



Clinical Practice Guidelines

National Heart Center/Saudi Heart Association 2025 Guidelines for Cardiovascular Diseases Prevention and Risk Assessment

Jamilah S AlRabimi^{a,b,c}, Shukri M. Al Saif^d, Laith Hussain-Alkbateeb^{e,f,g}, Ali M. Albarrati^h, Owayed M. Alshammeriⁱ, Talal S. Alghamdi^j, Khalid A. Al Faraidy^k, Ada M Al-Qunaibet^l, Nada A. Alnaji^m, Rasha A. Alfawazⁿ, Waleed M. Alharbi^o, Waleed A. AlHabeeb^p, Fahad M. Alnouri^q, Adel A. Tash^r

^a Department of Cardiac Sciences, King Abdulaziz Medical City, Ministry of the National Guard - Health Affairs, Jeddah, Saudi Arabia

^b King Abdullah International Medical Research Center, Jeddah, Saudi Arabia

^c Collage of Medicine, King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia

^d Seha Virtual Hospital, Saudi Arabia

^e Global Health Research Group, School of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden

^f Population Health Research Department, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia

^g College of Public Health & Health Informatics, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

^h Professor and Consultant of Rehabilitation and Cardiopulmonary Rehabilitation, Rehabilitation Sciences Department, King Saud University, Riyadh, Saudi Arabia

ⁱ Dr. Sulaiman Al Habib Hospitals, Alrayyan Hospital, Riyadh, Saudi Arabia

^j Consultant of Family Medicine and Preventive Cardiology, Head of Family Medicine & Primary Health Care Services, Al Hammadi Hospitals Group, Riyadh, Saudi Arabia

^k King Fahad Military Medical Complex, Dhahran, Saudi Arabia

^l Public Health Authority, Riyadh, Saudi Arabia

^m Manager, Non-Communicable Disease Programs and Policies, Gulf Center for Diseases Prevention and Control, Riyadh, Saudi Arabia

ⁿ Director, Public Health Programs and Policies, Gulf Center for Disease Prevention and Control, Riyadh, Saudi Arabia

^o Department of Cardiac Sciences, College of Medicine, King Fahad Cardiac Center, King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia

^p Department of Cardiac Sciences, King Saud University, Riyadh, Saudi Arabia

^q Head of the Cardiovascular Prevention Unit, Prince Sultan Cardiac Centre, Riyadh, Saudi Arabia

^r Director, National Heart Center, Saudi Health Council, Riyadh, Saudi Arabia

Objectives: To develop an evidence-based clinical guideline for the prevention and management of cardiovascular diseases (CVDs) in Saudi Arabia, tailored to local epidemiology and healthcare needs.

Methods: A multidisciplinary task force comprising cardiologists, public health specialists, and epidemiologists from different healthcare sectors in Saudi Arabia developed the guideline. Evidence synthesis was based on a comprehensive literature review and adaptation of international guidelines, particularly the 2021 European Society of Cardiology recommendations, contextualized to the Saudi setting.

Results: The guideline provides recommendations for both primary and secondary CVD prevention. Primary prevention emphasizes risk assessment incorporating genetic, lifestyle, and clinical factors, as well as lipid and glucose profiling. Lifestyle modifications, including dietary changes, smoking cessation, physical activity, weight management, and psychosocial support, are

prioritized. Pharmacologic therapy targets lipid levels, blood pressure, and glycemic control, tailored to individual risk categories. For secondary prevention, strategies include post-event risk stratification, comorbidity management (diabetes, hypertension, chronic kidney disease), and optimization of pharmacologic therapy for coronary artery disease, heart failure, cerebrovascular disease, and peripheral artery disease. Lifestyle interventions, supervised cardiac rehabilitation, and routine follow-up for complication monitoring and treatment adjustment are integral components.

Conclusion: This guideline presents an updated, evidence-based framework specifically designed for the Saudi population, underscoring prevention, lifestyle modification, and optimized pharmacologic management to address the rising burden of CVDs.

Keywords: Cardiovascular disease, Primary, Secondary, Prevention, Guideline, Saudi Arabia, risk assessment, lifestyle modification

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Address correspondence and reprint request to: Dr. Jamilah AlRahimi, Department of Cardiology, King AbdulAziz Medical City- Ministry of National Guard Health Affairs, King Abdullah International Medical Research Center, College of Medicine, King Saud bin AbdulAziz University for Health Sciences, Jeddah, Kingdom of Saudi Arabi. E-mail: alrahimija@gmail.com

Introduction.

Definition and rationale. Atherosclerotic cardiovascular disease (ASCVD) remains one of the most significant health challenges worldwide. The rising prevalence of ASCVD risk factors such as obesity, diabetes mellitus, and hypertension in Saudi Arabia has led to an increased burden of the disease [1]. With cardiovascular diseases (CVDs) accounting for about 45% of all deaths in the country, it has become clear that preventive measures and effective risk management strategies are urgently needed [2]. The rationale behind the **National Heart Center/Saudi Heart Association 2025 Guidelines for Cardiovascular Diseases Prevention and Risk Assessment** is to address this escalating health concern by providing a comprehensive framework for the prevention, early detection, and management of ASCVD, specifically tailored to the needs of the Saudi population.

Development. The Guidelines were developed by a multidisciplinary task force consisting of local and international experts from a variety of healthcare disciplines. These experts integrated the most current evidence from global research with data specific to Saudi Arabia's population, ensuring that the guidelines would be culturally relevant and scientifically robust. The development process involved a rigorous evaluation of existing clinical practices, consultations with national healthcare leaders, and the incorporation of findings from national epidemiological studies. The task force utilized advanced methodologies, including GRADE (Grading of Recommendations Assessment, Development, and Evaluation), to ensure that the recommendations were based on high-quality evidence and that each recommendation was carefully graded according to its strength and relevance to clinical practice.

Cost-effectiveness. The guidelines are designed to be cost-effective by emphasizing preventive measures and evidence-based interventions that can be widely implemented across healthcare systems. Interventions such as lifestyle modification (e.g., smoking cessation, dietary changes, and increased physical activity) and the use of generic medications for managing dyslipidemia, hypertension, and diabetes mellitus are central to reducing the

financial burden of ASCVD in Saudi Arabia. The focus on prevention and early detection helps to avoid costly treatments for advanced ASCVD stages and potentially reduces long-term healthcare expenditures.

Target Audience. The target audience for these guidelines includes all healthcare professionals involved in the management of ASCVD patients (including cardiologists, non-cardiologists, nursing staff, and pharmacists), policymakers involved in developing Saudi national population health programs, and healthcare leaders planning for CVD prevention and management in Saudi Arabia.

What is New?. The first edition of the NHC /SHA 2025 Cardiovascular Prevention Guidelines introduces significant advancements, establishing a new benchmark for CVD prevention and management in Saudi Arabia. These guidelines reflect the latest global evidence while tailoring recommendations to the unique needs of the local population. A major focus is on multidisciplinary care teams, highlighting the roles of the physicians, care coordinators, and patients in setting and collaboratively achieving treatment goals through medical and non-pharmacological interventions. This patient-centered strategy supports a comprehensive and effective CVD prevention and management approach. Key updates in the guidelines include:

1. Updated Evidence-Based Treatment Strategies: The guidelines now include updated recommendations for managing low-density lipoprotein cholesterol (LDL-C), optimizing blood pressure (BP) control, and improving glycemic management in diabetic patients. In addition, new insights into antithrombotic therapies have been incorporated to enhance treatment outcomes and minimize risks.
2. Personalized, Stepwise Approach: This patient-centered framework focuses on tailoring interventions to individual risk profiles and preferences. Physicians are encouraged to adopt a gradual escalation of therapeutic measures to ensure comprehensive care for both primary and secondary prevention of CVD. This approach allows for more precise, impactful, and sustainable outcomes (Figures 1 and 2).
3. Risk-Specific Considerations for the Saudi Population: These risk-specific recommendations address conditions such as the high prevalence of diabetes and obesity while considering demographic variables like gender and age. The goal is to ensure targeted interventions that are both effective and relevant to the local population.
4. Cultural Relevance: Special attention has been paid to aligning recommendations with dietary

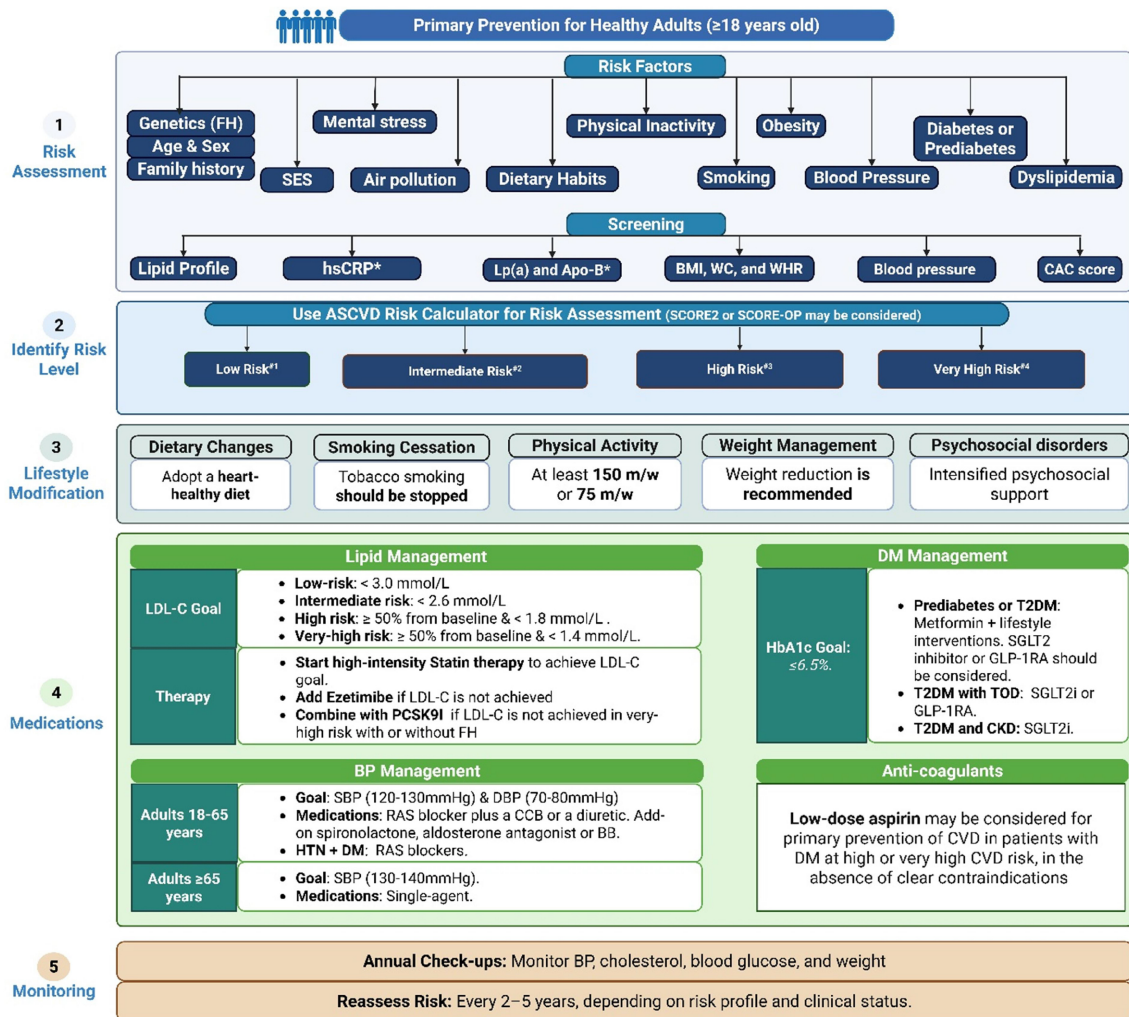


Figure 1 - Framework for primary prevention of cardiovascular disease in healthy adults (≥18 years). The pathway integrates: (1) risk assessment of genetic, demographic, lifestyle, and metabolic factors; (2) risk stratification using ASCVD risk calculators and biomarkers; (3) lifestyle modification through diet, smoking cessation, physical activity, weight management, and psychosocial support; (4) pharmacologic therapy including lipid-lowering agents, antihypertensives, diabetes management, and antiplatelet therapy when indicated; and (5) monitoring with regular follow-up and reassessment every 2–5 years. Figure created with professional assistance from Advocacy for HealthCare Consultancy (medical writing support). Abbreviations: ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; WC = waist circumference; WHR = waist-hip ratio; CAC = coronary artery calcium; hsCRP = high-sensitivity C-reactive protein; Apo-B = apolipoprotein B; LDL-C = low-density lipoprotein cholesterol; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; SBP = systolic blood pressure; DBP = diastolic blood pressure; RAS = renin-angiotensin system; CCB = calcium channel blocker; BB = beta-blocker; T2DM = type 2 diabetes mellitus; SGLT2i = sodium-glucose cotransporter 2 inhibitor; GLP-1RA = glucagon-like peptide 1 receptor agonist; CKD = chronic kidney disease. #1: Low-risk group: individuals with a calculated SCORE2 of less than 2.5 % (or SCORE-OP <5%) for the 10-year risk of fatal CVD. #2: Moderate-risk group: individuals with milder conditions, including young patients with T1DM diagnosed before the age of 35 years or T2DM diagnosed before the age of 50 years, with a disease duration of less than 10 years and no additional risk factors; and individuals with a calculated SCORE2 of ≥2.5 to 7.5% (or SCORE-OP ≥5% to <10%) for the 10-year risk of fatal CVD. #3: High-risk: individuals with markedly elevated single risk factors, such as total cholesterol levels greater than 8 mmol/L (310 mg/dL), LDL-C levels exceeding 4.9 mmol/L (190 mg/dL), or BP at or above 180/110 mmHg; patients with FH without other major risk factors; those with DM without target organ damage but with a duration of 10 years or more or another additional risk factor; individuals with moderate CKD; or individuals with a calculated SCORE2 of ≥7.5% to <10% (or SCORE-OP ≥10% to <15%) for the 10-year risk of fatal CVD. #4: Very high risk: Individuals with documented ASCVD, either clinically diagnosed or unequivocally detected on imaging; patients with DM who have target organ damage, at least three major risk factors, or early-onset T1DM of long duration exceeding 20 years; individuals with severe CKD; a calculated SCORE2 of ≥10% (or SCORE-OP ≥15% in older adults) for the 10-year risk of fatal CVD; or FH with ASCVD or another major risk factor.

habits, lifestyle practices, and healthcare accessibility unique to Saudi Arabia. This culturally sensitive approach ensures that the guidelines are practical and impactful within the local context.

