requires interpretable ECG at baseline	• May not detect balanced MVD • Flow reserve measurements using dedicated canners • Higher radiation exposure (10 to 20 mSv)	• Exercise or pharmacological stress • Use of contrast for image enhancement	• Plaque, perfusion and viability imaging • Myocardial blood flow and flow reserve measurements • Low radiation exposure (0.9-2.0 mSv)	• Pharmacological stress • High costs with long scan time • Not for patients with claustrophobia	• β-blocker to lower heart rate • Potential risks of contrast agent • Radiation exposure (3 to 5 mSv range)
Taiwan's NHI reimbursement	(+)	(+)	(+)	(-)	(-)	(-)
Sensitivity (95% CI)	0.58 (0.46-0.69)	0.87 (0.83-0.90)	0.85 (0.80-0.89)	0.83 (0.74-0.89)	0.89 (0.88-0.91)	0.97 (0.93-0.99)
Specificity (95% CI)	0.62 (0.54-0.69)	0.70 (0.63-0.76)	0.82 (0.72-0.89)	0.91 (0.81-0.96)	0.80 (0.78-0.83)	0.78 (0.67-0.86)
Findings indicating high risk	• > 2-mm ST-segment depressions at low workload • Duke treadmill score ≤ -11	• Perfusion defect in > 10 of LV myocardium • Baseline LVEF < 40%	• Peak wall motion score index > 1.7 • Stress-induced hypokinesia or akinesia: ≥ 3 of 16 segments • Baseline LVEF < 40% or decrease in LVEF > 10% under stress	• Perfusion defect in > 10% of LV myocardium • Baseline LVEF < 40% • Stress induced transient LV dilation • Low CFR	• ≥ 2 of 16 segments with stress perfusion defects • ≥ 3/16 segmennts with dobutamine-induced dysfunction	• Multiple coronary arteries with ≥ 80% stenosis • Left main stenosis ≥ 50%

Modified from Yang K, et al.[45] and Xu J, et al.[46]

CCTA, coronary computed tomographic angiography; CFR, coronary flow reserve; CI, confidence interval; CMR, cardiac magnetic resonance imaging; ECG, electrocardiogram; LV, left ventricle; LVEF, left ventricular ejection fraction; MPI, myocardial perfusion imaging; NHI, National Health Insurance; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

resting ECG. Therefore, the current role of exercise ECG for symptomatic patients with suspected obstructive CAD has been replaced to a level below stress imaging tests and can be considered as an initial non-invasive study only when stress imaging tests are not possible or available. However, exercise ECG still remains a recommended initial diagnostic test for patients with low to intermediate PTP with an interpretable ECG and who can exercise maximally.

6.2 Stress imaging tests in the evaluation of symptomatic patients with suspected CCS

Myocardial ischemia assessment with non-invasive stress tests provides useful information to diagnose CAD and evaluate overall cardiac and coronary risk other than purely a decision to refer for an intervention. Before revascularization decisions can be made, functional evaluation of ischemia is required in most patients. As a rule, patients with suspected CCS should have a stress test before cardiac catheterization if the PTP of obstructive CAD lies in the range of 5% to 15%. Therefore, stress testing may be preferred in symptomatic patients at the higher end of the range of PTP if revascularization is likely or the patient has previously confirmed CAD.

6.2.1 Stress echocardiography

Echocardiography can identify related wall-motion abnormalities, assess systolic and diastolic function, and

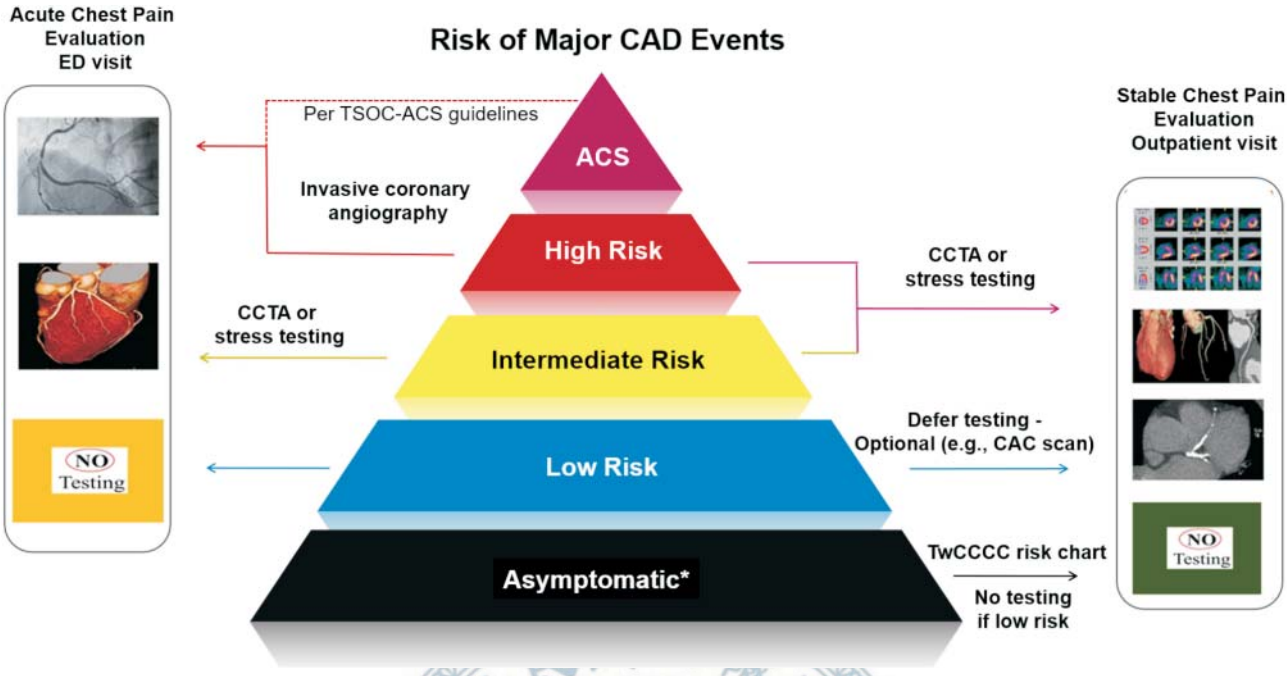


Figure 3. *The diagnostic work-up according to risk assessment in patients with suspected CAD. Modified from Gulati M, et al.[103] * Also see Figure 6 for asymptomatic subjects without known CAD. ACS, acute coronary syndrome; CAC, coronary artery calcium; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; ED, emergent department; TSOC, Taiwan Society of Cardiology; TwCCCC, Taiwan Chin-Shan Community Cardiovascular Cohort.*

detect potential alternative causes of the symptoms. Stress echo using exercise (treadmill or bicycle) or pharmacological (most commonly, dobutamine) stressors represents a unique functional imaging test to evaluate patients with suspected myocardial ischemia. Stress echo is widely available and allows for a rapid, nonionizing evaluation of myocardial ischemia to support therapeutic decisions, with potential for bedside applications. The test has good accuracy for induced myocardial ischemia in patients with intermediate-high PTP, with higher diagnostic sensitivity and specificity compared with exercise ECG test.[45] Stress echo yields prognostic information for risk stratification of patients with known or suspected CCS. A normal stress echo study with a peak wall motion score index of 1.0 confers a benign prognosis (0.9%/year cardiac event rate). A peak wall motion score index > 1.7 and impaired left ventricular ejection fraction (LVEF) ≤ 40% are independent markers of patients at high risk of an adverse clinical outcome.[46] Stress-induced hypokinesia or akinesia in ≥ 3 of 16 segments is considered high risk.[47] However, despite its clinical usefulness, stress echo is not applicable for coronary stenosis severity analysis and lacks the automated quantification of perfusion studies.[48]

6.2.2 Radionuclide myocardial perfusion imaging with single photon emission tomography

Among the wide range of functional imaging tests, SPECT-MPI has emerged as the most commonly used modality. There is no doubt that the volume of studies performed in Taiwan has increased significantly over the last few years. According to the National Health Insurance (NHI) administration database, the total number of SPECT-MPI tests significantly increased from 34,016 in 2000 to 151,254 in 2016 with an annual growth rate of 21.5%, much higher than the 7.9% growth of overall nuclear medicine tests during this period.[50] In the setting of an invasive strategy for CCS patients in Taiwan, 79.1% of the patients had MPI, 66.4% had exercise ECG, and only 0.05% had stress echo within the preceding 90 days prior to percutaneous coronary intervention (PCI).[51] In SPECT-MPI, patients are injected with radioactive agents (such as Tc-99m or Thallium 201), and their passage through the heart is viewed with a SPECT camera. Early SPECT studies indicated that myocardial perfusion is reduced in the presence of ≥ 70% intraluminal epicardial stenosis. The incidence of cardiac events increases with an increase in the extent of ischemic myocardium, and

the prognosis improves with a decrease in ischemic myocardium after coronary revascularization. Demonstration of myocardial ischemia affecting > 10% of the LV on stress SPECT-MPI is recommended as the indication for revascularization. However, the COURAGE nuclear substudy,[52] performed in the context of modern medical therapy, did not demonstrate a significant increase in events with an increasing extent of ischemia or a benefit from revascularization, even in patients with a moderate-severe ischemic burden. Consequently, it is not clear whether revascularization driven by the extent of inducible ischemia on a functional test improves clinical outcomes in CCS patients. Furthermore, SPECT-MPI has not been shown to be significantly superior to stress echo in terms of sensitivity and detecting the extent of CAD.[53] It should be acknowledged that SPECT-MPI does have limitations, including high false-positive results due to certain artifacts, false-negative results due to balanced ischemia resulting from multiple vessel disease (MVD), inability to detect non-obstructive early disease complexity, and adverse reactions arising from current pharmacological stressors, the time consuming nature of the imaging procedure, and relatively high radiation exposure ranging from around 10 to 20 mSv.[54] Recent developments in MPI using cadmium zinc telluride (CZT) scanners have improved performance so that the procedure is faster and requires less radiation exposure (3-11 mSv)[55,56] compared with standard gamma cameras. Myocardial blood flow and flow reserve assessment with dynamic CZT SPECT provides similar diagnostic value to PET, ICA and fractional flow reserve (FFR).[57-62]

6.2.3 Cardiac positron emission tomography

PET-MPI is the non-invasive gold standard for the assessment of myocardial blood flow and coronary microvascular disease. PET uses higher energy photons than SPECT and has a higher count sensitivity resulting in studies with higher overall counts and better spatial resolution than SPECT-MPI[63] or CCTA.[64] In addition, PET tracers have shorter half-lives and lower radiation exposure (0.9-2.0 mSv) compared to SPECT,[56,65] and PET-MPI protocols are shorter (~30 minutes) than SPECT-MPI protocols (2.5-4 hours), especially if the study requires both stress and rest imaging. With advances in scanner technology and the development of novel tracers, the applications of PET for the study of CAD have been gaining momentum in the last few years. Compared with the most commonly used nuclear test, SPECT, PET has higher resolution imaging, and the addition of quantitative information yields incremental prognostic value. Most importantly, PET-MPI allows for dynamic imaging to quantify absolute coronary blood flow, which is a significant advantage over conventional SPECT-MPI. PET-MPI is a powerful tool to identify and quantify risk, and to guide therapy in patients with known or suspected CAD. A large body of evidence supports the prognostic value of PET-MPI in women, and in intermediate-high risk, obese, and post-coronary artery bypass grafting (CABG) individuals.[66-68] The myocardial perfusion reserve provided by PET-MPI has been shown to be significantly associated with the development of MACEs.[69] Cardiac PET can comprehensively assess all aspects of CAD, from coronary atherosclerotic plaque (plaque imaging) to myocardial tissue characterization (perfusion and viability imaging).[70] With the wider availability of PET scanners and the routine use of quantitative blood flow imaging, the clinical use of PET-MPI is expected to increase further. Despite its superiority over conventional SPECT, PET has several disadvantages: PET cameras are not as widely available as SPECT cameras limiting access; PET tracers are more expensive than SPECT tracers, and an on-site cyclotron is needed for the short half-life PET tracers. Despite its technical appropriateness for the assessment of myocardial ischemia, PET is currently limited by reduced availability and lower spatial resolution in comparison with stress-CMR.[71]

6.2.4 Stress cardiac magnetic resonance imaging

CMR is a multiparametric imaging modality which yields high spatial resolution images that can be acquired in any plane for the assessment of global and regional cardiac function, myocardial perfusion and viability and tissue characterization, all within a single study protocol and without exposure to ionizing radiation. Stress CMR requires the induction of hyperemia using a vasodilator, such as adenosine or dipyridamole, before the use of a gadolinium-based contrast agent for the assessment of myocardial perfusion. It has overall high sensitivity and specificity for the detection of anatomically significant CAD (90% and 80%, respectively) and functionally significant CAD (89% and 87%, respectively).[72] The diagnostic superiority of stress CMR with a high

rule-in power in detecting functionally significant coronary artery stenosis compared to other stress tests has been validated against ICA with FFR in patients suspected of having CCS.[73,74] The appropriate selection of patients for stress CMR can potentially further strengthen its diagnostic accuracy. This has been widely validated in a large body of evidence, and it has more recently demonstrated clinical effectiveness in directly guiding revascularization in the presence of myocardial ischemia. In fact, stress magnetic resonance imaging (MRI) provides more precise guidance concerning the need for PCI than ICA with invasive pressure-wire measurements. In one study, the use of stress MRI lowered the rate of an indication for PCI from 45.0% to 35.7% (p = 0.005), without any unfavorable effects on symptoms or clinical outcomes at 1 year.[75] Large registry data have shown stress CMR to be a prognostic imaging modality that should be considered in patients with an intermediate PTP of CAD.[76,77] However, this technique has several limitations, including its limited availability, requirement for patients to hold their breath, high cost with long scan times, contraindications for patients with claustrophobia, or severe renal dysfunction due to the injection of gadolinium-based contrast agent. Nevertheless, with the use of stress T1 mapping, CMR holds promise for the detection of ischemia without the need for gadolinium.[78] CMR for this purpose, however, is not currently reimbursed by the NHI in Taiwan.

6.3 Non-invasive anatomic testing: cardiac computed tomography

Cardiac CT is a heart-imaging test that uses CT technology with or without intravenous contrast to visualize the heart anatomy, coronary circulation, and great vessels (including the aorta, pulmonary veins, and arteries). There are two types of CT scans that use different techniques and provide different information for the diagnosis of CAD: CAC screening heart scan, and CCTA.

6.3.1 Coronary artery calcium testing

CT for the quantification of CAC is a simple non-invasive tool to assess overall atherosclerotic plaque burden. CAC is highly correlated with coronary atherosclerosis and is a robust predictor of all-cause and CVD mortality in all studied ethnic groups, including Asians.[79-81] Agatston's original scoring system based simply on calcium area and density remains the gold standard for CAC quantification and is the basis for standardized scoring categories[82] as well as percentiles distributed by age, sex, and ethnicity.[83] When calcium is present, the higher the score, the higher the risk of CAD. The risk categories of MI and coronary mortality at 10 years by CAC are listed in Table 6.[84] CAC testing is widely available and does not require the use of iodinated contrast agents. CAC scanning images are rapidly obtained (< 10-second breath hold), and the results can be interpreted quickly in order to inform further diagnostic decisions.

6.3.1.1 CAC for symptomatic patients with suspected CCS

For patients presenting with stable chest pain or equivalent, the appropriate risk assessment strategy to identify individuals likely to benefit from further imaging testing is important. Routine testing of CAC is not recommended in symptomatic patients with suspected CCS. However, increasing evidence supports the role of CAC testing as an effective gatekeeper to further testing in low-intermediate risk patients with stable chest pain. CAC score is a simple risk modifier which may help to identify such patients with PTP of obstructive CAD < 15% who may benefit from primary prevention as per SCOT-Heart. CAC score permits a reclassification of risk incremental to conventional risk markers alone.[85] Patients with moderate-high risk based on CAC score (i.e., > 100) should be considered to receive preventative medical therapy such as statins. The PROMISE study was a RCT that evaluated individuals with stable chest pain or dyspnea plus an intermediate PTP for obstructive CAD. Quantification of CAC was performed in over 4,000 trial participants,[86] and the results showed that obstructive CAD was very uncommon in patients with a CAC score of 0 (CAC zero). Specifically, 15 of 1457 patients

Table 6. The risk category of myocardial infarction and coronary mortality at 10 years by coronary artery calcium score

CAC score	Risk
0	A zero score confers a very low risk
1-99	Low risk
100-399	Intermediate risk
100-399 & > 75th centile	Moderately high risk
≥ 400	High risk

Modified from Greenland P, et al.[84]
CAC, coronary artery calclium.

with CAC zero had 50-70% stenosis on CCTA, and 7 of 1457 patients had > 70% stenosis on CCTA [negative predictive value (NPV) 99.8% for ≥ 50% stenosis; 99.9% for ≥ 70% stenosis]. Over a 2-year follow-up period, MACEs occurred in 1.4% of the patients without CAC, which was a lower rate than those randomized to the stress-testing arm who had normal results (2.1%). A CAC zero effectively rules out significant epicardial CAD in low-risk symptomatic patients (NPV ~99%) and is associated with a very low risk of future CV events. CAC zero is a unique negative risk marker for symptomatic low-intermediate risk patients, referred to as the "power of zero" given its association with an exceedingly low event rate.[87] Accordingly, CAC zero would eliminate the need for further cardiac testing in those without high-risk features, whereas CAC > 100 would necessitate additional assessment. Moreover, a positive CAC would likely provide additional prognostic information to whatever additional testing is pursued, such as stress imaging.[88] With time and budget constraints as well as contraindications inherent to clinical testing, CAC possesses several advantages that may allow for the responsible stewardship of medical resources in lower-risk patients with stable chest pain. Notably, using CAC zero as a gatekeeper in symptomatic high-risk patients is not without potential concerns. Nevertheless, CAC zero does not entirely exclude obstructive CAD, because non-contrast CT does not detect noncalcified atherosclerotic plaque. Noncalcified plaque formation can be dynamic, with a preponderance to develop and bring about symptoms in younger patients.[89] In the CORE64 substudy,[90] 19% of symptomatic CAC zero patients had at least one ≥ 50% stenotic vessel, and 20% of the occluded vessels had no CAC. In the CONFIRM study,[91] CAC and CCTA showed that approximately 51% of 10,037 patients with chest pain but no known CAD had a CAC score of 0, of whom 13% had non-obstructive disease, 3.5% had ≥ 50% arterial stenosis, and 6% had 3-vessel CAD. Accordingly, CAC should not be relied on to exclude CAD in symptomatic patients with high-risk features, and is therefore not routinely recommended in high-risk individuals.

Key Recommendations:

- CAC should be considered as a risk modifier in symptomatic patients with low-intermediate PTP of obstructive CAD (COR IIa, LOE B).
- CAC is not recommended for patients with high-risk features to identify symptomatic individuals with obstructive CAD (COR III, LOE B).
- CAC is not recommended for patients with previously documented CAD (COR III, LOE C).
- CAC zero cannot exclude obstructive CAD in symptomatic patients with high PTP of CAD (COR III, LOE B).

6.3.2 CCTA in symptomatic patients with suspected CCS

CCTA has been shown to have the highest diagnostic accuracy compared with all available non-invasive stress tests for the detection of significant stenosis on ICA. The EVINCI trial enrolled 252 subjects with an intermediate pretest likelihood of disease, and found that CCTA had sensitivity and specificity of 91% and 92%, respectively, compared with SPECT/PET MPI (sensitivity 74%, specificity 73%) for the detection of significant CAD (> 50% LM, > 70% non-LM or FFR < 0.80) on ICA.[92] When using invasive FFR as the reference, CCTA again has demonstrated a very high per-patient sensitivity. In the PACIFIC trial, 208 patients with suspected CAD underwent CCTA, SPECT, PET, and ICA with FFR of all coronary arteries.[64] The results showed that the specificity of CCTA (60%) was lower compared with SPECT MPI (94%) and PET MPI (84%). Importantly, CCTA provides very high (~98%) negative predictive value and is a definitive test to help rule out the possibility of CAD. CCTA has been used as a first-line tool to evaluate patients exhibiting symptoms of CAD. It is effective for the diagnosis of CAD, risk stratification, and guiding treatment decisions. CCTA is also appropriate after inconclusive stress tests, such as SPECT tests and stress echo, when considering revascularization strategies. One feature of using CCTA to evaluate for CAD is that it provides information on the presence and extent of both obstructive and non-obstructive CAD. Although non-obstructive disease is unlikely to be detected by stress imaging techniques, emerging data suggest that non-obstructive plaques play an important role in the development of acute coronary events and that it is a predictor of all-cause mortality.[93-95] More recently, the 2021 American chest pain guidelines[96] redefined "known" CVD to include any coronary plaque on CCTA, in addition to the conventional definition based on obstructive CAD or clinical CV events. This new definition significantly expands the known CVD population and highlights the prognostic importance and preventive therapeutic im-

plications of CCTA for coronary atherosclerosis. The large-scale PROMISE RCT (n = 10,003) established that performing CCTA first was at least as effective as functional imaging (67% stress SPECT, 22% stress echo, 10% exercise ECG) strategies for all studied CV outcomes.[97] In the CCTA group, there was greater use of ICA but fewer normal coronary angiograms. Remarkably, 67% of MIs and CV deaths in the PROMISE trial occurred in patients with normal stress test findings at baseline, and the presence of high-risk plaque (positive remodeling, low CT attenuation, or napkin ring sign) on CCTA was associated with significantly increased MACE risk [adjusted hazard ratio (HR): 1.73; 95% confidence interval (CI): 1.13-2.62] even after adjusting for stenosis severity. In addition, CCTA was shown to be safe in the PROMISE trial with lower radiation exposure than nuclear stress imaging.[98] In the SCOT-HEART study, CCTA-guided management of symptomatic low-intermediate risk patients with stable chest pain on top of standard care (85% on baseline exercise ECG) resulted in lower coronary death or nonfatal MI rate (2.3% vs. 3.9%) at 5 years than standard care alone, without a higher rate of ICA or revascularization procedures.[99] Compared with standard care, CCTA increased early diagnostic certainty [risk ratio (RR) 2.56, 95% CI 2.33 to 2.79] and the frequency (RR: 1.09, 95% CI: 1.02 to 1.17) of a diagnosis of CAD at 6 weeks. Furthermore, this trial demonstrated that coronary plaque imaging by CCTA could lead to an improved clinical course by intensifying OMT and LSM, offering a novel intervention strategy.[100] In a meta-analysis of RCTs, stable chest pain patients (n= ~15,000) who underwent CCTA were noted to have a 31% lower risk of MI (pooled HR: 0.69; 95% CI: 0.49-0.98), which was likely related to a more accurate early diagnosis leading to more appropriate use of preventive therapies, a finding that is consistent across the PROMISE and SCOT-HEART studies.[101] In the ISCHEMIA trial, a total of 5179 patients with moderate-severe ischemia (core laboratory validated) were randomized (after a blinded CCTA to exclude LM or non-obstructive disease) to an invasive strategy of revascularization with OMT versus OMT alone. Very high-risk patients, including those with unacceptable angina despite OMT, LVEF < 35%, recent ACS or revascularization, and LM disease on a blinded CCTA, were excluded. After a median follow-up of 3.2 years, there was no difference in the primary endpoint. Overall, revascularization did not offer any "hard outcome" advantages over OMT. On the other hand, there was a durable improvement in symptoms. In this trial of stable subjects, the anatomic severity of CAD detected by CCTA, but not the severity of ischemia induced by stress tests, could predict 4-year MI and mortality.[102] In the light of these large clinical trials, the latest international guidelines[19,103] have redefined the role of CCTA in diagnostic strategies. For example, the National Institute for Health and Care Excellence (NICE) guidelines updated its chest pain guidelines and made CCTA the first test for all patients without established CAD who present with typical or atypical angina or with non-anginal chest pain plus an abnormal resting ECG.[104]

6.3.3 CCTA-first clinical chest pain pathway

Recent clinical trials and observational data provide compelling evidence for a CCTA-first strategy. Furthermore, some have advocated combining CCTA and the patients' symptoms as a first-line testing strategy for symptomatic patients without known CAD. With this approach, symptomatic patients with stable chest pain will receive CCTA to exclude LM disease or high-risk features while commencing medical therapy, with ICA deferred unless the patient has severe ongoing symptoms, or symptoms not controlled by OMT. This CCTA-first strategy may lead to substantial improvements in clinical efficiency and healthcare cost savings in triaging chest pain patients for either conservative OMT or invasive work-up. Most stress tests do not detect non-obstructive disease, and many patients who have non-obstructive disease detected on CCTA will have a normal stress test. Thus, the detection of plaque by CCTA offers an important opportunity for secondary prevention in patients with underlying non-obstructive CAD. The 2021 American Heart Association/American College of Cardiology (AHA/ACC),[103] 2019 ESC[105] and 2018 Japan Circulation Society (JCS)[106] guidelines make a recommendation for its use in clinical practice. Taken together, mounting evidence supports the use of CCTA as the first-line test for symptomatic patients with stable chest pain. Thus, the Task Force recommends that the first-line diagnostic tests for symptomatic subjects in Taiwan should include CCTA, an increasingly used anatomic imaging modality capable of detecting not only obstructive but also non-obstructive coronary plaques that may be missed with

stress tests. A CCTA-first strategy has the benefit of assisting in implementing a patient-centered approach by providing tangible evidence of the presence of plaque and increasing the likelihood of implementing and adhering to lifestyle changes and pharmacotherapies.

6.3.4 FFR-CT in patients with suspected or known CAD

More recently, the invasive assessment of coronary physiology through FFR and iwFR has been shown to be able to identify hemodynamically significant stenoses, assist in planning revascularization to improve outcomes, and avoid unnecessary interventional procedures.[7,107,108] Given the fact that physiology-guided revascularization results in improved outcomes compared with angiography-guided revascularization, the next step in CCTA evaluation seems to involve the determination of FFR by computed tomography (FFR-CT). Modern FFR-CT artificial intelligence analysis uses powerful computer algorithms and deep learning technology to solve millions of complex equations to simulate blood flow and provide FFR-CT values along the coronary arteries. FFR-CT has been validated against ICA and pressure wire assessment, and it shows considerable promise as a test for the diagnosis and management of patients presenting with chest pain.[109,110] A large multinational registry examined the use of FFR-CT with regards to driving clinical decision-making regarding the use of follow-up ICA and the safety of deferring coronary revascularization in patients with negative FFR-CT findings. In analysis of the ADVANCE registry, FFR-CT changed treatment recommendations in two-thirds of 5083 chest pain patients with less revascularization, and patients with negative FFR-CT findings had a significantly lower CV death or MI rate at 1 year compared to patients with abnormal FFR-CT values.[111] Thus, FFR-CT can add physiologic insights of the anatomy to provide actionable information to enable physicians to non-invasively diagnose lesion-specific ischemia and guide decision-making regarding revascularization in stenoses of 50-80% by CCTA. An active area of clinical research has been to identify a “one-stop shop” that is capable of concurrently detecting “functionally significant” stenoses by a single non-invasive examination. The 2021 AHA/ACC guidelines[103] now highlight the use of FFR-CT as a front-line pathway, and it has been shown to provide higher diagnostic accuracy compared to other non-invasive diagnostic tests,[112] to be able to assess long-term outcomes,[113] and to be a dominant strategy in a real-world registry.[114] The newly updated 2021 ACC/AHA guidelines reflect growing support for the FFR-CT pathway combining anatomic and physiologic information in a single non-invasive test worldwide – including in the 2019 ESC guidelines,[19] and 2018 Japan Circulation Society guidelines[106] – suggesting that a revolutionary paradigm shift in the diagnosis and management of CAD is underway. To date, FFR-CT analysis platforms are not available at the point of care in Taiwan. In the SYNTAX 3 REVOLUTION trial,[115] FFR-CT was shown to reduce the proportion of patients with hemodynamically significant MVD from 92% to 78%, and reclassify 15% of patients to a lower SYNTAX Score. In this trial, FFR-CT changed the Heart Team’s treatment decision-making and procedural planning in one-fifth of the MVD patients. Although it is already used in the clinical arena, further data, particularly in the form of large RCTs, are required. The FORECAST trial, a 1400 patient multicenter RCT in the United Kingdom (UK), demonstrated that a strategy of CCTA with selective FFR-CT in patients with stable chest pain did not differ significantly from standard clinical care pathways in cost or clinical outcomes, but did reduce the use of ICA.[116] In the future, incorporating the use of FFR-CT and CCTA has the potential to select those who would benefit from undergoing ICA and limit unnecessary procedures in patients for whom a medical management strategy is effective.

6.3.5 Limitations of CCTA

Despite the promise of CCTA (with and without FFR-CT), technical and patient-related limitations exist for the widespread application of this technology. Poor image quality and severe calcifications (i.e., CAC > 400) may lead to overestimation of stenosis severity by CCTA. Multiple patient-specific factors may result in suboptimal images, including a higher body mass index, frequent ectopy, atrial fibrillation (AF), and an inability to achieve optimal heart rate control. Additionally, patients with overt renal insufficiency or an allergy to contrast agents are unable to undergo CCTA. The negative effects of radiation are still a consideration despite improvements in technology with current radiation dosimetry ranging from 3 to 5 mSv, but this is much lower than traditional SPECT-MPI.[117] Another limitation of CCTA is its interpretation in elderly patients presenting with

dense coronary calcifications, particularly with a CAC score ≥ 400. The choice of non-invasive tests should always be individualized, accounting for local expertise, results of prior testing, and patient factors that influence test appropriateness and accuracy. However, CCTA should at least always be an option available to patients and providers. The Taiwanese NHI does not currently reimburse CCTA for evaluating CAD, limiting its utilization in the routine work-up for CAD.

