National Guideline for Risk Assessment and Primary Prevention of Cardiovascular Diseases For Secondary and Tertiary Healthcare level

Directorate of Non-Communicable Diseases

Ministry of Health

2021

First Edition 2021

Electronic version is available on www.health.gov.lk

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National Guideline for Risk Assessment and Primary Prevention of Cardiovascular Diseases

For Secondary and Tertiary healthcare level

Published by the Directorate for Non-Communicable Diseases with the technical support by the Ceylon College of Physicians and financial support by the World Health Organization (WHO)
to serve as a reference to the doctors managing this common condition at secondary and tertiary healthcare level.
This document was reviewed by the Directorate of NCD to be in line with the National policies, strategies and regulations.
Feedback of relevant professional colleges and institution was also incorporated into this guideline

ISBN: 978 – 624- 5719- 51-9

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Abbreviations

ABI	Ankle-brachial index
ACE-I	Angiotensin converting enzyme inhibitors
ApoA	Apolipoprotein A
ApoB	Apolipoprotein B
ARB	Angiotensin receptor blockers
ASCVD	Atherosclerotic cardiovascular disease
AU	Agatston score
BMI	Body mass index
CAD	Coronary artery disease
CCS	Coronary calcium score
CKD	Chronic kidney disease
COR	Class of recommendation
CTCA	Computerized Tomography Coronary Angiography
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
ECG	Electrocardiogram
ED	Erectile dysfunction
GLP-1R	Glucagon-like peptide-1 receptor
HDL	High density lipoprotein
hsCRP	High-sensitivity C-reactive protein
IMT	Intima-media thickness
ISH	International Society of Hypertension
LDL	Low density lipoprotein
Lp(a)	Lipoprotein(a)
LOE	Level of evidence
LVH	Left ventricular hypertrophy
MPI	Myocardial perfusion imaging
MRI	Magnetic resonance imaging
NNT	Number needed to treat
NRT	Nicotine replacement therapy
OSA	Obstructive sleep apnea
PET	Positron emission tomography
SBP	Systolic blood pressure
SGLT-2	Sodium-glucose cotransporter 2
SPECT	Single-photon emission computed tomography
WHO	World Health Organization
WHR	Waist to hip ratio

Introduction

This guideline is an attempt to translate scientific evidence into clinical practice with a view to improve cardiovascular health in Sri Lankan population.

This guideline attempts to help healthcare practitioners in cardiovascular risk assessment on most patients in most situations. However, the final judgment on assessment procedures and investigations for a particular patient must be made by the healthcare practitioner and it may be appropriate to have deviations from these guidelines on special circumstances.

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death worldwide. A number of studies have suggested that South Asian (India, Pakistan, Bangladesh and Sri Lanka) patients have a higher incidence of ASCVD than Caucasian patients.[1,2] ASCVD is the leading cause of death in Sri Lanka.[3] The life expectancy is estimated to increase by almost 7 years if all forms of major ASCVD were eliminated.[4] Coronary artery disease (CAD) has a long asymptomatic latent period, which provides an excellent opportunity for early detection and prevention. There is established evidence by meta-analysis of randomized clinical trials that absolute risk reduction is larger when individuals with higher baseline risk are detected and treated with antihypertensive medications.[5,6,7] The number of individuals need to treat (NNT) to prevent one adverse outcome decreases with increasing baseline ASCVD risk.

The aim of this guideline is to provide an evidence-based approach to risk assessment with a view to reduce ASCVD related morbidity and mortality in asymptomatic adults. Every effort was made to keep the guidelines concise and user friendly.

Assessment of the ASCVD risk for Sri Lankan adults should be started from the age of 20 years considering the incidence of ASCVD outcomes in young adults in Sri Lanka and in other South Asian countries. From age 20 to 39 years, it may be reasonable to assess conventional ASCVD risk factors every 4-6 years.[8,9] However, this risk should be assessed routinely form age 40 to 75 years.[5]

The recommendations published in this guideline are based on established scientific evidence as much as possible. An extensive literature search on published clinical trials, meta-analysis, case studies, consensus opinions and standards of care on cardiovascular risk assessment were reviewed during August to November 2020. The review was limited to the articles published in English language and research done on human subjects.

The key words used for the literature search included ankle-brachial index, apolipoproteins, arterial stiffness, atrial fibrillation, autoimmune diseases, cardiovascular risk, carotid intima-media thickness, carotid ultrasound scans, chemotherapy, chronic kidney disease, computed tomography coronary angiography, coronary calcium score, diabetes, erectile dysfunction, exercise electrocardiogram, genotype testing, global risk sores, hemoglobin A1c, high-sensitivity C-reactive protein, hypercholesterolemia, hyperlipidemia, hypertension, lipoprotein-associated phospholipase A2, lipoproteins, magnetic resonance imaging of plaques, microalbuminuria, myocardial perfusion imaging, natriuretic peptides, obstructive sleep apnea, radiotherapy, resting electrocardiogram, smoking, stress echocardiography, transthoracic echocardiography and weight control.

Scope of the Guidelines

The main focus of this guideline is risk assessment and primary prevention of CVD in asymptomatic men and women to prevent cardiovascular outcomes. These cardiovascular outcomes include CAD (chronic stable angina, unstable angina, coronary revascularization and fatal and non-fatal myocardial infarction), heart failure and atrial fibrillation.

Class of recommendation (COR)

The writing committee performed a formal literature review and weighed the strength of evidence for and against particular procedures, investigations and expected health outcomes. The strengths of evidence for efficacy of interventions were classified as follows.

- **Class I** – Strong evidence to confirm that the benefit of the intervention is much more than the risk.
- **Class IIa** – Moderately strong evidence to suggest that the benefit of the intervention is more than the risk.
- **Class IIb** – Weak evidence to suggest that the benefit of the intervention is more than the risk.
- **Class III (No Benefit)** – Either no evidence to confirm a benefit or the benefit is equal to the risk.
- **Class III (Harm)** – Strong evidence to confirm harm or the risk is more than the benefit.

Level of Evidence (LOE)

The review included ranking of the weight evidence to support recommendations. The evidence was ranked as follows.

- **Level A** - if the data were derived from multiple randomized clinical trials or meta-analyses.
- **Level B** - when the evidence was derived from a single randomized trial or non-randomized studies.
- **Level C** - when the recommendations are based on consensus opinion, retrospective studies, registries, case studies or standard of care.

Key Message

Individuals who have a low-risk for clinical events are unlikely to gain a substantial benefit from pharmacological therapy or revascularization procedures and therefore best be managed with lifestyle modifications only. Individuals who have a high-risk for clinical events are more likely to benefit from pharmacological therapy or revascularization procedures and therefore best managed with such treatment methods. Investigations for cardiovascular risk assessment may be indicated for individuals at borderline intermediate risk and intermediate risk to assess the need for lifestyle modifications and pharmacological therapy.

Chapter 1

Cardiovascular Risk Assessment

1.1 Global Risk Score (GRS) Assessment

Non-modifiable risk factors such as age and gender and modifiable risk factors such as smoking status, diabetes, systolic blood pressure or treatment for hypertension and serum total cholesterol levels can be combined together to develop a predictive model to estimate the risk of morbidity and mortality related to ASCVD.[10] These scores combine multiple risk factors in to a single quantitative risk estimate.[11] There are many global risk assessment scores available and are used all over the world. The writing committee recommends to use WHO (World Health Organization) risk prediction chart of 2019 for South East Asia for global risk score calculation for Sri Lankan population.

WHO CVD risk prediction chart for South East Asia is specially designed to assess 10-year combined myocardial infarction and stroke (fatal and non-fatal) in South East Asian countries including Sri Lanka.[12] This risk score is a product of a multiple ASCVD risk factors including gender, age, systolic blood pressure, total blood cholesterol, smoking status and presence or absence of diabetes. However, like many other charts, this chart cannot be used to assess GRS in young individuals < 40 years of age.

Other risk calculators, such as ASCVD Risk Estimator[13] by American College of Cardiology and American Heart association and Systematic Coronary Risk Estimation (SCORE)[14] used by European Society of Cardiology, are also widely used in Sri Lanka for ASCVD risk assessment. However, ASCVD Risk Estimator and SCORE may predict lower risk estimations for South Asians as they are primarily established for risk assessment in American and European populations respectively. Therefore, correction factors should be applied for more realistic risk estimation when these are used for South Asian populations. For example, SCORE risk estimation should be multiplied by 1.4 for correction to South Asian populations.[15]

Individuals can be categorized into low, intermediate and high-risk according to their global risk estimates of fatal or non-fatal outcomes from CVD during next 10 years. Traditionally, GRS of 0-10% are considered as low-risk, 10-<20% as intermediate risk and > 20% as high-risk.[16]

The GRC assessments should be interpreted together with the knowledge and the experience of the clinician and in view of the factors that may modify the ASCVD risk. Even if the 10-year absolute risk may be low, the relative risk can be high in young persons as events usually occur later in the life.

Table 1. 1 Global Risk Score (GRS) Assessment

COR	LOE	Recommendation
I	C	Calculation of GRS (such as WHO CVD risk prediction chart for Southeast Asia) using multiple, traditional cardiovascular risk factors should be done for all asymptomatic men and women above 40 years of age and have no clinical history of ASCVD.

1.2 Obtaining Family History of Premature ASCVD

Family history of premature ASCVD is an independent risk factor for development of the same disease in asymptomatic men and women.[17] The association of family history may be both the genetic trait and the environment share among family members.[18] Premature ASCVD is defined as a cardiovascular event occurring in a first-degree male relative of age < 55 years and/or in a first-degree female relative of age < 65 years. A family history of premature ASCVD is a simple, inexpensive but valuable information and therefore should be included in cardiovascular risk assessment in all individuals.