5. Supporting government-led public health initiatives: the guidelines align with these initiatives aimed at reducing CVD prevalence and enhancing population health.

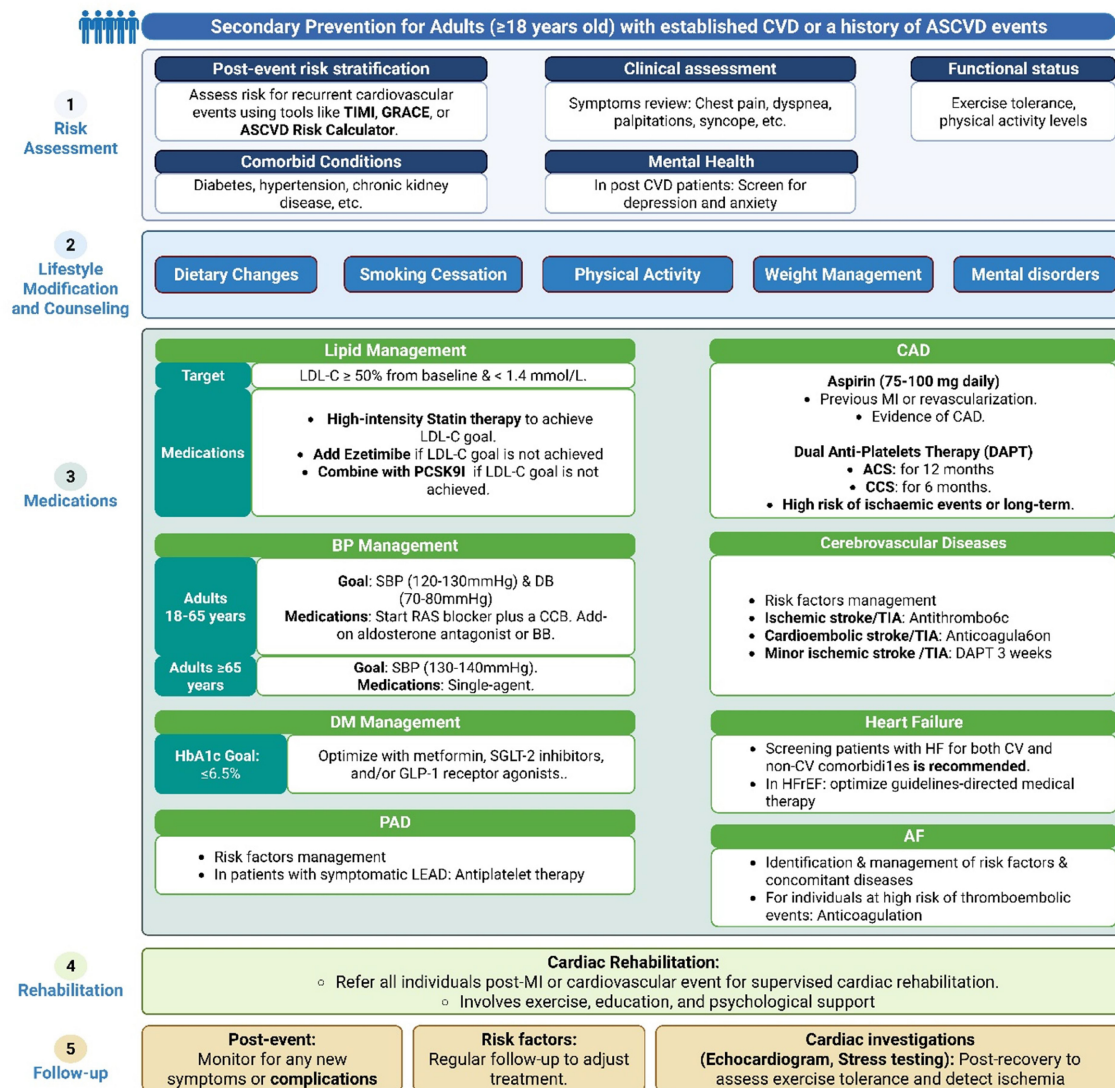


Figure 2 - Framework for secondary prevention of cardiovascular disease in adults (≥18 years) with established CVD or a history of ASCVD events. The pathway includes: (1) risk assessment through post-event stratification, clinical and functional evaluation, and screening for comorbidities and mental health conditions; (2) lifestyle modification and counseling on diet, smoking cessation, physical activity, weight control, and psychosocial support; (3) pharmacologic therapy targeting lipids, blood pressure, diabetes, and condition-specific management of CAD, cerebrovascular disease, heart failure, peripheral artery disease, and atrial fibrillation; (4) rehabilitation through supervised cardiac rehabilitation with exercise, education, and psychosocial support; and (5) follow-up with routine reassessment, complication monitoring, and cardiovascular investigations as indicated. Figure created with professional assistance from Advocacy for HealthCare Consultancy (medical writing support). Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; TIMI = Thrombolysis in Myocardial Infarction; GRACE = Global Registry of Acute Coronary Events; LDL-C = low-density lipoprotein cholesterol; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; SBP = systolic blood pressure; DBP = diastolic blood pressure; RAS = renin-angiotensin system; CCB = calcium channel blocker; BB = beta-blocker; DM = diabetes mellitus; HbA1c = glycated hemoglobin; T2DM = type 2 diabetes mellitus; SGLT2i = sodium-glucose cotransporter 2 inhibitor; GLP-1RA = glucagon-like peptide 1 receptor agonist; PAD = peripheral artery disease; LEAD = lower extremity artery disease; DAPT = dual antiplatelet therapy; ACS = acute coronary syndrome; CCS = chronic coronary syndrome; TIA = transient ischemic attack; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; AF = atrial fibrillation.

Purpose and scope. The primary aim of this guideline is to provide a structured, evidence-based framework for the prevention and management of CVDs tailored to the Saudi population and healthcare providers (HCPs). By incorporating insights from local research and addressing regional evidence gaps, the

guidelines address both primary and secondary CVD prevention strategies, with recommendations designed to be implemented across various healthcare settings in Saudi Arabia. By targeting modifiable risk factors, enhancing screening and early detection, optimizing resource allocation and utilization, and providing

structured management plans, these guidelines will help to reduce the prevalence and impact of CVDs. Additionally, these guidelines will help promote public health by emphasizing lifestyle modifications, community health programs, and public awareness campaigns to tackle CVD risk factors.

Methods. The guideline was developed by a multi-disciplinary group of experts, including cardiologists, public health specialists, and epidemiologists from various healthcare sectors in Saudi Arabia. The Task Force was supported by an international team contracted by Advocacy for HealthCare Consultancy, responsible for evidence searches, administrative support, and guidelines drafting. Communication between the Task Force and the Guideline Support Team was primarily via email and WhatsApp, with remote working sessions held to define the scope, prioritize outcomes, and form recommendations. A series of working sessions was conducted to select clinical questions, prioritize outcomes, and formulate recommendations.

Funding for the guideline development was provided through a contract between Advocacy for HealthCare Consultancy and another organization, and no financial incentives were provided to Task Force members. All participants declared potential conflicts of interest, which were reviewed to ensure impartiality in the development process. The CVD Task Force used the 2021 European Society of Cardiology (ESC) Guidelines on CVD prevention as the primary source for clinical questions due to their relevance to the Saudi healthcare setting, particularly in CVD burden and lifestyle-related risk factors. A systematic search on the MEDLINE database through PubMed (**from October 2023 to January 2025**) for local and international evidence was conducted, and studies were reviewed using the GRADE methodology, ensuring a robust and comprehensive evidence synthesis. The Class of Recommendation indicates the strength of the recommendation, based on the estimated magnitude of the benefit-to-risk ratio (**Table 1**). The Level of Evidence rates and the quality of scientific evidence supporting the intervention were based on the type, quantity, and consistency of data from clinical trials and other sources (**Table 2**).

Recommendations were formulated based on the evidence. Consensus for each clinical question was achieved when at least 70% of Task Force members were in agreement. The guideline draft was created by the Guideline Support Team, incorporating the evidence and Task Force input. After review by the Task Force, the draft was submitted to two external independent reviewers for further review and feedback. The finalized guidelines are intended to assist healthcare professionals in decision-making, allowing for flexibility based on individual patient needs and the specific circumstances of clinical practice.

The full description of our guidelines development methodology is presented in **Appendix A**. Also, all data underlying the evidence syntheses presented in this guideline are provided as manuscript appendices. Chapter-specific PICO frameworks used to guide literature identification and synthesis are available in **Appendix B** (Chapter 4), **Appendix C** (Chapter 5), and **Appendix D** (Chapter 6). **Appendix E** contains the complete set of GRADEpro outputs, including evidence profiles, certainty assessments, and evidence-to-decision tables for Chapters 5 and 6. These files provide full transparency into the review process, data extraction, and evidence grading methodology supporting the recommendations.

Chapter 1. The epidemiology of cardiovascular diseases and associated risk factors in Saudi Arabia.

Cardiovascular diseases in transition. CVD is an umbrella term encompassing various conditions affecting the heart and blood vessels, while ASCVD specifically refers to a subset of CVD caused by atherosclerosis in the arteries, such as coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular disease.

The rapid economic development and urbanization in Saudi Arabia, accompanied by significant lifestyle changes, have contributed to the country's rising burden of CVD. Both modifiable and non-modifiable cardiovascular risk factors are highly prevalent among Saudi nationals and foreign residents [1].

With limited administrative health data in Saudi Arabia, the true burden of CVD is challenging to

Table 1 - Classes of recommendation and definitions.

Class I	Strongly supported by evidence or consensus opinion. Such a treatment is strongly recommended.
Class IIa	Evidence or consensus opinion is mostly in favor. Such a treatment is reasonable to consider.
Class IIb	Evidence or consensus opinion conflict or is less well established. Such a treatment may be reasonable to consider.
Class III	Evidence or consensus opinion is against the treatment as it is not effective or harmful. Such a treatment should be avoided.

This classification system defines the strength of recommendations according to the benefit-to-risk ratio.

Table 2 - Levels of evidence and definitions.

Level of Evidence	Definitions
A	Data derived from multiple randomized clinical trials or meta-analyses
B	Data derived from a single randomized clinical trial or nonrandomized studies
C	consensus opinion or case reports. Clinical evidence lacking

This grading reflects the quality and consistency of evidence supporting clinical recommendations.

quantify. Current insights are predominantly derived from observational research, including cohort and cross-sectional studies, as well as exploratory analyses and review articles that were published in the last 15 years.

The causal pathways framework of cardiovascular disease risk factors. This guideline on the primary and secondary prevention of CVD aims to promote patient-centred care for adults aged 18 years and older, both with and without CVD. Understanding the epidemiology of CVD, the interactions among its risk factors, and the acquired susceptibility to the disease is fundamental to effective prevention and management. Utilizing appropriate causal models is essential, as gaps in knowledge regarding causal pathways can hinder the identification of contributing factors and, consequently, affect the design of effective public health interventions.

Epidemiologists and medical practitioners are encouraged to focus on factors that induce acquired susceptibility to disease, highlight the role of multiple exposures and their sequence in determining CVD, and examine their interaction through models of biological causation.

For complex chronic diseases like CVD, adopting a framework that incorporates multiple causative risk factors is crucial for understanding etiology. Such a framework can link social determinants and metabolic, behavioral, and psychosocial factors with biomedical causes, enabling the identification of key determinants and guiding the development of targeted interventional programs. [Figure 3](#), illustrates an adapted “web of causation” framework tailored to classify cardiovascular (CV) risk factors and their pathways in Saudi Arabia. In this model, the distal risk factors represent underlying vulnerability, while the proximal factors are the immediate triggers directly responsible for observed outcomes.

Modifiable risk factors

CVD risk factors involve complex mechanisms and perspectives. Hence, this guide classifies these risk factors into two categories: modifiable and non-modifiable. Modifiable cardiovascular risk factors include metabolic, behavioral, and psychosocial/socioeconomic factors that can be controlled or reduced by altering the individual's behavior.

Examples of modifiable risk factor interventions include reducing the intake of carbohydrates and fatty acids, quitting smoking, increasing physical activity (PA) and exercise, and improving sleep quality [3, 4]. These lifestyle modifications play a critical role in mitigating CVD risk and improving overall health outcomes.