Key Recommendations:

- CCTA is recommended as the initial first-line test to diagnose CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone (COR I, LOE B).
- CCTA may be considered as an alternative to ICA if a stress test is equivocal or non-diagnostic (COR IIb, LOE C).
- CCTA may be considered as an alternative to ICA to screen for CAD in patients with HFrEF (COR IIb, LOE B).
- A reduction in coronary arterial luminal diameter of ≥ 50% on CCTA should require further non-invasive stress testing(COR I, LOE A).
- Significant stenosis (≥ 50%) of the LM coronary artery, high-grade (≥ 80%) stenosis of the proximal LAD or three-vessel obstructive disease indicates a high risk and ICA should be considered (COR IIa, LOE B).
- FFR-CT should be considered to determine the hemodynamic relevance of coronary stenosis (COR IIa, LOE B).

7. PCI VERSUS MEDICAL TREATMENT

The advent of coronary revascularization techniques, with first CABG surgery in the 1960s and then PCI in the 1970s, represents one of the major breakthroughs in medicine during the last century. The benefit provided by PCI has been crucial in lowering mortality rates in ACS. However, in the setting of CAD where CCS is most prevalent, the reduction in MI or total death provided by coronary revascularization is unclear.

7.1 Cardiovascular outcomes

Over more than several decades, several milestone RCTs[5,8,118,119] have been carried out comparing OMT alone with a strategy of routine coronary revascularization on top of OMT. The COURAGE trial included 2287 CCS patients who had angiographic coronary stenosis > 70% with positive stress tests for ischemia or typical anginal symptoms. This trial failed to demonstrate significant differences in the risk of death, MI, or other MACEs between the two groups, but they did find a higher rate of acute MI complications derived from PCI. Extended follow-up analysis of the COURAGE trial for up to 15 years involving 1211 participants did not find a difference in long-term survival between both groups.[120] In the BARI 2D trial, 2368 diabetic patients with coronary stenosis > 50% documented on angiography were randomized to undergo revascularization (PCI or CABG) on top of OMT or intensive OMT alone. Again, the results of the PCI group showed a similar risk of all-cause death or MACEs regardless of whether the participants received PCI or OMT.[6] Both COURAGE and BARI 2D trials were conducted in the bare metal stent (BMS) era. Although important, there are concerns that these trials did not reflect the contemporary practice of PCI with new-generation drug-eluting stent (DES) (NG-DES). Contemporary trials with newer diagnostic modalities, physiologic assessment tools, and interventional devices would provide more solid conclusions. In the FAME 2 trial, 1220 patients with at least one functionally significant stenosis as identified by an FFR value < 0.8 were randomly assigned to PCI plus OMT or OMT alone.[7] The FFR-guided PCI strategy was more effective than OMT alone in reducing the risk of a combined endpoint (death, MI, or unplanned revascularization), mainly driven by a lower risk of urgent revascularization (HR: 0.23, 95% CI: 0.14-0.38) instead of death or MI. Of note, PCI was associated with a higher risk of the primary composite endpoint and death/MI rates in the early period (8 days) after randomization. Extended 5-year follow-up analysis of the FAME 2 trial still showed the consistent benefits of the PCI strategy with respect to urgent revascularization (HR: 0.27, 95% CI: 0.18-0.41), and again a neutral effect on all-cause death. Interestingly, the FAME 2 study reported that PCI plus OMT was associated with a higher angina-free rate than OMT alone at up to 3 years, but the difference was no longer significant at 5 years.[121]] The ISCHEMIA trial included 5179 CCS patients who had moderate or severe ischemia on stress testing.[8] All patients without contraindications underwent blinded

CCTA to identify those with obstructive CAD and exclude those with LM stenosis > 50%. This trial is very important owing to the comprehensive implementation of contemporary diagnostic testing and intervention devices, FFR/iwFR-guided approach, and randomization before ICA to eliminate potential bias. In the ISCHEMIA trial, even among the CCS patients with moderate to severe ischemia on non-invasive stress testing, routine invasive therapy failed to reduce MACEs compared with OMT. In contrast to the lack of benefits on definite CV events, the invasive strategy led to modest improvements in angina burden as measured by Seattle Angina Questionnaire (SAQ) scores (range, 0 to 100) over the short term (4.1-point improvement with PCI over 3 months [95% CI, 3.2 to 5.0 points]) and long term (2.9-point improvement with PCI over 36 months [95% CI: 2.2 to 3.7 points]). Routine invasive therapy was associated with harm at 6 months (increase in periprocedural MI) and associated with benefits at 4 years (reduction in spontaneous MI). Indeed, unprotected LM stenosis, LVEF < 35%, and unacceptable angina were excluded in the ISCHEMIA trial. Accordingly, these results do not apply to highly symptomatic patients, patients with LM disease, or LVEF < 35%. The ISCHEMIA-CKD trial had a similar study design to the ISCHEMIA trial and exclusively included 777 CCS patients who had ≥ stage 4 CKD at baseline.[119] The results showed that the cumulative event rate was similar with respect to the primary composite endpoint or key secondary outcome between both groups at a median follow-up of 2.2 years. However, the event rate of stroke and death or initiation of dialysis was significantly higher in the patients undergoing an invasive approach. A meta-analysis of 14 RCTs including nearly 15,000 participants with CCS demonstrated no significant association of routine revascularization with mortality compared with initial OMT and for MI overall, but found a significant association with lower rates of unstable angina (RR: 0.64, 95% CI: 0.45 to 0.92) and an association with fewer angina symptoms (RR: 1.10, 95% CI: 1.05 to 1.15).[122] Taken together, initial PCI plus OMT for CCS does not improve longevity or the risk of MI over OMT alone. These findings are not surprising, as studies have shown that the lesions which are responsible for ACS in CCS patients are not necessarily the ones that are more hemodynamically limiting. In fact, most infarcts are generated by nonflow-limiting and non-obstructive lesions, but PCI solely focuses on treating flow-limiting stenoses. This finding was validated by the PROSPECT trial,[123] which enrolled patients with ACS who had extensive 3-vessel imaging at their index hospitalization. When these patients presented with ACS during follow-up, more than half of these lesions were not significant at all at the index presentation. Interestingly, several of these management changes involved stenoses at the extremes; 30% of vessels with > 90% stenosis were surprisingly found to be functionally insignificant, and 5% of stenoses < 50% were actually found to be significant.[124] Thus, for patients with CCS, emphasis should be placed on optimizing LSM and controlling risk factors with preventive medications such as lipid-lowering and antiplatelet agents to reduce the risk of CV events and death. In the absence of high-risk features such as LV dysfunction, significant LM disease or high-grade MVD, invasive PCI therapy for CCS needs to be carefully considered in the context of angina burden.

7.2 Indication for coronary revascularization in CCS

Due to the heterogeneity of CCS, it is a challenge to determine in clinical practice which patients may benefit from PCI. A nuclear sub-study of the COURAGE trial revealed that adding PCI to OMT resulted in a greater reduction in ischemic area as assessed by nuclear MPI compared with OMT alone. Furthermore, these beneficial effects were more profound in patients with 10% or more ischemic myocardium at baseline.[125] The results of sub-analysis of the ORBITA trial also showed that baseline stress echo score was positively associated with better placebo-controlled efficacy of PCI with respect to angina-related health outcomes.[126] Based on dobutamine stress echo, a higher peak stress wall motion index score can also be used as the threshold for consideration of PCI. A post hoc analysis of the ISCHEMIA trial showed that the HF subgroup with LVEF < 40% could benefit from an invasive strategy with respect to the primary composite endpoint and CV death or MI, although p values for interaction were not statistically significant (0.055 and 0.061, respectively).[127] The appropriate use of coronary revascularization is determined by symptom status, non-invasive imaging findings, and coronary anatomy. Coronary revascularization is only deemed appropriate in patients with persistent symptoms despite OMT, high ischemic area ≥ 10% of the LV myocardium on stress

tests, high-risk anatomy features (LM stenosis ≥ 50% stenosis, proximal LAD ≥ 80% stenosis or 3-vessel disease on CCTA), and/or clinically HFrEF with suspected ischemic cardiomyopathy.

7.3 Physiology-guided PCI

The FAME 2 trial demonstrated that coronary revascularization improved QoL and reduced the use of anti-anginal medication compared to OMT in CCS patients with coronary stenosis and an FFR ≤ 0.80. At 5 years, the benefit of FFR-guided angioplasty vs. medical therapy was seen, with lower rates of urgent revascularization (HR: 0.27, 95% CI: 0.18-0.41) and spontaneous MI (HR: 0.62, 95% CI: 0.39-0.99).[121] Similar results were observed in a meta-analysis, in which contemporary FFR-guided PCI reduced the risk of MI or cardiac death by 28% compared to OMT in CCS patients (HR: 0.72, 95% CI: 0.54-0.96).[128] Avoiding hasty decisions particularly at borderline lesions is crucial, and if the potential benefit of revascularization is unclear, the use of invasive functional testing such as FFR or instantaneous wave-free ratio (iwFR) can be extremely helpful. Recent studies have investigated the use of iwFR, a pressure-derived index of stenosis severity that is obtained at rest without the use of adenosine, and identified a cut-off point of 0.89 compared to 0.80 for FFR. Regarding periprocedural complications as well as the prognosis, iwFR showed non-inferiority to FFR in the SWEDEHEART[129] and DEFINE-FLAIR[108] trials. These two RCTs found that the rates of short- and long-term MACEs were lower among patients who had PCI guided by physiology with either FFR or iwFR. Furthermore, Intravascular ultrasound (IVUS) and OCT, intravascular imaging technologies used to guide decision-making, can significantly improve clinical outcomes in contemporary PCI.[130,131]

Key Recommendations:

- OMT is recommended before considering ICA (COR I, LOE A) and ≥ 2 anti-anginal drugs should be used (COR IIa, LOE B).
- An invasive strategy for CCS patients fulfilling the appropriate criteria for ICA is associated with significantly better improvements in anginal symptoms and angina-related health status outcomes than OMT alone, especially in patients with more severe angina (COR I, LOE A).
- A routine invasive strategy for CCS patients with advanced CKD is not recommended (COR III, LOE B).
- A routine invasive strategy is not recommended for CCS patients to reduce total death, CV death, or MI (COR III, LOE A).
- A FFR ≤ 0.8 or an iwFR ≤ 0.89 indicates a high-risk lesion (COR I, LOE A).
- An invasive strategy should only be considered in CCS patients with high-risk features related to LV dysfunction (LVEF < 35%), coronary anatomy (LM or MVD with proximal epicardial lesions), or functional ischemia assessment (high ischemic area ≥ 10% of the LV myocardium on stress tests, or high peak stress wall motion index score > 1.7 on stress echo) (COR IIa, LOE B).

7.4 Selecting PCI or CABG

Both PCI and CABG are established strategies for coronary revascularization in the clinical setting. RCTs have also been performed to compare the safety and efficacy of CABG vs. PCI in CCS patients. Results from early studies demonstrated the benefit of CABG in CCS patients with high-risk features. In an important head-to-head comparison of the two revascularization strategies, the SYNTAX trial showed a higher incidence of MACEs and total deaths in the PCI group than in the CABG group. These results were particularly true for patients with high SYNTAX scores at 1, 3, and 5 years of follow-up. These results were subsequently supported by the FREEDOM trial[132] and BARI trial,[6] which demonstrated the superiority of CABG over PCI driven primarily by the advantage seen in patients with high-risk lesions (LM stenosis, complex MVD, or proximal LAD disease). A meta-analysis of 11 RCTs (n = 11,518 patients)[133] comparing PCI using first-generation DES with CABG for complex CAD showed that all-cause mortality was significantly higher with PCI compared with CABG. Specifically, the all-cause mortality rate observed after CABG was lower than that observed after PCI in patients with a diffuse CAD – associated high SYNTAX score of ≥ 33. In patients with SYNTAX scores < 33, PCI was as safe and effective as CABG. Similarly, patients with non-complex LM disease had similar survival with PCI and CABG. Based on a meta-analysis of six RCTs in patients with MVD, PCI with DES was not significantly associated with death or MI at 1 or 2 years. However, PCI was associated with a higher incidence of death and MI. In patients with MVD, PCI was

consistently associated with higher rates of repeat revascularization but with fewer strokes compared with CABG at 5 years. The rates of death and MI were significantly higher in the diabetic patients treated with PCI.[134] These RCTs were conducted before the widespread use of contemporary PCI, and showed the superiority of CABG over PCI in patients with higher disease burden and lesion complexity, and particularly in the presence of diabetes or LV dysfunction. However, the results of these early studies have been challenged in the current era. In the years since the SYNTAX results were first reported, advances in PCI technology and adjunctive therapies have significantly improved clinical outcomes. When comparing outcomes among patients undergoing PCI in the original SYNTAX I cohort (2005-2007), patients with de novo MVD who underwent contemporary PCI (2014-2015) in the SYNTAX II study had lower rates of repeat revascularization, MI, and mortality at 5 years. A prespecified analysis of the SYNTAX II PCI and matched SYNTAX I CABG cohorts showed similar MACCE outcomes at 5 years.[135] Recent data also imply that with improvements in technology and procedural techniques, the efficacy of PCI for LM revascularization may approach that seen with surgery. An updated meta-analysis of 4595 participants with LM disease from five RCTs comparing contemporary PCI with CABG who were followed up for more than 5 years[136] found that among patients with LM disease and, largely low or intermediate coronary anatomical complexity, there was no statistically significant difference in 5-year total death between PCI and CABG. Compared with CABG, PCI was associated with higher rates of repeat revascularization after PCI (OR: 1.89; 95% CI: 1.58-2.26), lower periprocedural MI at 30 days, non-periprocedural MI (OR: 2.32; 95% CI: 1.62-3.31) at 5 years, but lower rates of stroke (OR: 0.39, 95% CI: 0.16-0.98) at 30 days and (OR: 0.39, 95% CI: 0.21-0.73) 1 year. However, In the FAME 3 trial, 1500 patients with 3-vessel disease were randomly assigned to undergo CABG or FFR-guided PCI with NG-DES. FFR-guided PCI was not found to be noninferior to CABG with respect to the incidence of a composite of death, MI, stroke, or repeat revascularization at 1 year.[137] The 1-year incidence of the composite primary endpoint was 10.6% among patients randomly assigned to undergo FFR-guided PCI and 6.9% among those assigned to undergo CABG (HR: 1.5; 95% CI: 1.1 to 2.2), findings that were not consistent with the noninferiority of FFR-guided PCI (p = 0.35 for noninferiority). The incidence of death, MI, or stroke was 7.3% in the FFR-guided PCI group and 5.2% in the CABG group (HR: 1.4; 95% CI: 0.9 to 2.1). PCI continues to play an important role among selected patients with severe CAD, unprotected LM or complex MVD, particularly when the risk of operative mortality or complications with CABG surgery is high. Contemporary PCI may include the liberal use of coronary physiology (FFR/iwFR), intravascular imaging (IVUS/OCT), NG-DES, and intensified OMT.

7.5 Role of the heart team in decision-making for coronary revascularization

Although the trials completed to date present a consistent message regarding the role of PCI to improve angina symptoms rather than reduce the risk of MI or death in CCS patients, it is more difficult to reach a clear conclusion regarding CABG surgery in the contemporary era, given improvements in medical therapies and accumulating expertise with complex PCI. In general, patients with less extensive CAD be treated with PCI, while those with more complex and severe disease can be referred for CABG. Patients with LM or complex MVD who have diabetes or systolic dysfunction may prefer to undergo surgical revascularization; PCI can be considered as an alternative if they are poor candidates for surgery. Shared decision-making between the patient and clinician should guide choices between PCI and CABG, and the patient should be informed of the procedural risks of PCI (such as peri-procedural MI, bleeding and contrast-induced kidney injury), risk of operative mortality or complications (such as stroke in the first month) with CABG, and their options for alternative medical treatments for angina relief. Revascularization decisions in high-risk patients with diabetes, LM disease, and complex MVD can be optimized using a Heart Team approach with consideration of LV function, disease complexity and technical feasibility of treatment and patient preferences.

Key Recommendations:

- In CCS patients with undetermined ischemia and angiographically intermediate stenoses, the use of FFR or iwFR is recommended to guide the decision prior to proceeding to PCI (COR I, LOE A).
- In CCS patients with LM stenosis or MVD with a SYN-

TAX score > 32. and LVEF < 35%, CABG should be considered as the preferred revascularization option (COR IIa, LOE B).

- CABG may be considered as the preferred option even in the presence of a lower SYNTAX score when multiple complex lesions are present and PCI remains technically limited to achieve complete revascularization (COR IIb, LOE B).
- In selected patients with CCS and 1- or 2-vessel disease involving the proximal LAD, isolated ostial or shaft LM disease, and MVD with simple lesions (a SYNTAX score < 23), PCI should be considered (COR IIa, LOE B).
- For patients with significant LM disease and a SYNTAX score > 32, CABG is better than PCI to improve survival (COR I, LOE A).
- PCI can be considered but tends to be inferior to CABG for a distal LM (bifurcation) lesion, especially in combination with MVD and a SYNTAX score < 32 (COR IIa, LOE B).

7.6 Algorithm for the appropriate use of cardiac catheterization for suspected CCS

A three-step approach is proposed for symptomatic patients with suspected CCS as shown in Figure 4. The first step is to assess the symptoms and signs to exclude ACS. In patients without ACS, the next step is to estimate the PTP and clinical likelihood of obstructive CAD. To determine the likelihood, PTP should be carefully assessed with other coronary risk factors, LV function, abnormal resting or exercise ECG changes, and CAC if available. Step 2 considers anatomic or stress testing for significant CAD. Once a diagnosis of obstructive CAD has been confirmed, the patient's event risk will be determined (Step 3) as it has a major impact on the subsequent therapeutic decisions. Recent evidence has shown that only subgroups classified as appropriate or uncertain benefit from PCI in terms of coronary revascularization compared to OMT alone. Angina frequency and physical limitations are reduced by PCI only in appropriately selected subgroups. In the ORBITA trial, a median of three anti-anginal drugs were used, and more than 97.5% of the participants achieved the pre-specified target (≥ 2 anti-anginal drugs).[138] It is reasonable to recommend ICA if CCS patients are still symptomatic while using ≥ 2 anti-anginal drugs. Another issue is to determine the cut-off values of luminal stenosis for CCTA in this algorithm. The term "obstructive CAD" is used to indicate

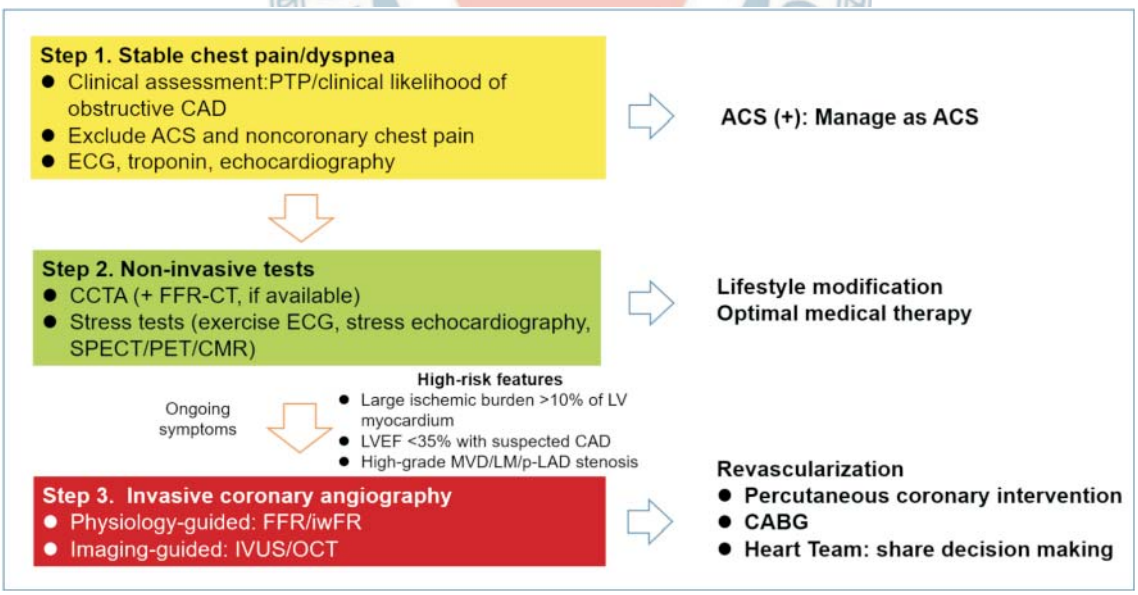


Figure 4. *The 3-step approach for the diagnosis of patients with stable symptoms and suspected obstructive CAD. ACS, acute coronary syndrome; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; ECG, electrocardiography; FFR, fractional flow reserve; FFR-CT, fractional flow reserve-computed tomography; IVUS, intravascular ultrasound; iwFR, instantaneous wave-free ratio; LM, left main; LV, left ventricle; LVEF, left ventricular ejection fraction; MVD, multi-vessel disease; OCT, optical coherence tomography; p-LAD, proximal-left anterior descending artery; PTP, pretest probability; PET, positron emission tomography; SPECT, single-photon emission computed tomography.*

CAD with ≥ 50% stenosis, and "non-obstructive CAD" is used to indicate CAD with < 50% stenosis. In addition, the term "high risk CAD" is used to denote patients with obstructive stenosis who have LM ≥ 50% or anatomically significant major epicardial disease ≥ 80% stenosis. Patients with non-LM lesions with ≥ 80% luminal stenosis can directly proceed to PCI without FFR/iwFR assessment, and lesions between 50-80% luminal stenosis should be assessed by FFR or iwFR to determine whether or not to proceed to PCI.[8] With the increasing effectiveness of prevention with OMT, invasive strategies should only be considered in patients with uncontrolled symptoms despite OMT or high-risk features related to LV dysfunction (LVEF < 35%), coronary anatomy (significant LM or MVD with proximal epicardial lesions), hemodynamically significant lesions with FFR ≤ 0.8 or iwFR ≤ 0.89, or functional ischemia assessment (high ischemic area ≥ 10% of the LV myocardium on stress tests or high peak stress wall motion index score > 1.7 on stress echo), taking into account the patient's expectations and preferences. A scheme for the appropriate use of cardiac catheterization for suspected CCS is shown in Figure 5.

8. SCREENING FOR CCS IN APPARENTLY HEALTHY ADULTS

Often MI or SCD is the first manifestation of CAD, suggesting the need for more effective screening of high-risk asymptomatic patients.[139,140] Furthermore, asymptomatic 'silent' myocardial ischemia increases the likelihood of future coronary events.[141,142] On the other hand, advanced obstructive CAD can exist with minimal or no symptoms, with manifestations that can progress suddenly and/or rapidly with either ACS or sudden death, emphasizing the importance of early detection and treatment of underlying subclinical coronary atherosclerosis.[143] The rationale for screening to identify existing critical disease and detect CAD during the non-obstructive stages of disease is the hope that appropriate treatment (medical therapy or coronary revascularization) may reduce the likelihood of future events. On the contrary, a common criticism of routine screening in general is the potential that false positive results may cause harm including unnecessary downstream invasive procedures and overtreatment. The current AHA/ACC primary pre-

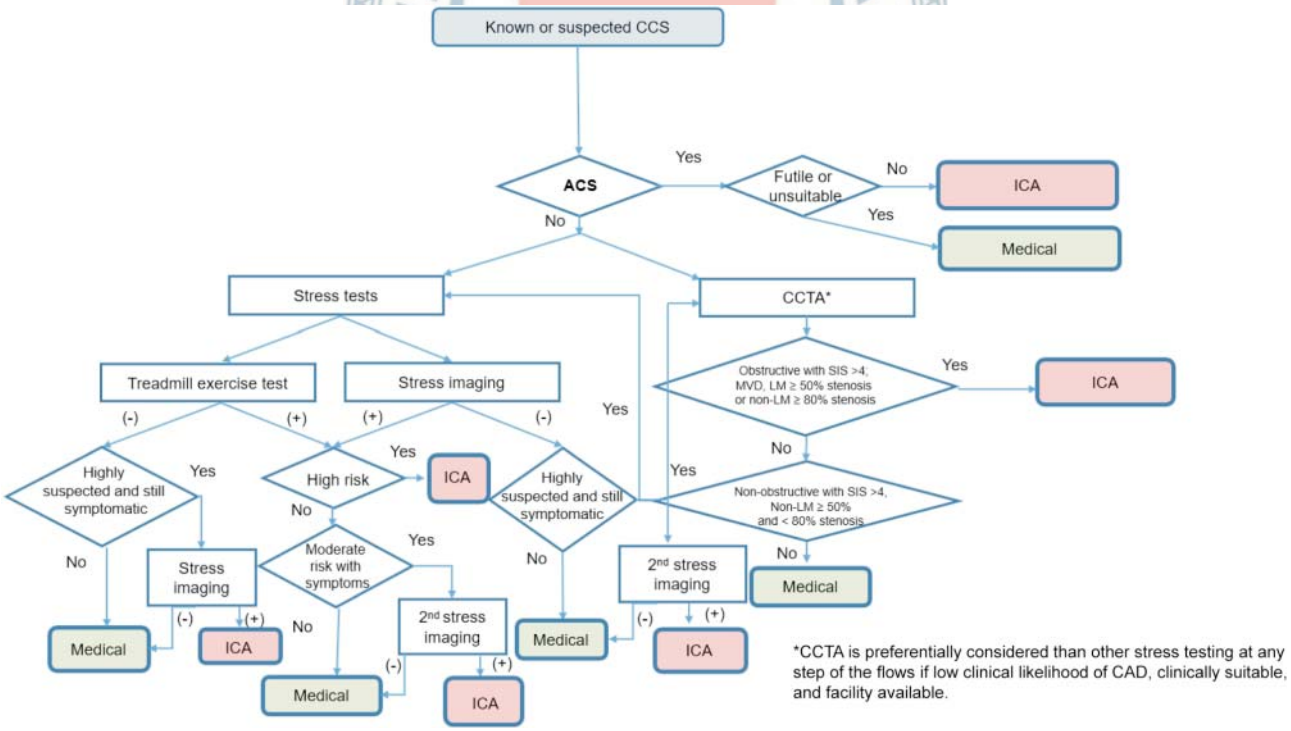


Figure 5. *The algorithm of appropriate use of cardiac catheterization for known or suspected CCS. ACS, acute coronary syndrome; CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; ICA, invasive coronary angiography, LM, left main; MVD, multiple vessel disease; SIS, segment involvement score.*

vention guidelines recommend atherosclerosis screening for those aged 40-75 years using clinical risk assessment algorithms.[144] With respect to screening for CCS, identifying patients at high risk could be central, since these are the patients in whom an intervention would likely have the greatest benefit. In an effort to lower the high burden of coronary deaths, screening tools using risk factors, laboratory markers and stress tests are often performed to predict the likelihood of acute CV events in asymptomatic individuals. A recent large population-based randomized screening (DANCAVAS) trial recruited 46,611 participants aged 65 to 74 years who underwent multifaceted screening (including CAC, resting 12-lead ECG, ankle-brachial index, BP recording and blood tests to detect diabetes mellitus and hypercholesterolemia) for subclinical CVD. After more than 5 years, the screening group did not have a significantly lower incidence of all-cause mortality.[145]

8.1 Screening for CCS in apparently healthy individuals without known ASCVD

Age is the major driver of CAD risk. People below 40 years of age are almost invariably at low 10-year CAD risk, but may have unfavorable modifiable risk factors that sharply increase their longer-term CAD risk. All people aged 40 years or older without established ASCVD should undergo CV risk assessments every 3 to 5 years.[146,147]

8.2 Screening for CCS in asymptomatic specific subgroups

It is important to note that patients with chronic inflammatory diseases (such as psoriasis and systemic lupus erythematosus), familial hypercholesterolemia, strong family history of premature MI, and CKD with estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, a population at higher risk of CAD, may deserve more intensive risk screening and management. In addition, individuals whose occupations involve public safety (e.g., airline pilots or bus drivers), or who are professional or high-profile athletes, commonly need to undergo periodic evaluations for possible CCS. Notably, CAD has been found in 85% of pilot autopsies after fatal accidents.[148]

8.3 Screening for CCS in asymptomatic patients with diabetes above 40 years of age

Recent guidelines no longer consider diabetes as a CAD risk equivalent and recommend CV risk stratification for primary prevention. Screening may be appropriate for certain diabetic patients who are generally a higher-risk population. Stratification may discriminate higher from lower-risk patients who may need intensive statin or aspirin prevention therapy, while avoiding overtreatment in lower risk cases. This also allows the clinician to decide whether to intensify risk reduction actions through specific newer cardiometabolic drugs such as SGLT2 inhibitors or GLP-1 receptor agonists, which have recently been shown to have additional CV protective effects. Several prospective RCTs have evaluated the impact of routine screening for subclinical CAD and the effect of therapy on the outcomes of asymptomatic diabetic patients, and found no significant improvement in outcomes among patients who underwent screening.[149,150] A meta-analysis of five RCTs, including 3314 patients with diabetes, showed that a screening strategy did not have an impact on all-cause mortality (OR: 1.00, 95% CI: 0.67-1.50), with non-significant trends for a lower risk of CV death (OR: 0.71, 95% CI: 0.40-1.27), and nonfatal MI (OR: 0.60, 95% CI: 0.23-1.52).[150] In the DIAD trial, 1123 diabetic patients with no symptoms of CAD were randomly assigned to be screened or not with stress MPI. After 4.8 years of follow-up, no additional benefits were observed. The event rate was 2.7% in the screened group and 3.0% in the non-screened group, which was not significantly different (HR: 0.88, 95% CI: 0.44-1.88).[151] Compared to the general population, data for patients with diabetes suggest that routine screening with MPI for all asymptomatic patients has a low yield and limited effect on outcomes.[152] In unselected asymptomatic diabetic patients who are being treated with appropriate risk factor reduction, screening for CAD has not been shown to improve clinical outcomes. As such, routine screening for CAD in asymptomatic diabetic patients is not recommend. However, high-risk subgroups who may benefit from screening (and revascularization) to improve outcomes, and the sequential use of CAC score followed by radionuclide MPI for screening may be considered in patients with severe atherosclerosis (i.e., CAC score $\geq$ 400).