Table 1. 2 Obtaining Family History of Premature ASCVD

COR	LOE	Recommendation
I	C	Family history of premature ASCVD should be obtained for risk assessment in all asymptomatic men and women.

1.3. Risk Assessment in Younger Individuals

Individuals < 40 years demonstrated a low ASCVD risk whenever 5- or 10-year their risk is calculated, using a standard risk calculator, regardless of their underlying risk factors. However, some individuals have high relative risk and are likely to experience fatal or non-fatal ASCVD events prematurely.

All the people < 40 years should be evaluated for cardiac risk factors. Men and women with a family history of premature CAD should be investigated for primary hypercholesterolemia using a validated clinical score.[19,20,21] They should also be evaluated every 4-6 years for other risk factors including smoking status, blood pressure and HbA1c.

Table 1. 3 Risk Assessment in Younger Individuals

COR	LOE	Recommendation
I	B	Screening of all men and women with a family history of premature ASCVD in a first degree relative is recommended for familial hypercholesterolaemia.

1.4. Assessment of Psychosocial Factors

Numerous psychosocial factors are associated with increased risk of ASCVD. These factors include low socio-economic status, chronic stress, mental disorders, personality traits and lack of social support. Poor adherence to treatment for risk factor control and lack of efforts to lifestyle changes may play a role in increased ASCVD risk in this group of individuals.

Low socio-economic status including low educational level, low job status, low income and living in poor residential facilities are associated with increased ASCVD risk.[22,23]

Chronic stress at work[24] and family life[25] are also associated with increased ASCVD risk. Also, clinical depression,[26] anxiety,[27] and schizophrenia[28] are associated with increased ASCVD risk. Individuals with hostility, which is characterized by mistrust, rage and anger are also associated with increased ASCVD risk.[29]

Social isolation and lack of social support are other psychosocial factors associated with increased ASCVD risk.[30]

Table 1. 4 Assessment of Psychosocial Factors

COR	LOE	Recommendation
IIa	B	Assessment of psychosocial factors in an interview by a clinician or using a standardized questionnaire[31] may be helpful for ASCVD risk assessment in all asymptomatic men and women.

1.5. Female Specific Conditions

Pre-eclampsia occurs in about 1-2% while pregnancy-induced hypertension occurs in about 10-15% of all the pregnancies as obstetric complications. Pre-eclampsia is associated with increased future risk of hypertension,[32] diabetes[33] and ASCVD[33] while pregnancy-induced hypertension is associated with increased future risk of hypertension[32] and ASCVD.[34]

Gestational diabetes is associated with increased risk of developing diabetes with up to 50% of them develop diabetes within the first 5 years after the preganacy.[35]

In a systematic review and a meta-analysis, women who experienced menopause younger than 45 years and women 45 years or older at onset were compared for CVD related outcomes.[36] The relative risks of overall CAD, fatal CAD, overall stroke, stroke mortality, CVD mortality and all-cause mortality were increased modestly.[36]

Polycystic ovarian syndrome is associated with increased future risk of developing diabetes[37] and may also be associated with increased ASCVD risk.

Table 1. 5 Female Specific Conditions

COR		LOE	Recommendation
IIa		B	Periodic screening for hypertension and diabetes mellitus can be helpful in women who developed pre-eclampsia, pregnancy-induced hypertension and premature menopause (≤ 40 years).
IIa		B	Periodic screening for diabetes mellitus can be helpful in women who has polycystic ovarian syndrome.

1.6. Chronic Kidney Disease (CKD)

CKD is associated with increased prevalence of hypertension, diabetes and hypercholesterolemia. CKD is also associated with increased risk of ASCVD, independent of conventional cardiac risk factors.[38]This increased risk could be due to vascular endothelial inflammation and coronary calcification caused by CKD.[38] As a result, eGFR is associated reciprocally with ASCVD. The ASCVD risk can be classified as "very high" for severe CKD (eGFR < 30 mL/min/1.73m^2) and as "high risk" for moderate CKD (eGFR < 30-59 mL/min/m^2) patients.

Table 1. 6 Chronic Kidney Disease (CKD)

COR	LOE	Recommendation
IIa	B	Measurement of eGFR can be useful for ASCVD risk assessment in asymptomatic men and women with chronic kidney disease.

1.7. Detection of Microalbuminuria

Urine analysis for microalbuminuria is a simple, inexpensive and widely available test, which can be helpful to assess ASCVD risk of both diabetic and nondiabetic patients.[39]An early morning, spot urine sample to measure urine albumin-to-creatinine ratio is effective in assessing ASCVD risk.[40] Microalbuminuria is defined as urine albumin-to-creatinine ratio of 30-300 mg/g.[41]

Microalbuminuria is an independent risk factor that is associated with doubling the risk of ASCVD when compared to the individuals without microalbuminuria.[42] This increased risk was demonstrated across subgroups of individuals including those with and without hypertension, with and without diabetes and with and without low estimated glomerular filtration rate.[39,41,42]

Individuals at intermediate-risk of ASCVD with microalbuminuria had a substantially high 5-year risk of ASCVD when compared to the individuals without microalbuminuria (20.1% versus 6.3% respectively).[43]

Table 1. 7 Detection of Microalbuminuria

COR	LOE	Recommendation
IIa	B	Detection of microalbuminuria by urine analysis can be useful for ASCVD risk assessment in asymptomatic men and women with diabetes and hypertension.
IIb	B	Detection of microalbuminuria by urine analysis may be useful for ASCVD risk assessment in asymptomatic men and women at intermediate risk without diabetes and hypertension.

1.8. Measurement of High-Sensitivity C-Reactive Protein (hsCRP)

Inflammation of the vascular endothelium plays a significant role in the pathogenesis of atherosclerosis. As a result, numerous biomarkers have been evaluated as risk markers of ASCVD. hsCRP is the most intensively studied biomarker for inflammation of vascular endothelium.

hsCRP is an independent risk factor for ASCVD.[44,45,46] hsCRP is also associated with increased risk for stroke, peripheral vascular disease, heart failure, atrial fibrillation, sudden cardiac death and all-cause mortality.[47,48,49,50,51]

Table 1. 8 Measurement of High-Sensitivity C-Reactive Protein (hsCRP)

COR	LOE	Recommendation
IIa	B	Measurement of hsCRP can be helpful for ASCVD risk assessment in men $\geq$ 50 years and women $\geq$ 60 years with no history of CAD, CKD, diabetes mellitus, severe inflammatory conditions and serum LDL cholesterol < 130 mg/dL with no contraindication to statin therapy.
IIb	B	Measurement of hsCRP may be helpful for ASCVD risk assessment in asymptomatic, intermediate-risk, men $\leq$ 50 years and women $\leq$ 60 years.
III No Benefit	B	Measurement of hsCRP is not recommended for ASCVD risk assessment in asymptomatic, high-risk, men and women.
III No Benefit	B	Measurement of hsCRP is not recommended for ASCVD risk assessment in asymptomatic, low-risk, men $\leq$ 50 years and women $\leq$ 60 years.

1.9. Coronary Calcium Score (CCS)

Although coronary artery atherosclerosis does not always show calcification, it may occur in late-stage subclinical coronary atherosclerosis.[52] The extent of coronary calcifications correlates with extent of atherosclerotic plaque burden.[52] The amount of calcium in the coronary artery walls is quantified by measuring the area of the calcium deposits on the scan multiplied by a weighing factor depending on the Hounsfield unit density of the calcium deposits.[53] The total amount of coronary calcium is usually expressed as Agatston score (AU).[54] The radiation dose is low (0.9-1.1

mSv) when the acquisition is prospectively triggered[55,56] but the radiation dose is higher when the retrospective imaging is used.[57]

Many published studies have reported that elevated CCS provides information on ASCVD risk over and above the information provided by conventional risk factors. Intermediate-risk patients with elevated CCS > 300 AU had 2.8% annual rate of fatal and non-fatal myocardial infarctions (roughly equal to 10-year risk of 28%).[53] Therefore, measurement of CCS may be helpful for ASCVD risk assessment in asymptomatic, intermediate-risk and borderline intermediate-risk, men and women.[58]

Measurement of CCS is not recommended for men < 40 years and women < 50 years considering the radiation dose and very low prevalence of detecting coronary calcium in these age groups.[58,59]

Table 1. 9 Coronary Calcium Score (CCS)

COR	LOE	Recommendation
IIa	B	CCS can be helpful for ASCVD risk assessment in asymptomatic, intermediate-risk, men and women.
IIb	B	CCS can be helpful for ASCVD risk assessment in asymptomatic, low to intermediate-risk (6%-10% 10-year risk), men and women.
III No Benefit	B	CCS is not recommended for ASCVD risk assessment in asymptomatic, low- risk, men and women.

1.10. Patients with Autoimmune Diseases

Active rheumatoid arthritis is associated with increased ASCVD risk in both men and women.[60]Other autoimmune diseases such as psoriasis, [61] ankylosing spondylitis and systemic lupus erythematosus are also associated with increased ASCVD risk. Systemic inflammation may be involved with accelerated atherosclerosis.[62] These inflammatory autoimmune diseases increase the relative risk of ASCVD by about 1.4 in men and 1.5 in women.[63]

Table 1. 10 Patients with Autoimmune Diseases

COR	LOE	Recommendation
IIa	B	The ASCVD risk can be calculated by multiplying the GRS by 1.5 in patients with active rheumatoid arthritis.
IIb	C	The ASCVD risk may be calculated by multiplying the GRS by 1.5 in patients with active non-rheumatoid arthritis conditions.