Metabolic/Co-morbid risk factors.

Hypertension. High BP is a major cause of both ASCVD and non-atherosclerotic CVD [5]. [Table 3](#) provides the classification of BP categories as per the ESC guideline, measured using validated auscultatory or semi-automatic devices in a seated office setting [6]. However, the latest Saudi National Guideline on the Management of HTN acknowledged the burden of HTN in Saudi Arabia by defining stage 1 HTN as office blood pressure $\geq 130/80$ mmHg (or equivalent thresholds using ambulatory or home measurements) [7]. Their intensive thresholds were also adopted by the American College of Cardiology/American Heart Association (ACC/AHA) recommendations, underscoring the importance of early recognition of high-risk patients [8]. Furthermore, they agreed that pharmacological treatment should be initiated when the repeated seated office systolic blood pressure (SBP) readings of ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg.

Hypertension contributes to nearly 24% of total deaths from cardiovascular and circulatory diseases [2]. Evidence shows that lowering BP effectively reduces the risk of CVD. Every 10 mmHg reduction in SBP significantly reduces the risk of major adverse cardiovascular events (MACE) and heart failure (HF). However, despite the proven benefits of BP-lowering treatments, the global rate of hypertension detection, treatment, and control remains suboptimal [5].

In Saudi Arabia, the burden of hypertension is particularly alarming. According to the Global Burden of Disease 2019 (GBD 2019) study, hypertension is the leading cause of CVD-related death in Saudi Arabia [9]. The PURE-Saudi study, conducted between 2012 and 2015, found that 30.3% of the 2047 included adults (aged 35 to 70 years) had hypertension. Older individ-

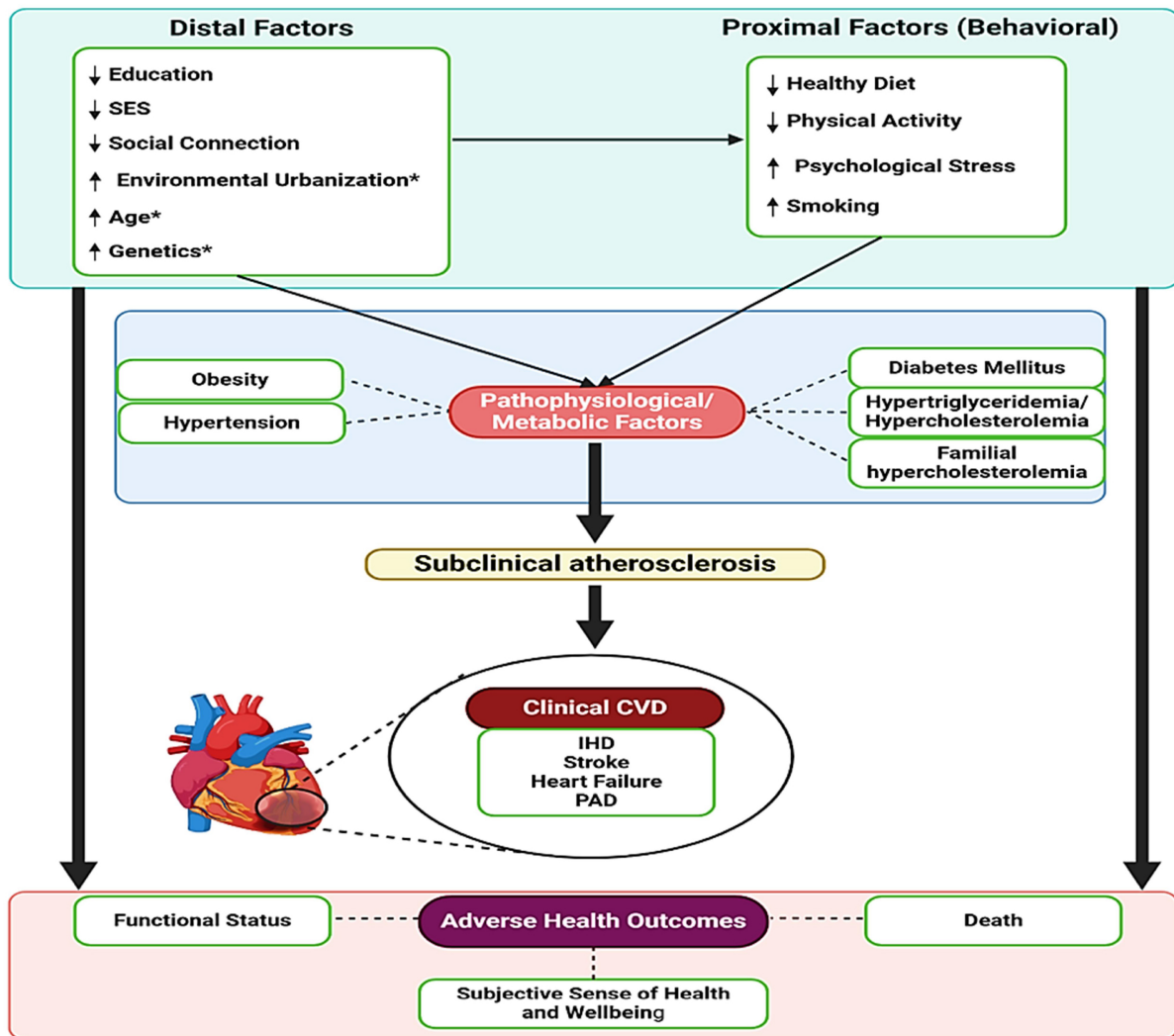


Figure 3 - Causal pathway framework for the classification of cardiovascular risk factors. *Presumably non-modified factors. CVD: Cardiovascular Disease; IHD: Ischemic Heart Disease; PAD: Peripheral Artery Disease; SES: Socioeconomic Status. Figure created with professional assistance from Advocacy for HealthCare Consultancy (medical writing support).

Table 3 - Categories for conventionally measured blood pressure.

Category*	office BP (mmHg)	Home BP (mmHg)	Daytime ABPM (mmHg)	24h ABPM (mmHg)	Night-time ABPM (mmHg)
Non-elevated BP	<120/70	<120/70	<120/70	<115/65	<110/60
Elevated BP	120/70–<140/90	120/70–<135/85	120/70–<135/85	115/65–<130/80	110/60–<120/70
Hypertension	≥140/90	≥135/85	≥135/85	≥130/80	≥120/70

ABPM; ambulatory blood pressure monitoring; BP; blood pressure. (Adapted from McEvoy et al. 2024 [6]).

*Physicians may use the tripartite structure (Stage I, II, or III Hypertension) to stage severity and tailor the intensity of antihypertensive therapy.

uals (aged 60 to 70 years) and rural residents were more likely to be hypertensive. Among those diagnosed, only 61.1% were aware of their condition, 58.9% received treatment, and just 30.7% achieved controlled BP [1].

Raising awareness about hypertension as a critical cardiovascular risk factor is essential, particularly among the younger population. Early detection, better education, and improved treatment adherence are vital steps

in reducing the prevalence and impact of hypertension in Saudi Arabia.

Dyslipidemia. In 2023, the population-based Western Denmark Heart Registry (n = 23,132 symptomatic CVD patients) firmly established LDL as a causal factor of ASCVD in adults [10]. Concurrently, the European Atherosclerosis Society Consensus Panel confirmed the

causality of LDL-C and ASCVD based on the following facts: 1) Greater absolute reduction in LDL-C—regardless of the treatment modality—corresponds to greater reductions in CVD risk. 2) Longer cumulative exposure to lower LDL-C levels is directly proportional to reduced risk of ASCVD. 3) The absolute benefit of LDL-C reduction depends on the individual's baseline ASCVD risk and the magnitude of LDL-C reduction. Notably, no threshold for LDL-C levels has been identified where benefits cease or harm begins, emphasizing the importance of achieving and maintaining lower LDL-C levels [11].

In the Middle East, dyslipidemia has a prevalence of 43.3% (95% confidence interval [CI] 21.5, 68%) [12]. Within Saudi Arabia, the Saudi subgroup analysis of the ACE (Africa Middle East Cardiovascular Epidemiological) study reported a higher prevalence of dyslipidemia at 55.1% (95% CI, 47.4–62.5), making it one of the most prevalent CVD risk factors. Interestingly, the prevalence was significantly lower among Saudi nationals compared to expatriates residing in the country, with the latter group exhibiting a prevalence of 75.5% (95% CI, 70.7–79.9%; $p < 0.001$) [13].

Additional studies provide varied prevalence estimates: the PURE-Saudi study documented a prevalence of 32.1% [1], while a national cross-sectional study using the World Health Organization (WHO) 'STEPwise' approach recorded prevalence rates ranging from 25% to 44% [14]. Despite these differences, the data unequivocally establish dyslipidemia as a major CVD risk factor in Saudi Arabia, underscoring its critical role in shaping the cardiovascular health landscape of the country.

Obesity. Obesity is a significant cardiovascular risk factor, strongly associated with adverse changes in cardiac structure and function starting during early adulthood [15, 16]. Across all grades of obesity, and particularly grades 2 and 3, the risk of all-cause mortality is significantly higher compared to individuals with normal weight [17]. Given its influence on other critical risk factors, such as BP, diabetes history, and cholesterol levels, controlling obesity is crucial for preventing CVD [5]. Key contributors to obesity include diets rich in processed foods, sugars, and carbohydrates, along with physical inactivity [18].

As per the 2021 American Heart Association (AHA) statement, obesity is associated with an increased risk of hypertension, dyslipidemia, and hyperglycemia in young adults [16]. The ESC further recognizes obesity as a disease causally linked to a wide spectrum of cardiovascular conditions, with two-thirds of obesity-related excess mortality attributed to CVDs [19].

Obesity is globally defined as a body mass index (BMI) $> 30 \text{ Kg/m}^2$ [5]. In Europe, the ESC recommends weight reduction in men and women with waist circumferences $\geq 102 \text{ cm}$ and $\geq 88 \text{ cm}$, respectively [5]. The 2024 ESC Guidelines stated that people with similar BMI may have different cardiometabolic risks as other factors share in the progression of CVD, such as abdominal adiposity (e.g., waist circumference, waist-to-height ratio, and waist-to-hip ratio) [5]. However, specific anthropometric cutoffs for Eastern Mediterranean and Middle Eastern (Arab) populations remain unavailable due to limited data [20]. Although multiple studies have proposed sensible cutoffs for the Saudi population, national adoption and endorsement by the Saudi Ministry of Health (MOH) are necessary [20].

A recent systematic review estimated the maximum prevalence of obesity among adults in Saudi Arabia to be 35.6%, with higher rates observed in older age groups [18]. This figure contrasts with the 2023 national estimate of 23.7% in adults [15, 21]. Nonetheless, even the lower national prevalence estimate surpasses the global average obesity prevalence of 16% in 2022 [22]. The Africa Middle East Cardiovascular Epidemiological (ACE) study highlighted disparities, showing higher rates of obesity and abdominal obesity among Saudi nationals compared to expatriates (52.6% vs 41.0% and 65.5% vs 52.2%, respectively) [13]. Among Saudi diabetic patients, the prevalence of obesity and overweight was particularly striking at 62.4% and 27.2%, respectively [23].

Despite variability across studies, these findings underscore obesity as a critical public health challenge and a major risk factor for non-communicable diseases in Saudi Arabia.

It is also worth mentioning that underweight (BMI $\leq 18.5 \text{ Kg/m}^2$) appears to have stronger effects on CVD and hypertension development than obesity. Wang et al. reported that individuals with BMI $\leq 18.5 \text{ Kg/m}^2$ had a higher risk of hypertension and coronary heart disease (CHD) (OR= 1.35; 95% CI 1.11–1.62) compared to those with a BMI of 30–34.9 kg/m^2 (OR= 1.29; 95% CI 1.06–1.56) [24].

Diabetes mellitus. Type 1 diabetes mellitus (T1DM), prediabetes, and type 2 diabetes mellitus (T2DM) are independent risk factors for CVD [5, 25]. Individuals with T2DM have more than twice the risk of CVD mortality compared to those without diabetes at any given age, with females exhibiting a particularly heightened susceptibility to stroke [26]. Effective glycemic control, achieved through dietary measures and pharmacological therapy, is recommended for reducing the risk of CVD among patients with diabetes.

Saudi Arabia is among the top ten countries projected to have the highest diabetes prevalence by 2030, with an estimated rate of 20.8%, as per the International Diabetes Federation (IDF) [27]. However, current studies provide varying prevalence rates, reflecting methodological differences and population heterogeneity. A large-scale study of 24,012 Saudi households estimated a national prevalence of diabetes at 8.5%, with a marked increase to 49.2% among individuals aged ≥ 60 years [28]. Conversely, the ACE study placed the prevalence of diabetes among Saudis at 23.6% [13].

The substantial burden of diabetes is underscored by its strong association with CVD. The CAPTURE cross-sectional study revealed that 18% of T2DM patients had established CVD, and 15% had ASCVD [29]. Another recent cross-sectional study reported that 37.8% of individuals with T2DM had experienced at least one cardiovascular event, while 15.5% were identified as being at risk for future events [25]. These findings emphasize both the high and increasing prevalence of diabetes in Saudi Arabia and its significant contribution to the national CVD burden, particularly among older adults.

Behavioral risk factors.