Key Recommendations:

- Routine screening for CAD is not recommended in asymptomatic patients with diabetes (COR III, LOE A).
- Screening for silent CAD by stress tests may be consid-

ered in selected high-risk diabetic patients with PAD, CKD with eGFR < 60 mL/min/1.73 m^2, proteinuria, or a high CAC score (i.e., > 400) (COR IIb, LOE C).

8.4 Taiwan CAD risk calculator in the primary prevention

Risk assessment is a central step in the current approach for the primary prevention of CAD. In asymptomatic individuals, the primary prevention of CAD is often based on the predicted 10-year risk of a coronary event. Knowledge of the 10-year risk of CAD identifies patients in higher-risk groups who are likely to have greater net benefit. Given that genetic predispositions may, to a varying extent, confer biological interactions with other risk factors, it is reasonable to derive population-specific models to optimally estimate CAD risk among different ethnicities. Various clinical risk scores have been developed and validated in different populations, including the Framingham Risk Score (FRS), AHA/ACC Pooled Cohort Equation (PCE), and ESC-Systematic COronary Risk Evaluation (SCORE) algorithm. Current US primary prevention guidelines recommend the use of the PCE,[153] which predicts 10-year ASCVD events (MI and stroke both fatal and nonfatal), with an elevated (moderate-high) risk defined as ≥ 7.5%. European guidance is based on the SCORE clinical algorithms that predict the 10-year risk of fatal CVD (fatal CAD, stroke or aneurysm), with an elevated risk (moderate-high) defined as > 1-5%.[154] However, the commonly used ASCVD risk estimation schemes to guide clinical decisions in primary prevention have mainly been derived and validated in Caucasian and African American populations, and their relevance to Asian populations has been questioned. For instance, the ACC/AHA ASCVD score tends to overestimate the risk in Asian populations.[155] Such imprecision in ASCVD risk estimation in different ethnic groups may result in a mismatch between ASCVD risk and treatment intensity. In the present guidelines, a point-based risk estimation tool using the Taiwan Chin-Shan Community Cardiovascular Cohort (TwCCCC) prediction model (Table 7) is recommended. This risk estimator was developed from the TwCCCC cohort study in the 1990s consisting of 3430 adults without a history of ASCVD at baseline; it specifically predicts the 10-year risk of CAD events consisting of fatal and nonfatal MI and coronary revascularization. As with the FRS, it relies on a set of traditional risk factors, namely, age, sex, hypertension, LDL-C, and HDL-C, and it was externally validated in an independent cohort of 22,193 individuals between 2003 and 2006.[156] To facilitate routine clinical practice to predict the 10-year CAD risk in Taiwan, an on-line point-based risk calculator is available at http://140.112.117.151/klchien/. 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. The estimation may help evaluate clinical risk status, assist in making logical management decisions, and avoid both under- and overtreatment. The clinician-patient discussion to utilize the tool to discuss the best ways to lower CAD risk is emphasized in these guidelines. Although clinical risk scores are useful for the initial estimation of risk, they may have limitations. Nevertheless, discordance between the FRS and atherosclerotic plaque burden has been noted.[157] To improve risk prediction, the guidelines suggest risk modifiers using non-invasive cardiac imaging (such as CAC by cardiac CT scan) in those deemed to be at low or intermediate risk. The guidelines suggest the use of CAC to up- or down-classify patients with borderline-intermediate risk and for initiating or intensifying preventive pharmacotherapies, as shown in Figure 6. As such, the CAC score may be incorporated along with current TwCCCC risk profiling to refine the risk on an absolute scale by combining imaging and clinical data to affect a more comprehensive calculation of CAD risk in a given individual. Some populations, such as those with a strong family history of premature MI, familial hypercholesterolemia, diabetes, CKD (eGFR < 60 mL/min/1.73 m^2), connective tissue diseases, autoimmune diseases and malignancy, may be at a higher risk than indicated in the TwCCCC chart. Notably, such individuals at high risk require immediate attention to control risk factors rather than a risk score assessment.

Key Recommendations:

- After the age of 40 years, it is reasonable to assess traditional CAD risk factors (COR IIa, LOE A).
- For adults 40 to 75 years of age without established ASCVD, chronic inflammatory diseases, diabetes, CKD (eGFR < 60 mL/min/1.73 m^2), or a family history of

Table 7. Estimate 10-year CAD risk by the TwCCCC point-based risk calculator

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
	< 110	5
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
0	0.000
1	0.001
2	0.001
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/).

CAD, coronary artery disease; BMI, body mass index; SBP, systolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprortein; TwCCCC, Taiwan Chin-Shan Community Cardiovascular Cohort.

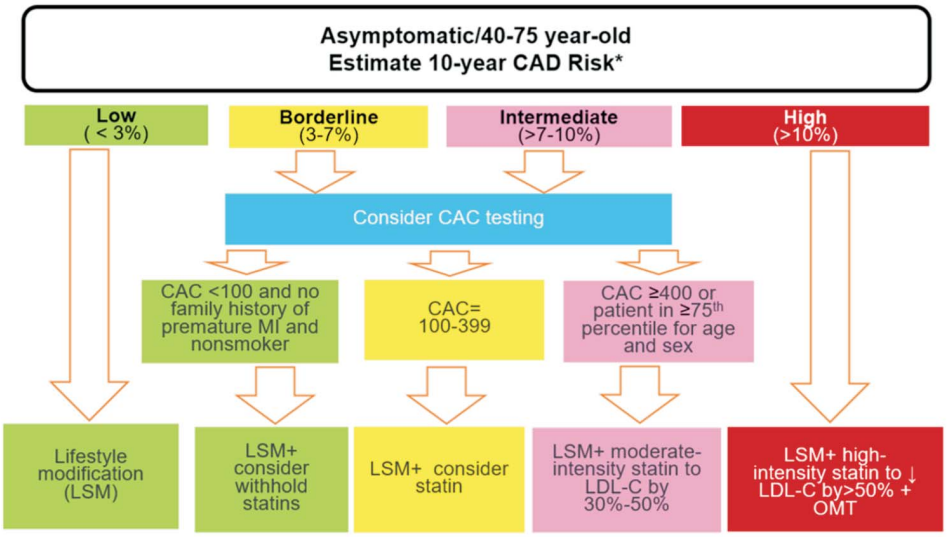
premature MI, clinicians should consider assessing traditional risk factors and calculate the 10-year risk of CAD by using the TwCCCC risk charts (COR IIa, LOE B).

8.5 Exercise ECG to screen for CCS in asymptomatic adults

RCTs have reported that routine screening with exercise ECG in asymptomatic adults aged 50 to 75 years did not result in improvements in CV outcomes compared to no screening.[158] Nevertheless, in asymptomatic adults at low risk of CAD, the potential harms of exercise ECG (e.g., arrhythmias, sudden death ~ 1/10000 and subsequent downstream ICA procedures after false-positive results) might be equal to or exceed the potential benefits.[159,160] Most asymptomatic patients who present with multiple risk factors without cardiac symptoms have a normal resting ECG. Such patients are more likely to have normal LV function and an excellent prognosis. For these reasons, these guidelines recommend against screening asymptomatic patients who are at low risk of CCS. However, a stepwise strategy is generally recommended in which an exercise ECG, and not a stress imaging procedure, is performed as the initial test in asymptomatic patients at intermediate-high risk of CAD. Standard Bruce protocol exercise stress testing is still a useful screening modality that does not require radiation, is inexpensive, and provides information about functional capacity. As such, in asymptomatic subjects at intermediate-high risk, an exercise ECG test, if tolerated, is the most appropriate and useful test.

Key recommendations:

- Exercise ECG is not recommended for low-risk, asymptomatic adults (10-year CAD risk < 3%), as determined by TwCCCC charts (COR III, LOE B).



The TwCCCC point-based 10-year CAD risk calculator

Risk factor	Points
Age	0-8
Sex	0, 3
Systolic blood pressure	0-4
LDL-C	0-2
HDL-C	0-5
BMI	0-2

10 year CAD Risk	Total points
Low	1-14
Borderline	15-17
Intermediate	18-19
High	20-24

*Estimate 10-year risk by the Taiwan Chin-Shan Community Cardiovascular Cohort (TwCCCC) risk calculator, available at http://140.112.117.151/klchien/

Figure 6. *The screening and management of subclinical CAD in apparently healthy adults. BMI, body mass index; CAC, coronary artery calcium; CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LSM, lifestyle modification; OMT, optimal medical therapy; TwCCC, Taiwan Chin-Shan Community Cardiovascular Cohort.*

- Exercise ECG, if tolerated, should be considered as the preferred test for asymptomatic adults at intermediate-high risk (10-year CAD risk, > 7%), as determined by TwCCCC charts (COR IIa, LOE C).

8.6 CAC for screening for CCS in asymptomatic adults

The latest European and American Societal guidelines incorporate the use of CAC score as a risk modifier or enhancer for asymptomatic adults at low-moderate risk.[105,144] Evidence from robust prospective studies has shown that advanced CAC, defined mainly as a CAC score ≥400 or > the 75th percentile for age and gender, can identify individuals at high risk of coronary events and mortality for primary prevention.[79] It is widely accepted that CAC severity is a more powerful CVD risk predictor than the PCE or FRS. In the Multi-Ethnic Study of Atherosclerosis (MESA) study, 6698 apparently healthy subjects with no risk factors and CAC score of 300 had an event rate 3.5 times higher than individuals with ≥ 3 risk factors and CAC score of 0 (10.9/1000 vs. 3.1/1000 person-years).[161] Although there were associations between the burden of coronary atherosclerosis, and either SCORE or PCE risk score, important subgroups were identified where atheroma burden was not accurately represented by either risk score. Clinical risk assessment tools may underestimate CAC, and hard coronary events significantly increase with an increase in CAC more than the extent with an increase in risk factors. In the MESA study, net reclassification improvement with the use of CAC score was achieved in more than half of the patients classified as intermediate risk by traditional risk factor assessment. Large long-term population-based observational studies in asymptomatic subjects have consistently shown that CAC provides incremental risk information beyond traditional risk calculators (e.g. FRS).[157,162] Based on a Taiwanese study which screened 509 asymptomatic subjects with at least one risk factor, significant coronary stenosis > 50% was found in 32% of the participants with a non-zero CAC score, and CAC score strata showed noteworthy correlations with significant coronary stenosis.[163] Moreover, the recent large-scale SCAPIS registry in the general population provided insights into the prevalence of severe coronary atherosclerosis stratified by CAC score. In asymptomatic persons with a high CAC score (≥ 400), it was remarkable that 1 of 5 had ≥ 50% lumen stenosis in the LM stem,

proximal LAD, or all three coronary arteries.[164] CAC is of most value in intermediate risk asymptomatic patients who do not have known CAD and are aged 40-75 years, where it can help to reclassify patients into lower or higher risk groups. Of note, CAC score should not be used in high-risk asymptomatic patients, because it can be low or even zero in middle-aged patients with soft non-calcified plaque.

Key recommendations:

- CAC score may be considered as a risk modifier in the CV risk assessment of asymptomatic individuals at low-moderate risk (COR IIb, LOE B).
- CAC score is not recommended for asymptomatic patients who are at high risk (COR I, LOE B).

8.6.1 CAC-guided medical therapy in primary prevention

Optimal diet and lifestyle measures are encouraged in all risk groups and form the basis of primary prevention strategies. Heterogeneity of CAD risk exists among asymptomatic primary prevention adults. The use of CAC testing may allow for more precise allocation of preventive therapies among adults without ASCVD. The concept of using CAC to help refine the risk/benefit balance for aspirin was studied by the MESA investigators.[165] The investigators recruited 4229 non-diabetic aspirin-naïve patients, all free of ASCVD, and determined that those with a CAC score > 100 had a net benefit from aspirin irrespective of their Framingham risk estimate, whereas those with a CAC score of zero had net harm from primary aspirin prevention regardless of FRS. The MESA trial demonstrated that the addition of CAC to traditional risk factors could improve risk classification, particularly in intermediate risk asymptomatic patients. Notably, clinical trials of low-dose aspirin in patients without CVD have inconsistently demonstrated improvements in CV outcomes, with potential benefits countered by increased risks of clinically significant bleeding.[166,167] Based on these findings, it may make sense to identify those with a CAC score of zero to avoid overtreatment (either with aspirin or statins) and those with a CAC score ≥ 400 to avoid undertreatment and ensure long-term adherence to a cost-effective treatment (aspirin and statin use).[168-170] The management of CAC requires shared decision-making with the patient considering the risks and benefits of medical therapies and patient preference. Patients with a CAC score ≥ 400 are recommended to receive preventative medical therapy such as aspirin and statins, unless otherwise deferred by the outcome of clinician-patient risk discussion. The evidence for pharmacotherapy is less robust in patients with intermediate CAC scores (100-399), with modest benefits with aspirin use, although statins may be reasonable if they are above the 75th centile. This leads to clinician-patient risk discussion to consider the pros and cons of low-dose aspirin therapy in primary prevention. These findings support the utility of CAC for decision-making by better defining high-risk CAC, for which the benefit of treatment most likely exceeds the risk in asymptomatic individuals. Thus, we suggest considering aspirin use only in patients with a CAC score ≥ 400 and low bleeding risk when the anticipated benefit exceeds the risk. Aspirin and statins are generally not recommended for asymptomatic patients with a CAC score < 100. The TSOC guidelines endorse CAC using the Agatston method as an adjunct to the TwCCCC model for enhanced risk assessment to guide management in asymptomatic individuals. Currently, the NHI does not reimburse for CAC testing in Taiwan.

8.6.2 CAC and statin use

Paradoxically, although sometimes the CAC increases with statin therapy, this does not increase CV risk. Statin therapy may modestly accelerate calcification of plaques leading to more stable, lower-risk composition.[171-173] It is therefore necessary for clinicians to take into account statins when interpreting subsequent CAC score. Recently, a report of 28,000 participants from the CAC Consortium showed that the association between CAC and outcomes in statin users was significantly attenuated compared to those in nonusers, however, the improvement in predictive value compared to risk factor models alone was similar in both groups. In statins users, the CAC score was shown to have prognostic utility for CAD risk, suggesting that CAC burden also predicts CAD risk in statin users.[174]

Key Recommendations:

- If the CAC score is zero, aspirin or statin therapy is not indicated in asymptomatic low-intermediate risk adults (COR III, LOE C).
- If the CAC score is 1-99, statin therapy may be consid-

ered for primary prevention (COR IIb, LOE B).

- If the CAC score is 1-99, aspirin therapy may be considered for primary prevention in those with a low bleeding risk (COR IIb, LOE C).
- For asymptomatic adults with a CAC score 100-399, statin use may be considered if they are above the 75th centile for age and gender (COR IIb, LOE B).
- For asymptomatic patients with a CAC score 100-399 and low bleeding risk, aspirin may be considered if they are above the 75th percentile for age and gender (COR IIb, LOE B).
- For asymptomatic subjects, if the CAC score is ≥ 400 or ≥ 75th percentile, statin therapy should be considered (COR IIa, LOE B).
- For asymptomatic subjects with a CAC score ≥ 400 and low bleeding risk, aspirin therapy may be considered (COR IIb, LOE B).

8.7 CCTA for screening for CCS in asymptomatic adults

In Taiwan, many institutions perform CCTA testing in asymptomatic individuals as part of health screening programs. Over the past few years, an increasing body of evidence on the potential role of CCTA in selected asymptomatic individuals has emerged. Although obstructive lesions are often believed to be more likely to cause clinical events, subclinical non-obstructive plaques were responsible for subsequent MI in 42% and 66% of future events in the SCOT-HEART and PROMISE trials, respectively.[87,175] It would seem appropriate, therefore to consider further management of subclinical CAD regardless of whether lesions are non-obstructive or obstructive. The CONFIRM registry is the latest and largest registry enrolling asymptomatic subjects, in which 27,125 consecutive patients and 7590 individuals were enrolled. During a median follow-up of 2 years, individuals with obstructive MVD or LM disease experienced higher rates of all-cause mortality and nonfatal MI (both $p < 0.05$) compared to individuals without evidence of CAD by CCTA.[176] In this trial, an adjusted HR of 3.9 (95% CI: 2.7-5.5) for death or nonfatal MI for the presence of obstructive CAD, and 1.18 (95% CI: 1.13-1.24) for the segment involvement score (SIS), a semi-quantitative measure of the extent of coronary atherosclerosis irrespective of plaque severity.[177] In a large-scale study of the general population including 25,182 individuals from SCAPIS registry, silent CAD was common (42%) with significant stenosis (≥ 50% by CCTA) in 5%, and more severe forms (significant LM, proximal LAD disease, or MVD) in 2% of individuals aged 50 to 64 years without known CAD.[164] Another study of 1000 asymptomatic patients evaluated the prevalence of occult CAD on CCTA and the ability to predict future adverse coronary events.[178] Atherosclerotic plaques were found in 22% of all patients, significant luminal stenosis (> 50%) in 5% of the patients, and stenosis > 75% in 2% of the patients. In patients with significant stenosis, 25% were initially classified as low risk, and 58% had a low CAC score < 100. At mid-term follow-up, all identified coronary events occurred in individuals in whom CCTA had detected CAD. In another study of 441 patients with suspected CAD, CCTA provided added incremental prognostic value compared with a combined clinical risk model and CAC. The presence of non-calcified or mixed plaques, independent of the lesion severity, was the strongest predictor of events ($p < 0.0001$).[179] A study of 1451 asymptomatic low-to-intermediate risk patients with CAC zero by CCTA reported that ~ 6% of patients had soft plaques of ≥ 50% luminal stenosis and 8% had high-risk plaque features.[180] At a mean follow-up of 6.6 years, the all-cause mortality rate was 2.7% in patients with CAC zero. Traditional risk scores may not be precise and may result in both unnecessary life-long therapies in those without disease and failure to initiate treatment in those at high risk. As with CAC, CCTA may serve as an additional risk stratification tool for primary prevention. CCTA can not only identify obstructive CAD, but also define non-obstructive lesions, soft non-calcified plaque with a zero calcium score and high-risk plaques, providing invaluable information for when and how to treat such individuals. A meta-analysis of 11 CCTA studies enrolling 9777 subjects found that the burden of atherosclerotic CAD as quantitatively assessed by SIS was a strong independent predictor of MACEs (HR: 1.25; CI: 1.16, 1.35; $p < 0.001$).[181] The SIS score was developed to determine the extent of coronary atherosclerosis irrespective of plaque severity as a measure of coronary atherosclerotic burden on CCTA imaging. The SIS score ranges from 0 to 16, and it is calculated as the total number of coronary artery segments exhibiting plaques, scored as absent or trace (score of 0) or present (score of 1), irrespective of the degree of luminal stenosis or its composition whether calcified or

not. ASIS score > 4 is defined as extensive atherosclerotic disease. Compared to CAC, CCTA is associated with a higher radiation dose and the risks of contrast media administration. These risks are real and need to be carefully weighed when considering CCTA as a screening test in large populations of asymptomatic individuals. Modern CT scanners and imaging protocols enable the rapid and accurate quantification of coronary atherosclerosis at a low radiation dose below < 5 mSv, and raise the possibility that CCTA could play a wider role in the targeting of preventative therapies through screening. Indeed, the latest ESC guidelines recommend a class IIB indication for CCTA for asymptomatic high-risk adults (diabetes, strong family history of CAD, high risk of CAD in non-invasive studies). In addition, the 2019 ESC guidelines highlighted the lack of evidence for the impact of CCTA on outcomes in asymptomatic patients. The upcoming SCOT-HEART II study may help answer key residual questions regarding whether the benefits of CCTA over and above CAC and/or current multivariate risk scores also result in meaningful restratification of management in asymptomatic individuals and are associated with clinical benefits.

Key Recommendations:

- In low-risk asymptomatic adults (TwCCCC 10-year CAD risk < 3%), CCTA is not indicated for CV risk assessment (COR III, LOE C).
- In intermediate-high risk asymptomatic adults (TwCCCC 10-year CAD risk > 7%), CCTA may be considered for CV risk assessment (COR IIb, LOE C).
- In high-risk asymptomatic adults (diabetes, strong family history of CAD, high risk of CAD in non-invasive tests, TwCCCC 10-year risk > 10%), CCTA should be considered for CV risk assessment (COR IIa, LOE C).

8.7.1 CCTA for screening for CCS in asymptomatic diabetic adults

The FACTOR-64 trial was a RCT in which 900 patients were randomized to receive CCTA screening or standard care to evaluate whether routine CCTA screening in a high-risk population affects changes in treatment and leads to a reduction in cardiac events.[182] High-risk asymptomatic patients with diabetes were randomized to receive either screening with CCTA with subsequent therapy directed by the imaging results, or standard treatment. CCTA showed no CAD in 31%, mild stenosis in 46%, moderate stenosis in 12%, and severe stenosis in 11% of the patients. There was a 20% lower rate of primary endpoint events (all-cause death, nonfatal MI, and hospitalization for ACS) in the CCTA group. CCTA screening led to more aggressive risk factor modification in 70% of the patients, including improvements in statin use and more aggressive treatment of serum lipids and blood pressure. In a study of 3370 diabetic patients and 6740 propensity-matched patients that evaluated the prognostic value of CCTA, mortality was significantly higher in the diabetic patients with both non-obstructive and obstructive CAD.[183] Interestingly, in 400 asymptomatic diabetic patients, the incremental prognostic value of CCTA over CAC was shown.[184] The major purpose of screening for CAD in diabetic patients is to identify patients whose prognosis could be improved with an intervention (e.g., aggressive medical therapy for risk factors or coronary revascularization). Screening of asymptomatic diabetic patients with a high risk of CAD by CCTA may be potentially useful clinically. Due to the potential overestimation of obstructive coronary disease by CCTA, it is advisable to perform additional stress testing for the presence of significant ischemia prior to ICA and revascularization in asymptomatic individuals.

Key Recommendations:

- In high-risk asymptomatic adults with diabetes (e.g., with a strong family history of MI, multiple risk factors, PAD, CKD with eGFR < 60 ml/min/1.73 m^2) stress imaging tests for myocardial ischemia may be considered for CAD risk assessment (COR IIa, LOE B).

8.7.2 CCTA-guided medical therapy in primary prevention

To date, there are little data to guide decisions regarding the use of aspirin after CCTA according to the burden of calcified or non-calcified plaque. The prognostic and therapeutic implications of statin and aspirin therapy in individuals with non-obstructive CAD detected by CCTA were explored in a substudy from the CONFIRM registry in subjects with normal or non-obstructive CAD at study entry. The data showed that aspirin therapy did not result in a statistically significant reduction in MACEs or all-cause mortality in people with non-obstructive CAD, but that statin use did ($p = 0.007$).[185] Neither aspirin nor statin therapy improved clinical out-

comes for patients with no detectable plaque. In this study, non-obstructive CAD involving more vessels was associated with reduced clinical survival during follow-up, and statin therapy only reduced the risk of mortality in those with plaque (HR 0.44: 0.28-0.68) but not in those without (HR 0.66: 0.30-1.43).[186] An increasing amount of plaque as determined by CCTA using SIS score was associated with increased all-cause mortality. Statin treatment in subjects with non-obstructive CAD and high burden with a SIS score > 4 has been associated with higher event-free survival during follow-up.[187] In particular, non-calcified plaque has been shown to have a higher tendency to regress in response to established medical therapies.[188] The prospective, multinational PARADIGM study registered consecutive patients without known CAD who underwent CCTA at an interval of ≥ 2 years, and found that statin treatment was associated with a significant reduction in annualized growth in percent atheroma volume. There was also a reduction in the rate of newly developed adverse atherosclerotic features.[173] Although the CONFIRM study did not show the benefits of aspirin for primary prevention, it seems reasonable to establish a non-obstructive coronary artery plaque burden (i.e., SIS score > 4) on CCTA at which the benefits of aspirin exceed the risk, representing an extension of plaque utilization to address specific patient preventive treatments. In summary, studies on CCTA-guided statin therapy in non-obstructive CAD have shown that statin use, or its intensification is beneficial in subjects with extensive plaque (SIS score > 4) or high-risk plaque features. In terms of the treatment target, no RCT has explored this issue. However, the treatment goal of an LDL-C level of 100 mg/dl for TwCCCC-based moderate-high risk subjects might be a reasonable target.

Key Recommendations:

- If no plaque is seen in CCTA, aspirin or statin therapy is not indicated in asymptomatic low-intermediate risk adults (COR III, LOE B).
- If non-obstructive plaques with SIS score > 4 are seen in CCTA, aspirin therapy may be considered for primary prevention in asymptomatic adults with a low bleeding risk (COR IIb, LOE B).
- If non-obstructive plaques with a SIS score > 4 are seen in CCTA, statin therapy should be considered for primary prevention (COR IIa, LOE B).

9. SPECIFIC POPULATIONS AND TREATMENT TARGETS

The primary goals of treatment for CCS are to reduce the risk of ASCVD events, to prevent progression to ACS, and to improve QoL by reducing angina symptoms. This can be best achieved through lifestyle modifications and OMT with the selective use of coronary revascularization. The PURE study enrolled 155,722 individuals from 21 countries, and reported population attributable fractions (PAF) for CVD and mortality associated with a cluster of behavioral factors (i.e., tobacco, alcohol, diet, and physical activity), metabolic factors (i.e., lipids, hypertension, diabetes) (41.2% of the PAF), socioeconomic and psychosocial factors (26.3% of the PAF), and environmental factors (i.e., ambient $PM_{2.5}$ air pollution) (13.9% of the PAF).[189] Among them, modifiable risk factors accounted for over 70% of CVD events worldwide, with hypertension, diabetes and dyslipidemia being particularly treatable contributors to population-attributable risk. OMT including managing reversible risk factors is the cornerstone of management for patients with both obstructive and non-obstructive CAD.

9.1 Patients with hypercholesterolemia

Extensive evidence from epidemiologic, genetic, and clinical intervention studies has clearly shown that LDL-C is the principal driving force for the initiation and progression of ASCVD, including CCS.[190,191] Pooled analysis of Mendelian genetic studies and pharmacological intervention trials indicated a log-linear relationship between the level of circulating LDL-C and the risk of ASCVD.