1.11. Erectile Dysfunction (ED)

Erectile dysfunction is common and may occur up to 40% of men after 40 years of age. ED and ASCVD share common risk factors including diabetes, hypertension, hypercholesterolemia, smoking and depression. Also, these two conditions share the same pathophysiologic mechanisms. Many studies have established that ED is associated with asymptomatic ASCVD in men.[64,65] A meta-analysis has established that ED is associated with 44% higher risk of ASCVD, 62% higher risk of myocardial infarction, 39% higher risk of stroke and 25% higher risk of all-cause mortality when compared with men without ED.[63]

Table 1. 11 Erectile Dysfunction (ED)

COR	LOE	Recommendation
IIa	C	Assessment for risk cardiac factors, and symptoms and signs of heart disease can be helpful for ASCVD risk assessment in men with ED.

1.12. Ankle-Brachial Index (ABI)

Ankle-Brachial Index is an easy-to-perform, bed side measurement performed by Doppler measurement of blood pressure in four extremities. It is the value of the highest blood pressure in lower extremity divided by highest blood pressure of upper extremity.

ABI < 0.9 is a reliable marker of peripheral arterial disease.[66] Many studies have demonstrated that ABI is also inversely related to the ASCVD risk.[67] Also, studies have demonstrated that measuring a low ABI of < 0.9 has an additive predictive value over GRS assessment.[68,69]

Table 1. 12 Ankle-Brachial Index (ABI)

COR	LOE	Recommendation
IIb	B	Measurement of ABI may be helpful for ASCVD risk assessment in asymptomatic, intermediate-risk, men and women.

1.13. Carotid Ultrasound

Evidence of atherosclerosis in one arterial territory may be associated with involvement of other arteries.[70] This can be used as a strategy by ultrasonographic assessment of carotid arteries to predict coronary atherosclerosis. Carotid ultrasonography can be used to measure intima-media thickness (IMT) and to determine presence and characteristics of atherosclerotic plaques.

Carotid IMT includes measurement of early atherosclerosis as well as smooth muscle hypertrophy/hyperplasia. However, lack of having a standardized definition for the measurement, high variability and low reproducibility of the measurement have made carotid IMT failing to demonstrate a value in ASCVD risk prediction.[71] Therefore, use of carotid IMT measurement for ASCVD risk prediction is not recommended.

Carotid ultrasound is used to detect atherosclerotic plaques causing > 50% stenosis. These plaques are associated with both coronary and cerebrovascular events.[72] Therefore, carotid artery plaque assessment by ultrasonography may be helpful for ASCVD risk prediction.

Table 1. 13 Carotid Ultrasound

COR	LOE	Recommendation
IIb	B	Carotid artery plaque assessment on ultrasonography may be helpful in ASCVD risk assessment in asymptomatic men and women.
III No Benefit	A	Measurement of carotid artery IMT is not recommended for ASCVD risk assessment in asymptomatic men and women.

1.14. Resting Electrocardiogram (ECG)

Population studies have shown that resting ECG abnormalities are predictors of ASCVD risk among asymptomatic individuals.[73] Novacode criteria divide resting ECG abnormalities in to major and minor types.[74] Major abnormalities include atrial fibrillation, atrial flutter, complete atrio-ventricular block, LVH with repolarization abnormalities, isolated ischemic changes and ventricular or supra ventricular tachycardia. Minor abnormalities include first and second degree atrio-ventricular blocks, partial bundle branch blocks and isolated minor Q wave and ST-T abnormalities.

Evidence of LVH on resting ECG may indicate severe or poorly controlled hypertension and is associated with increased ASCVD risk.[75] Addition of resting ECG to the standard GRS assessment may be helpful to reclassify ASCVD risk especially in patients with hypertension.[74,76]

Table 1. 14 Resting Electrocardiogram (ECG)

COR	LOE	Recommendation
IIa	C	A resting ECG can be helpful for ASCVD risk assessment in asymptomatic men and women with hypertension and/or diabetes.
IIb	C	A resting ECG may be helpful for ASCVD risk assessment in asymptomatic men and women without hypertension and diabetes.

1.15. Measurement of Hemoglobin A1c (HbA1c)

HbA_1C can be used to diagnose diabetes (HbA1c > 6,5%) and also to identify individuals who are at risk for developing diabetes (HbA1c 5.7% to 6.4%).[77] Some studies have observed that higher levels of HbA_1C are associated with an increased risk of ASCVD in non-diabetic patients.[78] For non-diabetic individuals, each 1% increase of HbA1c is associated with an adjusted 40% higher risk of ASCVD.[79] HbA1c is a better predictor to improve risk assessment and reclassification compared to fasting blood glucose.[80]

Table 1. 15 Measurement of Haemoglobin A1c (HbA1c)

COR	LOE	Recommendation
IIb	B	Measurement of HbA1c can be helpful for ASCVD risk assessment in asymptomatic men and women without diabetes.

1.16. Measurement of hemoglobin A1c (HbA1c)

Treadmill test is the most commonly used method for exercise testing and a number of exercise protocols are used during which, the walking speed and the grade are gradually increased in stages. Although the most important abnormality is ST-segment depression during and post exercise, other abnormalities such as exercise capacity, chronotropic response, heart rate recovery and exercise induced arrhythmia are also considered to be associated with increased ASCVD risk.[81,82] Duke score that incorporates exercise capacity, exercise induced angina and ST segment depression is used to synthesize a score to predict the risk.[83]

An exercise ECG may be helpful for ASCVD risk assessment in asymptomatic, intermediate-risk, men and women.[84,85,86] Particular attention should be paid to non-ECG abnormalities such as exercise capacity for risk prediction.[84,85,86]

Table 1. 16 Performing of Exercise ECG

COR	LOE	Recommendation
IIb	B	Exercise ECG may be helpful for ASCVD risk assessment in asymptomatic, intermediate-risk, men and women.

1.17. Transthoracic Echocardiography

Regional wall motion abnormalities are the most common echocardiographic manifestations of CAD but are only present during or recent (myocardial stunning) of an ischemic event or previous myocardial infarction as evident by loss of muscle mass and/or scar tissue. Additional echocardiographic manifestations of CAD include ischemic mitral regurgitation, reduced left and right ventricular systolic dysfunction. None of the abnormalities mentioned above have satisfactory sensitivity and specificity to consider transthoracic echocardiography for risk assessment of ASCVD.

LVH is associated with increased risk of ASCVD and all-cause mortality independent of blood pressure.[87,88,89] Echocardiography is more sensitive than resting ECG in diagnosing LVH and also able to measure left ventricular mass index. Patients with uncomplicated essential hypertension has a 40% higher risk of ASCVD for each 39 g/m2 greater left ventricular mass index.[90] Therefore, transthoracic echocardiography to detect LVH for ASCVD risk assessment is only recommended for patients with hypertension.[90,91]

Table 1. 17 Table Transthoracic Echocardiography

COR	LOE	Recommendation
IIb	B	Transthoracic echocardiography to detect LVH may be helpful for ASCVD risk assessment in asymptomatic men and women with hypertension.
III No Benefit	C	Transthoracic echocardiography is not recommended for ASCVD risk assessment in asymptomatic men and women without hypertension.

1.18. Myocardial perfusion Imaging (MPI)

Exercise or pharmacological stress MPI using single-photon emission computed tomography (SPECT) or positron emission tomography (PET) may be used for ASCVD risk assessment in asymptomatic individuals. However, both SPECT and PET scans involve considerable exposure to ionizing radiation. The average radiation exposure for stress MPI SPECT is about 5 mSv while for stress MPI PET is about 5 mSv after using dose reduction strategies.[92,93]

There is a well-established correlation between the CCS and the presence of silent ischemia detected by stress MPI.[94] The presence of silent ischemia is significantly high among patients with higher CCS and diabetes[95] or higher CCS and individuals with strong family history of premature CAD.[96]

Stress MPI may be helpful in the advanced assessment of asymptomatic individuals who have been evaluated with other risk assessment modalities and found to be at high-risk of silent ischemia. These individuals include patients with diabetes and those with strong family history of premature CAD and having high coronary calcium scores of > 400 AU. Stress MPI is not recommended for ASCVD risk assessment in asymptomatic, low or intermediate-risk, individuals. A special consideration should be made about the amount of radiation exposure when deciding the benefit of stress MPI in an asymptomatic individual against the potential risk.

Table 1. 18 Myocardial perfusion Imaging (MPI)

COR	LOE	Recommendation
IIb	C	Stress MPI may be helpful for ASCVD risk assessment in asymptomatic men and women with diabetes, strong family history of premature ASCVD or other risk assessments suggest high risk of ASCD (e.g., CCS ≥ 400 AU).
III No Benefit	C	Stress MPI is not recommended for ASCVD risk assessment in asymptomatic, low or intermediate risk, men and women.

1.19. Obstructive Sleep Apnea (OSA)

OSA affects 25% of men and 9% of women and is associated with increased cardiovascular morbidity and mortality.[97] Hypertension, myocardial infarction, stroke, heart failure and arrhythmia including atrial fibrillation are associated with OSA.

The increased CVD risk of OSA may be due to increased sympathetic activity, elevated blood pressure and increased oxidative stress secondary to episodic hypoxemia. The oxidative stress increases circulating levels of inflammatory markers causing endothelial dysfunction and atherosclerosis.[97]

Table 1. 19 Obstructive Sleep Apnoea (OSA)

COR	LOE	Recommendation
IIb	C	Assessment for cardiac risk factors (e.g., hypertension, diabetes, hypercholesterolemia, obesity and non-sustained atrial or ventricular arrhythmia) and symptoms and signs (e.g., angina or dyspnea on exertion and poor exercise tolerance) of heart disease can be helpful for CVD risk assessment in men and women with OSA.