Diet. Low-quality dietary patterns, characterized by an excess of refined grains, added sugars, excessive salt, unhealthy fats, and a deficiency in whole grains, fruits, vegetables, legumes, fish, and nuts, are strongly associated with increased CVD morbidity and mortality [30, 31]. The adoption of heart-healthy dietary patterns early in life and their consistent maintenance throughout the lifespan is crucial for reducing CVD risk [32].

While excessive saturated fatty intake was historically considered a major contributor to CHD, recent evidence highlights refined carbohydrates, particularly sugars, as a more significant risk factor. A 2016 systematic review revealed that the consumption of soft drinks and sweetened beverages was associated with a 22% higher risk of myocardial infarction (MI) and a 13% higher risk of stroke [33]. Similarly, a national prospective cohort study of 11,733 American adults demonstrated that individuals consuming 10% and 24.9% or $\geq 25\%$ of their daily calories from added sugar had adjusted hazard ratios (HR) for CVD mortality of 1.30 (95% CI, 1.09-1.55) and 2.75 (1.40-5.42; $P = .004$), respectively, compared to those consuming less than 10% daily [34]. Additionally, a consistent link has been found between the consumption of 50 - 100 grams per day of red and processed meat and an increased risk of CHD and cardiovascular events [35, 36].

In Saudi Arabia, a recent systematic review found that 34.4% of the population consumed unhealthy diets [37]. Although Saudi dietary guidelines are intended to mitigate CVD risk, there was no significant difference in adherence scores between CVD patients and non-CVD individuals [38, 39]. Furthermore, foods rich in polyphenols and fibers, such as fruits, olive oil, and non-alcoholic beer, are associated with a reduced risk of CVD but are consumed less by CVD patients [38].

Smoking. Smoking is the leading cause of preventable deaths globally and locally, as evidenced by multiple reports and studies [5, 40, 41]. It is estimated that over 8 million people die annually from smoking-related diseases worldwide [41]. The inhalation of a complex chemical mixture of chemical compounds from tobacco smoke contributes to adverse health outcomes, including CVD, through mechanisms such as DNA damage, inflammation, and oxidative stress [42, 43]. The risk of CVD increases with any increased intensity and duration of smoking [44]. While primary smoking poses the greatest risk, second-hand smoking and smokeless tobacco are also significantly associated with increased CVD risk [45]. Even minimal exposure to tobacco smoke through second-hand inhalation leads to a rapid and substantial increase in endothelial dysfunction and inflammation, which often results in acute cardiovascular events and thrombosis [45].

In Saudi Arabia, the prevalence of smoking among males nearly doubled between 1996 and 2012, rising from 21% to 37%, which was estimated to have contributed to over 280,000 premature deaths during that time [46]. However, the 2019 Global Adult Tobacco Survey (GATS) recorded a slight reduction in the prevalence of tobacco use among males in Saudi Arabia, declining to 30% [47]. The ACE study reported a smoking prevalence of 21.6% among Saudi patients [13]. Geographically, smoking is more common in the northern, eastern, and western regions of Saudi Arabia compared to other regions and is not significantly associated with income or occupation [48].

In addition to conventional cigarette smoking, other forms of smoking are uprising in the Middle-Eastern populations, such as vaping (e-cigarettes) and waterpipe (hookah). This was noticed among youth and university students in Saudi Arabia [49]. National surveys estimated a prevalence of e-cigarette use ranging from 10% to nearly 28% among Saudi college students, with higher use among males [50, 51]. This trend was mainly attributed to the misconception regarding the relative safety of e-cigarettes compared to conventional smoking, maximizing the burden of overall tobacco use in Saudi Arabia [49].

Physical activity and cardiovascular risk. A sedentary lifestyle and low PA are well-established risk factors for CVD. Physical inactivity is estimated to contribute to 6% of CHD cases, and over five million deaths could be prevented annually if inactive individuals adopted an active lifestyle [52]. Various forms of PA, including moderate-to-intense activity, light activity, and total activity, are associated with a lower incidence of CVD, particularly among middle-aged and elderly populations [53].

The 2021 ESC guidelines recommend 150 to 300 minutes per week of moderate-intensity PA along with resistance training (RT) at least twice a week to reduce all-cause and cardiovascular mortality and morbidity [5]. Examples of light, moderate, and vigorous physical activities are provided in Table 4.

In Saudi Arabia, the prevalence of physical inactivity remains alarmingly high. A 2018 systematic review reported inactivity rates ranging from 26% to 85% in Saudi males and 43% to 91% in Saudi females, both significantly below the recommended activity level. Most studies were conducted in urban areas, with limited data available on PA levels in rural regions [54]. The PURE-Saudi study revealed low PA prevalence in 69.4% of participants [1]. Furthermore, a multi-ethnic cross-sectional study conducted in Saudi Arabia identified the highest rate of physical inactivity among Saudi participants (41.5%). Compared to individuals from other countries, Saudis had a significantly higher likelihood of being physically inactive, with an adjusted odds ratio (OR) = 10.50 [55].

Psychosocial risk factors. Mental stress is increasingly recognized as a significant independent risk factor for CVD, regardless of traditional risk factors [56, 57]. Emotional stimuli can trigger transient myocardial ischemia, termed mental stress-induced myocardial ischemia (MSIMI), even in the absence of coronary obstruction. Clinical manifestations of MSIMI may include angina, MI, arrhythmias, and left ventricular (LV) dysfunction. Despite its association with increased cardiovascular mortality risk, MSIMI remains underdiagnosed due to its often painless presentation [56].

The impact of stress on CVD risk is complex and multifactorial. Stress is often intertwined with other

health behaviors, and the underlying biological mechanisms through which it increases CVD risk are not yet fully understood. Consequently, most clinical guidelines do not consider stress as an independent risk factor, and specific therapeutic targets for stress-related CVD are not yet established [58].

Raising public awareness about the effects of urbanization on mental health is a fundamental public health strategy [1]. In the PURE-Saudi study, 17% of participants reported experiencing stress episodes, while 7% experienced chronic stress. Women were more likely to experience the latter, though both episodic and chronic stress were more prevalent in younger individuals and those living in urban areas [1].

Non-modifiable risk factors

Non-modifiable risk factors are those that cannot be directly controlled or altered, including aging, sex, genetics, and race/ethnicity [3, 4]. However, their impact on health can be mitigated through targeted interventions and lifestyle modifications [2]. For example, while advancing age is inherently associated with an increased risk of CVD, this risk can be reduced by promoting healthy longevity. Key strategies include engaging in regular PA, incorporating RT to maintain muscle mass, reducing calorie intake, and prioritizing adequate protein consumption. These approaches can help prevent obesity, diabetes, and dyslipidemia, all of which are significant contributors to CVD [2, 59]. Similarly, early screening for genetically driven conditions, such as familial hyperlipidemia, allows for timely identification and proactive management of at-risk individuals. This can significantly reduce the long-term burden of CVD and related complications [2].

Age. In the Saudi context, the Heart Health Promotion study (HHP) revealed a significant increase in the prevalence of cardiovascular and metabolic risk factors with increasing age in both males and females. Among individuals aged 60 years or older, females had a higher prevalence of diabetes and metabolic syndrome compared to their male counterparts. Obesity prevalence also demonstrated an age-related increase, with females aged 40 years and above showing a significantly higher prevalence of obesity compared to males in the same

Table 4 - Examples of physical activities of various intensities [5, 417].

PA Intensity	Examples
Light	Walking, light household work
Moderate	Brisk walking, gardening, vacuuming, slow cycling
Vigorous	Race-walking, jogging, running, fast cycling, fast swimming, brisk elevated walking, heavy gardening, swimming laps

Intensity classification is based on metabolic demand, and examples provided illustrate common activities at each level.

age group. Similarly, the prevalence of dyslipidemia is higher with age and was observed to be more prominent in males [60].

Familial hypercholesterolemia. Familial hypercholesterolemia (FH) is a life-threatening autosomal dominant disorder of lipid metabolism characterized by lifelong elevated LDL-C levels [61]. It is among the most common inherited metabolic disorders worldwide. Due to its asymptomatic nature, many individuals with FH remain unaware of their condition until they experience ASCVD symptoms later in life, typically in their forties or fifties [62]. According to the Gulf FH registry, the prevalence of FH in Gulf Cooperation Council (GCC) countries, including Saudi Arabia, is estimated to be less than 1% [63]. Diagnosis is based on a combination of clinical and laboratory criteria, including severe lipid abnormalities, family history, and the Dutch Lipid Clinic Network (DLCN) criteria. Genetic testing can be used to confirm the diagnosis [5, 62].

Genetic. In addition to FH, other rare genetic variants predispose individuals to ASCVD. Monogenic disorders, such as Marfan syndrome, directly increase the risk of CVD [64]. Beyond single-gene disorders, polygenic inheritance also significantly contributes to CVD. Polygenic risk scores (PRS) combine the cumulative effects of multiple genetic variants to estimate an individual's genetic predisposition to conditions such as CAD or stroke. While research on the clinical applications of PRS for CVD risk stratification and prevention is ongoing, it holds promise for personalized medicine [5].

The relationship between genetic and environmental factors is crucial in determining CVD risk. Genetic predispositions, such as susceptibility to hypertension or diabetes, can be exacerbated by unfavorable lifestyle choices, including poor diet, smoking, physical inactivity, and stress. Conversely, a healthy lifestyle can help mitigate some genetic risks, highlighting the importance of an integrated approach to prevention [65].

Environmental factors

Air pollution. Air pollution, a mix of particulate matter (PM) and gases (such as ozone, nitrogen dioxide, carbon monoxide, and sulfur dioxide), is primarily caused by the combustion of fossil fuels and has been linked to CVD [5, 66].

Exposome, which refers to the totality of our environmental exposures to harmful biochemical and metabolic changes during our life course, plays a significant role in the development and progression of CVD. Exposure to harmful environmental factors accounts for up to two-thirds of all chronic non-communicable dis-

eases, and chemical pollution alone accounts for 16% of global deaths [67]. This increased CVD risk associated with harmful environmental exposure is synergistically increased with age, genetic predisposition, and pre-existing chronic diseases [68].

It is widely recognized as an environmental risk factor for CVD [5, 69]. In Saudi Arabia, PM levels, particularly PM_{2.5}, have consistently exceeded the WHO's recommended exposure limits. In 2017, the annual PM_{2.5} exposure in Saudi Arabia was 87.9 $\mu\text{g}/\text{m}^3$, marking a 24% increase from 1990, far surpassing the WHO's annual air quality guideline of 5 $\mu\text{g}/\text{m}^3$ [66, 70].

This high pollution level has been correlated with increased hospital admissions for acute CVD, particularly in the Eastern region, where a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10-2.5} was associated with up to a 1.1% rise in CVD admissions. In the Western region, air pollution is associated with a higher risk of cardiopulmonary morbidity [71]. Further, a study from Italy found that micro- and nanoparticles in carotid artery plaques were associated with a higher risk of MI, stroke, and mortality over 34 months of follow-up compared to individuals without such particles in their plaques [72]. These findings emphasize the urgent need for national air pollution governance, including stringent regulations to control industrial emissions and mitigate the harmful effects of air pollution on cardiovascular health.

Pedestrian mobility. In the process of urban development, prioritizing integrated modes of transportation, such as public transit, carpooling, cycling, walking, and wheeling, can significantly enhance public health, mobility, and air quality. These measures promote cleaner air and reduce greenhouse gas emissions, which, in turn, can help lower the prevalence of CVDs in the Saudi population [73]. By fostering these sustainable transportation options, urban areas can create a healthier, more efficient, and environmentally friendly infrastructure, benefiting both individuals and the broader community.

Interaction of cardiovascular disease risk factors. CVD risk factors are often analyzed independently, but an individual's overall risk is determined by the severity of a specific risk factor as well as the clustering of other factors. The interactions among these clustered risk factors can significantly amplify the risk of CVD. For example, metabolic risk factors interact to increase CHD risk. This is revealed by the additive interaction observed between hypertension and body weight in patients with T2DM, particularly in those with low body weight, where the risk of CHD is markedly heightened [24]. Gene-gene and gene-environment interactions can also influence CVD risk [24]. An example of this is the

interaction between smoking status and the deletion of the glutathione S-transferase M1 (GSTM1) gene, which significantly increases the risk of CHD compared to the individual impact of each factor alone [74]. These findings highlight the importance of considering both the presence and interaction of multiple risk factors rather than evaluating them in isolation when assessing CVD risk.

Public health interventions in Saudi Arabia. Prevention and management of CVD require a multidisciplinary approach supported by healthcare professionals who counsel patients on self-care. A community's perception of the causes of CVD and its associated risks is critical, as knowledge of these factors enables individuals to take actionable steps to manage their health. Enhancing awareness can improve the effectiveness of clinical and public health interventions.

Despite this, knowledge of CVD risk factors remains inadequate among Saudi adults. A recent cross-sectional study in Riyadh revealed that only 56% of participants had a strong understanding of CVD [3], and a similar rate (47.1%) was reported in another study conducted across universities, primary health centers (PHC), and social media platforms [75]. These findings highlight the urgent need for robust educational initiatives to raise awareness about CVD in Saudi Arabia.