9.1.1 LDL-C target in general patients with CCS

More intensive control of LDL-C not only improves the clinical outcomes of ASCVD, but also causes regression of coronary atheroma.[192,193] For patients with CCS without prior ACS, no target-driven RCTs have specifically examined the optimal treatment target of LDL-C. Most results from previous statin clinical trials and IVUS studies have shown great benefits in lowering circulating LDL-C to a level around 70 mg/dl.[194] The recent large-scale REAL-CAD RCT included only Japanese patients with stable CAD. This study demonstrated that patients with stable CAD receiving intensive statin therapy to achieve an LDL-C level around 73 mg/dl had

better clinical outcomes than those with less intensive statin therapy and LDL-C level around 90 mg/dl.[195] The REAL-CAD study demonstrated that an LDL-C level around 70 mg/ dl also provides clinical benefits in Asian CCS patients. In general, treatment for LDL-C and other dyslipidemia should follow the Taiwan lipid guidelines for high-risk patients, and an LDL-C target < 70 mg/dl is a reasonable recommendation for established CCS in Taiwan.[194]

9.1.2 New LDL-C target < 50 mg/dl for extremely high-risk CCS patients

In the present guidelines, the Task Force recommends that a lower LDL-C target of < 50 mg/dl should be considered in extremely high-risk CCS patients. The scientific evidence for lowering LDL-C levels to < 50 mg/dl in these patients is principally based on three adequately powered RCTs (i.e., IMPROVE-IT, FOURIER and ODYSSEY OUTCOMES). The IMPROVE-IT trial showed that in 18,144 post-ACS patients (hospitalization for ACS < 10 days), ezetimibe 10 mg/simvastatin 40 mg was superior to simvastatin 40 mg alone in reducing long-term CV events. A reduction was observed in the first as well as recurrent events. In addition, diabetic patients appeared to have a greater treatment effect than patients without DM.[196] A benefit was noted irrespective of baseline LDL-C level, including among those with a baseline LDL-C level < 70 mg/dl. Intensive lipid lowering therapy (LLT) with simvastatin plus ezetimibe achieved a lower median LDL-C level of 49 mg/dl in the diabetic group. The largest risk reductions in diabetic patients were for MI (24%) and ischemic stroke (39%). Interestingly, reduction to even lower levels (< 30 mg/dl) appeared to be safe. Moreover, these patients also had the lowest event rates over a 7-year period compared to patients with higher LDL-C concentrations.[197] PCSK9 inhibitors are monoclonal antibodies that bind to PCSK9, an important metabolic regulator of LDL-C, and allow plasma LDL-C concentrations to be reduced by up to 80% when used with high-intensity statins. The FOURIER study included 27,546 patients with stable ASCVD (81% of the participants had a history of prior MI, 13% had PAD at enrollment) with a baseline LDL-C level ≥ 70 mg/dl who were treated with statins and randomized to receive evolocumab or placebo.[198] Evolocumab plus statins reduced the LDL-C level to a median of 30 mg/dL compared with 92 mg/dl with statin therapy only. There was a 15% significant risk reduction in MACEs (HR: 0.85, 95% CI: 0.79 to 0.92) over a mean follow-up of 2.2 years. The ODYSSEY OUTCOMES study included 18,924 recent ACS (< 12 months) patients who received statin therapy but had an LDL-C level ≥ 70 mg/dl.[199] Importantly, the study was an LDL-C target-driven trial and used alirocumab dose adjustment to achieve the LDL-C target of 25-50 mg/dl. The mean achieved LDL-C level was 40 mg/dl at 4 weeks and 53 mg/dl at 48 weeks in the alirocumab plus statin group compared to 94 mg/dl in the statin therapy group. Alirocumab was associated with a 15% significant risk reduction in MACEs over a median 2.8 years of follow-up (HR: 0.85, 95% CI: 0.78-0.93). In addition, alirocumab decreased the risk of stroke, irrespective of baseline LDL-C and history of cerebrovascular disease. Furthermore, the risk of hemorrhagic stroke did not depend on achieved LDL-C levels in the alirocumab group.[200] Subgroup analyses found that the patients with polyvascular disease (including extremity or carotid artery stenosis)[201] or patients with diabetes[202] were at a higher risk of MACEs, and that intensive LDL-C lowering with alirocumab resulted in a larger risk reduction. A meta-analysis of 39 RCTs showed that combination therapy of PCSK9 inhibitors (alirocumab or evolocumab) with statins was associated with a reduced risk of ischemic stroke and no increase in hemorrhagic stroke.[203] Recently, a propensity score-matched analysis of the ODYSSEY OUTCOMES trial evaluated the impact of lowering LDL-C with alirocumab in three strata of LDL-C level (< 25, 25 to 50, > 50 mg/dl) on the risk of MACEs in post-ACS patients receiving optimized statin treatment. The results indicated that patients who achieved an LDL-C level < 25 mg/dl with alirocumab had a reduction in MACE rate similar to those who achieved levels of 25 to 50 mg/dl, and that patients who achieved LDL-C > 50 mg/dl derived less benefit.[204] Given the design of ODYSSEY OUTCOMES trial, these data may can answer the question of whether the LDL-C threshold for adding non-statin therapy should be lowered to ≥ 50 mg/dl among individuals at an extremely high risk. Although PCSK9 inhibitors are more potent and can achieve even lower LDL levels, the higher price and need to receive an injection has limited their use. From the landmark intervention studies on PCSK9 inhibitors, it is reasonable to identify subgroups of patients who may benefit the most

from such therapy. Focusing the use of PCSK9 inhibitors in individuals at highest risk is likely to provide maximal clinical benefits and improve the cost-effectiveness. In the present guidelines, CCS patients with a history of recent ACS (within the past 12 months), multiple prior MI events, multivessel CAD (> 50% stenosis in ≥ 2 epicardial vessels), post-ACS plus diabetes, or polyvascular disease with concomitant PAD (including extremities or carotid artery) are defined as being at extremely high risk, and more intensive LDL-C reduction to a target < 50 mg/dl is recommended.

Key Recommendations:

- In general, the LDL-C target is < 70 mg/dl in CCS patients (COR I, LOE B).
- In extremely high-risk CCS patients, defined as those with recent MI (< 12 months), multiple prior MIs, MVD disease, post-ACS plus diabetes, or CAD with polyvascular disease (including extremities or carotid artery), a lower target of LDL-C < 50 mg/dl should be considered (COR IIa, LOE A).

9.1.3 Pharmacological treatment to lower LDL-C

The major LDL-C lowering agents include statins, ezetimibe and PCSK9 inhibitors. Statins are the first-line treatment for all CCS patients as there is abundant scientific evidence showing that LDL-C reduction with statins can significantly improve CV outcomes. According to the patients' baseline LDL-C levels and clinical conditions, the initiation of moderate-intensity statins (LDL-C reduction by 30% to < 50%) or high-intensity statins (LDL-C reduction ≥ 50%) is recommended. The intensity of LDL-C reduction with different LLT regimens is listed in Table 8. Due to the different pharmacogenetic background between East Asian and Caucasian populations, East Asian patients are more sensitive to atorvastatin and rosuvastatin.[205-207] For safety reasons, atorvastatin 40 mg/day and rosuvastatin 20 mg/day are the two recommended high-intensity statins in Taiwan. When the LDL-C target cannot be achieved while taking high-intensity statins or maximally tolerated statins, the addition of ezetimibe is necessary. If the patient's general condition is not suitable for or they cannot tolerate high-intensity statins, it is reasonable to use moderate-intensity therapy plus ezetimibe directly. PCSK9 inhibitors can be considered if the LDL-C target is not achieved after combination therapy of high-intensity statins or maximally tolerated statins and ezetimibe. PCSK9 inhibitors should also be considered when statin intolerance occurs in CCS patients.

9.1.4 Upfront combination of statin and non-statin agents in CCS patients at extremely high risk

The causal effect of LDL-C on atherosclerosis is well established. Lifelong exposure to lower LDL-C is associated with an ~3-fold greater reduction in the risk of CV events per unit change in LDL-C as compared with short-term reductions in LDL-C during treatment with a statin.[208] Moreover, recent RCTs using non-statin LLTs (ezetimibe and/or PCSK9 inhibitors), a meta-analysis,[209] and Mendelian randomization data,[210,211] support the concept of "the earlier the better", "the lower the better" and "the longer the better". Most guidelines recommend the use of high-intensity statins to lower LDL-C by at least 50% in patients with CVD and those at high risk.[212] Current international guidelines still recommend using high-intensity statin monotherapy before considering combination therapy. Based on the rule of "the earlier, the better", upfront combination therapy should be the new standard of care to achieve the LDL-C target, particularly

Table 8. Expected LDL-C reduction for statin and/or non-statin combination therapies

Treatment regimen	Average LDL-C reduction
Moderate-intensity statins	≈ 30-50%
High-intensity statins	> 50%
Ezetimibe	≈ 15-20%
High-intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high-intensity statin	≈ 75%
PCSK9 inhibitor plus high-intensity statin plus ezetimibe	≈ 85%

LDL-C, low-density lipoprotein-cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

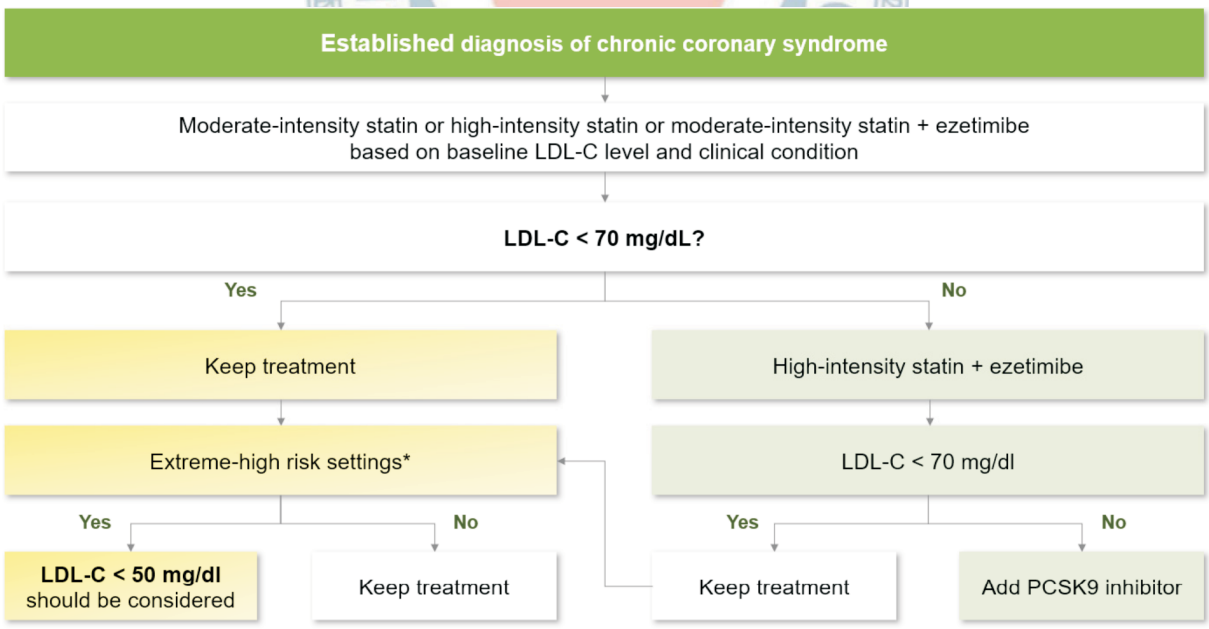
in patents at the higher risk. In the past years, RCTs have evaluated the earlier initiation of aggressive statin therapy following an ACS event, and have reported a corresponding early MACE reduction.[213-215] Evidence from these Mendelian randomization studies has been critical in driving a change to earlier treatment in patients at an extremely high risk, also supported by the ODYSSEY OUTCOMES trial which confirmed that earlier combination therapy of PCSK9 inhibitors with statins within 6 (even < 2) months after ACS resulted in better CV outcomes.[199] More recently, the PACMAN-AMI trial demonstrated that, compared with daily high-intensity rosuvastatin 20 mg, the early administration of alirocumab within 24 hours after PCI in 300 MI patients resulted in greater coronary atheroma volume regression, lower lipid core burden index, and larger increase in fibrous cap thickness in nonculprit lesions as assessed by serial multimodality imaging at 52 weeks.[216] Given the increasing importance of reducing lifetime exposure to LDL-C, the Task Force strongly suggests following the concept of "the lower the better," but also "the earlier the better" and "the longer the better." Figure 7 shows the algorithm for pharmacological LDL-C lowering therapy for CCS patients in Taiwan.

Key Recommendations:

- Moderate-high intensity statins are the first-line treatment for CCS (COR I, LOE A).
- Moderate-intensity statins plus ezetimibe can be used as the first-line treatment, especially if the patient's general condition is not suitable for or they cannot tolerate high-intensity statins (COR IIa, LOE B).
- PCSK9 inhibitors can be considered if the LDL-C target is not achieved after combination therapy of high-intensity statins and ezetimibe, or statin intolerance occurs (COR I, LOE B).
- Earlier initiation of PCSK9 inhibitors should be considered if the LDL-C target is not achieved after statin plus ezetimibe therapy in extremely high-risk CCS patients (COR IIa, LOE B).
- In extremely high-risk CCS patients, upfront combination treatment of high-intensity statins first with ezetimibe and then a PCSK9 inhibitor to achieve an LDL-C target of < 50 mg/dl should be considered (COR IIa, LOE A).

9.2 Patients with diabetes

A close link exists between diabetes and ASCVD, which is the most prevalent cause of morbidity and mor-



*Extreme risk defined as clinical settings with a history of recent ACS, multiple prior MI events, complex MVD, post- ACS plus diabetes, polyvascular disease with concomitant PAD. In such patients, upfront combination treatment of high intensity statins first with ezetimibe and then a PCSK9 inhibitor to achieve the target should be considered.

Figure 7. *LDL-C target and pharmacological treatment. ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; MVD, multiple vessel disease; PAD, peripheral artery disease; PCSK9, proprotein convertase subtilisin-kexin type 9.*

tality in diabetic patients. Traditional CV risk factors such as obesity, hypertension and dyslipidemia are common in patients with diabetes, placing them at increased risk of coronary events.

9.2.1 Glycated hemoglobin target (HbA1c)

Previous cohort studies have shown a linear relationship between CV events and all-cause death with the level of HbA1c.[217,218] However, RCTs comparing intensive to conventional glucose-lowering strategies have not confirmed this finding.[219-222] Why a lower blood glucose level does not translate into clinical benefits is still known. While hypoglycemia was an independent factor for excess morbidity and mortality in these trials,[220] a meta-analysis demonstrated that intensive glucose control reduced the risk of MACEs by 9% (HR: 0.91, 95% CI: 0.84-0.99).[223] All novel antidiabetic agents, including DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors, have a very low risk of hypoglycemia, and hypoglycemia-related adverse events would not be a concern when a lower glucose target is advocated. FDA issued a mandate in 2008 that all new anti-diabetic agents needed to show their CV safety in RCTs.[224] Twenty-three RCTs have since been published.[225] These trials were not target-driven in design and the target HbA1c level cannot be obtained. Among these trials, the final achieved HbA1c levels were all > 7.0% except in the REWIND trial, in which the final achieved HbA1c level was < 7%. On the other hand, a more recent meta-analysis showed the benefits of a lower glucose level with safer anti-diabetic agents, such as DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors, and the decrease in HbA1c was positively related to the reduction in CV endpoints.[226] Given that most of the new antidiabetic agents have superior safety profiles, the Task Force recommends an HbA1c level < 7.0% as the treatment target for diabetic patients with CCS. An HbA1c level < 6.5% may be considered in selected patients who are younger, highly educated and highly motivated, and have a low hypoglycemic risk, fewer comorbidities, and short diabetes duration.[225]

9.2.2 Pharmacological treatment of diabetes in patients with CCS

Traditional antidiabetic agents, including sulfonylureas, glinides, alpha-glucosidase inhibitors, and insulin, were not able to decrease CV events in respective trials.[227-230] In the UKPDS trial, metformin use in overweight patients reduced MI and total mortality rates compared with conventional lifestyle therapy (HR: 0.61, 95% CI: 0.41-0.89; HR: 0.64, 95% CI: 0.45-0.81, respectively).[231] In a meta-analysis of 35 clinical trials, a significant benefit was observed in the metformin group vs. placebo/no therapy group (OR: 0.79, 95% CI: 0.64-0.98).[232] Moreover, an updated meta-analysis of 40 studies comprising 1,066,408 CAD patients showed that metformin reduced the rates of CV mortality, all-cause mortality and incidence of CV events (HR: 0.81, 0.67, and 0.83, respectively). Subgroup analysis showed that metformin reduced all-cause mortality in patients with a history of MI (HR = 0.79). In the prospective nationwide ACS-DM TSOC registry from Taiwan, metformin users had a lower all-cause mortality rate (HR: 0.50, 95% CI: 0.26-0.95) over the 2-year follow-up period among 1157 patients with type 2 diabetes and a history of ACS.[233] Based on these findings, the Task Force recommend metformin as the first-line therapy for patients with diabetes and CAD. The efficacy of pioglitazone in patients with pre-existing CAD is partly supported by the PROactive trial, in which patients with diabetes and macrovascular disease who were randomized to receive pioglitazone had a low risk of the secondary endpoint (all-cause mortality, nonfatal MI, and stroke) (HR: 0.84, 0.72-0.98, p = 0.027).[234] The subgroup of patients who had a previous MI had lower risks of fatal and nonfatal MI (HR: 0.72, 95% CI: 0.52-0.99) and ACS (HR: 0.63, 95% CI: 0.41-0.97).[235] The finding of the beneficial effects of pioglitazone on CV outcomes was supported by two meta-analyses of controlled trials,[236,237] and two imaging studies.[238,239] The Task Force gives high priority to pioglitazone and recommends that it could be used in the combination therapy for patients with CAD. DPP-4 inhibitors, including saxagliptin, alogliptin, sitagliptin and linagliptin, have been tested in individual RCTs (SAVOR, EXAMINE, TECOS, and CAMELINA, respectively).[227,240-242] In general, their effects on MACEs and all-cause mortality were neutral, although there were no safety issues. The Task Force maintains a neutral position with regards to DPP-4 inhibitor treatment for diabetic patients with CAD. Eight RCTs of GLP-1 receptor agonists (i.e., ELIXA,[243] LEADER,[244] SUSTAIN-6,[245] EXSCEL,[246] HARMONY,[247] REWIND,[248] PIONEER 6,[249] and AMPLITUDE-O[250]) have been reported, of which five including liraglutide, semaglu-

tide, albiglutide, dulaglutide, and efpeglenatide were shown to decrease the MACE rate. Albiglutide was withdrawn from the market by the company in July 2018 and will thus not be discussed in these guidelines. A meta-analysis of seven trials of GLP-1 receptor agonists provided solid evidence to support the role of GLP-1 receptor agonists in reducing MACEs.[251] The efficacy was consistent in patients with ASCVD (secondary prevention) or with risk factors alone (primary prevention) with a p value for interaction of 0.24. The Task Force gives high priority to GLP-1 receptor agonists for diabetic patients with CAD, but only recommends those with proven efficacy in RCTs. Empagliflozin, canagliflozin, and dapagliflozin are SGLT2 inhibitors with proven benefits in reducing primary endpoints in diabetic patients.[252-254] Two meta-analyses demonstrated the beneficial effects of SGLT2 inhibitors on MACE and other CV endpoints.[255,256] SGLT2 inhibitors, when compared with placebo, reduced MACEs only in patients with ASCVD (secondary prevention), but not in patients with risk factors alone (primary prevention). The Task Force gives high priority to SGLT2 inhibitors in patients with diabetes and a history of CAD, but only recommends those with proven efficacy in RCTs. No previous RCT has compared SGLT2 inhibitors with GLP-1 receptor agonists. Two network meta-analyses compared SGLT2 inhibitors with GLP-1 receptor agonists.[257,258] The network meta-analysis by Yamada et al. demonstrated that SGLT2 inhibitors, when compared with GLP-1 receptor agonists, had similar effects on MACEs (RR: 0.94, 95% CI: 0.78-1.12), but were associated with a lower risk of renal events (RR: 0.79, 95% CI: 0.63-0.99).[257] A more comprehensive network meta-analysis included a total of 421,346 patients from 764 trials.[258] The investigators estimated the absolute effects of treatment per 1000 patients treated for 5 years at very low risk (no risk factors), low risk (three or more risk factors), moderate risk (ASCVD), high risk (CKD), and very high risk (ASCVD + CKD). Six endpoints of interest were examined: all-cause death, CV death, nonfatal MI, nonfatal stroke, kidney failure, and hospitalization for HF. For patients with moderate risk (ASCVD), SGLT2 inhibitors were more effective than GLP-1 receptor agonists in reducing all-cause death, and hospitalization for HF. The Task Force gives SGLT2 inhibitors a higher priority than GLP-1 receptor agonists in patients with diabetes and CAD.

Key Recommendations:

- For patients with CCS and diabetes, the target HbA1c level is < 7.0% (COR I, LOE C).
- GLP1 receptor agonists and SGLT2 inhibitors are preferred medications in patients with CCS and diabetes (COR I, LOE A).
- In patients with CCS and a history of ischemic stroke, GLP-1 receptor agonists are more effective than SGLT2 inhibitors (COR IIa, LOE B).
- In patients with CCS and a history of HF or CKD, SGLT2 inhibitors are the preferred medications (COR I, LOE A).

9.3 Patients with hypertension

Large-scale prospective trials have demonstrated that elevated BP promotes the progression of coronary atherothrombosis.[259,260] Based on a threshold of hypertension of 140/90 mmHg, its prevalence ranges from 30% to 70% in individuals with pre-existing CCS.[261] Most clinical studies of hypertension have reported that lowering systolic blood pressure (SBP) by approximately 10-20 mmHg or diastolic blood pressure (DBP) by approximately 5-10 mmHg can reduce the occurrence of coronary events by 15-20%.[262]

9.3.1 BP target for CCS patients

To date, no target-driven clinical trials have been primarily designed to evaluate optimal BP targets in CCS patients. The following recommendation is mainly based on large-scale registry, subgroup analysis, post hoc analysis or meta-analysis of RCTs. Three large RCTs [HOPE,[263] EUROPA,[264] and PEACE[265] evaluated the effects of angiotensin-converting enzyme (ACE) inhibitors versus placebo in CCS patients. Baseline traditional office BP values in all three of these trials were in the range of previously defined prehypertension (139/ 79, 137/82, and 133/78 mmHg for HOPE, EUROPA, and PEACE, respectively). The final BP values were 136/76, 132/80, and 129/74 mmHg, respectively. Primary endpoints decreased by 22% in the HOPE trial ($p < 0.001$), 20% in the EUROPA trial ($p = 0.0003$), and 4% in the PEACE trial ($p > 0.05$). No J-curve phenomenon was noted. The CAMELOT trial compared amlodipine and enalapril versus placebo in CCS patients, and reported that BP decreased from a baseline of 129/78 mmHg to 124/75 mmHg.[266] In addition, the primary endpoints decreased by 31% (p =

0.003) in the amlodipine group. In a substudy of the CAMELOT trial using intra-vascular ultrasound, patients with a final office BP > 140/90 mmHg had a significant increase in atheroma volume.[267] Of note, those who had a final BP in the range of 120-139/ 80-89 mmHg had no major progression in atheroma volume. Interestingly, those with a final BP < 120/80 mmHg had a significant decrease in atheroma volume. The CLARIFY registry enrolled 22,672 hypertensive patients with CCS from 45 countries, and categorized SBP and DBP before each event into 10 mmHg increments, using the 120-129 mmHg SBP and 70-79 mmHg DBP subgroups as reference. After a median follow-up of 5.0 years, this large international CAD registry demonstrated that subjects with SBP 120-129 mmHg and DBP 70-79 mmHg were associated with the lowest risk of the primary endpoints, a composite of CV death, MI, or stroke.[268] Further evidence comes from CCS subgroup analysis of the SPRINT trial which included 1206 participants with CCS, of whom 692 underwent coronary revascularization.[269] After a median follow-up of 3.9 years, intensive treatment to reduce SBP below 120 mmHg was shown to provide a protective effect against all-cause death (HR: 0.60, 95% CI: 0.37-0.96) in the CCS subgroup, although the primary outcome (composite of CV events) was similar (HR: 1.05, 95% CI: 0.76-1.46) between groups. Furthermore, a DBP around 65 mmHg seemed to be even safer and did not increase CVD events in patients with CCS. In the CCS subgroup, intensive BP treatment did not increase the risk of serious adverse events (HR: 1.03, 95% CI: 0.88-1.20). One important meta-analysis was conducted after our 2017 hypertension guidelines, and it supported intensive BP lowering for subjects with CCS. This meta-analysis was conducted by the well-respected Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) using individual participant-level data from 48 randomized trials of BP lowering medications.[270] Data obtained from 344,716 participants were pooled to investigate the stratified effects of BP-lowering treatment across seven SBP categories (ranging from < 120 to ≥ 170 mmHg). Among the participants with previous CVD (n = 157,728), 113,970 (74.9%) had CCS. Pre-randomization mean SBP/DBPs were 146/84 mmHg (with a SBP of < 130 mmHg in 19.8% and DBP < 80 mmHg in 31.0%) in the secondary prevention subgroup. The relative effects of BP-lowering treatment were proportional to the intensity of SBP reduction. At 4.15 years, the hazard ratio associated with a reduction in SBP by 5 mmHg (even true with an achieved SBP < 120 mmHg) for a MACE was 0.89 (95% CI: 0.86-0.92) for patients with pre-existing CVD.[270] These findings do not substantiate concerns about a J-shaped association between BP and CV outcomes in previous observational studies. Lately, the importance of out-of-office BP measurements has been highlighted in the diagnostic confirmation of hypertension. Of note, the TSOC updated 2022 hypertension guidelines revised the diagnostic thresholds to 130/80 mmHg measured by home BP monitoring.

Key Recommendation:

- For CCS patients with hypertension, BP targets are < 130/80 mmHg using home BP monitoring [preferred] (COR I, LOE A).

9.3.2 Pharmacological treatment of hypertension in patients with CCS

Therapy is directed toward preventing disease progression, MI, CV death, and reducing symptoms of angina and the occurrence of ischemia. The mainstays of angina treatment include β-blockers and calcium channel blockers (CCBs) when not contraindicated. Meta-analyses of antihypertensive trials have demonstrated that BP lowering is more important than the particular drug class used in the primary prevention of the complications of hypertension, including CCS. Combination antihypertensive drug therapy is typically needed to achieve and to sustain effective long-term BP control. Thus, there is no evidence to support initiating therapy with any one antihypertensive drug class over another for the primary prevention of CAD. In contrast, for secondary protection in individuals with underlying comorbid illnesses such as diabetes, CKD, or recurrent stroke, not all drug classes have been proven to confer optimal or even the same level of benefit. In hypertensive CCS individuals with "compelling indications", some specific classes of antihypertensive drugs through mechanisms independent of their BP-lowering action have greater anti-atherosclerotic and disease-modifying actions (such as long-acting dihydropyridine CCBs or RAS inhibitors) and/or anti-ischemic effects (such as CCBs or β-blockers) than others.[271] In general, pharmacological strategies for

the prevention of CV events in CCS patients include RAS inhibitors, β-blockers (particularly after MI) and CCBs. The choice of BP-lowering regimen for patients with CCS and hypertension largely depends on the presence of underlying comorbid illnesses such as diabetes, CKD, history of prior MI, and HF.

Key Recommendations:

- For hypertensive subjects with symptomatic angina, β-blockers and/or CCBs are recommended (COR IIa, LOE C).
- For hypertensive CCS patients with previous MI or HFrEF, β-blockers, RAS inhibitors, and aldosterone receptor antagonists are preferred (COR I, LOE A).
- For CCS subjects with a requirement for multiple antihypertensive agents for BP control, the combination of a RAS inhibitor and a dihydropyridine CCB may be preferable to a RAS inhibitor and a thiazide/thiazide-like diuretic (COR IIa, LOE B).
- The combination of a β-blocker and either of the non-dihydropyridine CCBs (diltiazem or verapamil) should be used with caution in patients with symptomatic CCS and hypertension because of the increased risk of significant bradyarrhythmia and HF (Class IIb, LOE C).
- Short-acting dihydropyridine CCBs should not be used for long-term therapy because of their potential to increase mortality (COR III, LOE B).

10. COMPREHENSIVE MANAGEMENT OF CCS

As an initial management strategy in CCS patients, PCI has not been shown to reduce the risk of death, MI, or other MACEs when added to OMT. The mainstay of treatment for CCS is the evidence-based use of contemporary OMT, and this approach is recommended for all CCS patients. The INTERHEART study determined the degree of effect a certain risk factor will have on the development of CVD.[272] More than half of the risk of MI could be attributed to lifestyle habits. The Task Force emphasizes the importance of comprehensive interventions, including better LSM and OMT. This management strategy for CCS can be summarized as **"ABCDE-PS2"**: **A**ntiplatelet therapy, **B**P target < 130 mmHg, LDL-**C**holesterol control to target, **D**iet adaptation, **E**xercise adoption, less **P**M2.5 exposure, **S**moking cessation, and less **S**tress (Figure 8).

10.1 Pharmacological treatment of CCS

Recent trials have highlighted the importance of OMT for the management of CAD irrespective of the revascularization strategy. In addition to LSM, better control of risk factors (i.e., hypertension, diabetes, and dyslipidemia) and optimal antithrombotic therapy are key components of OMT. The beneficial effect of NG-DES on the outcomes of patients with CAD has led to substantial changes in the strategy of OMT after revascularization. Despite recent advances in revascularization, there are multiple reasons to support the alterna-

Figure 8. *An "ABCDE-PS2" steps for heart and vascular wellness. BP, blood pressure; LDL-C, low-density lipoprotein cholesterol.*

tive of providing OMT alone for the initial management of patients with a presumptive or confirmed diagnosis of CCS. OMT may include both preventive medications designed to favorably influence the natural history of coronary atherosclerosis, pathophysiology of myocardial ischemia and anti-anginal medications such as β-blockers, CCBs, nitrates, ranolazine, and ivabradine, which reduce angina frequency and improve QoL and CV outcomes. Various disease modifying agents can improve adverse clinical outcomes, including antiplatelets, statins, and RAS inhibitors. Various antithrombotic therapies for the management of CCS, including single antiplatelet and dual antiplatelet therapy (DAPT) have been clinically validated. A recent RCT demonstrated the benefits of a dual pathway inhibition (DPI) strategy with aspirin and very-low dose rivaroxaban, a new option for CCS treatment.