1.20. Genotype Testing

Many genetic tests are currently available to identify the genetic risk for CVD. However, there is no agreement regarding which genetic markers to use and how to calculate genetic risk scores. There is no evidence to demonstrate that genotype testing is helpful in decision making to alter management and to improve outcomes in asymptomatic men and women.[98] Epigenetics involve the chemical alteration of DNA that affect expression of genes. Higher methylation of DNA is involved with higher risk of ASCVD while lower methylation of DNA is associated with higher-risk.[99] However, there is no evidence to confirm that epigenetic screening is helpful ASCVD risk prediction beyond conventional risk factors.

Table 1. 20 Genotype Testing

COR	LOE	Recommendation
III No Benefit	B	Genotype testing and epigenetic screening for ASCVD risk assessment in asymptomatic men and women are not recommended.

1.21. Measurement of Natriuretic Peptide Levels

Atrial natriuretic peptides, B-type natriuretic peptides and their precursors are measured to diagnose and to assess prognosis of heart failure in symptomatic patients. Increased levels of these markers are also associated with poor prognosis in patients with acute coronary syndrome and stable CAD. However, the value of natriuretic peptides in predicting development of CVD in asymptomatic individuals who are free from CAD and heart failure is not confirmed.[100] Therefore, measurement of natriuretic peptide levels for assessment of CVD risk in asymptomatic individuals is not recommended.

Table 1. 21 Measurement of Natriuretic Peptide Levels

COR	LOE	Recommendation
III No Benefit	B	Measurement of natriuretic peptide levels for CVD risk assessment in asymptomatic men and women is not recommended.

1.22. Measurement of Lipoprotein-Associated Phospholipase A_2 Level

Lipoprotein-associated phospholipase A_2 is an enzyme produced by macrophages and lymphocytes. This is a proatherogenic enzyme that hydrolyses oxidative phospholipids in LDL, generating proatherogenic phospholipids, non-esterified fatty acids and inflammatory markers.[101]

In a meta-analysis of 14 studies, there was no significant association between lipoprotein-associated phospholipase A_2 enzyme levels and ASCVD risk.[102] Therefore, measurement of lipoprotein-associated phospholipase A_2 level for ASCVD risk assessment in asymptomatic individuals is not recommended.

Table 1. 22 Measurement of Lipoprotein-Associated Phospholipase A2 Level

COR	LOE	Recommendation
III No Benefit	B	Measurement of lipoprotein-associated phospholipase A_2 level for ASCVD risk assessment in asymptomatic men and women is not recommended.

1.23. Measurement of Arterial Stiffness

An increase in arterial stiffness is associated with arterial wall damage, especially in hypertensive patients.[103] Arterial stiffness is usually measured by either aortic pulse wave velocity or arterial augmentation index.[104] However, the use of arterial stiffness for risk prediction of ASCVD is restricted only to research setting.[104] Therefore, systematic use of arterial stiffness for ASCVD risk assessment in general public is not recommended.

Table 1. 23 Measurement of Arterial Stiffness

COR	LOE	Recommendation
III No Benefit	B	Measurement of arterial stiffness for ASCVD risk assessment in asymptomatic men and women is not recommended.

1.24. Computerized Tomography Coronary Angiography (CTCA)

CTCA has been compared with conventional invasive coronary angiography for detection of significant coronary stenosis of > 50% in many studies.[105] Most of these studies show sensitivity and specificity in the range of 85% to 95% and has a high negative predictive value of > 98%.[105]

In a study of asymptomatic adults without a history of established CAD, coronary calcium was detected in 18% of participants while identifiable atheromatous plaques were detected in 22% of participants.[106] The prevalence of significant coronary stenosis in low, intermediate and high-risk groups were 2%, 7% and 16% respectively. During the next 18-month follow-up, 15 cardiac events occurred but 14 of these were revascularization procedures based on CTCA results. The utility of CTCA for risk assessment of ASCVD in asymptomatic adults could not be established as there was only one non-procedural cardiac event in this study.

Table 1. 24 Computerized Tomography Coronary Angiography (CTCA)

COR	LOE	Recommendation
III No Benefit	C	CTCA for ASCVD risk assessment in asymptomatic men and women is not recommended.

1.25. Stress Echocardiography

Exercise or pharmacological stress echocardiography is usually performed in symptomatic patients to assist in the diagnosis of obstructive CAD. Stress echocardiography may be considered for testing asymptomatic individuals during pre-operative assessment,[107] for patients with atrial fibrillation and investigation following an episode of ventricular tachycardia or syncope. However, there is little published data on use of stress echocardiography in asymptomatic patients for ASCVD risk assessment.

Table 1. 25 Stress Echocardiography

COR	LOE	Recommendation
III No Benefit	C	Stress echocardiography for CVD risk assessment in asymptomatic, low or intermediate risk, men and women is not recommended.

1.26. Magnetic Resonance Imaging (MRI) of Plaque

MRI is a non-invasive method of assessment of the size and characteristics of atheromatous plaques in aorta, carotid and femoral arteries.[108,109] Also, MRI does not require exposure to ionizing radiation. The capability of MRI in detection and quantification of atheromatous plaques can be used for risk assessment of ASCVD.[110] However, there is no published data to date to confirm the benefit on using MRI plaque assessment in aorta, carotid and femoral arteries for ASCVD risk assessment.

Table 1. 26 Magnetic Resonance Imaging (MRI) of Plaque

COR	LOE	Recommendation
III No Benefit	C	MRI for detection and quantification of atheromatous plaques in aorta, carotid and femoral arteries as ASCVD risk assessment in asymptomatic men and women is not recommended.

1.27. Measurement of Lipoproteins and Apolipoproteins

Additional lipid parameters such as apolipoprotein B (ApoB) is related closely with LDL cholesterol level while apolipoprotein A (ApoA) is related with HDL cholesterol levels. Therefore, measuring these particles beyond standard fasting lipid profile is not beneficial as measurement of non-HDL cholesterol reflects the total concentration of atherogenic peptides and particle number.[111] Non-HDL cholesterol is a simple measurement, which is calculated as the difference between total and the HDL cholesterol level. There is no publish data to demonstrate an incremental predictive value of LDL subfractions beyond that of conventional CVD risk factors.[112]

In the Framingham Heart Study, only a marginal additional risk prediction could be done from ApoB and ApoB/A-1 ratio when compared with total/HDL cholesterol ratio.[113]

Lipoprotein (a) [Lp (a)] is a large glycoprotein attached to an LDL like particle and is believed to be associated with increased ASCVD risk that is independent of conventional lipid parameters. A meta-analysis of prospective studies involving 126,634 participants and a follow-up of 1.3 million person-years demonstrated that Lp(a) concentration is weakly correlated with several conventional CVD risk factors.[114] There was a continuous, independent but modest association of Lp(a) concentration with risk of ASCVD and stroke. However, the information of independent risk prediction by measuring Lp(a) concentration beyond fasting lipid profile measurement is lacking. Also, there are concerns about measurement and standardization of Lp(a) concentration in a clinical setting.[11]
Therefore, measurement of apolipoprotein levels, particle size and density and lipoproteins for ASCVD risk assessment in asymptomatic individuals is not recommended.

Table 1. 27 Measurement of Lipoproteins and Apolipoproteins

COR	LOE	Recommendation
III No Benefit	C	Measurement of apolipoprotein levels, particle size and density and lipoproteins for CVD risk assessment in asymptomatic men and women is not recommended.

Chapter 2

Measures for Primordial and Primary Prevention of Cardiovascular Events

2.1. Diet and Nutrition

Specific nutrients in the diet, specific foods and dietary patterns influence ASCVD risk by both their effect on risk factors such as diabetes, hypertension, hypercholesterolemia and obesity and through direct effect.[116]

Fats and fatty acids

The types of fatty acids consumed are more important than the amount of total fat for ASCVD risk reduction. Intake of saturated fatty acids should be reduced to less than 10% of total energy intake by replacing it with polyunsaturated fatty acids.[117] polyunsaturated fatty acids lower LDL cholesterol and also HDL cholesterol to a lesser extent. Monounsaturated fatty acids increase HDL cholesterol level. There is only weak evidence to confirm that both polyunsaturated and monounsaturated fatty acids lower ASCVD risk.[118]

Trans fatty acids are a subclass of saturated fatty acids that forms during industrial processing of fats. Trans fats increases total cholesterol and reduces HDL cholesterol level. Increasing the energy intake from trans fats by 2% leads to increase ASCVD risk by 23%.[119] It is recommended to reduce trans fats to < 1% of total energy intake.

The impact of the amount of dietary cholesterol to serum cholesterol is weak compared to composition of fatty acids in the diet. However, it is recommended to reduce cholesterol intake to < 300 mg per day.

Minerals

The Dietary Approaches to Stop Hypertension (DASH) trial demonstrated the association between sodium restriction and blood pressure reduction.[120] Almost 80% of the total salt comes from processed food while remaining is added during cooking or at the dining table. It is recommended to limit salt intake to < 5 g per day.

Increasing potassium intake contributes to lower blood pressure.[121] Higher consumption of fruits and vegetables, which are high in potassium should be considered in addition to salt restriction to control high blood pressure.

Vitamins

Serum levels of vitamin A, B, C and E have been shown no association between these vitamins and ASCVD risk. Vitamin D_3 level has shown a small beneficial effect by reducing all-cause mortality by 11%.[122] However, it is not clear whether Vitamin D_3 specifically reduces CVD related mortality. Therefore, Vitamin D_3 supplements for ASCVD risk reduction is not recommended.