Public health interventions are crucial for improving cardiovascular health. These include health education, promoting PA, encouraging healthy eating habits, implementing smoking cessation programs, and stress management initiatives in workplaces and other settings [37]. Recognizing the significance of CVD, Saudi Arabia has prioritized it as a public health issue. In 2022, the government allocated \$3000 per patient for screening tests, dyslipidemia treatments, and other preventive measures, aiming to reduce the burden of CVD over five years [2]. Several initiatives have been implemented to address modifiable CVD risk factors. For instance, the Obesity Control & Strategy 2020 focuses on monitoring and managing obesity while promoting healthier lifestyles [2]. The government has also encouraged the early adoption of day-case bariatric procedures and emphasized the need for national clinical trials to explore weight loss interventions, including pharmacological approaches (e.g., Glucagon-like peptide-1 [GLP-1] analogs), lifestyle changes, and surgical options [18]. Additionally, efforts to address non-modifiable risk factors, such as genetic testing for familial hyperlipidemia, are underway. These comprehensive strategies reflect the government's commitment to reducing the prevalence of CVD and improving the overall cardiovascular health of the population.

Chapter 2. Health conditions and risk factors associated with increased cardiovascular risk. Certain clinical conditions, beyond traditional risk factors, can significantly elevate CVD risk and worsen its prognosis (Figure 4). These conditions often exhibit a bidirectional relationship with CVD. Although not included in conventional risk assessment tools, they should be recognized, closely monitored, and managed effectively to mitigate CVD risk and enhance patient outcomes.

Chronic kidney disease. Chronic kidney disease (CKD) is a major public health issue in Saudi Arabia. Defined by abnormalities in kidney structure or function lasting over three months with health implications [5]. CVD is the leading cause of morbidity and mortality in patients with CKD [76]. CKD not only increases the risk of CVD and its associated traditional risk factors, but it also increases the risk of non-traditional ones, such as inflammation, oxidative stress, and vascular calcification [77].

In Saudi Arabia, the prevalence of CKD has grown significantly. In 2010, it was estimated at 5.7% using the estimated glomerular filtration rate (eGFR) MDRD-3 equation [78]. Over the past decade, CKD cases increased by 25.1%, with two million cases and 3,818 deaths reported in 2017 [79]. Recent data reveal an age-standardized CKD prevalence (excluding renal replacement therapy) of 9,892 per 100,000, indicating a rising burden [80]. However, a more recent study found a lower prevalence of 1.9% [81], though data from the country remain limited.

Chronic-kidney-metabolic syndrome. Cardiovascular-kidney-metabolic (CKM) syndrome describes the clustering of insulin resistance, adiposity, CKD, and cardiovascular risk [82]. The AHA defines five stages of CKM syndrome that reflect disease progression (stages 0–4), from early risk to overt end-organ damage. The AHA emphasizes that CKM syndrome is a progressive condition beginning in early life stages, often remaining undetected until advanced stages. The syndrome significantly increases the risk of adverse cardiovascular events, kidney failure, and mortality; therefore, early identification and intervention are crucial. The AHA advocates for routine screening of kidney and metabolic health indicators, even in individuals without overt symptoms, to initiate protective therapies as early as possible and prevent disease progression [82].

The use of clinical tools for identifying and managing CKM syndrome, especially in high-risk Saudi subpopulations, is recommended. Recommendations include integrated screening (e.g., HbA1c, eGFR, lipids) and lifestyle interventions tied to Vision 2030 health goals.

CVD-associated Conditions

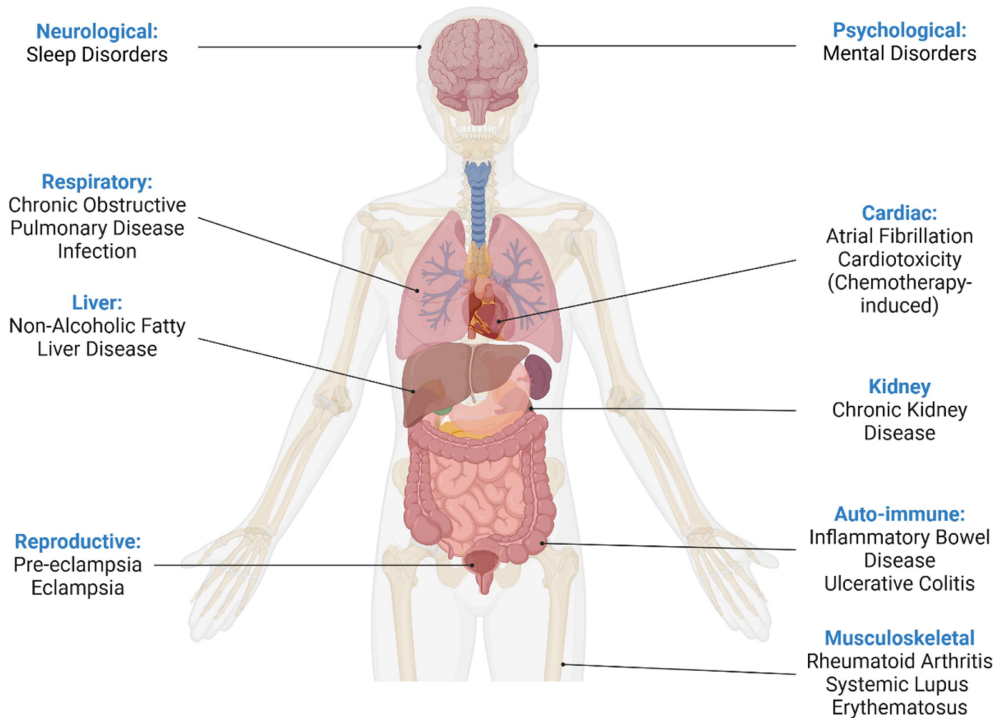


Figure 4 - Conditions Associated with An Increased Cardiovascular Risk. Figure created with professional assistance from Advocacy for HealthCare Consultancy (medical writing support).

Atrial fibrillation. Atrial fibrillation (AF) is associated with an increased risk of CVD and death, with this risk being higher in females compared to males [83, 84]. The likelihood of developing AF increases with age, comorbidities, and the patient's ASCVD risk factor profile [85]. Managing modifiable CVD risk factors through targeted and comprehensive treatment of underlying conditions, rather than focusing on isolated risk factors, could reduce the incidence of AF [86].

In 2019, the global age-standardized incidence rate of AF was 39.8 per 100,000 population, and the age-standardized mortality rate was 4.3 per 100,000 population [87]. In Saudi Arabia, data from the Saudi Atrial Fibrillation Survey registry indicated that AF patients are younger compared to those in Western countries, with a higher prevalence of diabetes and rheumatic heart disease [88]. A retrospective study conducted in a single hospital in the western Saudi region found that AF was more prevalent among females. The most common risk factors identified in AF patients were hypertension, valvular heart disease, and type 2 diabetes [89]. These findings highlight the need for tailored interventions to address modifiable risk factors and improve outcomes for AF patients in Saudi Arabia.

Infections. CVD and influenza are closely linked as their incidence peaks during winter. Cardiovascular mortality increases during influenza pandemics due to influenza-related cardiac complications, such as myocarditis, acute MI, ischemic heart disease (IHD), and stroke [5]. Visits to the Emergency Department for influenza-like illness are also predictive of CVD mortality [90]. In Saudi Arabia, 4.58% of total deaths in 2020 were attributed to seasonal influenza and pneumonia, with a mortality rate of 30.9 per 100,000 persons, ranking the country 82nd globally [91]. Evidence from a recent systematic review and meta-analysis highlights the role of influenza vaccination in reducing cardiovascular mortality and cardiovascular events in patients with CVD [92]. Cardiologists and primary care physicians (PCPs) should actively promote influenza vaccination, especially among CVD patients, who often show suboptimum vaccine uptake [93].

Pre-existing CVD significantly increases the risk of severe COVID-19 infection and mortality. Patients with adverse COVID-19 outcomes frequently have a high prevalence of cardiovascular risk factors, with older age and diabetes particularly associated with elevated mortality risks [94]. In two tertiary hospitals in Saudi Arabia,

older age, CKD, and acute respiratory distress syndrome (ARDS) were identified as key predictors of COVID-19 mortality [95]. Since many associated cardiovascular risk factors are modifiable, prevention strategies targeting these factors could improve outcomes in post-COVID-19 recovery [96].

COVID-19 also directly affects cardiac health, causing conditions such as acute coronary syndrome (ACS), arterial and venous thrombosis, acutely decompensated HF, myopericarditis, stress-induced cardiomyopathy, and arrhythmia. While cardiovascular events related to COVID-19 vaccination have been reported, studies have shown that vaccination with BNT162b2 or CoronaVac does not increase the risk of heart attacks or strokes in patients with existing CVD [97–99]. The benefits of COVID-19 vaccination outweigh the potential risks; however, vaccination decisions should be individualized, taking into account the patient's cardiovascular risk profile and the vaccine type [100].

Chronic obstructive pulmonary disease. Chronic obstructive pulmonary disease (COPD), though treatable and preventable, is the fourth leading cause of death globally [101]. It is characterized by chronic airflow limitation, an enhanced inflammatory response, and airway abnormalities and narrowing [5].

COPD and CVD share common risk factors, such as smoking, hypertension, dyslipidemia, and ageing. This overlap explains the high prevalence of CVD among COPD patients, who are more likely to have CVD compared with age-matched controls, even after adjusting for tobacco smoking [102]. In addition, patients with mild to moderate COPD are 8–10 times more likely to die from ASCVD than from respiratory failure [103].

In Saudi Arabia, the prevalence and incidence of COPD have steadily increased over the past three decades. By 2019, around 434,560.64 people had COPD, and the age-standardized prevalence rate was 2053 cases per 100,000. The mortality rate due to COPD in 2019 was 19.6 deaths per 100,000, accounting for 1.65% of the total deaths in the country [104]. These trends highlight the growing burden of COPD in Saudi Arabia and the need for integrated strategies to address both COPD and its cardiovascular comorbidities.

Inflammation. Inflammation is a significant risk factor for developing CVD. Chronic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus, periodontitis, and atopic dermatitis are associated with an increased risk of CVD [105]. Inflammatory biomarkers, such as C-reactive protein (CRP) levels, can independently predict CVD risk and are associated with worse survival outcomes during ACS [106, 107]. The transcription factor NFκB plays a key role in

the relationship between inflammation and CVD [108]. All stages of atherosclerosis involve interactions between the innate and adaptive immune systems, bone marrow, and spleen, which regulate the pro-inflammatory and anti-inflammatory activities of protein mediators (e.g., cytokines) and immune cells (e.g., leukocytes, macrophages, and lymphocytes) [109].

In Saudi Arabia, studies have reinforced the link between inflammation and CVD. A strong association was observed between high Disease Activity Score-28 for Rheumatoid Arthritis with CRP (DAS28-CRP) and CVD [110]. Similarly, Saudi patients with psoriatic arthritis exhibited a higher prevalence of cardiovascular risk factors (hypertension, dyslipidemia, diabetes, obesity, and elevated inflammatory biomarkers) compared to the general population [111].

The European League Against Rheumatism (EULAR) has recommended annual cardiovascular risk assessments for patients with inflammatory diseases, coupled with management of traditional CVD risk factors and aggressive suppression of inflammation and disease activity. Although better management of inflammation lowers the risk of CVD, certain medications, such as glucocorticoids, may paradoxically increase CVD risk, potentially negating the anti-inflammatory benefit. To address this, EULAR provides specific recommendations for balancing the benefits and risks of such treatments, ensuring comprehensive care for patients with inflammatory diseases [112]. Furthermore, other medications, particularly colchicine, can be used as anti-inflammatory agents for cardiovascular risk reduction, as evidenced by major trials such as COLCOT and LoDoCo2 [113, 114].

Cancer. Cardiovascular risk in cancer patients emerges from a combination of shared biological mechanisms and risk factors between cancer and CVD, treatment-related toxicities, and patient-specific factors [5]. Chemotherapy and radiotherapy can directly affect vascular health, increasing the likelihood of atherosclerosis-related CVD outcomes. Additionally, novel anticancer drugs are linked to a spectrum of CVD adverse events, including cardiomyopathy, LV dysfunction, HF, hypertension, CAD, and arrhythmias [5].

In Saudi Arabia, a cross-sectional study on adult cancer patients receiving chemotherapy reported a cardiotoxicity rate of 12.5%. Significant factors associated with cardiotoxicity included the use of anthracycline or trastuzumab and receiving more than ten chemotherapy cycles. The development of cardiotoxicity was challenging to predict and appeared independent of baseline systolic function [115]. Another study by Alzahrani et al. identified a history of stroke and CVD as a major risk

factor for new cardiac adverse events (AEs) in prostate cancer patients receiving androgen deprivation therapy (ADT) [116].

Given these findings, predicting and preventing CVD toxicity in cancer patients undergoing potentially cardiotoxic treatments is crucial. Regular monitoring for symptoms of cardiac dysfunction during and after treatment is essential to detect early abnormalities and initiate timely interventions [5]. Proactive management strategies, including baseline cardiovascular risk assessment, patient-specific treatment modifications, and ongoing surveillance, can help mitigate the burden of CVD in this vulnerable population.

Sleep disorders. Sleep duration and quality are vital to cardiovascular health. Deviations from the optimal seven hours of sleep per night and sleep disturbances, such as insomnia, parasomnia, hypersomnolence, limb movements during sleep, and sleep-related breathing disorders, significantly increase cardiovascular risk [117]. These sleep disturbances are associated with mental health disorders, further compounding cardiovascular risk [118]. Moreover, sleep impairments are prevalent among patients with existing CVD, with conditions such as insomnia and sleep-breathing disorders being the most common [119].