10.2 Antiplatelet therapy

Platelet activation and aggregation are drivers of symptomatic coronary thrombosis, forming the basis for the use of antiplatelet drugs in patients with CCS in view of a favorable balance between the prevention of ischemic events and increased risk of bleeding. Antiplatelet drugs are a key part of secondary prevention in patients with CCS, and their use warrants careful consideration. Because guidelines and recommendations rapidly change in response to RCTs of new strategies, antithrombotic therapies for patients after ACS or PCI are becoming more complex in daily clinical practice.

10.2.1 Anti-platelet drugs for patients with CCS without PCI

10.2.1.1 Low-dose aspirin

Aspirin acts via irreversible inhibition of platelet cyclooxygenase-1 and thus thromboxane production, with a chronic dosing ≥ 75 mg daily. Aspirin has been the gold standard of single antiplatelet therapy in CCS patients; however, aspirin is associated with a higher risk of gastrointestinal bleeding than P2Y12 inhibitors because it acts by inhibiting cyclooxygenase.[273] The gastrointestinal side effects of aspirin increase at higher doses, and current evidence supports a daily dose of 75-100 mg for the prevention of ischemic events in CAD patients with or without a history of MI.[274,275] Recently the MESA study showed that implementing the 2019 ACC/AHA guideline recommendations for ASCVD risk together with CAC for further risk assessment may provide a more personalized, safer allocation of aspirin in CCS primary prevention.[170] As with earlier recommendations in this article (see also section 8.6.1), aspirin may be considered in patients with a CAC score 100-399 and is indicated if the CAC score is ≥ 400 for asymptomatic patients. The recent ADAPTABLE trial confirmed no significant differences in CV events or major bleeding between 81 mg and 325 mg of aspirin daily in patients with established ASCVD.[276]

10.2.1.2 Oral P2Y12 inhibitors

P2Y12 inhibitors block platelet receptors, which play a key role in platelet activation and the amplification of arterial thrombus formation. Clopidogrel and prasugrel are thienopyridine prodrugs that irreversibly block P2Y12 via active metabolites. Ticagrelor is a reversibly binding P2Y12 inhibitor that does not require metabolic activation. Clopidogrel is limited by various pharmacodynamic effects related to the variable efficiency of conversion to its active metabolite, which is partly associated with loss-of-function variants in the CYP2C19 gene leading to a lack of efficacy in some patients.[277] Prasugrel and ticagrelor have more rapid, more predictable, and greater antiplatelet effects compared with clopidogrel, and they are not susceptible to the effect of CYP2C19 loss-of function variants. The CAPRIE trial[278] showed a slight benefit with clopidogrel (75 mg once daily) compared with aspirin (325 mg once daily), with a similar overall safety profile, in preventing CV events in patients with previous MI, previous stroke, or PAD. Subgroup analysis suggested greater benefits of clopidogrel in patients with PAD but not in patients with previous MI. A recent meta-analysis also reported that P2Y12 inhibitor monotherapy reduced the risk of MI and was associated with a comparable risk of stroke compared to aspirin among patients with established atherosclerosis.[279] The CHARISMA trial investigated the use of DAPT with low-dose aspirin plus clopidogrel compared with aspirin monotherapy in patients with either multiple RFs or clinically evident CVD.[280] Overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rates of MI, stroke, or CV death. Several RCTs have strongly indicated the use of prasugrel[281] and tica-

grelor[282] in patients with ACS. The THEMIS study assigned patients with CCS and diabetes to receive either ticagrelor plus aspirin or placebo plus aspirin to investigate the composite of 3P-MACEs and bleeding outcomes.[283] In subgroups analysis of patients who did not receive PCI, ticagrelor plus aspirin did not significantly lower ischemic events (HR: 0.98, 95% CI: 0.84-1.14) but significantly increased TIMI major bleeding (HR: 2.79, 95% CI: 1.91-4.06).

Key Recommendations:

- Aspirin 75-100 mg daily is recommended for CCS patients with previous MI, stroke or PAD (COR I, LOE A).
- Clopidogrel 75 mg daily may be preferred to aspirin in CCS patients with either PAD or a history of ischemic stroke (COR IIb, LOE B).
- Routine DAPT therapy for CCS patients without PCI is not recommended (COR III, LOE B).

10.2.2 Antiplatelet drug in patients with CCS after PCI

After PCI with stent placement, at least a 1 month course of DAPT is the standard of care reported in previous studies[284,285] and current international guidelines.[286] No dedicated study has yet focused on CCS patients undergoing PCI and exposed to different DAPT durations. Hence, recommendations regarding CCS patients undergoing PCI are derived from subgroup analyses from pertinent RCTs.[287,288] Ticagrelor 60 mg or 90 mg twice daily has been shown to provide greater and more consistent platelet inhibition than clopidogrel in CCS patients undergoing elective PCI.[289] However, further studies of ticagrelor 60 mg twice daily are warranted in CCS patients undergoing PCI. Prasugrel was approved in both Taiwan and Japan at lower doses [loading dose (LD)/maintenance dose (MD), 20/3.75 mg] than the standard prasugrel doses (LD/MD, 60/10 mg) for Western populations, mainly because of the lower body weight and higher bleeding risk in East Asian patients. These reduced doses of prasugrel were selected from a phase II, dose-finding study,[290] and was subsequently proved to be safe and efficacious in the PRASFIT-Elective phase III trial of CCS patients who had received PCI.[291] Since its approval in Japan and Taiwan, prasugrel use has been reported in real-world practice in both countries. The Japanese PRASFIT-PRACTICE II study revealed a 2-year cumulative 3.3% MACE rate and 1.6% TIMI major bleeding rate in CAD patients undergoing PCI.[292] Similarly, the Taiwanese Switch Study reported a 1.0% MACE rate and 2.0% TIMI major bleeding rate in ACS patients undergoing PCI.[293] In pharmacodynamic and pharmacogenetic studies in Japan and Taiwan, reduced-dose prasugrel has consistently shown superior platelet inhibition and thus lower rates of patients with high on-treatment platelet reactivity (HPR) than clopidogrel.[293-295]

10.2.2.1 Short-term DAPT versus 12 months of DAPT after PCI

In the past decade, many RCTs have demonstrated that short-term DAPT (3-6 months) after PCI was non-inferior compared to 12 months of DAPT in terms of the ischemic endpoint, while some trials have also shown a significant reduction in bleeding complications.[296-305] Of note, almost all of these studies used PCI with NG-DES. In addition, although patients in most studies had a relatively low risk of recurrent ischemia, no dedicated study has focused on CCS patients undergoing PCI with different durations of DAPT. For example, the ISAR-SAFE trial is the largest double-blind study with 4005 randomized patients after DES implantation. It confirmed that a 12-month course of clopidogrel-based DAPT did not provide any additional benefits on ischemic endpoints compared to a 6-month course. Likewise, the net clinical benefit (composite of death, MI, stent thrombosis, stroke, and TIMI major bleeding) was neutral. In subgroup analysis, there was no heterogeneity with respect to the primary study endpoint among the 2394 patients who presented with CCS compared to the 1601 patients with ACS.[301] The more recent STOPDAPT-2 trial randomized 3045 Japanese patients to receive either 1 month of DAPT followed by clopidogrel monotherapy or 12 months of DAPT with aspirin and clopidogrel. The results showed that 1 month of DAPT was superior to 12 months of DAPT for the primary endpoint (composite of CV death, MI, stroke, definite stent thrombosis, or major or minor bleeding at 12 months). Although there was no interaction between thrombotic risk scores and the effect of DAPT duration in subgroup analysis, the benefit of short-term DAPT was more significant among the 1861 patients who presented with CCS (HR: 0.59; 95% CI: 0.33-1.03) than the 1148 ACS patients (HR: 0.72; 95% CI: 0.38-1.36).[302] Nonetheless, these studies collectively suggest that short-term DAPT may improve the outcomes in patients with a relatively

low thrombotic risk and/or high bleeding risk. Accordingly, current guidelines recommend that short-term DAPT should be considered in patients at high bleeding risk.

10.2.2.2 Short-term DAPT followed by aspirin or P2Y12 inhibitor monotherapy

No previous RCT has compared P2Y12 inhibitor monotherapy to aspirin monotherapy after a short course of DAPT or experience with P2Y12 inhibitor monotherapy beyond 1 year after stent implantation. In recent years, the status of aspirin as the mainstay of antithrombotic therapy has been challenged. Aspirin use is associated with an increased risk of bleeding (in particular gastrointestinal bleeding), especially in the elderly and those who concurrently use other antithrombotic agents.[306] Previous studies of short-term DAPT followed by aspirin monotherapy have demonstrated that 3-6 months of DAPT did not increase composite ischemic and bleeding events when compared to 12 months of DAPT after PCI.[296,297,300,301] In recent years, the strategies of similar studies have mainly shifted aspirin to P2Y12 inhibitor monotherapy after an initial shorter course of DAPT (1-3 months).[302-305] The results of these trials consistently demonstrated that a shorter course of DAPT was associated with similar ischemic events and fewer bleeding complications than a longer course of DAPT. Of note, according to subgroup analysis, clopidogrel was the favored choice in low ischemic risk and CCS patients, and new P2Y12 inhibitors (mostly ticagrelor) were more suitable for high ischemic risk and ACS patients. This concept was also demonstrated in the ALPHEUS trial, which found that ticagrelor was not superior to clopidogrel in reducing periprocedural myocardial necrosis after elective PCI but did increase the rate of minor bleeding at 30 days.[307] Based on the available evidence, P2Y12 inhibitor monotherapy after an initial short course of DAPT should be considered as an alternative to standard DAPT in patients without high ischemic risk undergoing PCI. Given continued refinement in stents and better PCI techniques, there is increasing evidence of the safety of discontinuing aspirin 1-3 months after uncomplicated NG-DES implantation, with continuation of P2Y12 monotherapy, especially if IVUS or OCT confirms optimized stent results. The PENDULUM-Mono Japanese registry enrolled high bleeding risk (HBR) patients undergoing PCI who were eligible to receive prasugrel SAPT based on the physicians' judgment.[308] Compared to patients receiving DAPT in historical controls, patients receiving SAPT had a comparable MACCE rate (HR: 0.85; 95% CI: 0.61-1.19; p = 0.34) but a significantly lower BARC type 2/3/5 bleeding rate (2.8% for SAPT vs. 4.1% for DAPT), 1 year after PCI.[309]

10.2.3 Complete omission of aspirin after PCI

An aspirin-free strategy is now emerging as a novel strategy for antiplatelet therapy after PCI. Recently, the ASET Study demonstrated that aspirin-free prasugrel monotherapy following successful NG-DES implantation was feasible and safe with no increase in stent thrombosis in low-risk patients with CCS.[310]

10.2.3.1 Extended DAPT for more than 12 months

Previous RCTs have not demonstrate a benefit of extended DAPT (18-48 months) over standard DAPT (6-12 months).[311-317] The majority of patients enrolled in these trials had CCS, and clopidogrel was used almost exclusively. In 2014, a large-scale DAPT trial with 9961 patients demonstrated that extended DAPT (30 months) with clopidogrel or prasugrel significantly reduced the risk of definite or probable stent thrombosis and MACEs, but that the clinical benefit was tempered by an increase in bleeding events.[315] In addition, there was a trend towards increased all-cause mortality (0.5% absolute increase) with extended DAPT. In 2019, the PEGASUS-TIMI 54 trial enrolled patients who had had MI 1-3 years previously and had at least one additional high-risk feature (age > 65 years, diabetes requiring medication, multiple prior MIs, MVD or renal impairment). The results showed that extended DAPT with ticagrelor 60 mg twice daily (median 33 months) plus aspirin 100 mg once daily compared to aspirin monotherapy reduced the risk of the composite of CV death, MI, or stroke (HR: 0.80; 95% CI: 0.70-0.91) and all-cause mortality (HR: 0.80; 95% CI: 0.67-0.96), but also largely increased the risk of TIMI major bleeding (HR: 2.36; 95% CI: 1.65-3.39).[318] In a pre-specified subgroup of patients with diabetes and CCS with previous PCI in the THEMIS trial, long-term DAPT with ticagrelor (60 mg twice daily) on top of aspirin (for a median of 3.3 years) was associated with a 1.3% absolute reduction in CV death, MI, and stroke (HR: 0.90; 95% CI: 0.81 to 0.99) coupled with an increase in TIMI major bleeding (HR: 2.32; 95% CI:

1.82 to 2.94) and intracranial hemorrhage (HR: 1.71; 95% CI: 1.18 to 2.48).[283] These results support extended DAPT in diabetic patients who have undergone PCI and are at a high ischemic risk without HBR. Accordingly, ticagrelor has been approved by the FDA to reduce the risk of MI or stroke in high-risk patients with CCS. A meta-analysis demonstrated that extended DAPT in patients with prior MI significantly reduced stent thrombosis, stroke, MI and CV death.[317] In contrast, other meta-analyses have shown that extended DAPT in lower-risk patients did not reduce CV death and was even associated with an increased risk of all-cause mortality.[319] Hence, current guidelines recommend that extended DAPT can be considered in patients with high thrombotic risk without HBR.[320]

10.2.3.2 Chronic maintenance monotherapy after PCI in patients with CCS

Aspirin is the most widely used antiplatelet agent and is recommended as standard therapy for patients after PCI. Clopidogrel is limited by variable pharmacodynamic effects related to the variable efficiency of conversion to its active metabolite, which is partly associated with loss-of-function variants in the CYP2C19 gene, leading to a lack of efficacy in some patients.[277] CCS patients treated with clopidogrel who carry CYP2C19 loss-of-function alleles undergoing PCI have been associated with a significantly increased risk of MACEs compared to non-carriers, and even markedly significant in Asian patients.[321] The CAPRIE trial showed that clopidogrel may have potential benefits in patients with ASCVD, such as reducing CV events with a reduced incidence of gastrointestinal complications.[278] However, the trial was published in 1996 and did not specifically address the post-PCI population and was not done in an era when NG-DES or high-intensity statins were available. A recent meta-analysis found that removing aspirin and continuing a P2Y12 inhibitor as monotherapy would be the preferred strategy in intermediate-high risk patients after PCI.[322] Before 2021, no head-to-head comparison RCT in the contemporary NG-DES era specifically addressed which antiplatelet agent might be the optimal choice during the period of indefinite antiplatelet monotherapy in patients after PCI. Recently, the large-scale HOST-EXAM trial randomly allocated 5530 patients who were event free for 6-18 months post-PCI and successfully received the intended duration of DAPT. The clinical diagnosis at the time of PCI was CCS in 1517 (27.4%) patients and ACS in 4013. During 24 months of follow-up, compared with aspirin, clopidogrel monotherapy significantly reduced the risk of the composite of all-cause death, nonfatal MI, stroke, readmission due to ACS, and BARC type bleeding 3 or higher. (HR: 0.7; 95% CI: 0.59-0.90). In addition, in patients requiring indefinite antiplatelet monotherapy after PCI with NG-DES, clopidogrel monotherapy was superior to aspirin monotherapy in preventing future adverse clinical events.[323] A recent US administrative claims data study identified 42,683 patients who filled a prescription for clopidogrel, ticagrelor, or prasugrel within 30 days of PCI from 2009 to 2016. Of these patients, ~7000 had a non-ACS indication for PCI. During the study period, the proportion of non-ACS PCI patients filling clopidogrel prescriptions decreased from 99% to 66%, while the proportion of patients filling a prescription for prasugrel or ticagrelor increased from 1.0% to 34%. Consequently, the study concluded that the off-label use of prasugrel and ticagrelor in elective PCI patients with CCS is common in clinical practice.[324]

Key Recommendations:

- Life-long aspirin use is recommended unless contraindicated in patients with CCS undergoing PCI (COR I, LOE A).
- Monotherapy with P2Y12 receptor inhibitors should be considered when aspirin is contraindicated in patients with CCS undergoing PCI (COR IIa, LOE B).
- In patients with CCS treated with PCI with NG-DES implantation, 1-3 months of DAPT with P2Y12 receptor inhibitors in addition to aspirin is recommended (COR I, LOE A).
- Shortening of DAPT to 1-3 months should be considered for patients with HBR and CCS undergoing PCI (COR IIa, LOE B).
- Monotherapy with P2Y12 receptor inhibitors should be considered in CCS patients with low thrombotic risk and HBR following 1-3 months of DAPT after PCI (COR IIa, LOE A).
- In patients with previous MI who are at low bleeding risk and high thrombotic risk, extended DAPT with ticagrelor 60 mg twice daily in addition to aspirin for > 12 months and < 36 months should be considered (COR IIa, LOE B).

10.3 Oral anticoagulant drugs

Secondary prevention with antiplatelet agents has become the cornerstone of treatment for CCS patients in recent decades due to their proven efficacy, acceptable safety, and convenient administration.[325] However, anticoagulants alone or in combination with antiplatelet agents have also been demonstrated to improve clinical outcomes in CCS patients. Previous studies have shown that the contribution of thrombin to the thrombosis of arteries is not only via the formation of fibrin, but also by activation of platelet aggregation.[326] During the past decades, many studies have been conducted to evaluate the role of warfarin in ACS or CCS patients. Due to differences in study designs, heterogenous efficacy results and increased bleeding risk, current evidence does not support the routine use of warfarin as alternative or add-on therapy to antiplatelet agents in these patients. However, adding very low-dose rivaroxaban with aspirin to patients with stable ASCVD has been shown to result in better CV outcomes than aspirin alone.[327]

10.3.1 Warfarin in patients with CAD

Three RCTs compared the efficacy and safety of warfarin to placebo in post-MI patients. With a mean follow-up duration from 24 to 37 months, the risk of recurrent MI was found to be reduced in all three studies, and the stroke rates were also significantly reduced in the WARIS and ASPECT trials, although increased major bleeding rates were noted.[328-330] Another two studies compared warfarin with aspirin in post-MI patients, and the results showed similar ischemic event rates between the two groups with a significantly increased bleeding risk in the patients treated with warfarin.[331,332] Other studies have tried to answer whether adding warfarin to aspirin provides additional clinical benefits in post-MI patients. In the CHAMP and the LoWASA studies, combination therapy with low-dose aspirin and low-intensity warfarin did not add extra clinical benefits when compared to aspirin alone.[333,334] Moreover, in the LoWASA study, major bleeding occurred more frequently in the combination group. The WARIS-II study compared moderate-intensity warfarin (PT INR 2-2.5) plus aspirin (75 mg/day) with aspirin alone (160 mg/day) in post-MI patients. The incidence rates of the primary endpoint, re-infarction, and thrombo-embolic stroke were all significantly reduced in the combination group, but at the cost of a higher major bleeding risk than in the patients receiving aspirin monotherapy.[335] Furthermore, in the BAAS study, the addition of warfarin (PT INR 2.1-4.8) to aspirin (100 mg/day) in symptomatic CCS patients receiving PCI was demonstrated to reduce the 1-year primary efficacy endpoint including death, MI, target vessel revascularization and stroke when compared to subjects receiving aspirin alone (3.4% vs. 6.4%, p = 0.04). However, the bleeding complication rate also increased significantly in the warfarin group.[336] In summary, the routine use of warfarin as an alternative or add-on therapy to aspirin in CCS patients is not recommended based on the currently available evidence. Further well-designed studies are needed to clarify the role of warfarin in CCS patients receiving PCI or treated medically.

10.3.2 Novel oral anticoagulants (NOACs) in patients with CAD

Three clinical trials have evaluated the efficacy and safety of NOACs in ACS patients, and reported different balances of efficacy and bleeding. In the APPRAISE-2 study, the addition of apixaban at a dose of 5 mg twice per day to standard antiplatelet therapy increased major bleeding risk without reducing ischemic events.[337] On the contrary, in the ATLAS ACS 2-TIMI 51 study, triple therapy with rivaroxaban 2.5 mg twice per day reduced composite efficacy endpoints at the cost of increased major bleeding risk when compared to standard DAPT.[338] Furthermore, when added to P2Y12 inhibitors, rivaroxaban 2.5 mg twice per day was shown to have a similar risk of significant bleeding to DAPT in the GEMINI-ACS-1 study.[339]

10.3.3 Dual pathway inhibition in patients with CAD

In the COMPASS study, DPI with rivaroxaban (2.5 mg twice per day) and aspirin (100 mg once daily) reduced the composite of CV death, stroke, and MI compared with aspirin alone in PAD and high-risk CCS patients, but at the cost of an increased ISTH major bleeding risk (HR: 1.70; 95% CI: 1.40 to 2.05).[327] Regarding the balance between efficacy and safety, the pre-specified net clinical benefit still statistically significantly favored DPI therapy, and rivaroxaban was also shown to reduce the all-cause mortality rate by 18%. In addition, a larger absolute risk reduction and highest net clinical benefits of rivaroxaban were found in high-risk groups, including patients

with diabetes, renal impairment, HFrEF or polyvascular disease.[327,340-342] In the present guidelines, CCS patients with at least one of the following (diabetes, CKD with eGFR < 60 ml/min/1.73 m^2, HFrEF, ischemic stroke, and PAD) are defined as being at high ischemic risk, and DPI with rivaroxaban 2.5 mg twice per day and aspirin 100 mg once daily may be considered.

Key Recommendations:

- Adding rivaroxaban 2.5 mg twice per day to aspirin 100 mg once daily may be considered in CCS patients with high ischemic risk and without HBR for long-term secondary prevention (COR IIb, LOE B).
- The routine use of warfarin as an alternative or add-on therapy to aspirin in CCS patients is not recommended (COR III, LOE A).

10.3.4 Consideration of DPI and DAPT in patients with CCS

The choice of antithrombotic medication may depend on the progression of atherosclerotic disease, the predominantly affected vascular bed, comorbidities, and concomitant medications. Mechanistically, DAPT aims to prevent thrombus formation by inhibiting the activation of platelets, while NOACs act on the coagulation cascade to inhibit thrombin and prevent fibrin formation.[282,343] The composition of coronary and peripheral thrombi differs, and therefore, they may respond differently to antithrombotic therapies.[344] In patients with CAD, PAD, or a mix of CAD and PAD, recent studies provide evidence for the use of DAPT with low-dose ticagrelor in patients with predominant CAD, and the use of very low-dose rivaroxaban plus aspirin in patients with predominant PAD (Figure 9).[283,345-347] DAPT with ticagrelor has consistently been shown to reduce the risk of MACEs, and particularly the risk of MI, in patients who are at high ischemic risk with ACS (PLATO-study like patients, all inclusive of STEMI and NSTEMI regardless of the choice of treatment strategy), post-MI (PEGASUS-study like patients with median prior MI at 1.7 years), or pre-MI (THEMIS-study like patients, no prior MI but all concomitant with diabetes).[283,318] This is also the case for patients with predominant CAD with concomitant PAD.[283,345,348] In patients with a predominant PAD burden, the use of rivaroxaban plus aspirin has shown benefits in reducing acute limb ischemia, major adverse limb events and stroke (COMPASS-study like patients with median prior MI at 7.1 years).[346] In PAD patients undergoing lower-extremity revascularization, treatment with rivaroxaban 2.5 mg twice daily with aspirin compared to aspirin alone has been shown to significantly reduce the risk of the composite outcome of acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, or CV death.[347] However, in this trial, rivaroxaban plus aspirin did not reduce the risk of CV death or MI in patients en-

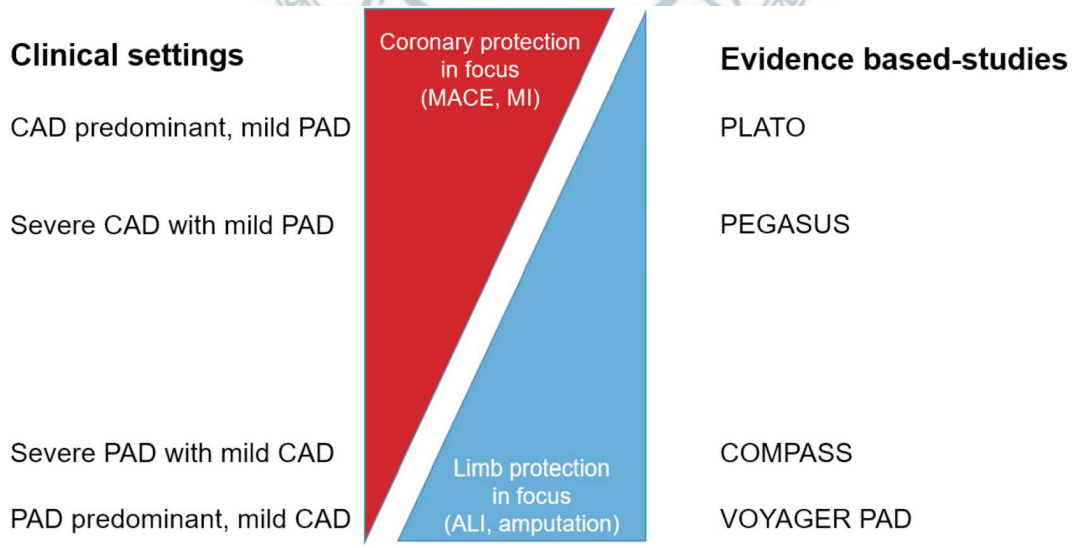


Figure 9. *The CAD-PAD continuum of managing CCS: Choice of DPI or DAPT in patients with high ischemic risk and low bleeding risk. ALI, acute limb ischemia; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; DPI, dual pathway inhibition; MACE, major adverse cardiovascular events; MI, myocardial infarction; PAD, peripheral artery disease.*

rolled based on PAD criteria (VOYAGER-PAD study like patients, all with documented lower-extremity PAD). In patients with CAD and PAD, the choice of therapy may be influenced by the secondary prevention focus (i.e., coronary vs. peripheral artery events). In patients with predominant CAD and concomitant PAD, the risk of MI is higher than the risk of acute limb ischemia.[345,346] Even in patients with predominant PAD, such as those undergoing revascularization, the risk of MI remains high in addition to the risk of acute limb ischemia.[347] Finally, besides the secondary prevention focus, the risk of mortality risk due to recurrent MI should also be taken into consideration. Notably, given that DAPT and DPI are associated with a significantly higher risk of bleeding, their use should only be considered for those with high ischemic risk and low bleeding risk. The Task Force proposes a treatment algorithm to guide the proper use of antithrombotic regimens for CCS based on the diverse clinical scenarios as shown in Figure 10. A one-size-fits-all approach is not suited to antithrombotic therapies for East Asian patients with CCS; a careful and individualized assessment of ischemic and bleeding risks is always recommended to determine the treatment strategy.