Fiber

Consuming > 7 g per day of fiber from whole grain products is associated with 9% reduction of ASCVD risk.[123]

Nuts

Daily consumption of 30 g of nuts reduces ASCVD risk by about 30%.[124]

Fruits and vegetables

Consumption of each additional serving (a palm full) of fruits and vegetables up to 5 sessions per day reduces the ASCVD related mortality by 4%.[125] Therefore, 5 servings of fruits or vegetables are recommended for ASCVD risk reduction.

Fish and fish oils

Eating fish at least once a week is associated with 16% reduction of ASCVD risk compared with eating less fish[126] and eating fish 2-4 times a week reduces the risk of stroke by 6% compared with eating fish less than once a week.[127]

However, using fish oil supplements have no benefit in reducing ASCVD risk or cardiac events.[128]

Alcohol

Alcohol is a colossal global health issue and small reductions in health-related harms at low levels of alcohol intake are outweighed by the increased risk of other health-related harms, including cancer. [129]

Sugar and sugar-sweetened soft drinks

Regular consumption of sugar and sugar-sweetened soft drinks is associated with obesity, diabetes and metabolic syndrome. The WHO recommends to limit the energy from sugar and sugar-sweetened soft drinks to < 10% of daily total energy intake.[130]

Table 2. 1 Sugar and sugar – sweetened soft drinks

COR	LOE	Recommendation
I	B	A diet containing higher amounts of vegetables, fruits, legumes, nuts, whole grains and fish is recommended for ASCVD risk reduction.
IIa	B	Replacement of saturated fat in the diet with monounsaturated and polyunsaturated fats can be helpful for ASCVD risk reduction.
IIa	B	Cholesterol and salt restriction in the diet can be helpful for ASCVD risk reduction.
IIa	B	Minimizing the intake of processed meats, refined carbohydrates and sweetened beverages can be helpful for ASCVD risk reduction.
III No Benefit	B	Using fish oil supplements are not recommended for ASCVD risk reduction.
III Harm	B	Trans fats should be avoided for ASCVD risk reduction.

2.2. Physical Activity and Exercises

Regular physical activities and exercises help to prevent and control many cardiovascular risk factors including hypertension, diabetes, LDL cholesterol and non-HDL cholesterol.[131] Regular physical activities and exercises also reduce CVD related mortality and all-cause mortality in healthy individuals and patients with cardiovascular risk factors.[132]

Aerobic physical activities and exercises have a dose-response effect on reduction of ASCVD risk and cardiac events.[133,134,135] These exercises consist of movement of large muscles in a rhythmic manner for a period of time. They include brisk walking, jogging, swimming, cycling, dancing, gardening and daily household and occupational activities.

Aerobic physical activities and exercises of moderate intensity for at least 150 minutes or vigorous intensity for at least 75 minutes per week is recommended for all healthy men and women for ASCVD risk reduction.[133,134,136] The frequency of each session should be at least 5 times a week but preferably every day.

The prescription for physical activity and exercises should be tailored to individuals to determine intensity, duration and frequency accordingly. Individuals who can do more exercises should be encouraged to do more exercises and should be encouraged to do up to 300 minutes of moderate intensity of 150 minutes of vigorous intensity exercises per week to gain additional benefits.[133,134] Similarly, individuals, who cannot perform minimum recommended level of physical activity and exercises should be encouraged to do some moderate or vigorous activities as even less than minimum recommended level of activities can be beneficial to reduce ASCVD risk.[137,138]

Sedentary individuals, especially those with high ASCVD risk should undergo a thorough clinical evaluation including exercise ECG before prescribing them physical activities and exercises.[139]

Each session of physical activity or exercises should include warm-up, conditioning and cool-down phases. Warming-up prior to exercises and cooling-down following exercises with stretching and flexing can be helpful to prevent injuries and adverse cardiac events.

Other types of exercises such as dynamic resistance exercises and isometric resistance exercises are associated with enhancing muscle mass, strength and power and exercise capacity.[140] Neuromotor exercises are also helpful to maintain and improve balance, coordination, agility and gait, especially in elderly individuals. However, the beneficial effects in terms of ASCVD risk reduction by these exercises have not been demonstrated.

Table 2. 2 Physical Activity and Exercises

COR	LOE	Recommendation
I	A	At least 150 minutes of moderate intensity or 75 minutes of vigorous intensity aerobic physical activity a week is recommended for healthy men and women of all ages for ASCVD risk prevention.
I	A	Gradual increase of aerobic physical activity to 300 minutes of moderate intensity or 150 minutes of vigorous intensity a week is recommended for healthy men and women for additional benefits in ASCVD risk prevention.
IIa	B	For men and women who are unable to meet minimum recommendations of physical activity, engaging some moderate or vigorous intensity physical activity, even if less than the recommended amount, can be helpful to reduce ASCVD risk.
IIa	C	Clinical evaluation, including PAR-Q screening and exercise ECG, should be considered for sedentary men and women with cardiovascular risk factors and intending to start vigorous physical activity or sports.

Whether to change the whole chart accordingly or do we need to have this separately as a new document.

2.3. Tobacco cessation

Tobacco affects vascular endothelial inflammation, oxidative processes, platelet functions, fibrinolytic mechanisms, lipid oxidation and vasomotor functions. These mechanisms enhance atherosclerotic process and prothrombotic phenomena increasing the risk of ASCVD and cardiac events.

Smoking cessation is the most cost-effective intervention for ASCVD risk reduction. The risk associated with smoking is related to the degree of smoking with no lower limit for its deleterious effects.[141] A long-standing smoker has a 50% risk of dying from his smoking habit and average loss of 10 years of his life.[142] The 10-year risk of mortality is approximately double in smokers compared to non-smokers. Even low-level smoking is associated with increased ASCVD risk.[143]

Passive smoking or environmental tobacco smoking is also associated with increased ASCVD risk.[144.145] The risk of ASCVD increases by 30% if an individual is exposed to passive smoking.

The risk of ASCVD is reduced almost close to the level of a non-smoker within 10-15 years of abstinence from smoking. There is no age limit to achieve the benefit of smoking cessation. Passive smoking should also be avoided.

Repeated advice, counselling including motivational interviews and support are important to help smokers to stop smoking. The pharmacological therapy to help smoking cessation includes nicotine replacement therapy (NRT), varenicline and bupropion.[146] In Sri Lanka consensus was agreed among the stakeholders i.e Ceylon college of Psychiatrist, NATA, Directorate of Mental Health not to recommend NRT based on evidence. [147]

Electronic cigarettes (e-cigarettes) are battery operated devices that vaporize nicotine and other chemicals to inhale and obtain the effects of combustible cigarettes. Studies have shown that the effects of e-cigarettes are similar to NRT trans dermal patches[148] and inhalers.[149] More research is required to study the long-term safety and health effects of e-cigarrets.[150] According to the National Authority on Tobacco and Alcohol Act, no 27 of 2006 gazette, dated 31st August 2016 e cigarettes are banned in Sri Lanka.

Table 2. 3 Tobacco Cessation

COR	LOE	Recommendation
I	A	All men and women should be advised to abstain from smoking tobacco, other herbal products and consuming smokeless tobacco products.
I	A	Repeated advice, counselling, support and medications including varenicline and bupropion individually or in combination are recommended for all smokers and people who use smokeless tobacco products to help tobacco cessation.
I	B	All men and women should be advised to avoid exposure to passive smoking (environmental tobacco smoking).

2.4. Weight Control

Overweight and obesity are associated with increase in blood pressure, insulin resistance, dyslipidemia, albuminuria and prothrombotic state. Both overweight and obesity are associated with development of diabetes, CAD, heart failure, atrial fibrillation, stroke, CVD related mortality and all-cause mortality. Therefore, weight loss is recommended for all overweight and obese individuals for ASCVD risk reduction.[151]

Body mass index (BMI) [weight (kg)/ (height (m)) ^{2}] is used extensively to identify overweight and obese men and women. Individuals with BMI of 25-29.9kg/m^2 are categorized as overweight while BMI > 30 kg/m^2 are categorized as obese. All-cause mortality is lowest with BMI of 20-25 kg/m^2. However, maintaining a BMI between 20-23 kg /m^2 is recommended for Sri Lankan population considering the higher risk of ASCVD among South Asians.

BMI 23-24.9kg/m^2 is considered as an increased risk for overweight. (Therefore, it is considered as a trigger point for life style modification)

The pattern of fat distribution is especially important for South Asians as their intra-abdominal fat deposition is associated with higher cardiometabolic and ASCVD risks. Waist circumference and waist to hip ratio (WHR) are used to identify individuals with abdominal obesity.[152] For South Asian populations, men with waist circumference $\geq$ 90 cm and WHR > 0.9 and women with waist circumference $\geq$ 80 cm and WHR > 0.8 are recommended weight loss to reduce cardiometabolic and ASCVD risk.[153]

Life style interventions, behavioral modifications, exercises and calorie restriction are important for weight loss.[151,154] Medical therapy for weight loss include orlistat and bariatric surgery. Patients who undergo bariatric surgery have a reduced risk of CVD events including myocardial infarction and stroke and mortality compared with non-surgical controls.[155]

Table 2. 4 Weight control

COR	LOE	Recommendation
I	B	Weight loss is recommended 0.5 kg/week until optimal BMI is reached to all men and women with overweight and obesity for ASCVD risk reduction.
I	B	Lifestyle interventions and counselling are recommended for men and women with overweight and obesity to achieve and maintain weight loss.
I	C	Measurement of BMI is recommended for all men and women to identify overweight and obesity for weight loss considerations.
IIa	B	Measurement of waist circumference can be helpful in identifying men and women with higher cardiometabolic risk.