Major risk factors for obstructive sleep apnea (OSA) include age > 35 years; BMI ≥ 25 kg/m², alcoholism, higher Epworth sleepiness scale (ESS) scores, prolonged apnea duration, oxygen desaturation index (ODI), and nocturnal oxygen desaturation (NOD) [120]. A higher sleep-breathing impairment index (SBII) score correlates with a higher 10-year Framingham CVD risk score [121].

In Saudi Arabia, around 50% of the population sleeps less than 7 hours per night [122], and the prevalence of insomnia in the general population is high at 37.6% [123]. Among patients with CVD attending atherosclerosis clinics at King Abdulaziz Cardiac Center, 16.6% had insomnia, and about 60% experienced poor-quality sleep [124]. These findings highlight a significant burden of sleep disturbances among the region's general and cardiovascular patient populations.

Findings from the Nationwide Swedish Twin Registry, which followed 12,268 CVD-free individuals for 18 years, further underscore the association between sleep patterns and CVD [125]. The study reported hazard ratios (HRs) of 1.14 for those sleeping less than 7 hours/night and 1.10 for those sleeping more than 10 hours/night, compared to individuals sleeping 7-9 hours/night. Additionally, napping for over 30 minutes and poor sleep patterns were associated with an increased CVD risk [125].

Inadequate sleep duration and poor sleep quality are significant contributors to cardiovascular morbidity and mortality. Recognizing and addressing sleep impairments in patients, particularly those with existing CVD, is critical. Clinicians should develop management plans incorporating both pharmacological and non-pharmacological therapies to improve sleep quality and ultimately enhance patients' cardiovascular health and overall prognosis.

Psychosocial and mental disorders. Psychosocial and mental disorders are strongly associated with the development of CVD and reduced life expectancy [126]. Patients with severe mental illness face a CVD mortality rate that is more than double that of the general population [127]. Simultaneously, the prevalence of mental disorders is higher among patients with CVD compared to the general population, highlighting a bidirectional relationship [5].

The link between mental disorders and CVD is complex and multifaceted, involving both direct and indirect pathways. Indirectly, mental disorders often lead to unhealthy lifestyle choices, such as smoking, poor diet, physical inactivity, or substance abuse (such as cocaine-induced myocardial ischemia), which increase CVD risk. Impaired healthcare utilization further delays the diagnosis and management of CVD risk factors. Direct mechanisms include neurobiological and neuroendocrine changes, autonomic and endothelial dysfunction, systemic inflammation, platelet activation and thrombosis, all of which are associated with mental disorders. Furthermore, medications used to treat mental disorders, such as antipsychotics and mood stabilizers, can contribute to cardiometabolic side effects, worsening the risk profile for CVD [128]. Barriers from HCPs, including a lack of recognition of the impact of mental disorders on CVD and stigmatized attitudes towards mental health patients, further compound the problem [129].

In Saudi Arabia, mental disorders pose a significant public health challenge, with approximately 5.1 million individuals affected in 2019 and an incidence rate of 2.4 million. Between 1990 and 2019, the burden of mental disorders in the country has risen, with increases in mortality rates, years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life-years (DALYs) [130].

Given this significant burden, clinicians should prioritize screening for mental health conditions in CVD patients and vice versa, address modifiable lifestyle factors, monitor psychotropic medication side effects, and promote collaboration between cardiology and psychiatry. Reducing stigma and improving healthcare

access are essential to enhancing outcomes and quality of life (QoL).

Frailty. Frailty, a multidimensional decline in physiological status marked by fatigue, weakness, and reduced tolerance to medical interventions, is independent of age and multimorbidity [5, 131]. While its incidence increases with age and comorbidities can exacerbate it, frailty is distinct from both [5]. It serves as a functional risk factor for both cardiovascular and non-cardiovascular morbidity and mortality [132], potentially modifying global CVD risk. Non-pharmacological interventions aimed at improving frailty can enhance CVD treatment outcomes [133], even though frailty assessment is not part of formal CVD risk evaluations [5].

Physical frailty and poor cardiovascular health are independently associated with an increased risk of all-cause mortality, including CVD, as shown in large cohort studies [134, 135]. Lifestyle modifications and improved cardiovascular health have demonstrated significant reductions in CVD risk [134].

In Saudi Arabia, frailty is prevalent among the elderly population. Among community-dwelling individuals aged over 60, the prevalence rates of pre-frailty and frailty using Fried's frailty phenotype were 47.3% and 21.4%, respectively [136]. Similarly, a study at a PHC reported frailty and pre-frailty rates of 25.4% and 24.6% in elderly patients aged 60 years and above [137]. A tertiary hospital study of patients aged 50 years and older reported mild, moderate, and severe frailty rates of 22%, 12%, and 4%, respectively [138].

Non-alcoholic fatty liver disease. Non-alcoholic fatty liver disease (NAFLD) is closely associated with major cardiovascular events and complications such as cardiomyopathy, cardiac valvular calcification, and cardiac arrhythmias, independent of traditional cardiovascular risk factors. It also significantly contributes to cardiovascular mortality [139, 140]. In Saudi Arabia, the prevalence of NAFLD is projected to exceed 30% by 2030 [139]. A model based on trends in adult obesity and DM prevalence estimates that there will be around 12.5 million cases of NAFLD in the country by 2030 [141].

Pre-eclampsia. Pre-eclampsia, a pregnancy-related condition characterized by hypertension and proteinuria, increases the risk of CVD by 1.5 to 2.7 times compared to all women. It also elevates the likelihood of developing traditional cardiovascular risk factors, with women experiencing pre-eclampsia having three times the risk of hypertension and twice the risk of diabetes mellitus (DM) [5]. In Saudi Arabia, pre-eclampsia affects approximately 5.37 out of every 10,000 women [142].

Polycystic ovary syndrome. Polycystic ovary syndrome (PCOS) is associated with an increased risk of CVD and DM [143]. Women with PCOS often have metabolic disorders such as insulin resistance, obesity, and dyslipidemia, which can contribute to these health risks. A recent cross-sectional study in Saudi Arabia found that the prevalence of PCOS among Saudi women is 16% [144]. This highlights the significance of PCOS as a public health concern in the region and emphasizes the need for targeted healthcare interventions to monitor and mitigate the associated risks of CVD and DM in affected individuals.

Pregnancy-related risk factors. Beyond pre-eclampsia and PCOS, several other pregnancy- and reproductive-related factors serve as crucial cardiovascular risk enhancers. These include gestational diabetes mellitus, which is associated with the increased risk of type 2 DM; premature menopause (<40 years), accompanied by reduced estrogen's vascular protection; and recurrent pregnancy loss or adverse pregnancy outcomes such as delivery of low birthweight or preterm infants, both of which have been linked to higher long-term maternal cardiovascular risk. Accordingly, obtaining a comprehensive pregnancy and reproductive history is essential for lifetime CVD risk assessment in women [145, 146].

Chapter 3. Prevention of cardiovascular disease. In this section, we focus on both primary and secondary prevention strategies for CVD, with an emphasis on addressing individual CVD risk factors.

Optimizing lifestyle and risk factors management. Primary cardiovascular prevention strategies focus on addressing common risk factors and promoting healthy lifestyles to reduce the incidence of CVD. The AHA developed Life Essential 8, which outlines key components that target lifestyle, behavioral, and biological factors contributing to cardiovascular and overall health [147].

Life's Essential 8 consists of four lifestyle components and four health measures aiming to improve cardiovascular health. These include a **healthy diet**, **PA**, **avoiding nicotine exposure**, and **healthy sleep**. The health measures are **maintaining a healthy weight (BMI)** and ensuring **normal levels of blood lipids, blood glucose, and BP** [147]. Together, these factors are critical for improving cardiovascular health and lowering the risk of cardiovascular-related mortality [148, 149].

Diet

Lowering saturated fat intake and replacing it with polyunsaturated fatty acids (PUFAs) can significantly reduce the risk of CHD. A meta-analysis of major

randomized controlled trials (RCTs), including the Wadsworth Hospital and Veterans Administration Center, Oslo-Diet-Heart, British Medical Research Council, and Finnish Mental Hospital studies, demonstrated that replacing saturated fats with PUFAs for at least two years lowered the risk of CHD by 29% (RR 0.71, 95% CI 0.62, 0.81) [150]. Since foods rich in saturated fats are also high in cholesterol, this replacement decreases dietary cholesterol intake, which in turn lowers serum cholesterol levels [151]. Additionally, the Hooper et al. meta-analysis showed that reducing saturated fat intake reduced the risk of combined CVD events by 17% (RR 0.83, 95% CI 0.70, 0.98), with a direct proportional relationship between the reduction in saturated fat and the reduced risk of CVD events [151].

High sodium intake, primarily from salt, plays a significant role in the pathophysiology of CVD. It raises BP, a major contributor to CVD, and negatively impacts LV mass, arterial stiffness, renal function, cardiac output, and sympathetic outflow [152]. Individuals with high sodium intake face a higher CVD risk than those with lower intake (rate ratio 1.19, 95% CI 1.08, 1.30), with each additional gram of sodium consumed daily increasing CVD risk by up to 6% [153]. Reducing sodium intake by 2.5 grams per day has been associated with a 20% reduction in CVD events (RR 0.80, 95% CI 0.66, 0.97) [154].

Consistent evidence links processed meat consumption to an increased risk of CHD and CVD. One meta-analysis of prospective cohort studies found that consuming 50 grams of processed meat per day is associated with a 27% increase in CHD incidence [155].

Increasing fiber intake is associated with a reduction in cardiovascular risk. For every 7 grams of fiber consumed daily, the risk of CAD decreases by 9% (RR 0.91) [156]. Additionally, consuming 10 grams more fiber daily is linked to a 16% reduction in stroke risk (RR 0.84) and a 6% reduction in the risk of T2DM (RR 0.94) [157]. High fiber intake also helps reduce

postprandial glucose (PPG) levels and lower triglyceride levels [158].

The California Teachers Study revealed that women who consumed sugar-sweetened beverages regularly (two servings per day compared to one serving per month) had a higher risk of developing CVD and revascularization [159].

Due to their rich nutrient profile, fruits and vegetables play a crucial role in CVD prevention. Packed with essential vitamins, minerals, and antioxidants, they help reduce inflammation and oxidative stress, protecting the heart. High fiber content aids in lowering LDL cholesterol and maintaining healthy BP levels. Additionally, the low-calorie density of fruits and vegetables supports weight management, further reducing CVD risk. Regular consumption of a variety of fruits and vegetables is strongly associated with a lower incidence of heart disease and stroke (Table 5) [160].

Smoking

The detrimental effects of smoking on CVD are well established, making smoking cessation a cornerstone of CVD prevention [5]. Among patients with CHD, those who quit smoking experience a 37% reduction in the relative risk of all-cause mortality compared to those who continued smoking [161]. The most recent Surgeon General's report on smoking cessation indicated that quitting smoking improves numerous pathogenetic factors involved in CVD and significantly reduces the risk of CVD-related morbidity and mortality [162].

Effective smoking cessation interventions often combine multiple strategies, including counselling, pharmacotherapy (e.g., nicotine replacement therapy, varenicline, and bupropion), and participation in support groups. This comprehensive approach targets both the physical and psychological aspects of smoking, thereby increasing cessation success rates and contributing to improved cardiovascular outcomes (Table 6) [163].

Smoking interventions must extend to the alternative forms of tobacco, such as vaping and hookah. There

Table 5 - Diet recommendation for CVD prevention.

Recommendation	Class	Level
A healthy diet focusing on replacing saturated with unsaturated fats, reducing salt intake, restricting processed meat and sugar, and increasing fiber, fruits, and vegetables is recommended to lower the risk of CVD.	I	B

This recommendation highlights the role of dietary modification in reducing cardiovascular risk through balanced nutrition and lifestyle adaptation. CVD= Cardiovascular disease.

Table 6 - Smoking cessation recommendation for CVD prevention.

Recommendation	Class	Level
It is recommended that all forms of tobacco smoking be discontinued to enhance the CVD risk profile.	I	A

This recommendation emphasizes smoking cessation as a cornerstone intervention in cardiovascular prevention, given its strong impact on risk reduction. CVD= Cardiovascular diseases.

Table 7 - Physical activity recommendation for CVD prevention.

Recommendation	Class	Level
Aerobic physical activity of moderate intensity for at least 150 to 300 minutes a week or vigorous intensity for at least 75 to 150 minutes a week – or an equivalent combination – is recommended for all adults to reduce all-cause mortality, CV mortality and morbidity.	I	A
Adults who are not able to perform the minimal moderate-intensity physical activity (150 minutes per week) are recommended to stay as active as their health condition allows.	I	B
Besides aerobic physical activity, resistance training is recommended at least twice per week to reduce all-cause mortality.	I	B

These recommendations emphasize both aerobic and resistance exercise as essential components of cardiovascular disease prevention, with flexibility for individuals limited by health status. CV= Cardiovascular.

is a critical need for targeted public education campaigns that can educate young people and raise their awareness about the use of these substances, particularly in light of the common misconception about their safety. Additionally, the assessment of vaping and waterpipe use should be considered in the routine CVD risk evaluation [164, 165].

Physical activity

There is extensive evidence supporting the benefits of moderate-to-vigorous physical activity (MVPA) in reducing all-cause mortality, CVD mortality, and atherosclerotic CVD events, including CHD, ischemic stroke, and HF [166]. Studies show no significant difference in the reduction of all-cause and CVD mortality between individuals performing MVPA in 1–2 sessions per week (≥ 150 minutes of moderate-intensity or ≥ 75 minutes of vigorous-intensity activity) and those spreading the same activity over 3–5 sessions per week [167–169].