10.4 Special considerations of antithrombotic therapy in East Asian patients: use of "C-V-D" and "A-B-O" criteria to assess the ischemic and bleeding risk

Optimal antithrombotic strategies are a cornerstone of the management of CCS or PCI and have constantly evolved to balance ischemia and bleeding. The proportion of Asian patients enrolled in landmark RCTs involving antithrombotic therapy for CAD is substantially low, which limits the direct application of trial findings into clinical practice in Asian countries. Compared with Caucasian patients, East Asian patients have been reported to have a different ischemia/bleeding propensity in response to antithrombotic therapy, known as the "East Asian paradox" (i.e., more bleeding events but fewer thromboembolic events). Notably, a number of characteristics may limit transferability of RCT results from predominantly Western trial populations to East Asian patients. These include, but are not limited to, reduced bioactivation of certain drugs (i.e., clopidogrel) and HPR from genetic polymorphisms, a lower risk of stent thrombosis/ischemic events and higher gastrointestinal bleeding risk, and a higher prevalence of diabetes among

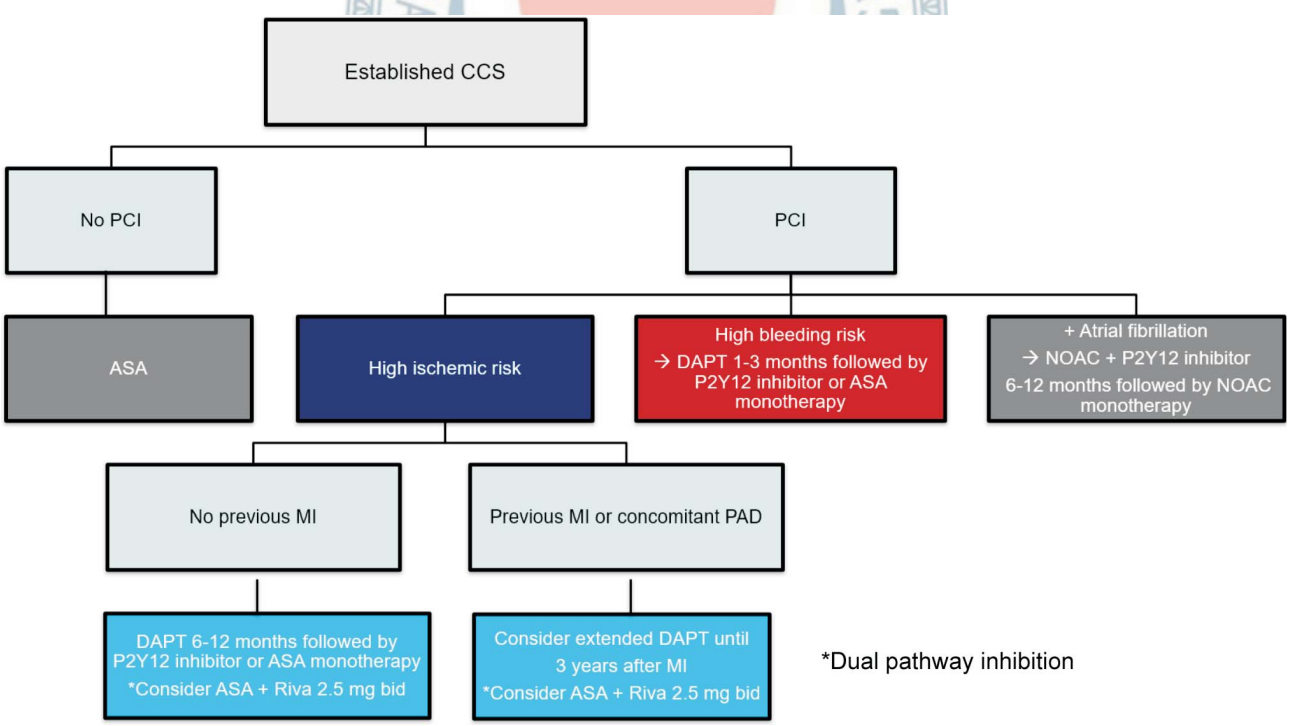


Figure 10. *Choice of antithrombotic regimens for CCS. ASA, aspirin; CCS, chronic coronary syndrome; DAPT: dual anti-platelet therapy; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; P2Y12, purinergic receptor type Y, subtype 12; MI, myocardial infarction; NOAC, novel oral anticoagulants; Riva, rivaroxaban.*

East Asian CAD patients. Advanced age, diabetes, and CKD not only increase the risk of ischemic events in patients with CCS but also confer a high bleeding risk during antithrombotic therapy. These special considerations may warrant modification of medical therapy, especially among East Asian populations, who have been shown to have clinically distinct characteristics from Western populations. Different tools for ischemic and bleeding risk assessment have been developed in trials of patients with CAD, and several risk calculators have been developed and validated to assess the risk of ischemic events and major bleeding in CAD patients. In these guidelines, the Task Force suggest simple **"C-V-D"** and **"A-B-O"** criteria to assess the ischemic and bleeding risk, respectively. The **"CVD"** criteria = **C**oronary-**V**ascular-**D**isease (**C**: Prior coronary event, high-risk coronary anatomy such as PCI involving LM, bifurcation lesions, MVD; **V**: CAD with concomitant PAD and or stroke (i.e., polyvascular disease), **D**: diabetes with micro- and macroalbuminuria, CKD with eGFR < 60 ml/min/1.73 m^2, HFrEF due to CAD); and the **"ABO"** criteria = **A**ge-**B**leeding-**O**rgan failure (**A**: advanced age; **B**: history of spontaneous intracranial hemorrhage, recurrent gastrointestinal bleeding, Hb < 9 g/dl; **O**: liver cirrhosis, advanced-stage renal failure, bone marrow failure, e.g. severe thrombocytopenia, platelet count < 50,000/μl, stroke in the last 6 months). The presence of any single factor listed would indicate high thrombotic or bleeding risk in a CCS patient. The presence of multiple factors would indicate an even higher ischemic or bleeding risk in such patients.

10.5 General strategy of pharmacological therapy

The aims of pharmacological therapy for CCS should include symptom relief, better QoL and preventing CV events – mainly MI and death. A more sophisticated approach may have additional benefits beyond angina relief. Mainly influenced by the results of the most recent large comparative RCTs of medical therapy versus revascularization treatment, the therapeutic scenario of CCS has evolved markedly over the past few years. The current TSOC guidelines for the management of patients with CCS recommend OMT as a key therapy for reducing symptoms, halting the progression of atherosclerosis and preventing ASCVD events. This strategy should be individualized for each patient, and there is no universal definition of optimal management for CCS.[349] Regarding pharmacological therapy, in addition to disease-modifying agents, CCS patient are often in need of antianginal therapies to prevent and treat anginal episodes that impair their functional capacity and QoL. Some agents, in addition to having antianginal effects, possess antiatherosclerotic properties that could be useful depending on the comorbidities present. Physicians communicating the indication for CCS treatment to their patients should emphasize its importance on reducing total CAD risk rather than focusing on symptom control only. Physicians should be aware of the disease-modifying potential of OMT, particularly given the incorporation of the most recent pharmacological lipid-lowering agents, novel antidiabetic drugs and antithrombotic agents into the current therapeutic armamentarium.

10.5.1 Tailored pharmacological approach beyond the angina paradigm

The TSOC guidelines recommend antianginal therapy to control symptoms, before considering coronary revascularization. The current ESC guidelines[19] recommend antianginal drugs classified as being first line (β-blockers, CCBs, short-acting nitrates) or second line (long-acting nitrates, ivabradine, nicorandil, and ranolazine). Second-line drugs are only indicated for patients who have contraindications to first-line agents, cannot tolerate them, or remain symptomatic. However, this approach is currently under debate. In fact, no direct comparisons between first-choice and second-choice treatments have demonstrated the superiority of one group of drugs over the other. Indeed, it appears that some newer antianginal drugs, which are classified as second choice, have more contemporary evidence-based clinical data to support their early use than the data available for first-choice drugs. A better understanding of the pathophysiologic mechanisms of myocardial ischemia and patient profiles may help to guide new therapeutic strategies to optimize the management of symptomatic CCS patients. Ideal medical therapy should be geared not only toward symptom control but also toward eliminating the occurrence of ischemia, treating ASCVD risk factors, and improving patients' CV outcomes. In this context, the present guidelines recommend a new approach for the medical treatment of patients taking into consideration comorbidities as well as the pathophysiology of myocardial ischemia. This approach can be sum-

marized into three steps: (1) disease-modifying therapy for all patients with CCS, (2) pathophysiology-based therapy for myocardial ischemia, and (3) symptomatic therapy in patients with chest pain. In contrast to other guidelines, the Task Force recommends this personalized three-step approach (Figure 11) to pharmacological therapy that does not simply add antianginal drugs on top of each other until resolution of angina, but targets specific aims at each step: Step 1 (disease-modifying therapy), the initiation of disease-modifying therapies ("A-C-S"; Antiplatelet therapy, Colchicine, Statins) that should be considered for all CCS patients, regardless of the presence of angina. Comorbidities play an important role to determine the best individual treatment strategies. In CCS patients with comorbidities, the choice of pharmacological therapy with proven antiatherosclerotic benefits (such as RAS inhibitors for hypertension; SGLT2 inhibitors and GLP-1 receptor agonists for diabetes) should be preferred first. Step 2 (pathophysiology-based therapy), the administration of agent according to the pathophysiology of myocardial ischemia. A consequence common to all precipitating mechanisms leading to myocardial ischemia at the cellular level is the development of a late inward sodium current in cardiomyocytes.[350, 351] This late sodium current increases intracellular calcium concentration, which in turn impairs relaxation and increases diastolic wall tension, thus worsening ischemia and creating a vicious circle. Ranolazine, an inhibitor of this abnormal late sodium current, should be considered a therapeutic target common to CCS patients. In addition, coronary microvascular angina due to dysfunction of the coronary microcirculation is the underlying cause of chest pain in almost 50% of CCS patients either with or without underlying obstructive CAD, and it is associated with a poor prognosis and poor QoL.[352] Ranolazine has shown additional beneficial effects on coronary

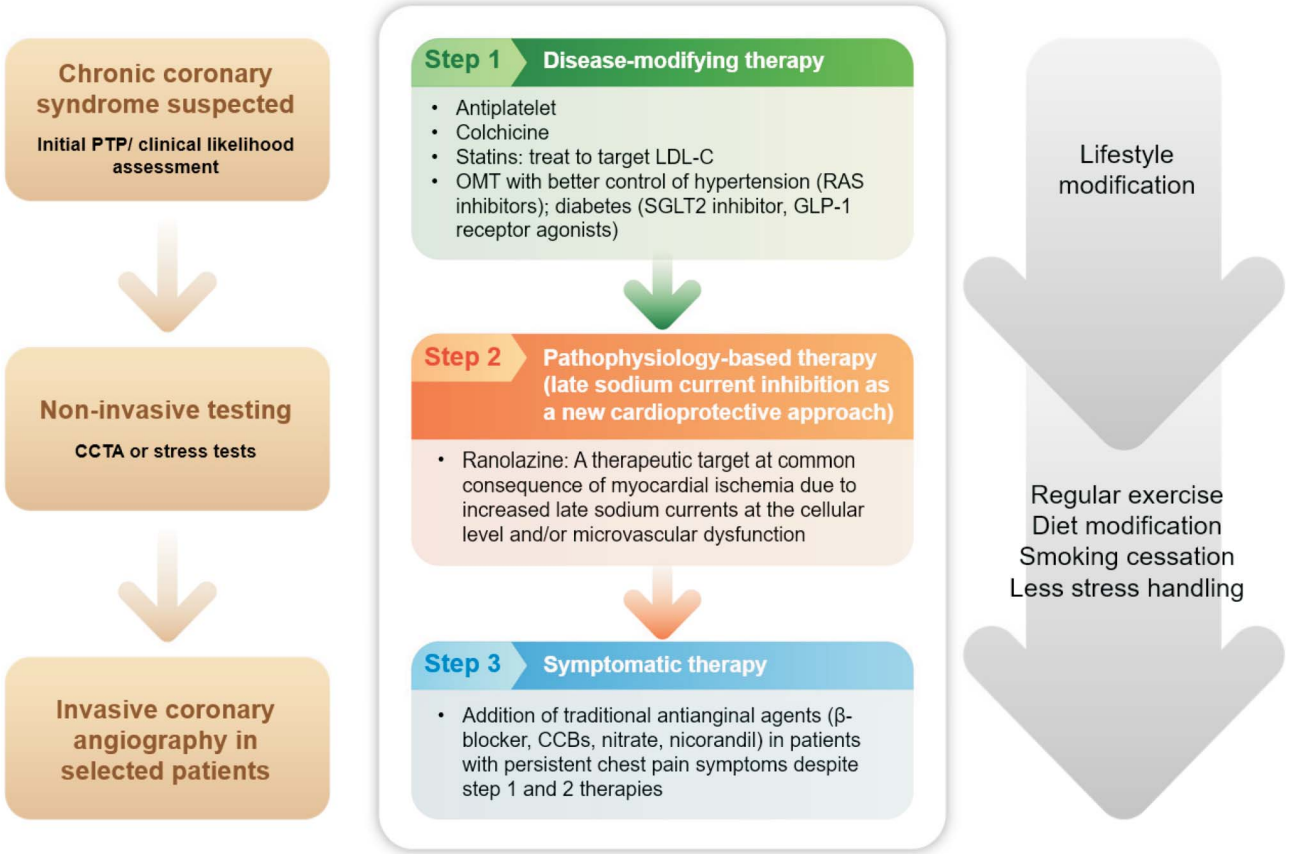


Figure 11. *Tailored pharmacological approach for CCS beyond the angina paradigm. CAD, coronary artery disease; CABG, coronary artery bypass graft surgery; CCBs, calcium channel blockers; CCTA, coronary computed tomography angiography; CCS, chronic coronary syndrome; GLP-1, glucagon-like peptide-1; LDL-C, low-density lipoprotein cholesterol; OMT, optimal medical therapy; PTP, pretest probability; RAS, renin-angiotensin system; SGLT2, sodium-glucose cotransporter 2.*

microvascular dysfunction in patients with CCS,[353,354] which suggests that it should be considered before the use of classic antianginal drugs in CCS patients. Step 3 (symptomatic therapy), the addition of supplementary antianginal agents in patients with persistent chest pain symptoms despite step 1 and 2 therapies. Finally, drug treatment should be tailored to individual patients and chosen according to the pathophysiology, hemodynamic profile, adverse effects, potential drug interactions and comorbidities. Such a tailored approach should be considered as a better option in most cases. The impacts on hemodynamics, pharmacology, symptom relief, and outcome benefits of antianginal drugs are presented in Table 9.

10.6 Antianginal drugs available in Taiwan

Angina is a most prevalent symptomatic manifestation of myocardial ischemia secondary to a number of potential factors, including epicardial coronary artery stenosis, thrombosis, changes in the coronary vasomotor tone, CMD, hemodynamic and metabolic factors and comorbidities contributing to an imbalance in oxygen supply and demand to the myocardium. Chronic chest pain greatly impairs the quality of life and is associated with an increased risk of adverse CV outcomes.[355]

10.6.1 Short-acting nitrate

Sublingual (SL) and spray nitroglycerin formulations provide immediate relief of angina symptoms, of which spray nitroglycerin acts more rapidly than SL nitroglycerin.[356] During an angina attack, patients should rest in a sitting position and avoid standing, which may lead to syncope. A lying position is not suggested due to increased venous return and increased preload which may exacerbate the symptoms of angina. SL nitrate should be taken sublingually instead of swallowing at 5-minutes interval until the pain improves, or to a maximum of 1.2 mg has been taken within 15 minutes. Immediate medical attention is suggested if angina persists for more than 15 minutes. The use of prophylactic nitrates before physical activity is accepted to prevent angina attack. Isosorbide dinitrate (5 mg sublingually) has a slightly slower onset of action than nitroglycerin due to hepatic conversion to isosorbide mononitrate. The effect of isosorbide dinitrate may last for less than 1 hour if the drug is taken sublingually, and will persist for a longer time (several hours) if the drug is taken by oral ingestion.

10.6.2 Long-acting nitrates

Traditionally, long-acting nitrate medications including nitroglycerin, isosorbide dinitrate, and isosorbide mononitrate should be considered as second-line therapy for angina relief if first-line medications fail to control symptoms or if they are poorly tolerated or contra-

Table 9. Impacts of antianginal drugs on hemodynamics, pharmacology, symptom relief, and outcomes benefits

Antianginal drug	HR	SBP	DBP	PVR	Cardiac contractility	Coronary vasodilatation	Symptom relief	Outcomes benefit
Nitrates								
Short-acting	↑–	↓↓	↓↓	↓–	–	↑↑↑	Yes	No
Long-acting	↑–	↓	↓	↓–	–	↑↑	Yes	No
β-blockers								
Noncardioselective	↓↓↓	↓↓	↓↓	↑–	↓↓	–	Yes	No
Cardioselective (preserved EF)	↓↓↓	↓↓	↓↓	–	↓↓	–	Yes	No
Cardioselective (reduced EF)	↓↓↓	↓↓	↓↓	–	↓↓	–	Yes	Yes
With vasodilatation (preserved EF)	↓↓	↓↓↓	↓↓↓	↓↓	↓	–	Yes	No
With vasodilatation (reduced EF)	↓↓	↓↓↓	↓↓↓	↓↓	↓	–	Yes	Yes
Calcium-channel blockers								
Dihydropyridines	↑–	↓↓↓	↓↓↓	↓↓↓	↑-	↑↑↑	Yes	No
Nondihydropyridines	↓↓	↓↓	↓↓	↓↓	↓↓	↑↑	Yes	No
Newer agents								
Ivabradine	↓↓	↓–	↓-	–	–	–	Yes	No
Nicorandil	↑	↓↓	↓↓	↓–	–	↑↑↑	Yes	No
Ranolazine	–	–	–	–	–	–	Yes	Yes, in ACS patients with prior chronic angina

DBP, diastolic blood pressure; EF, ejection fraction; HR, heart rate; NA, not available; PVR, peripheral vascular resistance; SBP, systolic blood pressure.

indicated. A nitrate-free or low-dose interval should be considered, as taking long-acting nitrates at 10-14-hour intervals such as transdermal nitrates through slow-release patch systems is also effective. The bioavailability of isosorbide dinitrate is lower than isosorbide mononitrate which is a directly active metabolite and is 100% bioavailable. Abrupt termination of long-acting nitrate therapy is not suggested to avoid angina attack.[357] Side effects of long-acting nitrates include headache, flushing and hypotension. Contraindications include hypertrophic obstructive cardiomyopathy, severe aortic stenosis, and co-administration of phosphodiesterase inhibitors (e.g., sildenafil, tadalafil, or vardenafil).

10.6.3 Beta (β)-blockers

By reducing contractility and heart rate, β-blockers are effective in reducing angina in CCS patients. The target resting heart rate is around 55-60 beats per minutes.[358] Abrupt discontinuation of β-blockers is not recommended. β-blockers can be combined with dihydropyridine (DHP)-CCBs to reduce DHP-induced reflex tachycardia, although the clinical benefit is uncertain. However, a combination of β-blockers with verapamil or diltiazem should be used with caution due to complications such as bradycardia, atrioventricular block or worsening of HF. Other side effects of β-blockers include fatigue, bradycardia, heart block, bronchospasm, peripheral vasoconstriction, postural hypotension, impotence, and depression. The symptoms of hypoglycemia may not obvious after the use of β-blockers. β-blockers are associated with lower risks of mortality and CV event in patients with recent MI or HFrEF.[359-361] In a retrospective analysis of the National Cardiovascular Data Registry (NCDR) of 755,215 patients age more than 65 years and with a history of CAD but without prior MI or HFrEF undergoing elective PCI, the use of β-blockers at discharge showed no benefit in reducing CV morbidity or mortality at 30 days and 3 years of follow-up.[362] However, in patients with CCS with/without prior MI who have undergone CABG, β-blockers have been associated with a reduced risk of long-term mortality and adverse CV events.[363] In CCS patients with prior MI, the long term (> 1 year) benefit of β-blockers remains unclear.[364-366]

10.6.4 Calcium channel blockers

While CCBs improve symptoms of angina and myocardial ischemia in CCS patients, they have not been shown to reduce morbidity or mortality.[367,368] Non-DHP CCB agents include verapamil and diltiazem. Verapamil has a large range of approved indications for all varieties of angina, including effort angina and vasospastic angina. The possible adverse effects include heart block, bradycardia, and worsening of HF. The anti-angina effect of verapamil is similar to metoprolol.[369] Verapamil is associated with a lower risk of diabetes and angina attack compared with atenolol in patients with hypertension with CCS[370] and less psychological depression.[371] A combination of verapamil and β-blockers is not recommended due to an increased risk of heart block. Another non-DHP CCB agent, diltiazem, has fewer side effects compared with verapamil, and may be the better choice to treat effort angina. The mechanism of verapamil is through peripheral vasodilation, which relieves exercise-induced coronary artery constriction, has a modest negative inotropic effect, and inhibits sinus node. No outcome study has compared verapamil and diltiazem. The use of non-DHP CCBs in patients with LV dysfunction is not advised, especially intravenous forms non-DHP CCB which may deteriorate LV function in patients with low LVEF. Long-acting nifedipine, a DHP CCB, is a useful arterial vasodilator with few serious side effects. Long-acting nifedipine is especially well tolerated in hypertensive patients with CCS. It is also well tolerated in combination with β-blockers. In the large ACTION trial, the addition of long-acting nifedipine to conventional antianginal treatment had no additional benefit on MACE-free survival. Long-acting nifedipine has been shown to be safe and beneficial in reducing the need for coronary interventions.[372] Contraindications for long-acting nifedipine included severe aortic stenosis, hypertrophic obstructive cardiomyopathy, or HF. Long-acting DHP can be considered in combination with β-blockers with a low risk of complications. The vasodilatory side effects include headache and ankle edema. Amlodipine with its very long half-life and good tolerability make it an effective once daily antianginal and antihypertensive agent, which is quite different from other CCBs taken either twice or three times daily. Amlodipine is associated with few side effects, of which ankle edema is most common. A 2-year trial showed that in patients with CCS and normal BP (of whom 75% were receiving β-blockers), amlodipine 10 mg per day could reduce coronary revascularization

zations and hospitalizations for angina.[266]

10.6.5 Ivabradine

Ivabradine has been reported to be non-inferior to atenolol or amlodipine in the management of angina and ischemia in patients with CCS.[373,374] Adding ivabradine 7.5 mg twice daily to atenolol therapy has been shown to provide better control of heart rate and anginal symptoms.[374] In the BEAUTIFUL trial of 10,917 patients with limited previous angina, ivabradine did not reduce the composite primary endpoint of CV death, hospitalization with MI, or HF.[375] In addition, the SIGNIFY study enrolled 19,102 CCS patients without clinical HF and a heart rate > 70 beats per minute, and showed no significant difference between the ivabradine group and endpoint of CV death or nonfatal MI.[376] Ivabradine was associated with an increase in the incidence of death from CV causes or nonfatal MI in patients with activity-limiting angina, but not among those without activity-limiting angina (p = 0.02 for interaction). The incidence of bradycardia was higher with ivabradine than with placebo (18.0% vs. 2.3%, p < 0.001).

10.6.6 Nicorandil

Nicorandil is a nitrate derivative of nicotinamide, which has an antianginal effect similar to nitrates and β-blockers.[377,378] The side effects of nicorandil include nausea, headache, vomiting, and potentially severe oral, intestinal, and mucosal ulcerations. In the placebo-controlled IONA trial (n = 5126), nicorandil significantly reduced the composite endpoints of coronary death, nonfatal MI, or unplanned hospital admission for suspected anginal symptoms in patients with CCS, but had no benefit on death from CAD or nonfatal MI.[379]

10.6.7 Ranolazine

There is increasing evidence that the late sodium current of the sodium channel in cardiomyocytes plays a critical role in the pathophysiology of myocardial ischemia, and is thus a preferred therapeutic target in symptomatic patients with CCS.[351,380] Ranolazine is an inhibitor of the late sodium current which prevents calcium overload-induced ischemia and therefore interrupts a major step in the pathophysiology of myocardial ischemia at a cellular level. It reduces the frequency and severity of anginal attacks and improves the QoL in patients with coronary microvascular dysfunction and severe refractory angina,[381] and unlike other antianginal drugs, ranolazine does not alter heart rate or BP.[382] In most cases, patients with chronic angina usually have a number of abnormalities, and by definition angina is always secondary to myocardial ischemia. In patients with myocardial ischemia, chest pain is often but not always present (silent ischemia), although other symptoms associated with ischemia may be present (such as exertional shortness of breath, diaphoresis, fatigue). In the last decade, the development of ranolazine has included multiple clinical trials enrolling more than 10,000 patients. The efficacy of ranolazine in reducing symptomatic angina in CCS patients has been demonstrated both as monotherapy in the MARISA trial[383] and in combination with amlodipine, atenolol or diltiazem in the CARISA[384] and ERICA trials.[385] Furthermore, ranolazine (500-1500 mg twice daily) has been shown to progressively improve exercise-induced ischemic ST-segment depression during submaximal and maximal exercise stress without inducing a substantial change in heart rate or rate-pressure product, suggesting that the anti-ischemic effects of ranolazine in patients with chronic angina are primarily due to an improvement in regional coronary perfusion in areas of myocardial ischemia.[385] The MERLIN-TIMI 36 trial randomized 6560 patients with recent NSTE-ACS to intravenous ranolazine or placebo within 48 h from the onset of ischemic symptoms. After a median follow-up of 348 days, ranolazine proved to be effective in preventing worsening angina and additional antianginal therapy and in reducing recurrent ischemia at 1 year, despite showing no effect on the composite endpoint (CV death, acute MI or recurrent ischemia).[386] However, in 3565 patients included in the trial with prior chronic angina, ranolazine significantly increased total exercise time and time to onset of angina or to 1-mm ST-segment depression, reduced worsening angina, new antianginal treatment and recurrent ischemia, and more importantly significantly improved the primary endpoint (CV death, MI, recurrent ischemia; HR: 0.78; 95% CI: 0.67-0.91) compared with placebo.[387] Moreover, ranolazine reduced recurrent ischemic events, regardless of whether patients received PCI within 30 days of NSTE-ACS.[388] The Ranolazine Refractory Angina Registry enrolled CCS patients with refractory angina. After 1 year, 43% of the patients had a ≥ 2 class improvement in an-

gina class and 57% remained on ranolazine (91% on 500 mg b.i.d.).[389] The short- and long-term benefits of ranolazine on cardiac-specific health status and quality of life after recent NSTE-ACS were evaluated in a prospective trial, and the results showed significant improvements from baseline, particularly in patents with a previous history of angina.[390] In the prospective TERISA study of symptomatic patients with type 2 diabetes and CCS with chronic angina recruited from 104 centers in 14 countries, the proportion of patients achieving ≥ 50% reduction in weekly angina and the Short Form-36 (SF-36) Physical Component Summary Score was significantly higher with ranolazine (target dose 1000 mg bid) than with placebo.[391] Interestingly, the significantly greater benefits of ranolazine versus placebo in terms of reduced weekly angina frequency were positively correlated with higher baseline HbA1c (p for interaction = 0.027). A prospective, multicenter, observational study at 88 sites across Austria with 12 weeks of follow-up in patients with refractory angina (ARETHA AT) was conducted to evaluate angina symptoms, nitrate use and QoL in a routine clinical setting.[392] Of the included patients, 94.0% reported improved exercise capacity and 93.7% reduced symptoms. A recent RCT compared the antianginal efficacy of ranolazine (daily 1000 mg) versus allopurinol (300 mg b.i.d.) for symptomatic CCS patients with a history of PCI. The results showed that both allopurinol and ranolazine improved chest pain severity and Duke Treadmill Score, but ranolazine had a statistically greater positive effect on ST depression reduction.[393] In the CARISA trial, ranolazine (750 and 1000 mg b.i.d.) reduced HbA1c versus placebo by 0.48% (p = 0.008) and 0.70% (p = 0.0002), respectively, and this effect remained unchanged during long-term follow-up.[394] In the MERLIN-TIMI 36 trial, in diabetic patients treated with ranolazine, HbA1c declined from 7.5% to 6.9% (p < 0.0001), and the patients were more likely to achieve an HbA1c value < 7% at 4 months compared with placebo (59 vs. 49%; p < 0.001).[395] A recent scientific statement from the AHA provided specific indications for CCS patients with type 2 diabetes, highlighting the possible negative effect of β-blockers and CCBs on glycemic control, and reported the clinical benefits on glucose control observed with ranolazine.[396] A meta-analysis of 46 studies evaluating 71 treatment comparisons quantified the clinical benefits of β-blockers, CCBs, long-acting nitrates, ranolazine, ivabradine or nicorandil added to first-line monotherapy for CCS patients with angina,[47] and found that the addition of ranolazine to CCBs or β-blockers improved angina frequency, sublingual nitroglycerin consumption, prolonged exercise duration as well as time to onset of ischemia and to onset of angina with no substantial effects on BP and heart rate. Coronary microvascular dysfunction (CMD) is a common cause of angina and exercise intolerance in CCS patients. In patients with CCS and evidence of myocardial ischemia, but no obstructive CAD, ranolazine has been shown to increase coronary flow reserve (CFR), probably due to improvement in abnormal coronary autoregulation, both reducing baseline diastolic coronary flow velocity and increasing hyperemic diastolic coronary flow velocity.[397] In a study with a crossover design of females with CMD diagnosed by CMR imaging perfusion, CMD patients were randomly assigned to either ranolazine or placebo. After 4 weeks of therapy, ranolazine resulted in significantly better SAQ scores and a trend toward improved myocardial perfusion.[398] In another study, 46 CMD patients were randomly assigned ivabradine, ranolazine or placebo, and were followed for angina symptoms, coronary microvascular dilation, exercise tolerance and ST-segment depression on stress testing.[381] The patients assigned ranolazine had greater improvements in angina, exercise duration, and time-to-ST-segment duration compared with the ivabradine and control groups. A recent meta-analysis of nine RCTs[399] showed that in the subgroups with a baseline CFR < 2.5 or a global myocardial perfusion reserve index (MPRI) < 2, ranolazine increased the MPRI (weighted mean difference: 0.19; 95% CI: 0.10 to 0.27) and reduced the IMR (weighted mean difference: -7.63; 95% CI: -11.8 to -3.4) compared with the control drugs (nicorandil, ivabradine). In addition, ranolazine improved 3 of the 5 SAQ domains and also reduced angina. Despite being effective in improving CFR, angina stability, physical functioning, and QoL, ranolazine was not shown to improve CV mortality (1000 mg twice daily, RR: 1.03, 95% CI: 0.56 to 1.88) or nonfatal MI incidence (any dose, RR: 0.88, 95% CI: 0.69 to 1.12) compared with placebo or control therapy.[354] Taken together, a better understanding of the pathophysiologic mechanisms of myocardial ischemia may permit new therapeutic strategies to optimize the pharmacological treatment of CCS patients. In contrast to other anti-

anginal agents, ranolazine targets the common consequence of myocardial ischemia at a cellular level regardless of the underlying causes or triggers.[400] In this respect and because of its peculiar mechanism of action, ranolazine represents a preferred therapeutic approach in symptomatic patients with CCS. Based on these reasons, symptomatic patients who complain of stable chest pain or its equivalent despite disease-modifying therapies in step I should proceed to step II anti-ischemic therapy, where ranolazine may be considered for all patients. Its side effects include dizziness, nausea, and constipation.[382] Ranolazine was shown to prolong the QTc interval by 2-7 ms in both healthy volunteers and patients with NSTE-ACS without increasing the risk of proarrhythmias.[401,402] In fact, in the MERLIN-TIMI 36 trial, ranolazine reduced the incidence of ventricular tachycardia ($p < 0.001$), without increasing the risk of torsades de pointes.[402] The ROLE trial enrolled 746 CCS patients and followed them for 2.82 years, and found that prolongation of the QTc increased from 419.9 ± 0.8 ms to 422.3 ± 0.7 ms, but no cases of torsades de pointes were reported.[403] Thus, dose-related prolongation of the QT interval does not seem to be a concern at the recommended therapeutic dose (500 mg b.i.d.). Moreover, ranolazine has been shown to exhibit anti-AF effects,[404,405] and a combination of ranolazine and amiodarone has been shown to significantly increase the sinus rhythm restoration rate in patients with AF and LV systolic dysfunction without increasing the risk of proarrhythmias.[406]

10.6.8 Allopurinol

A RCT investigating the effect of high-dose (up to 600 mg daily) allopurinol on exercise in patients with CCS reported that high-dose allopurinol increased the time to chest pain attack compared with placebo, with a mean increase of 38 seconds, without significantly increasing side effects.[407] However, when using allopurinol, hypersensitivity with toxic epidermal necrolysis (TEN) and Stevens-Johnsons syndrome (SJS) should be taken into consideration. Screening of HLA-B*5801 may help patients to prevent the occurrence of allopurinol-induced TEN/SJS, especially in those with a higher ($\geq 5\%$) risk allele frequency.[408] When considering allopurinol use for CCS patients, a full risk-benefit assessment, dosage adjustment, and careful monitoring may be warranted. In a population-based cohort study and meta-analysis in Asian patients, febuxostat was found to have fewer hypersensitivity effects with similar CV risk.[409] Another meta-analysis also showed no difference in the occurrence of MACEs in hyperuricemia patients between allopurinol and febuxostat groups.[410]

10.6.9 Colchicine

Hyperuricemia has been linked to an increased risk of CVD, possibly through a proinflammatory milieu. However, not all drugs used to treat hyperuricemia improve CV outcomes. Recent evidence suggests the potential benefits of low-dose colchicine (< 1 mg per day) in atherogenesis and secondary prevention of CAD via inhibition of cytokine production. Interest in colchicine has grown following publication of the COLCOT[411] and LoDoCo2[412] trials, and colchicine has been shown to improve CV outcomes in patients with recent MI (mean of 13.5 days after MI) and CCS independently of lipid-lowering effects. The COLCOT and LoDoCo2 trials included > 10,000 patients and found that colchicine reduced CV risk both in patients after MI and in those with CCS. In the LoDoCo2 trial, 5522 patients underwent randomization; 2762 were assigned to the colchicine (0.5 mg once daily) group and 2760 to the placebo group. The colchicine group had a lower rate of the composite endpoint of CV death, nonprocedural MI, ischemic stroke, or ischemia-driven coronary revascularization (95% CI: 0.57 to 0.83). The composite of CV death, spontaneous MI, or ischemic stroke was also lower in the colchicine group (4.2%) than in the placebo group (5.7%) (HR: 0.72; 95% CI: 0.57 to 0.92).[412] Furthermore, a recently published meta-analysis of 13 trials comparing colchicine in CCS patients showed that colchicine versus placebo/standard therapy reduced the risks of MI (OR: 0.64; 95% CI: 0.46-0.90) and stroke (OR: 0.50; 95% CI: 0.31-0.81), but that treatment with colchicine had no influence on all-cause and CV mortality.[413] In addition, colchicine increased the risk of gastrointestinal side effects. Colchicine represents a promising supplementary drug for the secondary prevention of ischemic events among CCS patients. With trials such as COLCOT and LoDoCo2 showing the benefits of colchicine in patients with CAD, its use may be extended to current practice in the secondary prevention of CAD.