2.5. Management of Diabetes

Patients with diabetes has double the risk of ASCVD when compared to non-diabetic patients.[156] Lifestyle modifications including heart-healthy diet for optimal glycemic control, weight management, regular exercises and physical activity and smoking cessation are of paramount importance for the management of diabetes.[157] The target $HbA1_C$ should be maintained below 7% in patients with both Type I and Type II diabetes.[158,159] In addition, optimal blood pressure control and lipid lowering therapy also play an important role in ASCVD risk reduction in diabetic patients.

The dietary plan of diabetic patients should include predominance of fruits, vegetables, green leaves, whole grain cereals and low-fat proteins while high-carbohydrate diets, sugar, sugar-sweetened drinks, salt, saturated fats, Trans fats and alcohol should be restricted.

At least 150 minutes per week of moderate-intensity exercises or 75 minutes per week high-intensity exercises are recommended for optimal glycemic control and ASCVD risk reduction. These exercises can be a combination of aerobic and resistance exercises.

Smoking should be strongly discouraged as this is associated with ASCVD and premature deaths among both diabetic and non-diabetic patients.[157,160]

Although short duration of diabetes does not increase the ASCVD risk significantly, the risk approaches to CAD risk equivalence after about a decade and in those with proteinuria and reduced eGFR.[161,162,163]

Meta-analyses involving data from multiple, large, randomized, controlled studies have shown that intense glucose control significantly reduces non-fatal myocardial infarction and CAD events but no effect on stroke or all-cause mortality.[164,165] Metformin is the first-line treatment recommended for glycemic control if this medication is tolerated and not contraindicated.[166] In a large, randomized, controlled study, metformin reduced microvascular and macrovascular complications by 32%, myocardial infarctions by 35% and all-cause mortality by 36% when compared with life-style modifications alone.[167]

Newer hypoglycemic agents, SGLT2 inhibitors and GLP-1R agonists may be effective in CVD risk reduction in diabetic patients. Addition of SGLT2 inhibitor, empagliflozin, to diabetes management was associated with reduction of CVD by 38%, hospitalization for heart failure by 35% and all-cause mortality by 35% when compared to patients with standard diabetic management without a SGLT2 inhibitor.[168] However, non-fatal myocardial infarctions and strokes were not reduced by empagliflozin. These results suggest that the mechanism of benefit was likely to be due to cardio-renal hemodynamic effects than hypoglycemic action or prevention of atherosclerosis. Two other randomized, controlled trials also showed significant reduction of CVD events and heart failure by other types of SGLT2 inhibitors, canagliflozin[169] and dapaglifloxin.[170]

GLP-1R agonists also have been shown to reduce ASCVD risk significantly. These effects have been demonstrated with liraglutide, [171] albiglutide[172] and semaglutide.[173]

There is clear evidence to confirm that intense lipid lowering therapy using simvastatin[174] or atorvastatin[175] is associated with a significant reduction of ASCVD events and related mortality in

diabetic patients who have no history of CAD or myocardial infarction. There is greater reduction of ASCVD risk with more intense lipid lowering therapy in diabetic patients.[176] Also, addition of ezetimibe to statin therapy for more intense LDL cholesterol control is associated with further reduction of ASCVD risk.[177] Lipid lowering therapy is recommended for all diabetic patients > 40 years of age with high-risk patients should achieve LDL cholesterol target of < 70 mg/dL (non-HDL cholesterol target < 100 mg/dL) while intermediate-risk patients should have a LDL cholesterol target of < 100 mg/dL (non-HDL cholesterol target < 130 mg/dL).

Optimal blood pressure control is also important alongside with glycemic control and lipid lowering therapy in diabetic patients. A systematic review and a meta-analysis of randomized trials of blood pressure lowering in > 100,000 diabetic patients confirmed that optimal blood pressure control reduces all-cause mortality, CVD events, strokes and heart failure in these patients.[178] Angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) are the first line anti-hypertensive therapy in diabetic patients as these medications are associated with initiation and prevention of diabetic nephropathy. A target blood pressure of < 130/80 mmHg should be achieved in both Type I and Type II diabetic patients to reduce ASCVD risk and diabetic nephropathy.

Low-dose aspirin is generally not indicated for primary prevention of ASCVD in diabetic patients. However, low-dose aspirin (75-100 mg daily) may be considered for diabetic patients with high-risk for ASCVD (See 5.10).

Intense glycemic control, lipid lowering therapy and blood pressure control are important for ASCVD risk reduction in type I diabetic patients as well. A Swedish study has demonstrated that type I diabetic patients with $HbA1_C$ < 6.9% have 2 times higher risk while patients with $HbA1_C$ > 9.7% has about 10 times higher risk of ASCVD when compared to general population.[179] Same $HbA1_C$, blood pressure and LDL cholesterol targets for type II diabetic patients are recommended for type I diabetic patients as well.

Table 2. 5 Management of Diabetes

COR	LOE	Recommendation
I	A	A heart-healthy dietary pattern is recommended for ASCVD risk reduction in all men and women with diabetes aiming at optimal glycemic control and weight maintenance.
I	A	At least 150 minutes per week of moderate-intensity exercises or 75 minutes per week of high-intensity exercises are recommended for ASCVD risk reduction in all men and women with diabetes.
I	A	A target $HbA1_C$ < 7% is recommended for reduction of ASCVD risk and microvascular complications in all men and non-pregnant women with both Type I and Type II diabetes.
I	A	Lipid lowering therapy, preferably with statins, is recommended for ASCVD risk reduction in all Type I and Type II diabetic patients above the age of 40 years. Diabetic patients with high-risk (10-year risk of fatal or non-fatal CVD event ≥20%) of ASCVD should have an LDL cholesterol target of < 70 mg/dL (non-HDL cholesterol target < 100 mg/dL) while intermediate-risk (10-year risk of fatal or non-fatal CVD event between 10- <20%) patients should have an LDL cholesterol target of < 100 mg/dL (non-HDL cholesterol target < 130 mg/dL).
I	B	Lowering of blood pressure to < 130/80 mmHg is recommended for patients with both Type I and Type II diabetes and hypertension.
IIa	B	Metformin can be helpful as the first-line drug therapy alongside with life-style modifications for optimal glycemic control and ASCVD risk reduction in men and women with type II diabetes.
IIb	A	Lipid lowering therapy, preferably with statins, may be helpful for ASCVD risk reduction in Type I and Type II diabetic patients below the age of 40 years but significantly elevated risk, based on the presence of albuminuria or multiple cardiovascular risk factors. Diabetic patients with high-risk of ASCVD should have an LDL cholesterol target of < 70 mg/dL (non-HDL cholesterol target < 100 mg/dL) while intermediate risk patients should have an LDL cholesterol target of < 100 mg/dL (non-HDL cholesterol target < 130 mg/dL).
IIb	B	SGLT-2 inhibitors or GLP-1R agonists may be helpful to achieve glycemic control and CVD risk reduction in type II diabetic patients when their life-style modifications and metformin therapy are insufficient for optimal glycemic control.

2.6. Management of Hypertension

Hypertension is defined as an office measurement of systolic blood pressure (SBP) $\geq$ 140 mmHg and/or diastolic blood pressure (DBP) $\geq$ 90 mmHg. Hypertension is a major risk factor for CAD, stroke, heart failure, CKD, atrial fibrillation and peripheral vascular disease. There is a log-linear relationship of mortality from CAD and stroke with increasing SBP from 115 mmHg and DBP from 75 mmHg upwards.[180]

The decision to start anti-hypertensive therapy is based on the measured blood pressure and total CVD risk of the patient. Lifestyle modifications including weight reduction, regular exercises,[181] salt restriction,[182] alcohol moderation and a dietary pattern[183] with increased consumption of fruits, vegetables and low-fat dairy products are recommended for all men and women with hypertension and borderline hypertension.

Anti-hypertensive therapy is recommended for patients with grade I hypertension (SBP 140-159 mmHg and/or DBP 90-99 mmHg) and grade II hypertension (SBP 160-179 mmHg and/or DBP 100-109 mmHg) if their blood pressure remain in this range during several office and/or ambulatory blood pressure measurements despite reasonable life-style modifications.[184]

Prompt commencement of anti-hypertensive therapy is recommended for patients with grade III hypertension (SBP $\geq$ 180 mmHg and/or DBP $\geq$ 110 mmHg) irrespective of their CVD risk.[185]

All major antihypertensive drug classes including ACE-I, ARBs, calcium channel blockers, diuretics and beta blockers are effective in lowering blood pressure and to reduce CVD morbidity and mortality when they are used either as monotherapy or in combination.[185,186] These benefits are mainly due to lowering of blood pressure per say independent of the class effect of the anti-hypertensive medication used.[185,186]

Anti-hypertensive medications with 24-hour efficacy improves compliance and reduce blood pressure variability, organ damage and CVD risk. ACE-I and ARBs should be used with caution in women of child bearing age due to potential teratogenic effects of these medications.[187]

Combinations of anti-hypertensive medications may be needed to achieve target blood pressure control in many patients. The additional blood pressure reduction by combining two anti-hypertensive medications from two different classes is approximately 5 times more than doubling the dose of one medication[188] and cause less side effects.