A meta-analysis revealed that even a low dose of MVPA (1–499 MET-minutes per week) led to a 22% reduction in mortality risk (RR 0.78, 95% CI 0.71–0.87) [170]. This highlights that any MVPA is preferable to a sedentary lifestyle, with no minimum activity level required to begin accruing health benefits. Therefore, even individuals unable to meet the recommended activity levels should be encouraged to engage in some form of PA [5, 171].

In addition to aerobic activities, RT independently lowers CVD risk through a U-shaped association and indirectly by reducing BMI. Engaging in RT two to three times per week reduces the risk of total CVD events by 43%–59%, CVD morbidity by 28%–42%, and all-cause mortality by 32% [172]. Furthermore, combining RT with aerobic activity yields additive benefits. Compared with no exercise, the combination of RT and aerobic PA was associated with a 40% reduction in all-cause mortality (HR 0.60, 95% CI 0.49–0.72) [173]. The Saudi Heart Association (SHA) Prevention and Cardiac Rehabilitation Group recommends RT in the form of 8–10 exercises targeting major muscle groups,

with 1–3 sets of 8–15 repetitions at an intensity of 40%–70% of one-repetition maximum (1 RM) [171].

Recent research has demonstrated that adhering to recommended PA levels increases life expectancy by over five years compared to inactivity [174].

Accordingly, the 2018 Physical Activity Guidelines, the 2021 ESC Guidelines, and the SHA Prevention and Cardiac Rehabilitation Group recommend 150 to 300 minutes per week of moderate-intensity activity, 75 to 150 minutes per week of vigorous-intensity activity, or a combination of both [5, 167, 171]. Similarly, a joint consensus statement of the Saudi Public Health Authority (PHA) recommends these activity levels for adults aged 18–64 years, along with muscle-strengthening activities twice a week [175]. The consensus statement also emphasizes minimizing prolonged sitting time by incorporating at least light PA interruptions throughout the day (Table 7) [175].

Obesity

Obesity, characterized by a BMI ≥ 30 , is a significant risk factor for CVD. Achieving a weight loss of 5–10% of body weight is typically the initial target to attain notable health benefits. Sustained lifestyle changes, such as adhering to a healthy diet and engaging in regular PA, are fundamental for long-term weight management. Beyond lifestyle interventions, drugs can play a pivotal role in obesity management. Glucagon-like peptide-1 receptor agonists (GLP1-RAs) and dual GIP/GLP1-RA agents (e.g., semaglutide, tirzepatide) were reported with promising benefits in terms of weight reduction and cardiometabolic outcomes. For instance, the SELECT trial concluded that once-weekly semaglutide (2.4 mg) was able to reduce mortality and cardiovascular morbidities in obese patients without diabetes [176–178].

A meta-analysis demonstrated that weight loss improves cardiovascular risk factors, including SBP, DBP, LDL cholesterol, triglycerides (TG), fasting blood glucose (FBG), and Hemoglobin A1C (HbA1c), with improvements observed in both mild ($<5\%$) and moderate (5– $<10\%$) weight loss, particularly during the first two years [179]. Another meta-analysis of RCTs showed

Table 8 - Weight Reduction Recommendation for CVD Prevention.

Recommendation	Class	Level
Weight reduction is recommended for all overweight and obese individuals to reduce their CVD risk factors and improve their CVD risk profile.	I	A

This recommendation underscores the importance of weight management as a cornerstone of cardiovascular prevention strategies. CVD= Cardiovascular disease.

Table 9 - Target glucose lowering recommendation for CVD prevention.

Recommendation	Class	Level
A target HbA1c of $\leq 6.5\%$ (48 mmol/L) is recommended for the majority of non-pregnant adults with either T1DM or T2DM, if it can be achieved safely, to reduce CVD risk and microvascular complications of DM.	I	B

This recommendation emphasizes the role of optimal glycemic control in reducing both cardiovascular and microvascular complications, provided targets can be achieved without undue risk. HbA1c = Hemoglobin A1c, T1DM = Type 1 diabetes mellitus, T2DM = Type 2 diabetes mellitus, CVD = Cardiovascular disease, DM = Diabetes mellitus.

that weight loss interventions among obese adults reduced all-cause mortality (risk ratio 0.82, 95% CI 0.71, 0.95), cardiovascular mortality (RR= 0.93, 95% CI 0.67, 1.31), and the incidence of new cardiovascular events (RR= 0.93, 95% CI 0.83, 1.04) [180].

Although weight regain is a common occurrence following initial weight loss, achieving a greater initial weight reduction should still be prioritized, as it has been shown to improve HbA1c levels in patients with T2DM [181]. Moreover, incorporating behavioral and psychological support into weight loss programs can enhance their effectiveness, improving the overall QoL and reducing the risk of other obesity-related conditions (Table 8) [182, 183].

Diabetes mellitus

Intensive glucose lowering is a critical component of CVD risk reduction in patients with DM [5, 184]. The 2022 American Association of Clinical Endocrinology (AACE) clinical practice guidelines recommend targeting an HbA1c level of $\leq 6.5\%$ (48 mmol/L) to prevent and/or reduce the risk of microvascular complications associated with DM [184]. To achieve this target, FBG should be maintained at < 100 mg/dL and 2-hour PPG at < 140 mg/dL [184].

The AACE emphasizes the importance of tailoring these glycemic targets to individual patient characteristics and prioritizing safety. Less stringent HbA1c goals may be appropriate in the following circumstances: limited life expectancy, hypoglycemia unawareness or a history of severe hypoglycemia, high CVD risk, long-standing DM, and challenges in achieving tight glycemic control [184, 185]. This patient-centered approach ensures that glycemic targets are both achievable and safe, balancing the benefits of intensive glucose control with the potential risks in vulnerable populations (Table 9).

Hypertension

The Systolic Blood Pressure Intervention Trial (SPRINT) found that intensive SBP reduction to less than 120 mmHg significantly reduced cardiovascular risks. Compared to a less intensive SBP target of less than 140 mmHg, intensive SBP control lowered the risk of the primary composite outcome—which includes first occurrences of MI, ACS, stroke, HF, or death from cardiovascular causes—by 25%. Additionally, it reduced the risk of HF by 38%, cardiovascular mortality by 43%, and all-cause mortality by 27% [186].

Furthermore, a 10-mmHg reduction in SBP was associated with a 20% reduction in major CVD events, 17% in CHD, 27% in stroke, 28% in HF, and 13% in all-cause mortality [187].

Achieving higher scores in components of "Life's Essential 8" among patients with hypertension has also been linked to reduced all-cause mortality, particularly from CVD [188].

Accordingly, the 2024 ESC Hypertension Guidelines recommend an SBP target of 120–129 mmHg for patients aged 18 to 65 years who are receiving BP-lowering medication [6].

According to the 2023 National Heart Center/Saudi Heart Association (NHC/SHA) guideline, a SBP target of < 130 mmHg is recommended for patients with DM [7]. However, recent evidence from the BROAD Research Group emphasizes the advantages of intensive BP control in this population. Their study showed that targeting an SBP below 120 mmHg significantly reduced MACE [189]. Reflecting this evidence, the 2024 ESC Hypertension Guidelines now recommend an SBP target of 120–129 mmHg for patients with hypertension and DM [6].

In patients with hypertension and CKD, evidence suggests clinical benefits in maintaining an SBP target of 130–140 mmHg. SBP is closely linked to the risk of renal

Table 10 - Target blood pressure recommendation for CVD prevention.

Recommendation	Class	Level
A SBP target of 120-130 mmHg is recommended in patients aged 18 to 65 years with stage 2 hypertension (BP >140/90 mmHg) and heart failure (HFrEF or HFpEF).	I	A
A SBP target of 130-140 mmHg is recommended in patients aged 18 to 65 years with hypertension and CKD.	I	A
A treatment SBP target of 120-130 mmHg and DBP target of 70-80 mmHg is recommended in patients aged 18 to 65 years with hypertension and CAD.	I	A
A treatment SBP target of 130-140 mmHg is recommended for older patients (≥ 65 years) with hypertension and CAD.	I	A

These recommendations reflect target blood pressure thresholds tailored to comorbid conditions including heart failure, chronic kidney disease, and coronary artery disease. SBP= Systolic blood pressure, BP= Blood pressure, HFrEF= Heart failure with reduced ejection fraction, HFpEF= Heart failure with preserved ejection fraction, CKD= Chronic kidney disease, DBP= Diastolic blood pressure, CAD= Coronary artery disease.

disease progression in individuals with nondiabetic kidney disease [7]. A prospective, randomised, controlled trial found that deviations from an SBP range of 130–139 mmHg, either higher or lower, were associated with worsened composite outcomes, including mortality and end-stage renal disease (ESRD) [190]. Similarly, a meta-analysis of RCTs found no additional benefit for renal outcomes with intensive BP control (<130/80 mmHg) compared to standard treatment (<140/90 mmHg) in patients with CKD without diabetes [191]. Based on this evidence, the 2023 NHC/SHA guidelines recommend an SBP target of 130–140 mmHg for managing hypertension in patients with CKD [7].

Lowering BP is strongly associated with potent reductions in the risk of CAD [7]. However, a J curve phenomenon has been observed, where both excessively high and excessively low BP targets are linked to adverse cardiovascular outcomes, including cardiovascular mortality, MI, or stroke. Specifically, BP levels exceeding 140/80 mmHg or falling below 120/70 mmHg are associated with increased adverse outcomes in patients with CAD and hypertension [192, 193]. Accordingly, the 2023 NHC/SHA guidelines recommend a target BP of 120/70 to 130/80 mmHg for patients with hypertension and CAD [7].

In elderly patients, lowering BP provides substantial benefits, including reduced cardiovascular morbidity, cardiovascular mortality, and all-cause mortality, even in frail individuals [7]. A meta-analysis demonstrated that lowering BP to less than 140 mmHg in individuals aged 60 years and older was associated with a reduced risk of stroke, HF, and cardiovascular and all-cause mortality [194]. Given these findings, the 2023 NHC/SHA and 2024 ESC guidelines recommend a higher systolic BP target range in elderly patients to balance the benefits of BP control with the risks of overly aggressive treatment (Table 10) [6, 7].

Lipids

Building on the findings from the Cholesterol Treatment Trialists (CTT) meta-analyses [195], the 2022

Saudi Guidelines for Dyslipidemia Management established updated lipid targets tailored to patients' risk stratification. These recommendations underscore the importance of individualized lipid management to optimize cardiovascular outcomes, emphasizing evidence-based thresholds for different risk categories [196]. By adopting this precision-driven strategy, HCPs can effectively mitigate cardiovascular risk and enhance overall patient care (Table 11).

Furthermore, the 2022 Saudi national guidelines for dyslipidemia endorsed the ESC suggestion regarding patients with recurrent ASCVD events or those considered at extremely high risk, for a more aggressive LDL-C target of <1.0 mmol/L (<40 mg/dL), as outlined in Table 11 [196, 197].

Psychosocial/Mental disorders

In high-income countries like Saudi Arabia, individuals with severe mental disorders are at an increased risk of CVD, including conditions like hypertrophic cardiomyopathy, which can also contribute to the development of mental health issues [198]. To mitigate this, evidence-based psychosocial interventions, including smoking cessation, weight loss programs, and addressing substance misuse and risky sexual behaviors, are recommended [199]. Additionally, psychological techniques like Mindfulness-Based Stress Reduction (MBSR) have shown significant benefits, reducing both systolic and DBP in prehypertensive patients after just two months, offering a promising approach to managing both mental health and cardiovascular risks (Table 12) [200].

Alcohol consumption

Despite the relatively low rates of alcohol consumption in Saudi Arabia, social factors and stressful lifestyles have contributed to the initiation of alcohol use among the population [201]. Heavy alcohol consumption, defined as more than 20 drinks per week for men and more than 13 drinks per week for women (or ≥ 200 g per week), has been associated with an increased risk of MACE. A meta-analysis has further confirmed that

Table 11 - Target LDL-C level recommendation for CVD prevention.

Recommendation	Class	Level
In secondary prevention of patients at very high risk, an LDL-C reduction of $\geq 50\%$ from baseline and an LDL-C goal of < 1.4 mmol/L (< 55 mg/dL) are recommended .	I	A
In primary prevention of individuals at very high risk and with no familial hypercholesterolemia (FH), an LDL-C reduction of $\geq 50\%$ from baseline and an LDL-C goal of < 1.4 mmol/L (< 55 mg/dL) are recommended .	I	C
In patients at high risk, an LDL-C reduction of $\geq 50\%$ from baseline and an LDL-C goal of < 1.8 mmol/L (< 70 mg/dL) are recommended .	I	A
An LDL-C goal of < 2.6 mmol/L (< 100 mg/dL) is recommended in individuals at moderate risk.	I	A
An LDL-C goal of < 3.0 mmol/L (< 116 mg/dL) should be considered in low-risk individuals.	IIa	A

- Extremely high risk: For patients with recurrent ASCVD events within 2 years despite optimal therapy, an LDL-C goal of < 1.0 mmol/L (< 40 mg/dL) is recommended, as endorsed by the ESC and the Saudi dyslipidemia guidelines [196, 197].
- Very high risk: Individuals with documented ASCVD, either clinically diagnosed or unequivocally detected on imaging; patients with DM who have target organ damage, at least three major risk factors, or early-onset T1DM of long duration exceeding 20 years; individuals with severe CKD; a calculated SCORE2 of $\geq 10\%$ (or SCORE-OP $\geq 15\%$ in older adults) for the 10-year risk of fatal CVD; or FH with ASCVD or another major risk factor.
- High-risk: individuals with markedly elevated single risk factors, such as total cholesterol levels greater than 8 mmol/L (310 mg/dL), LDL-C levels exceeding 4.9 mmol/L (190 mg/dL), or BP at or above 180/110 mmHg; patients with FH without other major risk factors; those with DM without target organ damage but with a duration of 10 years or more or another additional risk factor; individuals with moderate CKD; or individuals with a calculated SCORE2 of $\geq 7.5\%$ to $< 10\%$ (or SCORE-OP $\geq 10\%$ to $< 15\%$) for the 10-year risk of fatal CVD.
- Moderate-risk group: individuals with milder conditions, including young patients with T1DM diagnosed before the age of 35 years or T2DM diagnosed before the age of 50 years, with a disease duration of less than 10 years and no additional risk factors; and individuals with a calculated SCORE2 of ≥ 2.5 to $< 7.5\%$ (or SCORE-OP $\geq 5\%$ to $< 10\%$) for the 10-year risk of fatal CVD.
- Low-risk group: individuals with a calculated SCORE2 of less than 2.5 % (or SCORE-OP $< 5\%$) for the 10-year risk of fatal CVD.