11. ISCHEMIA WITH NO OBSTRUCTIVE CORONARY ARTERY DISEASE (INOCA)

Angina in the absence of a hemodynamically significant stenosis is a conundrum that physicians frequently encounter in their daily practice. Recognition of suspected myocardial ischemia with no significant obstructive CAD – termed INOCA – has increased in recent years.[414] The term INOCA encompasses a large number of clinical scenarios characterized by reduced CFR in the absence of anatomical obstructive epicardial disease. In INOCA, the mismatch between blood supply and myocardial oxygen demand may be caused by coronary microvascular dysfunction (CMD) and/or epicardial coronary artery spasm. Coronary vasomotion disorders represent a frequent cause of microvascular angina (MVA) and/or dyspnea in INOCA patients. The highly complex interplay of vasodilatation and vasoconstriction can be assessed via an invasive diagnostic procedure. The spasm provocation test involves injecting acetylcholine and/or ergonovine into the coronary artery to induce epicardial coronary vasospasm > 90% and/or reproducibility of symptoms with ECG changes.[415] Clinically, CMD is responsible for chest pain in a wide range of patients, including those with obstructive or non-obstructive CAD and persistent symptoms despite revascularization, or those with myocardial diseases such as Fabry disease, hypertrophic or dilated cardiomyopathy without coronary stenosis. Therefore, patients with INOCA can have symptoms from CMD and/or epicardial coronary artery spasm (vasospastic angina, also known as variant angina). CMD is characterized by reduced CFR, microvascular spasm, and/or coronary endothelial dysfunction. Importantly, CMD is associated with a significantly higher rate of MACEs including MI, stroke, HFpEF and death, especially in women.[416-418] Recent meta-analyses of CMD across a broad range of ACS and CCS patients detected through invasive or non-invasive testing showed that reduced CFR was associated with a remarkable 3- to 5-fold higher incidence of all-cause mortality and MACEs.[419, 420] In practice, once obstructive epicardial CAD has been ruled out with angiography or other testing such as CCTA, the diagnosis of CMD becomes more likely. The demographic and clinical risk factors for CMD include younger age,[421] female sex,[417] anxiety disorder,[422] and traditional atherosclerotic risk factors such as diabetes, hypertension, hypercholesterolemia and cigarette smoking.[423]

11.1 Diagnosis of CMD

Diagnostic testing for CMD includes invasive and non-invasive methods aimed at detecting low CFR, provoked microvascular spasm, and microvascular dysfunction. Noninvasive clinical workup comprises both anatomical and physiological testing using CCTA, PET, stress echo, MRI, and their combinations. PET can provide an estimate of CFR by comparing myocardial blood flow at rest with blood flow acquired during stress,[417] which represents the gold standard for diagnosing microvascular abnormalities. CMR provides a measure of CFR by comparing perfusion (first-pass gadolinium uptake) at rest with perfusion during vasodilator or dobutamine stress.[424] Echocardiographic CFR is measured by comparing velocities obtained from the LAD at rest with velocities obtained during stress.[425] Echocardiographic myocardial perfusion reserve is measured by comparing contrast echo-derived myocardial replenishment curves obtained at rest with curves obtained with peak adenosine infusion. Recently, CCTA with myocardial perfusion imaging (CCTA-MPI) has been shown to have good performance in the assessment of microvascular disease.[426-428] CCTA-MPI evaluates the passage of contrast medium from the vascular to the myocardial compartment at rest and after adenosine administration. Considering that CCTA allows for optimal investigation of epicardial coronary artery and microvascular function in the same study, it could be a promising technique for a “one-stop shop” assessment. In patients with CMD, ICA shows normal epicardial coronary arteries or mild coronary artery disease (< 30% stenosis). In patients with lesions between 30% and 50%, further evaluation with FFR should be carried out to make sure that lesions are not hemodynamically significant. For patients without obstructive CAD as the cause of myocardial ischemia and in whom the diagnosis of CMD is considered, additional testing should be performed, usually at the time of ICA. Local availability and expertise will dictate which test is chosen, and it may be necessary to perform more than one to establish the diagnosis of CMD due to the heterogeneity of underlying mechanisms. According to the Coronary Vasomotion Disorders International Study Group (COVADIS) proposed standardized criteria, definitive MVA is only diagnosed if all four criteria are present, in-

cluding the presence of symptoms, absence of obstructive/flow limiting coronary stenosis (> 50% diameter reduction or FFR < 0.80), objective evidence of myocardial ischemia on non-invasive testing, and evidence of CMD on coronary function testing.[429] Impaired coronary microvascular function includes low CFR (< 2 to < 2.5), coronary microvascular vasospasm (reproduction of symptoms and ischemic ECG changes but no epicardial vasospasm during acetylcholine testing), and/or high index of microcirculatory resistance (IMR) ≥ 25.

11.2 Management of INOCA

The management strategy of INOCA remains largely empirical, and optimal therapy may vary with the mechanism of CMD. In CMD patients with abnormal CFR < 2.0 or IMR ≥ 25 units and a negative acetylcholine provocation test, β-blockers, ACE inhibitors, and statins, along with lifestyle changes and weight loss, may be considered.[19] Microvascular spasm can also be treated like vasospastic angina.[19,429] Certain β-blockers, including atenolol carvedilol and nebivolol, have been evaluated in clinical studies.[430-432] β-blockers seem to be effective in reducing the frequency and severity of angina and in improving exercise tolerance.[433] The Women's Ischemia Syndrome Evaluation (WISE) study showed that after 16 weeks, treatment of women with CMD with quinapril was significantly associated with improvements in angina symptoms and CFR compared with the placebo group.[434] Furthermore, in patients with hypertensive disease who were treated for 12 weeks with cilazapril, cardiac PET showed a 42% improvement in CFR.[435] In pilot studies, atorvastatin improved CFR at 2 and 6 months.[436,437] A recent meta-analysis of 46 RCTs assessing the effect of statins on coronary endothelial function showed that treatment with statins was associated with a significant improvement in endothelial function, with a standardized mean difference of 0.66 (95% CI: 0.46-0.85; p < 0.001).[438] The efficacy of ranolazine, a late sodium channel blocker, in patients with symptomatic obstructive CAD is well established. In CMD, ranolazine may be associated with improvements in CFR and angina stability, physical functioning, and QOL (see section 10.4.2.7). Abnormal cardiac nociception is a condition primarily studied in women with suspected CMD, and is characterized by abnormal cardiac pain perception.[439] Imipramine, a tricyclic antidepressant medication, may be effective in some patients with MVA when used at a low dose. One study evaluated 60 patients with chest pain and normal coronary angiograms.[440] The patients were randomly assigned to imipramine (50 mg nightly), clonidine (0.1 mg twice daily), or placebo. A benefit was seen only with imipramine, which reduced the frequency of chest pain in patients with CMD by approximately 50%.

12. LIFESTYLE MANAGEMENT

Lifestyle management is the cornerstone of both primary and secondary prevention of CAD, and the importance of lifestyle management is emphasized by all major guidelines. The LSM interventions include smoking cessation, dietary change, increasing physical activity, and stress management. The interventions for CV risk reduction in CCS patients are summarized in Table 10.[441-446]

12.1 Diet and CCS

Several observational and RCTs have demonstrated an association between a lower CVD risk and healthy dietary patterns, including a Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH) diet, healthy Taiwanese eating approach, and Taiwanese vegetarian diet.[447-450] The role of food and dietary patterns in the prevention of ASCVD are still incompletely understood, and nutritional science continues to evolve. Unhealthy diets are a leading contributor to CAD and its progression, and changes to healthy eating patterns in patients with CCS have resulted in a reduction in mortality and CV events.[451] Although evidence of the association between nutrition and ASCVD outcomes is limited due to the lack of large-scale prospective RCTs, numerous observational studies have shown the effect of dietary pattern on CVD mortality.[144] Trans and saturated fats have been associated with a higher risk of total and cause-specific death.[452] Southern dietary patterns, characterized by added fats, fried food, eggs, organ and processed meats, and sugar-sweetened beverages has been associated with a 56% higher hazard of ACS.[453] A slightly elevated risk of nonfatal MI has been associated with the intake of 1 or more eggs per day among US veterans.[454] Using meat for protein has been associated with a 61% increase in CV mortality rate, whereas replacing meat with nuts and seeds has been associated with a 40% reduction.[455] Plant-based and Mediterranean dietary pat-

Table 10. Interventions for CV risk reduction in subjects with established or at high risk of CAD

Therapy	Study details	Relative risk reduction	Risk ratio (95% CI)
Smoking cessation[441]	Meta-analysis of 6 cohort studies comparing smoking cessation vs. ongoing smoking in participants with CAD and > 2 years of follow-up (n = 8408).	29% for all-cause mortality	0.71 (0.65-0.77)
Mediterranean diet[442]	Umbrella meta-analysis of RCTs comparing Mediterranean dietary pattern vs usual diet (n = 12,894; not limited to CAD).	38% for MACE plus ≥ 1 other event	0.62 (0.45-0.86)
Physical activity[443]	Meta-analysis of 85 RCTs comparing exercise vs. no exercise among patients with CAD (n = 23,430).	28% for myocardial infarction	0.72 (0.55-0.93)
Stress training[444]	Meta-analyses of 35 trials comparing psychological interventions vs control in patients (n = 10,703).	21% for cardiovascular mortality	0.79 (0.63-0.98)
Influenza vaccination[445]	Meta-analysis of 16 studies comparing influenza vaccine vs. placebo in participants with cardiovascular disease (n = 237,058).	18% for cardiovascular mortality	0.82 (0.80-0.84)
Pneumococcal vaccination[446]	Pooled results from 11 studies comparing pneumococcal vaccination vs. control (n = 332,267).	14% for cardiovascular events	0.86 (0.76-0.97)

CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; MACE, major adverse cardiovascular events; RCT, randomized control trial.

terns high in fruit, nut, vegetable, legume, fiber and lean vegetable or animal protein (preferably fish) consumption have consistently been associated with a lower risk of all-cause mortality than control or standard diets.[144,212] As a part of a healthy diet, it is reasonable to minimize the intake of processed meats, refined carbohydrates, red meat, dairy, and saturated fat to reduce ASCVD risk.[212]

Key Recommendations

- A plant-based diet high in fruit, nut, vegetable, legume, fiber and lean vegetable or animal protein (preferably fish) consumption is recommended to decrease CAD risk (COR I, LOE B).
- Minimizing the intake of processed meats, and replacing saturated fat with dietary monounsaturated and polyunsaturated fats can be beneficial to reduce CAD risk (COR IIa, LOE B).
- A diet containing reduced amounts of sodium can be beneficial to decrease CAD risk (COR IIa, LOE B).
- As a part of a healthy diet, the intake of trans fats should be avoided to reduce CAD risk (COR III, LOE B).

12.2 Alcohol consumption and CCS

Modest alcohol drinking has been repeatedly discussed in scientific papers as protective against CVD, but in most cases, alcohol worsens health conditions, especially when consumed at high risk levels. The complexity of the risk relationship between alcohol consumption and CV conditions has confused clinicians as to whether it should be recommended. To reduce the risk of alcohol-related harms, the 2020-2025 American Dietary Guidelines[456] recommend that adults can choose not to drink, or to drink in moderation by limiting intake to 1-2 drinks (1 drink = 14 g pure alcohol) per day or less for men or 1 drink or less per day for women, on days when alcohol is consumed. Although some studies have suggested that modest alcohol consumption (< 14 g/day or 1 drink/day) is associated with a decreased CV risk,[457,458] recent trials have challenged this view. In a combined analysis of individual-participant data for 599,912 current drinkers in 83 prospective studies, alcohol consumption was linearly associated with an increased risk of stroke (HR: 1.14, 95% CI: 1.10-1.17) and CAD (HR: 1.06, 95% CI: 1.00-1.11) with per 100 g/week alcohol consumption.[459] More recently, a cohort study of UK Biobank data including 371,463 participants reported that alcohol consumption of all amounts, in linear Mendelian randomization analyses, a 1-standard deviation increase in genetically predicted alcohol consumption was associated with 1.4-fold (95% CI: 1.1-1.8) higher risk of CAD.[460] Of note, marked risk differences exist across levels of alcohol intake, including those accepted by current national

guidelines. Meaning in this analysis, alcohol consumption at all levels was associated with an increased risk of CAD. The Global Burden of Disease 1990-2016 analysis concluded that **"zero alcohol intake"** was the level at which the risk of death and disability was minimized.[461] Another population-based cohort study of 430,016 adults recruited from a standard health-screening program since 1994 reported that even modest drinking significantly increased the risk of mortality due to esophageal cancer by 3.83 folds (HR: 3.83, 95% CI: 1.90-7.73) and the risk of oral cancer by 2.35 folds (HR: 2.35, 95% CI: 1.38-4.01).[462] The potential detrimental effect of alcohol drinking could be more pronounced in nearly 30-50% of Taiwanese and other East Asians who carry the aldehyde dehydrogenase-2 (ALDH2) dysfunctional allele (ALDH2*2 variant).[463,464] The ALDH2*2 dysfunctional allele delays acetaldehyde metabolism following alcohol drinking and leads to "Asian alcohol flushing syndrome (AAFS)".[465] A Korean meta-analysis proposed that even mild alcohol consumption had no protective effect on all-cause death and CV mortality.[466] A large-scale cohort study from the Taiwan Precision Medicine Initiative database enrolled 42,665 participants, and reported strong evidence of significant associations between ALDH2 variants and cancer of the larynx, pharynx, and esophagus.[467] In addition, a Japanese pooled analysis of five cohort studies revealed an increased dose – response relationship between alcohol consumption and colorectal cancer incidence, and the relationship was more apparent in Japanese than in Western populations.[468] Given the growing evidence for the detrimental effect of alcohol consumption, the Task Force recommends people without a habit of alcohol drinking should avoid starting drinking for any reason. Alcohol consumption, even when modest, sits at the point at which the health benefits of alcohol clearly outweigh the risks. The latest consensus places this point at no more than 1 drink a day for men or 1/2 a drink a day for women in Taiwan. As such, a limited alcohol consumption of < 100 g/week (14 g/day or 1 drink/day) for men and < 50 g/week (7 g/day or 0.5 drink/day) for women who do not carrying the ALDH2*2 dysfunctional allele or AAFS is recommended. Alcohol abstention is strongly advised for those who carry the ALDH2*2 dysfunctional allele or have AAFS. If this population consume alcohol, more limited alcohol consumption < 64 g/week (9 g/day or 4 drinks/week) for men and < 28 g/week (4 g/day or 2 drinks/week) for women is recommended.[469]

Key Recommendations:

- Individuals who do not have a habit of alcohol consumption should avoid starting drinking for any reason (COR I, LOE C).
- Alcohol drinking 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 who do not have the ALDH2*2 dysfunctional allele or AAFS (COR I, LOE A). (one drink = 14 g pure alcohol)
- 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 who have the ALDH2*2 dysfunctional allele or AAFS (COR IIa, LOE B).

12.3 Physical activity and CCS

Appropriate physical activity has many beneficial effects on the CV system, including hemodynamic, metabolic, and bioenergetic effects.[470] Obviously, regular physical activity can reduce a variety of atherosclerotic risk factors such as decreasing LDL-C and TG levels, reducing BP and increasing insulin sensitivity etc. A detailed pooled analysis showed a dose-response relationship of physical activity with mortality, and that moderate-to-vigorous physical activity lowered the risk of mortality by 31-37%.[471] A meta-analysis of patients with previous MI, angina pectoris or CAD detected by angiography demonstrated that exercise-based cardiac rehabilitation could reduce cardiac mortality.[472] In contrast to the effects of regular physical activity, a sedentary lifestyle is associated with increased all-cause mortality and CV disease mortality.[473] Nonetheless, high levels of moderate-intensity physical activity can reduce the detrimental risks of a sedentary lifestyle.[474] Therefore, regular physical activity is recommended in CCS patients. However, sedentary individuals should start a lower intensity of exercise and gradually progress to recommended levels to decrease the risk of CVD.[475] Despite the benefits of physical activity on CV events, patients suffering heart diseases may hesitate to increase exercise level, especially in those who are male or with comorbid conditions, poor general health, fewer years of education, older age, or obesity.[476] Consequently, physical activity counseling plays a critical role for these patients to re-

cognize the levels or patterns of physical activity they can follow. Exercise-based rehabilitation programs can encourage them to perform adequate physical activity and decrease CV events.[477] Several studies have reported that when the mean intensity of aerobic training reaches 65% of maximal HR, those in the cardiac rehabilitation group were associated with improved survival and decreased hospitalization.[478,479] Home-based programs for secondary prevention of CAD are as effective as hospital-based cardiac rehabilitation programs to improve the quality of life.[480] Moderate-to-vigorous intensity aerobic physical activity is required for CCS patients to obtain CV benefits. The Task Force strongly recommends at least 150 minutes per week of moderate-intensity physical activity or 75 minutes per week of vigorous-intensity aerobic physical activity (or an equivalent combination of moderate and vigorous activity).[144,481] Even physical activity with a shorter duration of either 5 or 10 minutes with 1- to 2-minute interruptions is as beneficial as a longer duration.[482] Meanwhile, education is also important for patients to maintain regular physical activity and to take appropriate steps to manage angina while doing physical activity.

Key Recommendations:

- Asymptomatic patients should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity (COR I, LOE B).
- Physical activity counseling is considered beneficial for those with a sedentary lifestyle and high-risk patients. Cardiac rehabilitation programs are indicated to improve compliance and persistence (COR I, LOE B).
- Education for symptom management during physical activity should be considered (COR IIa, LOE C).

12.4 Sexual activity and CCS

Sexual dysfunction is common in patients with CCS and is caused by risk factors shared with ischemic heart disease. A review study reported that 46% of men with CAD have erectile dysfunction.[483] The prevalence of sexual dysfunction is also high in adult women at around 40-45%, and it increases with age.[484] An observational study of postmenopausal women with heart diseases showed that at least 52% had sexual problems.[485] Erectile dysfunction in men can be present 2-3 years before CV events occur[486] and is a strong risk factor for all-cause and CV mortality.[487] Data analysis from the Massachusetts Male Aging Study showed that a sedentary lifestyle was associated with the highest risk of erectile dysfunction, and that the risk of erectile dysfunction was lower among those who were physically active (20).[488] A report from the National Health and Nutrition Examination Survey (NHANES) demonstrated that a lack of physical activity was a significant independent factor for erectile dysfunction.[489] Appropriate exercise has a significant beneficial effect on CV risk and is considered to improve sexual activity in CCS patients.[490] People with episodic sexual or physical activity have been shown to have a 2.7 relative risk of MI compared to those who are not physically active.[491] However, the risk of sexual activity-induced MI is extremely low, and sexual activity is not the main cause of AMI. Furthermore, regular exercise will decrease the risk of MI induced by sexual activity.[492] Sexual activity is safe in CCS patients who can perform physical activity $\geq$ 3-5 METs without symptoms including angina, hypotension, arrhythmia or excessive dyspnea.[493] Therefore, physical activity is beneficial not only on CV risk reduction but also to improve sexual safety.

Key Recommendation:

- Sexual activity is acceptable for those who can perform physical activities more than 3 to 5 METs without symptoms, such as angina, excessive dyspnea, hypotension or arrhythmia (COR IIa, LOE B).

12.5 Psychological interventions in CCS patients

Many epidemiologic and human studies have demonstrated the effects of psychological factors on cardiac pathology and pathophysiology.[494-496] Anxiety, depression, and stress are associated with compromised quality of life, and increased recurrent coronary events and are independent risk factors for CVD morbidity and mortality. Previous studies have demonstrated that acute and chronic stress may promote the development and progression of CAD,[497] and an association between perceived work stress or strength of exposure to job strain and CAD incidence or prevalence.[498] The large-scale INTERHEART study compared 11,119 CAD and 13,648 matched control subjects from 52 countries, and demonstrated that psychosocial factors (perceived stress at work or home, financial stress, depression, and so on)

were associated with the risk of the first AMI.[499] These psychosocial effects were comparable with those of traditional risk factors, and were independent of socioeconomic status and smoking. Of 12,461 cases of AMI in a case-control study of first AMI, 14% (n = 1752) were angry or emotionally upset in the case period (i.e., 1 hour before symptom onset), and anger or emotional upset in the case period was associated with an increased risk of AMI (OR: 2.44; 99% CI: 2.06-2.89) with a population-attributable risk (PAR) of 8.5% (95% CI: 7.0-9.6).[500] Emotional upset may cause sympathetic activation, catecholamine secretion, systemic vasoconstriction, and increased heart rate and BP, thereby modifying myocardial oxygen demand, which may precipitate the rupture of an already vulnerable coronary atherosclerotic plaque. Another follow-up study of over 7000 women found that those who had moderate to severe perceived stress were more likely to have a new diagnosis of CAD at follow-up compared to those with no perceived stress.[501] Notably, one RCT demonstrated that stress management training conferred an incremental benefit when combined with comprehensive cardiac rehabilitation.[502] More recently, a meta-analysis corroborated the benefits of stress management training in cardiac rehabilitation, underscoring the need to adopt a stress management program in routine cardiac care.[503] Several psychological therapies have been used as part of secondary prevention to improve CV outcomes. These include relaxation and stress management, enhancement of coping skills, and cognitive behavioral therapy, many of which are incorporated into cardiac rehabilitation programs. Considering the extensive evidence validating the beneficial effects of stress management in improving cardiac health, it should be included as a part of routine cardiac rehabilitation.

Key Recommendations:

- Acute and chronic stress are risk factors for the development and progression of coronary atherosclerosis (COR IIa, LOE B).
- For patients with CCS, stress management training should be considered as a part of routine cardiac rehabilitation (COR IIb, LOE B).