Reduction of blood pressure to a target of < 140 mmHg of SBP and < 90 mmHg of DBP is recommended for all hypertensive patients < 60 years of age.[189] Reduction of SBP to a target between 140 to 150 mmHg is recommended for all hypertensive patients > 60 years of age and > 80 years with good physical and mental conditions when they are found to have a SBP > 160 mmHg.[190]

Reduction of blood pressure to a target of < 130 mmHg of SBP and < 80 mmHg of DBP is recommended for all hypertensive patients with CKD[191,192,193] and diabetes.[192]

Table 2. 6 Management of Hypertension

COR	LOE	Recommendation
I	A	Lifestyle modifications including weight reduction, regular exercises, salt restriction, and increased consumption of fruits, vegetables and low-fat dairy products are recommended for all men and women with hypertension and borderline hypertension.
I	A	All major antihypertensive drug classes including ACE-I, ARBs, calcium channel blockers, diuretics and beta blockers are recommended for blood pressure lowering as they do not differ significantly in their blood pressure lowering efficacy.
I	B	Reduction of blood pressure to a target of < 140 mmHg of SBP and < 90 mmHg of DBP is recommended for all the hypertensive men and women < 60 years of age.
I	B	Reduction of blood pressure to a target SBP between 140 to 150 mmHg is recommended for all the hypertensive men and women > 60 years of age and SBP > 160 mmHg.
I	B	Reduction of blood pressure to a target SBP between 140 to 150 mmHg is recommended for all the hypertensive men and women > 80 years of age and SBP > 160 mmHg provided they are in good physical and mental conditions.
I	B	Reduction of blood pressure to a target of < 130 mmHg of SBP and < 80 mmHg of DBP is recommended for all the hypertensive men and women with CKD.
I	B	Reduction of blood pressure to a target of < 130 mmHg of SBP and < 80 mmHg of DBP is recommended for all the hypertensive men and women with diabetes.

2.7. Management of Dyslipidemia

There is a strong association between total cholesterol as well as LDL cholesterol levels and ASCVD risk.[194] This association applies to men and women with and without CAD. Meta-analysis of several trials of lipid lowering therapy with statins clearly show a linear relationship of lipid lowering and reduction of ASCVD. The ASCVD mortality and non-fatal myocardial infarctions are reduced by 20-25% with each 40 mg/dL (1.0 mmol/L) reduction of LDL cholesterol.[195]

Non-HDL cholesterol comprises of all pro-atherogenic lipoproteins including LDL cholesterol, intermediate-density lipoprotein cholesterol and very low-density lipoprotein cholesterol. This can be calculated easily by subtracting HDL cholesterol from total cholesterol level. It is a better prediction of ASCVD than LDL cholesterol.[196] non-HDL cholesterol is a more accurate measurement than calculated LDL cholesterol values when triglyceride levels > 400 mg/dL (> 4.5 mmol/L) and also has the advantage of not requiring patients to fast before giving the blood sample.

Low HDL cholesterol is associated with increased ASCVD rsik.[197] HDL cholesterol < 40 mg/dL (< 1.0 mmol/L) in men and < 45 mg/dL (< 1.2 mmol/L) in women are regarded as levels of increased risk

for ASCVD. Lifestyle interventions, especially regular exercises and physical activity, are more important than drug therapy to elevate HDL cholesterol levels.

Elevated triglyceride also has an independent but weak association with ASCVD risk.[198] Combination of elevated triglycerides and low HDL cholesterol levels are associated with physical inactivity, abdominal obesity, insulin resistance and type II diabetes. Although, there are no randomized trials to decide on a target level to lower serum triglyceride, fasting triglyceride > 150 mg/dL (> 1.0 mmol/L) is considered as a marker for increased ASCVD risk.

Statins are the first line medications to treat hypercholesterolemia and combined hyperlipidemia. Cholesterol lowering with statin therapy is associated with significantly reduced risk of needing coronary revascularization and ASCVD related morbidity and mortality.[199,200] In high-risk patients, addition of ezetimibe to statins may provide an additional benefit in ASCVD risk reduction when the highest recommended or maximum tolerated dose of statins is inadequate to lower the LDL cholesterol to the target limits.[177] Addition of fenofibrates to statins are also helpful in lowering triglycerides, increasing HDL cholesterol and reducing LDL cholesterol levels. However, there is no convincing evidence to show that combination of stains and fenofibrate reduce ASCVD risk.

Most patients of 40-75 years with type II diabetes are either intermediate or high-risk for ASCVD. Large RCTs on primary prevention of ASCVD in diabetic patients show a significant risk reduction of ASCVD by lipid lowering using statin therapy.[201,202,203] Therefore, moderate-intensity statin therapy to reduce LDL cholesterol to < 100 mg/dL (< 2.6 mmol/L) or at least 50% reduction of the respective baseline cholesterol levels if LDL cholesterol is between 100-200 mg/dL (2.6-5.1 mmol/L) is recommended for reduction of ASCVD risk in all diabetic men and women of age 40-75 years irrespective of their estimated cardiovascular risk.[204] Similarly, moderate-intensity statin therapy to reduce non-HDL cholesterol to < 130 mg/dL (< 3.4 mmol/L) or at least 50% reduction of the respective baseline cholesterol levels if non-HDL cholesterol is between 130-230 mg/dL (3.4-6.0 mmol/L) is recommended for reduction of ASCVD risk in all diabetic men and women of age 40-75 years irrespective of their estimated cardiovascular risk.

The risk of ASCVD events go even higher when diabetic patients develop additional risk modifiers including long duration of diabetes (type I diabetes > 10 years or type II diabetes > 20 years), microalbuminuria, eGFR < 60 mL/min/1.73m^2, retinopathy, neuropathy or ABI < 0.9. Therefore, high-intensity statin therapy to reduce LDL cholesterol to < 70 mg/dL (< 1.8 mmol/L) or at least 50% reduction of the respective baseline cholesterol levels if LDL cholesterol is between 70-135 mg/dL (1.8-3.5 mmol/L) is recommended for reduction of ASCVD risk in all men and women with multiple CVD risk factors.[204,205,206,207] Similarly, high-intensity statin therapy to reduce non-HDL cholesterol to < 100 mg/dL (< 2.6 mmol/L) or at least 50% reduction of the respective baseline cholesterol levels if non-HDL cholesterol is between 100-165 mg/dL (2.6-4.3 mmol/L) is recommended for reduction of ASCVD risk in all men and women with multiple CVD risk factors.

Individuals who have severe primary hypercholesterolemia with LDL cholesterol $\geq$ 190 mg/dL ($\geq$ 4.9 mmol/L) is associated with high ASCVD risk[208] with premature and recurrent coronary events. Because high-intensity statin therapy is associated with greater reduction of ASCVD risk,[205] highest recommended or maximum tolerable statin dose should be recommended for these individuals. High-intensity statin therapy to reduce LDL cholesterol to < 70 mg/dL (< 1.8 mmol/L) is recommended for reduction of ASCVD risk in all men and women of age 20-75 years if their

baseline LDL cholesterol is ≥ 190 mg/dL (≥ 4.9 mmol/L).[204] Similarly, high-intensity statin therapy to reduce non-HDL cholesterol to < 100 mg/dL (< 2.6 mmol/L) is recommended for reduction of ASCVD risk in all men and women of age 20-75 years if their baseline non-HDL cholesterol is > 220 mg/dL (> 5.7 mmol/L).

The benefit of statin therapy depends on the initial global risk of ASCVD and the intensity of the treatment.[194,195] High-intensity statin therapy to reduce LDL cholesterol to < 70 mg/dL (< 1.8 mmol/L) or at least 50% reduction of the respective baseline cholesterol levels if LDL cholesterol is between 70-135 mg/dL (1.8-3.5 mmol/L) is recommended for reduction of ASCVD risk in all men and women with 10-year estimated GRS for cardiovascular events is > 20%. Similarly, high-intensity statin therapy to reduce non-HDL cholesterol to < 100 mg/dL (< 2.6 mmol/L) or at least 50% reduction of the respective baseline cholesterol levels if non-HDL cholesterol is between 100-165 mg/dL (2.6-4.3 mmol/L) is recommended for reduction of ASCVD risk in all men and women with 10-year estimated GRS for cardiovascular events is > 20%.

Moderate-intensity statin therapy to reduce LDL cholesterol to < 100 mg/dL (< 2.6 mmol/L) or at least 50% reduction of the respective baseline cholesterol levels if LDL cholesterol is between 100-200 mg/dL (2.6-5.1 mmol/L) is recommended for reduction of ASCVD risk in all men and women with 10-year estimated GRS for cardiovascular events is between 10 - <20%. Similarly, moderate-intensity statin therapy to reduce non-HDL cholesterol to < 130 mg/dL (< 3.4 mmol/L) or at least 50% reduction of the respective baseline cholesterol levels if non-HDL cholesterol is between 130-230 mg/dL (3.4-6.0 mmol/L) is recommended for reduction of ASCVD risk in all men and women with 10-year estimated GRS for cardiovascular events is between 10 - <20%. Individuals with intermediate-risk according to GRS may be reclassified in to high-risk considering their concomitant risk factors including coronary calcium score ≥ 100 AU,[209] inflammatory disease (e.g., rheumatoid arthritis, psoriasis[210]), history of cancer chemotherapy and human immunodeficiency virus infection when treated with protease inhibitors.[211]

Table 2. 7 Management of Dyslipidaemia

COR	LOE	Recommendation
I	A	Moderate-intensity statin therapy to reduce LDL cholesterol to < 100 mg/dL (< 2.6 mmol/L) and/or to reduce non-HDL cholesterol to < 130 mg/dL (< 3.4 mmol/L) or at least 50% reduction of the respective baseline cholesterol levels if LDL cholesterol is between 100-200 mg/dL (2.6-5.1 mmol/L) and/or non-HDL cholesterol is between 130-230 mg/dL (3.4-6.0 mmol/L) is recommended for reduction of ASCVD risk in all diabetic men and women of age 40-75 years irrespective of their estimated cardiovascular risk.
I	B	High-intensity statin therapy to reduce LDL cholesterol to < 70 mg/dL (< 1.8 mmol/L) and/or to reduce non-HDL cholesterol to < 100 mg/dL (< 2.6 mmol/L) is recommended for reduction of ASCVD risk in all men and women of age 20-75 years if their baseline LDL cholesterol is > 190 mg/dL (> 4.9 mmol/L) and/or non-HDL cholesterol is > 220 mg/dL (> 5.7 mmol/L). This is for men and women with familial hypercholesterolemia.
I	B	High-intensity statin therapy to reduce LDL cholesterol to < 70 mg/dL (< 1.8 mmol/L) and/or to reduce non-HDL cholesterol to < 100 mg/dL (< 2.6 mmol/L) or at least 50% reduction of the respective baseline cholesterol levels if LDL cholesterol is between 70-135 mg/dL (1.8-3.5 mmol/L) and/or non-HDL cholesterol is between 100-165 mg/dL (2.6-4.3 mmol/L) is recommended for reduction of ASCVD risk in all men and women with multiple CVD risk factors including long duration (type I diabetes > 10 years or type II diabetes > 20 years), microalbuminuria, eGFR < 60 mL/min/1.73m^2, retinopathy, neuropathy or ABI < 0.9.
I	B	High-intensity statin therapy to reduce LDL cholesterol to < 70 mg/dL (< 1.8 mmol/L) and/or to reduce non-HDL cholesterol to < 100 mg/dL (< 2.6 mmol/L) or at least 50% reduction of the respective baseline cholesterol levels if LDL cholesterol is between 70-135 mg/dL (1.8-3.5 mmol/L) and/or non-HDL cholesterol is between 100-165 mg/dL (2.6-4.3 mmol/L) is recommended for reduction of ASCVD risk in all men and women with 10-year estimated GRS for cardiovascular events is ≥ 20%.
I	B	Moderate-intensity statin therapy to reduce LDL cholesterol to < 100 mg/dL (< 2.6 mmol/L) and/or to reduce non-HDL cholesterol to < 130 mg/dL (< 3.4 mmol/L) or at least 50% reduction of the respective baseline cholesterol levels if LDL cholesterol is between 100-200 mg/dL (2.6-5.1 mmol/L) and/or non-HDL cholesterol is between 130-230 mg/dL (3.4-6.0 mmol/L) is recommended for reduction of ASCVD risk in all men and women with 10-year estimated GRS for cardiovascular events is between 10 - <20%.

2.8. Behavioral Change

Life-styles of individuals are usually based on their behavioral patterns and the social environment they live. Individualized counselling is important for motivation and commitment to change life-style. Cognitive behavioral interventions such as "motivational interviewing" increase motivation and commitment.[212] changing the life-style by a small but a steady step at a time is key to change long-term behaviour.[213]

Combining the expertise of a multi-disciplinary team including physicians, nurses, dieticians, physical training instructors, psychologists and social workers into a multi-model behavioral intervention can tremendously improve the preventative efforts of ASCVD. Multi-model behavioral interventions include health education, smoking cessation, healthy diet, regular exercises, weight reduction and stress management and counselling for psychosocial risk factors. These types of interventions are especially important in high-risk individuals of ASCVD.

Table 2. 8 Behavioural Change

COR		LOE	Recommendation
I		A	Cognitive behavioral strategies such as "motivational interviewing" are recommended for life-style modifications to reduce ASCVD risk.
I		A	Approach by multidisciplinary health care professionals such as physicians, nurses, dietitians, physical training instructors, psychologists and social workers is important for life-style and behavioral modifications to reduce ASCVD risk.
I		A	Multi model interventions including health education, smoking cessation, healthy diet, regular exercises, weight reduction and stress management and counselling for psychosocial risk factors are recommended for ASCVD risk reduction in high-risk individuals.

2.9. Management of Psychosocial Factors

Individuals with psychological and psychiatric issues such as stress, anxiety, depression, social isolation and negative emotions need special efforts and interventions by psychologists and psychiatrists as these factors act as barriers against their behavioral change.[214,215] Females, older persons and individuals of low socio-economic status also need programs in order to meet their special needs.

Table 2. 9 Management of Psychosocial Factors

COR	LOE	Recommendation
IIa	A	Referral for psychiatric assessment, psychotherapy, medications and multi-disciplinary management can be helpful for ASCVD risk reduction in patients with depression, anxiety and other psychiatric conditions.

2.10. Low-Dose Aspirin Therapy

The benefit of aspirin in secondary prevention of ASCVD and stroke is well established.[216] However, the use of aspirin in primary prevention of ASCVD is controversial as it is difficult to balance the benefits and the potential harm. Also, the value of aspirin in primary prevention of ASCVD is becoming less important with the improvements of the co-administration of other primary preventative methods in hypertension, lipid lowering and diabetes management therapies.[217,218,219]

In terms of primary prevention of ASCVD, aspirin therapy may be helpful only in high-risk individuals with age 40-70 years.[218,221,222] They include individuals with strong family history of premature myocardial infarction, high coronary artery calcium score,[222] diabetes for > 10 years, micro albuminuria, CKD and inability to achieve target lipid, blood pressure and blood glucose control.[223] Their bleeding risk should also be assessed before commencing aspirin therapy.

Prophylactic use of aspirin is not recommended for primary prevention of ASCVD in individuals > 70 years because of high-risk of bleeding in this age group outweigh the benefits.[224] Also, aspirin is not recommended for primary prevention of ASCVD in individuals < 40 years of age as there is insufficient evidence to justify the benefits of aspirin over potential risks of this therapy. Although, routine use is not recommended, aspirin may be given to selected high-risk patients in these age groups after discussing the risks and benefits with the patients. The eligible high-risk patients are as mentioned above. Their bleeding risk should also be assessed before commencing aspirin therapy.

Low-dose aspirin is not recommended as a primary preventative measure in ASCVD risk reduction in individuals who have a high-risk of bleeding.[225] Individuals with high-risk of bleeding include those with a history of gastrointestinal bleeding and peptic ulcers, bleeding from other sites, age > 70 years, thrombocytopenia, coagulopathy, CKD and concomitant use of other medications that increases bleeding risks. The medications that increase bleeding risk include non-steroidal anti-inflammatory drugs, steroids, warfarin and direct oral anticoagulants.

Table 2. 10 Low-Dose Aspirin Therapy

COR	LOE	Recommendation
IIb	A	Low-dose aspirin (75-100 mg daily) may be helpful for primary prevention of ASCVD in high-risk patients (e.g., individuals with strong family history of premature myocardial infarction, high coronary artery calcium score, diabetes for > 10 years, micro albuminuria, CKD and inability to achieve target lipid, blood pressure and blood glucose control) of age 40-70 years.
III Harm	B	Low-dose aspirin (75-100 mg daily) is not recommended routinely for primary prevention of ASCVD in in men and women < 40 years and > 70 years of age.
III Harm	B	Low-dose aspirin (75-100 mg daily) is not recommended for primary prevention of ASCVD in individuals of any age with increased risk of bleeding.

2.11. Prevention of Heart Disease in Patients Treated for Cancer

Surviving cancer patients, who had been treated with chemotherapy or radiotherapy, have an increased risk of CVD. The increased risk of CVD also depends on the type and the dose of treatment given. The risk further increases when these patients also have other risk factors for CVD.[226]

There are 2 types of chemotherapy-associated cardiotoxicity. Type I cardiotoxicity occurs with agents causing irreversible cardiotoxicity (e.g., anthracyclines) while type II cardiotoxicity occurs with agents causing partially reversible cardiotoxicity (e.g., trastuzmab).[227]

Both chemotherapy[227] and chest radiotherapy[228] are associated with accelerated atherosclerosis and increased risk of ASCVD. Type I cardiotoxicity mainly causes left ventricular dysfunction. Pretreatment assessment for left ventricular is important[229] and clinical features should be monitored during the treatment for early detection of left ventricular dysfunction in patients receiving potentially cardiotoxic chemotherapy.[230] Beta blockers, angiotensin converting enzyme (ACE) inhibitors and statins have been tested and complied to prevent chemotherapy induced left ventricular dysfunction.[231] Early preventative treatment is paramount to exert the maximum benefit.[229]

Table 2. 11 Prevention of Heart Disease in Patients Treated for Cancer

COR	LOE	Recommendation
IIa	B	Prophylactic treatment with beta blockers, ACE inhibitors and statins can be helpful for prevention of left ventricular dysfunction in patients receiving high cumulative doses of type I chemotherapy.
IIa	C	Optimization of CVD risk profile can be helpful for minimizing the CVD risk in cancer patients who are receiving chemotherapy or chest radiotherapy.

Chapter 3

Gaps in Evidence

1. There are no recent RCTs for a global risk score assessment approach.

2. Young individuals (< 40 years), elderly (> 75 years) and women are underrepresented in clinical trials.

3. The association between routine screenings for psychosocial risk factors with future ASCVD events needs further evaluation.

4. The role of biomarkers such as hsCRP, natriuretic peptides in risk prediction of ASCVD needs further research and evaluation.

5. ASCVD risk reduction in patients treated with lipid or blood pressure lowering medications as a result of reclassification by CCS or ABI measurements are needed to be proven.

6. No data available on age to commence ASCVD risk assessment and the interval of repeating the assessment.

7. Inadequate data to confirm that pre-eclampsia, pregnancy-induced hypertension and polycystic ovarian disease are causing a risk that is independent to conventional ASCVD risk.

8. Inadequate data on non-rheumatoid arthritis autoimmune diseases with increased ASCVD risk.

9. No evidence on the relationship between anti-rheumatic drugs and ASCVD risk.

10. Inconclusive evidence on the efficacy of early preventative measures to reduce chemotherapy induced Type I cardiotoxicity.

11. Inadequate information of relative roles of life style interventions, exercise and calory restriction in the management of overweight and obesity.

12. Inadequate information on management and treatment goals of white coat hypertension.

13. No randomized trial evidence to decide on target levels to lower triglycerides.

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Appendix

Supplementary Data and Links

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