12.6 Smoking cession in CCS

Tobacco use is one of the major public health concerns worldwide, and it is responsible for over 6 million deaths annually – almost 12% of all global deaths.[504] The Osaka Acute Coronary Insufficiency Study reported that nonsmokers in Japan had a 61% lower risk of all-cause death than smokers.[505] According to the 2019 report of Taiwan's Health Promotion Administration, 24,000 people die of smoking-related heart disease every year in Taiwan, with 1 person dying of smoking-induced harm every 22 min.[506] The report also stated that in 2008 the prevalence of smoking among people aged over 15 years was 21.9%, but that it decreased to 14.5% in 2017. Smoking induces CVD via endothelial dysfunction, atherosclerosis, inflammation by cytokines and an activated prothrombotic state. These effects are mediated by three principal constituents: nicotine, carbon monoxide, and oxidant gases.[507] In the brain, nicotine binds to $\alpha 4\beta 2$ nicotinic cholinergic receptors acting as a sympathomimetic agent. This stimulates the release of catecholamines, resulting in tachycardia, hypertension and myocardial stress, which induce an imbalance in myocardial work and oxygen demand.[508] Carbon monoxide can cause relative hypoxemia that precipitates ischemic events. The high levels of nitrogen oxides and free radicals in cigarette smoke induce inflammation, decreased cellular production of nitric oxide, dysfunction of the endothelial system, activation of a prothrombotic state, and activation of lipid oxidation, which are associated with CVD pathogenesis. Consequently, smoking increases the risk of CAD (HR: 3.2-3.5) and cerebrovascular disease (HR: 1.7-3.2).[509] The sex-specific relative risk of smoking mortality in Taiwan is the same as that in international reports. Mortality from all causes, all cancers, CVD, and respiratory disease is significantly higher in women than in men.[510] Observational epidemiological research and clinical studies have demonstrated a non-linear dose effect for exposure to cigarette smoke in CVD.[511,512] In the INTERHEART study,[513] the odds of CVD was 9-fold higher in those who smoked over 40 cigarettes per day (OR: 9.16, 95% CI: 6.70-12.3) than in never smokers, and the risk increased by 5.6% for every additional cigarette smoked. The influence of smoking on younger individuals (OR: 3.53, 95% CI: 3.23-3.86) was higher compared to older individuals (OR: 2.55, 95% CI: 2.35- 2.76). In restricted analysis, among heavy smokers ($\geq$ 20 cigarettes per day), the OR was 5.60 (OR: 5.60, 95% CI: 5.10-6.20) for younger individuals, and 3.60 (OR: 3.60, 95% CI: 3.25-3.98) for older individuals. When heavy smokers

stopped smoking, the largest decline in CVD risk was noted in the first 3 years, but the risk of AMI was still higher than that in never smokers. The U.S. National Health Interview Survey[509] demonstrated that adults who stopped smoking aged 25 to 34, 35 to 44, and 45 to 54 years extended their life span by approximately 10, 9, and 6 years, respectively, when compared to individuals who continued smoking. The NIH-AARP Diet and Health Study[514] included 160, 113 individuals aged 70 years and older, and found that even smokers aged over 70 years were still far more likely to die in the next 6 years than nonsmokers. Therefore, quitting smoking even when older than 70 years of age can meaningfully reduce mortality, and it is never too late to stop smoking. These findings reveal that with regards to smoking cessation: the younger, the better; the earlier, the better; the lighter, the better; with never smoking being the best. In conclusion, evidence indicates that smoking cessation improves the health prognosis of CCS patients, with an associated 36% risk reduction in mortality in individuals who stop smoking.[441] The use of LSM for CCS has superior effects to repeated coronary interventions.[515]

12.6.1 Secondhand smoke and CCS

Secondhand smoke (SHS) is the combination of smoke from the burning end of a cigarette and smoke breathed out by smokers. SHS contains more than 7000 chemicals and causes almost 34,000 premature deaths from heart disease every year in the United States.[516] The impacts of SHS are 80% to 90% those of active smoking, including increased platelet aggregation, endothelial dysfunction, arterial stiffness, atherosclerosis, oxidative stress and decreased antioxidant protection.[517] The INTERHEART study provided evidence that SHS was associated with a graded increase in exposure-related AMI risk, with an OR of 1.24 (1.17-1.32) in individuals with a lower exposure (1-7 hours per week) and 1.62 (1.45-1.81) in those with higher exposure (> 21 hours per week).[513] A systematic review and meta-analysis reported that pooled relative risks for never smokers exposed to SHS 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.[518]

12.6.2 Electronic cigarettes and CCS

Electronic cigarettes (E-cigarettes) use electronic nicotine delivery systems and differ from cigarettes and other combustible tobacco products in that they do not produce smoke by burning tobacco. E-cigarettes have emerged as a popular way to facilitate tobacco cessation in recent years. However, several large-scale meta-analyses about whether E-cigarettes are superior to non-E-cigarette methods for tobacco cessation have reported inconsistent results.[519,520] Even though E-cigarettes are expected to be less harmful than smoking combustible tobacco products in the short term, their long-term safety is uncertain due to other constituent chemicals (e.g., nicotine, propylene glycol, and glycerin).[521] Currently, 60% of adult E-cigarette users do not completely stop smoking.[522] In the American Health eHeart Study on cigarette and E-cigarette users, dual users had higher risks of arrhythmia, CAD, and asthma than single cigarette users due to the two different sources of poison.[523] According to the Health Promotion Administration, the use of E-cigarettes among adolescents in Taiwan increased by more than 50% in 1 year – from 2.7% in 2018 to 4.2% in 2019.[506] Thus, limiting the use of E-cigarettes is crucial. In a systematic review study with a meta-analysis of E-cigarette use and smoking cessation in adults (including 55 observational studies and 9 RCTs), E-cigarette use was not associated with quitting in observational studies of all adult smokers (OR: 0.94; 95% CI: 0.77-1.16) or motivation to quit smoking (OR: 0.85; 95% CI: 0.68-1.05).[524] The RCTs that compared smoking cessation among smokers who were provided E-cigarettes to smokers who received conventional therapy found that E-cigarette use was associated with a higher rate of quitting (OR: 1.55; 95% CI: 1.17-2.06). Thus, E-cigarettes should not be approved as consumer products but may warrant consideration as a prescription treatment. In the National Health Interview Surveys of 2014 (n = 36,697) and 2016 (n = 33,028), daily E-cigarette use was independently associated with increased odds of MI (OR: 1.79, 95% CI: 1.20-2.66) as was daily conventional cigarette smoking (OR: 2.72, 95% CI: 2.29-3.24).[525] However, a RCT of E-cigarettes versus nicotine-replacement therapy (NRT) including 886 participants reported that the 1-year abstinence rate was 18.0% in the E-cigarette group compared with 9.9% in the NRT group (OR: 1.83; 95% CI: 1.30-2.58).[526] As a result, there is no solid evidence supporting that E-cigarettes are a safer alternative for tobacco cessation, or sufficient evidence to claim their long-term CV safety.[521]

12.6.3 Pharmacological and nonpharmacological behavioral treatment

For smoking cessation, physicians should follow the **5 A**'s: **A**sk about smoking, **A**dvise to quit, **A**ssess readiness to quit, **A**ssist with smoking cessation, and **A**rrange follow-up. Pharmacotherapy combined with nonpharmacological behavioral treatment can increase cessation rates by 50% to 300% compared with unassisted quitting.[521] The pharmacological effect of nicotine is to stimulate the sympathetic nervous system, increase heart rate, increase BP, and contract coronary arteries. Currently, varenicline and bupropion are the main pharmacological options for NRT.[527] In an early NRT study, mortality rate, AMI, cardiac arrest, CVD hospitalization rate were not obviously increased in CCS patients who received NRT.[528] Meta-analyses[529,530] and recent large RCTs (EAGLES and its extension trial)[527,531] have shown that these medications are more effective than placebo in promoting smoking cessation for ≥ 6 months and are safe for use in patients with CCS and psychiatric disorders. Therefore, the U.S. FDA has approved bupropion, varenicline, and five NRT products for smoking cessation. Additionally, package inserts for NRT have not previously recommended its use for patients with ACS, severe arrhythmia and recent stroke. However, a hospital-initiated smoking cessation program (Ottawa model) showed that NRT significantly reduced all-cause readmissions and smoking-related readmissions.[532] In addition, varenicline has been shown to be more effective for smoking cessation, with similar major adverse CV events other than placebo.[533] Furthermore, the FDA has withdrawn black box warnings about neuropsychiatric events, and the benefits are still greater than the harm. In a meta-analysis published in the Cochrane library network (267 studies, 101,804 participants), both NRT and bupropion were superior to placebo in smoking cessation (OR: 1.84 and 1.82, respectively).[534] Varenicline, a partial nicotinic receptor agonist specific for the alpha-4 beta-2 receptor, has been associated with a higher odds of quitting compared with placebo, and it has been shown to be superior to individual NRT products and bupropion.[535-538] Evidence has shown that the net benefit of behavioral interventions for smoking cessation on perinatal outcomes and smoking abstinence in pregnant women who smoke is substantial. Continued medical education with group training of physicians and counselors regarding knowledge and skills to help patients quit smoking followed by smoking cessation service contests and annual award ceremonies among hospitals has been proven effective to promote smoking cessation for high CVD risk smokers in Taiwan.[539]

Key Recommendations:

- As a recommendation to reduce the risk of ASCVD, smoking cessation should be advised for individuals with CCS (COR I, LOE A).
- To reduce the risk of ASCVD, all subjects with CCS are advised to avoid exposure to secondhand smoke (COR III, LOE A).
- As a method of smoking cessation, E-cigarettes should not be recommended (COR I, LOE B).
- Varenicline is recommended over a nicotine patch and bupropion for nicotine-dependent adults in whom treatment is being initiated (COR I, LOE A).

13. VACCINATION IN PATIENTS WITH CCS

13.1 Influenza vaccination in patients with CCS

Influenza viruses belong to the Orthomyxoviridae family and are classified into influenza A, B, C, and D. However, only influenza A and B viruses cause human infective diseases, including viral pneumonia, myocarditis, pericarditis, encephalitis and Reye syndrome.[540] Influenza A is classified into subtypes based on hemagglutinin (H) and neuraminidase (N) antigens present on the surface of the viral envelope. To date, 18 hemagglutinin subtypes and 11 neuraminidase subtypes have been recognized. Influenza B is divided into lineages based on hemagglutinin (i.e., Yamagata and Victoria). Influenza C mainly infects humans and influenza D mainly infects pigs and cattle, and they possess only one glycoprotein (hemagglutinin-esterase-fusion protein, HEF) with no obvious clinical symptoms. Because of antigenetic shift and antigenic drift in the influenza virus, influenza A (H1N1, H2N2 or H3N2) and influenza B can cause pandemics or seasonal epidemics in humans. In the United States, the Centers for Disease Control and Prevention estimates that influenza has caused about 9-45 million illnesses, 140,000-810,000 hospitalizations, and 12,000-61,000 deaths annually since 2010. In Taiwan, 14% of the general population seek medical atten-

tion for pneumonia or influenza annually, and 8% of these admitted patients require intensive care. Influenza cases with severe complications are defined as those with influenza infection complicated with myocarditis, pericarditis, encephalopathy or acute respiratory distress syndrome. The mortality rate of influenza cases with severe complication is about 20% in Taiwan. The total loss of overall social productivity due to pneumonia and influenza was estimated at 30.9 billion USD between 2008 and 2011.[541] Most influenza vaccines can protect against three ("trivalent") or four ("quadrivalent") different influenza viruses.[542] The vaccines include inactivated influenza vaccine, recombinant influenza vaccine, or live attenuated influenza vaccine selected by the World Health Organization, Global Influenza Surveillance, and Response System.[543] Additionally, quadrivalent vaccines can prevent an influenza A (H1N1) virus, influenza A (H3N2) virus, and two influenza B viruses. Trivalent vaccines protect against three flu viruses, including two influenza A viruses (H1N1 and H3N2) and one influenza B virus. The influenza virus acts through many mechanisms such as cytokine inflammation, prothrombotic status, coronary atheroma rupture, vasoconstriction, hypoxia, and tachycardia. The pathophysiology induces arrhythmia, HF, MI, and MACEs.[544] Many meta-analyses and RCTs have shown that influenza vaccine can reduce CV morbidity and mortality in patients receiving secondary prevention, especially in the elderly.[106,545] The EPIVAC trial[546] included 1340 Spanish community-dwelling individuals aged 65 years or older, and found that influenza vaccination was associated with a significant reduction of 37% in the adjusted risk of mortality. In a meta-analysis of influenza vaccination and CV outcomes in high-risk patients (n = 6735 in 6 RCTs), influenza vaccination was related to a lower risk of composite CV events (2.9% vs. 4.7%; RR: 0.64, 95% CI: 0.48-0.86).[547] Another propensity score-matched follow-up study[548] on influenza vaccination and secondary prevention of CVD among older Taiwanese adults reported lower incidence rates of all-cause mortality (HR: 0.82, 95% CI: 0.73-0.92), MI or CV mortality (HR: 0.84, 95% CI: 0.74-0.96), and HF hospitalization (HR: 0.83, 95% CI: 0.74-0.92) in the vaccine cohort. Additionally, the effect of influenza vaccination on COVID-19 infection rates and severity has been discussed in recent years. A recent retrospective cohort study (n = 27,201) reported that influenza vaccination was associated with decreased positive COVID-19 testing rate and improved clinical outcomes with a lower likelihood of requiring hospitalization (OR: 0.58, 95% CI: 0.46-0.73) or mechanical ventilation (OR: 0.45, 95% CI: 0.27-0.78), and a shorter hospital length of stay (RR: 0.76, 95% CI: 0.65-0.89).[549]

13.2 Pneumococcal vaccination in patients with CCS

Community-acquired pneumonia (CAP) is a leading infectious etiology of hospitalization and death among American adults.[550] In the Etiology of Pneumonia in the Community Study, the most common pathogens were human rhinovirus (9% of patients), influenza virus (6% of patients), and Streptococcus pneumoniae (5% of patients). In Taiwan, a microbiologic diagnosis has been confirmed in as high as 75% of pneumonia cases.[551] The three most significant pathogens for CAP in Taiwan are S. pneumoniae (23-26%), Mycoplasma pneumoniae (14-20%), and Chlamydophila pneumoniae (8-13%). In a previous observation study,[552] patients with pneumococcal pneumonia were at a substantial risk of concurrent acute CV events (19.4%), such as MI, severe arrhythmia, or new or worsening HF. According to another registry-based cohort study,[553] sepsis or pneumonia in adults was associated with an increased risk of CVD in the years following infection. The risk was at its highest during the first year after infection, with an adjusted HR of 6.33. The pathogenesis of cardiac events in pneumococcal pneumonia is related to an imbalance in oxygen demand and supply, cytokine production, procoagulant activation, and the inhibition of anticoagulant pathways. S. pneumoniae bacteria are lancet-shaped, gram-positive, facultative anaerobes. One hundred serotypes had been identified by polysaccharide capsule by 2020.[554] Two types of S. pneumoniae vaccine, the 23-valent pneumococcal polysaccharide vaccine (PPV23) and 13-valent pneumococcal conjugate vaccine (PCV13), have been licensed since 1977. PPV23 (Pneumovax 23) contains 23 purified capsular polysaccharide antigens of S. pneumoniae (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F).[555] PPV23 induces antibodies primarily using T-cell independent mechanisms, and therefore induces an immune system response that is neither long-lasting nor characterized by an anamnestic response upon subse-

quent challenge with native polysaccharides. Thus, the antibody response to PPV23 is poor in children aged < 2 years with immature immune systems. Additionally, polysaccharide vaccines do not reduce nasopharyngeal carriage of S. pneumoniae in children, and therefore they are not associated with herd immunity. The effectiveness of preventing invasive pneumococcal infections caused by vaccine serotypes is about 56% to 75%.[556] For adults over 65 years of age, the effectiveness of PPV23 has been reported to be 27.4% (95% CI: 3.2-45.6) against all pneumococcal pneumonia, and 33.5% (95% CI: 5.6-53.1) against PPV23 vaccine-type pneumococcal pneumonia.[556] In addition, immune hyporesponsiveness should be noted with vaccination using the pneumococcal polysaccharide vaccine. Re-vaccination with PPV23 in a short time can result in low antibody production (immune hyporesponsiveness) due to the immune consumption of polysaccharide antigens, resulting in a greater depletion of pre-existing antigen-specific memory B cells than at the initial vaccination.[557] PCV13 (Prevnar 13) contains 13 serotypes of S. pneumoniae (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) conjugated to a nontoxic variant of diphtheria toxin. This antigen complex stimulates a T-helper cell response, leading to a substantial primary response among infants and a strong booster response at re-exposure. The Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) study[558] included 84,496 adults aged 65 or older, and showed 45.6% and 45.0% efficacy rates against vaccine-type pneumococcal pneumonia and vaccine-type nonbacteremic pneumococcal pneumoniae, respectively, in older adults receiving PCV13. Additionally, 25.4%, 12.5%, and 10.2% of the older patients developed some degree of clinical underlying disease, including heart disease, diabetes, and lung disease, respectively. Even though pneumococcal vaccines are an effective weapon against vaccine-type pneumococcal pneumoniae, the efficacy of pneumococcal vaccination in patients with CVD has not been well established due to the lack of prospective RCTs and the neutral results of many studies on this issue.[559,560] In the two systematic reviews and meta-analyses of the effect of PPV vaccines on CVD,[561,562] the PPV23 vaccination was associated with lower risks of any CV event (RR: 0.91; 95% CI: 0.84-0.99), all-cause mortality (RR: 0.78; 95% CI: 0.68-0.88), and MI (RR: 0.88, 95% CI: 0.79-0.98) in all age groups, with a significant effect in those aged over 65 years, but not in the younger group. In another systematic review and meta-analysis on pneumococcal vaccinations (PPV23 or PCV13) in adults with CVD,[563] the pooled results from five studies enrolling a total of 163,756 participants showed a significant decrease in all-cause mortality (HR: 0.78, 95% CI: 0.73-0.83). Therefore, pneumococcal infection increases the risk of CV events, possibly due to pro-inflammatory mediators, sympathetic stimulation, and activation of the coagulation cascade which may prompt the rupture of atherosclerotic plaques.

13.3 COVID-19 vaccination in patients with CCS

The COVID-19 pandemic has brought unprecedented changes to our healthcare system. Recent studies have reported an increased incidence of AMI after COVID-19 infection related to an increased risk of thrombosis.[564,565] Recently, a large cohort study (including 62,727 never vaccinated and 168,310 fully vaccinated people) compared the incidence of AMI and ischemic stroke after COVID-19 infection. The median follow-up duration starting 30 days after COVID-19 was 90 days in the unvaccinated group and 84 days in the fully vaccinated group. The adjusted risk was significantly lower in the fully vaccinated patients for both AMI (aHR: 0.48; 95% CI: 0.25-0.94) and ischemic stroke (aHR: 0.40; 95% CI: 0.26-0.63).[566] On the other hand, there are limited data on the risk of thrombotic events and AMI following COVID-19 mRNA vaccination.[567,568] Data from 40 U.S. healthcare systems (N = 15,215,178 persons) participating in a large network demonstrated that the risk of cardiac complications was significantly higher after COVID-19 infection than after mRNA COVID-19 vaccination for both males and females in all age groups.[569] These findings support the continued use of recommended mRNA COVID-19 vaccines among all eligible persons with CCS.

Key Recommendations:

- Annual influenza vaccination is recommended for patients with CCS, especially in the elderly (COR I, LOE B).
- In adults ≥ 65 years of age who have not previously received a pneumococcal vaccine, the administration of PCV13 followed by PPV23 1 year or later is recommended (COR I, LOE B).
- In adults who have been vaccinated with PPV23 after the age of 65 years, the administration of PCV13 is

recommended at least 1 year following the PPV23 dose (COR I, LOE B).

- Adults who received PPV23 before the age 65 years and who are ≥ 65 years of age at the time of their visit should receive a dose of PCV13 at least 1 year after their last PPV23 dose, followed by a dose of PPV23 at least 1 year after the PCV13 dose and at least 5 years following the previous PPV23 dose (COR I, LOE B).
- For adults > 19 years of age and < 65 years of age with CCS, the administration of PCV13 followed by PPV23 8 weeks or later is recommended (COR I, LOE B).

14. DIETARY SUPPLEMENTS AND NUTRACEUTICALS

14.1 Coenzyme Q10

Nutraceuticals, a term combining nutrition and pharmaceuticals, are products that are used to prevent and treat diseases. Several RCTs have investigated the CV benefits of nutraceuticals for patients with CAD in the recent two decades. Coenzyme Q10 (CoQ10) is a naturally occurring compound that has a role in cellular energy production. Tissue depletion of CoQ10 resulting in muscle symptoms can occur in patients taking statins for the prevention of CAD. CoQ10 can be an effective supplement for some patients with statin-induced muscle symptoms.[570] The Q-SYMBIO RCT evaluated CoQ10 as adjunctive treatment for patients with chronic HF.[571] The primary 2-year endpoint was reached by 15% of the patients in the CoQ10 group versus 26% in the placebo group (HR: 0.50; 95% CI: 0.32 to 0.80). However, the small event numbers, difficulties in patient recruitment, and an unexpectedly large treatment effect with wide CI limits the interpretability of the results.[572] The ACC/AHA guidelines currently do not recommend initiating CoQ10 as treatment in HF patients (level of evidence B, class III recommendation). No RCTs have evaluated the effect of CoQ10 in patients with CCS.

14.2 Vitamins

Some studies have found that vitamins have antioxidative and anti-inflammatory effects which may affect the risk of CVD.[573-575] In the Physicians' Health Study II RCT, 14,641 US male physicians were enrolled, including 754 men (5.1%) with prevalent CVD at randomization. Compared with placebo, neither vitamin E nor vitamin C had an effect on the incidence of MACEs, total MI, total stroke, or CV mortality.[576] In the same cohort, there were no significant effects of a daily multivitamin on MACEs, total MI, total stroke, or CV mortality compared with placebo. The effect of a daily multivitamin on MACEs did not differ between subjects with or without a baseline history of CVD.[577] A cross-sectional study found that vitamin D deficiency was significantly associated with the severity of CAD.[578] In the VITAL trial, a total of 25,871 participants with no history of CVD underwent randomization. Supplementation with vitamin D was not associated with a lower risk of MACEs, a composite of MI, stroke, or CV death during a median follow-up of 5.3 years (HR: 0.97, 95% CI: 0.85 to 1.12).[579] No RCT has evaluated the CV effects of vitamin D in patients with CCS.

14.3 Red yeast rice

Red yeast rice is a traditional Chinese nutritional supplement. Daily consumption of red yeast rice has been shown to cause a reduction in LDL-C plasma levels by up to 15% to 25% within 6 to 8 weeks. This lipid-lowering effect is mainly due to monacolin K, a weak reversible inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase.[580] In the Chinese Coronary Secondary Prevention Study trial, 4870 Chinese patients were randomly assigned either to extract of red yeast rice daily or placebo for an average of 4.5 years. The results showed that the frequencies of the primary endpoint, a major coronary event that included nonfatal MI and death from CAD, were 10.4% in the placebo group and 5.7% in the treated group, with absolute and relative decreases of 4.7% and 45%, respectively. Treatment with extract of red yeast also significantly decreased CV and total mortality by 30% and 33%, and the need for coronary revascularization by one-third.[581] Meta-analysis showed that the lipid-lowering effect of extract of red yeast was not statistically significant when standard dose statins were used as background treatment. Red yeast rice might contain monacolin K, the same ingredient that is in the prescription cholesterol-lowering drug lovastatin. Therefore, red yeast rice might be an effective treatment option for dyslipidemia and CV risk reduction in statin-intolerant patients.[582] Nonetheless, the quality of red yeast rice products in the market varies and it may carry the risk of pharmacological interactions; moreover, its safety outcomes have not been extensively studied as yet. Based on scientific opinion on the safety of monacolins in red yeast

rice,[583] restrictions on daily doses and mandatory label warnings now apply to dietary supplements containing monacolins from red yeast rice in Europe.

14.4 Omega-3 fatty acids

In addition to lower plasma triglyceride levels, omega-3 fatty acids can reduce inflammation, thrombosis and oxidation.[584] Omega-3 fatty acids include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which differ in their effects on membrane structure, rates of lipid oxidation, inflammatory biomarkers, and endothelial function as well as tissue distributions.[585] Several clinical studies using different types of formula (EPA only or EPA + DHA) have demonstrated conflicting results with regards to CV protection. In the GISSI-Prevenzione trial, 11,324 Italian MI patients were randomly assigned to supplements of n-3 polyunsaturated fatty acids (PUFA) (1 g daily), vitamin E (300 mg daily), both (n = 2830), or none (n = 2828) for 3.5 years. Treatment with n-3 PUFA, but not vitamin E, significantly lowered the risk of the primary endpoints including death, nonfatal MI, and stroke. The benefit was attributed to a decrease in the risk of death and CV death.[586] In the JELIS randomized trial, 18,645 Japanese patients were randomly assigned to receive either 1800 mg of EPA daily with statins or statins only. At a mean follow-up of 4.6 years, the primary endpoint was reached in 2.8% of the patients in the EPA group and 3.5% in the control group – a 19% relative reduction in major coronary events (p = 0.011). In patients with a history of CAD who were given EPA treatment, major coronary events were reduced by 19% (8.7% in the EPA group vs. 10.7% in the control group; p = 0.048).[587] In the REDUCE-IT trial, patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo. A total of 8179 patients were enrolled including 70.7% for the secondary prevention of CV events and were followed for a median of 4.9 years. A primary endpoint event occurred in 17.2% of the patients in the icosapent ethyl group, compared with 22.0% of the patients in the placebo group (HR: 0.75, 95% CI: 0.68 to 0.83).[588] In JELIS and REDUCE-IT trials, the CV risk was significantly lower among the patients who received EPA than among those who received placebo despite the background use of statins. In addition, icosapent ethyl also demonstrated beneficial effects on the regression of coronary plaque volume detected by serial multidetector CT compared with placebo in the EVAPORATE trial.[589] In contrast there have been some neutral trials of omega-3 fatty acids. In the multicenter, double-blind, placebo-controlled Alpha Omega Trial, 4837 MI patients were randomly assigned to receive one of four trial margarines for 40 months: a margarine supplemented with a combination of 400 mg of EPA-DHA, 2 g of alpha-linolenic acid (ALA), EPA-DHA and ALA, or a placebo. Neither EPA-DHA nor ALA reduced the primary endpoint.[590] In the STRENGTH trial participants were randomized to receive 4 g/d of a carboxylic acid formulation of EPA and DHA (omega-3 CA) (n = 6539) or corn oil (n = 6539) in addition to usual background therapies, including statins. When 1384 patients had experienced a primary endpoint event (of a planned 1600 events), the trial was prematurely halted based on an interim analysis that indicated a low probability of clinical benefit of omega-3 CA vs. the corn oil comparator. Among the 13,078 treated patients, the primary endpoint occurred in 785 patients (12.0%) treated with omega-3 CA vs. 795 (12.2%) treated with corn oil (HR: 0.99, 95% CI: 0.90-1.09). Prespecified subgroup analyses revealed an HR for the primary endpoint of 0.94 (95% CI: 0.84-1.05) in the secondary prevention population.[591] The contradictory results between these studies may be due to different types of omega-3 fatty acids (only EPA or combination of EPA + DHA), dose (higher vs. lower dose) of omega-3 fatty acids, or different comparators (corn oil or mineral oil), as well as the underlying severity of the CVD risk or use of statins.

Key Recommendations:

- For high-risk populations (i.e., patients with ASCVD, or diabetes with additional risk factor) under statin treatment, high-dose EPA should be considered if the TG level is > 150 mg/dl (COR IIa, LOE B).
- Red yeast can be considered for secondary prevention without background statin treatment (COR IIb, LOE B).
- CoQ10, vitamins C, D, E and multivitamin are not recommended for CAD prevention (COR III, LOE A).

15. AMBIENT FINE PARTICULATE MATTER EXPOSURE AND CCS

Increasing evidence has shown that long-term expo-

sure to air pollution is associated with all-cause and CV mortality.[592-594] A recent air pollution consensus report by the AHA suggested that the inhalation of particulate matter (PM) accelerates or enhances the development of atherosclerosis, and triggers clinical CV events.[594] In the Multi-Ethnic Study of Atherosclerosis and Air Pollution longitudinal cohort study,[595] increased concentrations of $PM_{2.5}$ (particulate matter of 2.5 μm in aerodynamic diameter) and traffic-related air pollution within metropolitan areas were associated with the progression of coronary artery calcification, consistent with the acceleration of atherosclerosis.

15.1 Evidence summary for short-term $PM_{2.5}$ exposure and risk of CAD

A short exposure period of a few hours to 1 day to high levels of $PM_{2.5}$ can trigger AMI. A recent study investigated the relationship between exposure to air pollutants and the mechanisms of coronary instability evaluated by OCT in 126 ACS patients, and found that $PM_{2.5}$ was independently associated with plaque rupture (OR: 1.19; 95% CI: 1.04 to 1.34), the presence of thin-cap fibroatheroma, and macrophage infiltrates at the culprit site.[596] This study provides novel insights into the missing link between air pollution and increased risk of coronary events. In particular, exposure to higher concentrations of air pollutants was associated with the presence of vulnerable plaque features and with plaque rupture as a mechanism of coronary instability. An early case crossover study in Boston reported an estimated OR of 1.48 for an increase of 25 $\mu g/m^3$ in $PM_{2.5}$ during a 2-hour period before the onset of MI, and an OR of 1.69 for an increase of 20 $\mu g/m^3$ in $PM_{2.5}$ in the 24-hour period before the onset of MI.[597] Evidence from time-series analyses conducted worldwide has shown that even a 10 $\mu g/m^3$ increase in short-term (< 24 h) $PM_{2.5}$ level increases the relative risk of daily CV mortality by ~0.4% to 1.0%.[598] The consistency of the evidence for adverse health effects after short-term exposure to $PM_{2.5}$ across a range of important health outcomes and diseases supports policy measures to control $PM_{2.5}$ concentrations.[599]

15.2 Evidence summary for long-term $PM_{2.5}$ exposure and risk of CAD

A recent study enrolled 3127 subjects undergoing serial CCTA between January 2007 and December 2017, and demonstrated that long-term cumulative exposure to $PM_{2.5}$ in ambient air was independently associated with CAC progression (adjusted OR: 1.09, $p < 0.001$), and its relative impact on coronary atherosclerosis was higher than that of traditional CV risk factors.[600] Evidence from cohort studies has demonstrated on average an approximate 10% increase in all-cause mortality per 10 $\mu g/m^3$ elevation in long-term average $PM_{2.5}$ exposure. The mortality risk specifically related to CVD appears to be elevated to a similar (or even greater) extent, ranging from 3% to 76%.[594]

15.3 Evidence summary for hospital admission due to $PM_{2.5}$ exposure

Both excess CV mortality and increased rates of hospitalizations have been associated with day-to-day changes in PM air pollution.[594] A national database study of daily time-series data for 1999 through 2002 on hospital admission rates in the United States also confirmed that short-term exposure to $PM_{2.5}$ increased the risk of hospital admission for CVD.[601] Reducing ambient $PM_{2.5}$ exposure may benefit human health and increase life expectancy. A long-term observational study in the United States confirmed that a reduction in exposure to ambient PM fine-particulate air pollution contributed to a reduction in CV events by a natural time course.

15.4 Cardiovascular and health benefits of reducing exposure to $PM_{2.5}$

A previous study reported that a decrease of 10 $\mu g/m^3$ in the concentration of $PM_{2.5}$ was associated with an estimated increase in mean life expectancy of 0.61 years.[602] Lelieveld et al. estimated that air pollution reduces the mean life expectancy in Europe by about 2.2 years, with an annual attributable per capita mortality rate of 133/100,000 per year. Replacing fossil fuels by clean, renewable energy sources could substantially reduce the reduction in life expectancy from air pollution.[603] There is now substantial evidence that air purifiers reduce indoor $PM_{2.5}$ concentrations and improve subclinical health indicators in areas with severe ambient particulate air pollution.[604,605] In an open randomized crossover trial, reducing personal exposure to air pollution using a highly efficient face mask appeared to reduce symptoms and improve a range of CV measures (maximal ST segment depression, mean arterial pres-

sure and heart rate variability) in patients with CCS.[606] Thus, interventions to reduce personal exposure to PM air pollution have the potential to decrease the incidence of CV events in highly susceptible populations. In this regard, the use of air purifiers with particle filters should be considered for CCS patients.

Key Recommendations:

- Both long-term and short-term ambient $PM_{2.5}$ exposure increase the risk of CAD (COR I, LOE A).
- Reducing ambient $PM_{2.5}$ exposure may benefit cardiopulmonary health and prolong life expectancy in patients with CAD (COR IIa, LOE B).

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DECLARATION OF CONFLICT OF INTEREST

Kwo-Chang Ueng, Chern-En Chiang have been on the speaker bureau for Astrazeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Novartis, Pfizer, Sanofi, Tanabe, and TSH biopharm. All other authors report no potential conflicts of interest in relation to these guidelines.

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