Table 12 - Psychosocial recommendation for CVD prevention.

Recommendation	Class	Level
Intensified psychosocial attention and support are recommended for patients with mental disorders to improve their adherence to CVD prevention or risk improvement measures (such as lifestyle changes and drug treatments).	I	C

This recommendation highlights the importance of integrating psychosocial support into cardiovascular prevention strategies to improve adherence and clinical outcomes. CVD= cardiovascular diseases.

heavy alcohol consumption raises cardiovascular risk [202]. Additionally, a multivariable Mendelian randomization study reported that alcohol use is associated with increased levels of high-density lipoprotein cholesterol (HDL-C), decreased TG, and higher BP levels, thus increasing the risk of CVD (Table 13) [203].

Cardiac rehabilitation. Cardiac rehabilitation (CR) is a comprehensive, multidisciplinary intervention designed for the secondary prevention of CVD by addressing and managing risk factors. It begins with a thorough patient assessment, followed by counselling on PA, exercise prescription, education, nutritional guidance, and psychosocial and vocational support [204]. The main goals of CR include lowering the risk of sudden death or reinfarction, managing cardiac symptoms, stabilizing or reversing the progression of atherosclerosis,

and enhancing psychosocial and vocational well-being. It also aims to improve physical function, including musculoskeletal function, cardiorespiratory fitness, and balance, reducing the risk of falls, sarcopenia, and frailty [133, 205, 206]. Modern CR programs emphasize enhancing patient well-being and health-related quality of life (HRQoL) [207, 208]. Table 14 lists all patients eligible for CR.

Benefits of cardiac rehabilitation

CR programs have proven to provide significant benefits following ASCVD events or revascularization, improving a variety of outcomes.

• Exercise-Based Cardiac Rehabilitation (EBCR)

Outcomes: EBCR significantly reduces cardiovascular mortality by 26% compared to no exercise

Table 13 - Alcohol consumption recommendation for cardiovascular prevention.

Recommendation	Class	Level
When addressing alcohol consumption, it is recommended to prioritize overall health and well-being. Individuals with comorbidities or a history of alcohol use disorder are strongly advised to abstain from alcohol to avoid potential harm.	I	A

This recommendation emphasizes abstinence in patients with comorbidities or a history of alcohol use disorder, aligning with evidence-based cardiovascular prevention strategies.

Table 14 - Eligible Patients For Cardiac Rehabilitation [205, 418–420].

1. Patients with acute coronary syndromes (ACS) (including those with non-ST elevation and ST-elevation myocardial infarction (MI) and unstable angina).
2. Patients undergoing reperfusion (such as coronary artery bypass surgery (CABG) and percutaneous coronary intervention (PCI)).
3. Patients undergoing revascularization, surgery for implantable cardiac devices, or heart valve replacements in non-ACS or HF settings.
4. Patients with heart failure (HF).
5. Patients with heart transplants and ventricular assist devices.
6. Patients with a confirmed diagnosis of exertional angina.

Cardiac rehabilitation is indicated for a broad spectrum of cardiovascular conditions and should be offered routinely to eligible patients. ACS = acute coronary syndrome; MI = myocardial infarction; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; HF = heart failure.

Table 15 - Exercise-Based Cardiac Rehabilitation Recommendation for CVD Prevention.

Recommendation	Class	Level
Comprehensive EBCR managing all recognized CV risk factors is recommended for all eligible patients immediately following a cardiac event or surgery.	I	A
Comprehensive EBCR programs lasting at least one year or a high CR dose (≥ 36 sessions) should be considered for patients with HF.	IIa	A

These recommendations highlight the role of structured EBCR in reducing risk and improving long-term outcomes in patients with cardiovascular disease and heart failure. EBCR= Exercise Based Cardiac Rehabilitation, CV= Cardiovascular, CR= Cardiac Rehabilitation, HF= Heart failure.

control (Risk ratio [RR] 0.74, 95% CI 0.64, 0.86) and hospital admissions by 18% (RR 0.82, 95% CI 0.70, 0.96) in patients with CHD [209]. Moreover, EBCR decreases cardiovascular mortality by 58% (95% CI 0.21, 0.88), MI by 30% (95% CI 0.54, 0.91), and cerebrovascular events by 60% (95% CI 0.22, 0.74) (Table 15) [210].

- **Comprehensive CR Programs:** In combination with cardioprotective medications targeting BP and lipids, comprehensive CR programs have been shown to reduce all-cause mortality. The Cardiac Rehabilitation Outcome Study (CROS II) confirmed that CR after ACS and coronary artery bypass grafting (CABG) results in reduced total mortality [211]. Additionally, the American Association for Cardiovascular and Pulmonary Rehabilitation (AACVPR) notes that CR can extend life expectancy by up to five years and lower all-cause mortality by up to 30% [212].
- **Improvement in Functional Capacity:** CR has a profound impact on improving functional capacity. Research by Prabhu and colleagues demonstrated that treadmill and cycle ergometry training significantly enhanced functional capacity and PA levels following coronary revascularization procedures [213].
- **Effects on Aging and CVD:** CR also helps mitigate the negative effects of aging and CVD by enhancing functional independence, musculoskeletal health, cardiorespiratory performance, and cognitive function [214].
- **Health-Related Quality of Life (HRQoL):** Beyond reducing hospitalizations, MI, and cardiovascular mortality, CR has been shown to improve disease-

specific HRQoL. For instance, in patients with HF, CR led to clinically important improvements in HRQoL, as indicated by a reduction in the Minnesota Living with Heart Failure (MLHF) questionnaire score [215].

- **Mental Health Benefits:** Research on the mental health effects of CR is growing. A randomized controlled trial (RCT) found that CR, when coupled with stress management, significantly reduced ASCVD events compared to standard CR alone (HR 0.49) [216]. Early mobilization after acute MI has also been shown to reduce depression, and systematic reviews suggest that CR can alleviate symptoms of depression and anxiety [217].
- **Impact on Heart Failure:** In patients with HF, CR has been shown to reduce both overall hospital admissions and HF-specific hospitalizations compared to no exercise control [218]. Long-term CR (lasting more than one year) may further improve all-cause mortality [218, 219].
- **Benefits for HFpEF and heart failure with mid-range ejection fraction (HFmrEF):** For patients with chronic HFpEF, supervised exercise training provides a range of pleiotropic effects, including improvements in exercise capacity, cardiorespiratory fitness, peripheral muscle function, and HRQoL, without significantly affecting LV function [220]. Similarly, exercise training in patients with HFmrEF enhances early-to-late mitral inflow velocity ratios and reduces the deceleration time of early filling [221].
- **Cardiac Pathophysiology and Autonomic Nervous System Recovery:** Early involvement in CR plays a critical role in reversing cardiac

pathophysiology and supporting the physiological recovery of the myocardium after cardiac events while also resynchronizing the autonomic nervous system [222]. Furthermore, CR enhances the capacity of circulating progenitor cells, which aids in restoring diseased endothelium and improving myocardial perfusion, flow-mediated dilation, endothelial function, skeletal muscle neovascularization, and LV function [223].

- **Autonomic Nervous System Health:** CR improves heart rate variability, which is a key indicator of autonomic nervous system function and overall cardiac health [224]. This effect is achieved by promoting parasympathetic activity and reducing sympathetic tone, further contributing to improved cardiovascular outcomes.

In conclusion, CR offers a broad range of benefits, including reductions in mortality, improvements in functional capacity, mental health, and HRQoL, as well as positive impacts on cardiac physiology and autonomic nervous system function. These benefits make CR a cornerstone of post-ASCVD care and recovery.

Components of cardiac rehabilitation

The major components of CR programs are outlined in Table 16. It is important to note that sarcopenia is closely associated with CVD and its risk factors, such as hypertension, dyslipidemia, and DM, independent of existing CVD. Furthermore, CVD exacerbates the negative outcomes of sarcopenia, including falls, frailty, increased hospitalization, and mortality [225–227]. Hence, early screening for falls and sarcopenia is crucial in identifying potential frailty, enabling timely therapeutic interventions that can help mitigate these adverse consequences and improve patient outcomes [133, 228].

Barriers to CR implementation in Saudi Arabia

Despite the proven benefits of CR, referral services remain underutilized in Saudi Arabia. Several factors contribute to the low participation rate in CR programs:

- **Patient-related factors** include characteristics such as age, sex, socio-economic status, competing obligations, limited awareness of CR, and other health issues that divert attention from the importance of CR [229, 230].
- **Physician-related factors** include low referral rates to CR programs and skepticism regarding the benefits of CR [230].
- **Logistical barriers** include a lack of transportation, long travel distances to CR centers (with cardiac centers mainly located in major cities), and com-

munication challenges between staff and patients [231], with a potential consideration of telehealth or telerehabilitation.

- **Lack of CR programs and centers**, coupled with a shortage of qualified healthcare professionals, further hinders access to CR [232].
- **Barriers at the health-system level:** the most significant barrier to nationwide CR implementation in Saudi Arabia. Currently, private hospitals in the country do not offer CR programs, and only a few government hospitals provide CR services, typically to selective cases [232]. Moreover, the absence of a well-structured and comprehensive CR program remains a key challenge.

Strategies to enhance the implementation, increase participation, and improve adherence to CR programs in Saudi Arabia are comprehensively outlined in Table 17.

Chapter 4. Screening and risk markers of cardiovascular diseases.

In this section, key recommendations for the screening and identification of risk markers for CVD prevention are systematically addressed in Table 18, providing evidence-based approaches to identify at-risk individuals early and implement targeted interventions to prevent CVD effectively.

In addition to conventional risk scores such as Framingham Risk Score (FRS), QRISK, and the Pooled Cohort Equations (PCE), there is a growing interest in genetic risk assessment. Polygenic risk scores (PRS), such as the Genome-wide Polygenic Score (GPS), can enhance prediction in young adults and patients with borderline risk. While not yet standard in Saudi Arabia, they hold promise for research and future clinical use [233–235].

High-sensitivity c-reactive protein and cardiovascular risk assessment. The high-sensitivity CRP (hsCRP) test detects very low levels of CRP, enabling more accuracy and precision in detecting chronic inflammation compared to standard CRP tests [196]. Elevated hsCRP (≥ 2.0 mg/L) influences the risk of ASCVD and warrants clinician-patient discussions about risk and potential management strategies [236]. A randomized controlled trial (RCT) in asymptomatic individuals with elevated hsCRP and normal LDL-C found a significant reduction in cardiovascular events following treatment with rosuvastatin for two years compared to placebo [237]. In Saudi Arabia, a cross-sectional study reported significantly higher hsCRP levels in patients with CAD compared to healthy individuals. This suggests that hsCRP measurement can improve coronary risk assessment in Saudi patients with CAD [238].

Table 16 - Main Components of Cardiac Rehabilitation Programs (adapted from Ambrosetti et al. 2021 and Brown et al. 2024 [204, 212]).

Component	Specification
Patient Assessment	Medical history (diagnosis, procedure, CV risk factors, comorbidities, disabilities, adherence); mental status, mood, cognition; sleep pattern and apnea risk; CVD symptoms (dyspnea, angina); daily activity and exercise level; fall risk; physical exam (cardiopulmonary, neuromuscular); CV function (ECG, HR variability, imaging); blood tests (HbA1c, lipid profile, renal panel, peptides); sarcopenia screening; frailty assessment; peak exercise capacity; HRQoL; literacy and education needs; goals of care, barriers, preferences; return-to-work planning.
Physical Activity Counselling	Educate on harms of inactivity; assess motivation and opportunities; recommend enjoyable, feasible activities; set realistic personal goals; advise on progression; address barriers (dyspnea, limitations); reduce sedentary time (active transport, breaks from sitting, chair-based/alternative exercises); recommend ≥ 150 min/week of moderate or ≥ 75 min/week vigorous aerobic activity; allow shorter bouts (<10 min) for deconditioned patients; add resistance training 2–3×/week.
Exercise Training	Individualized prescription using FITT (frequency, intensity, time, type) with progression (FITT+VP). Frequency: Aerobic 2–3 days/week → progress to 6–7; Resistance 2–3 non-consecutive days/week. Intensity: Low (30–39% VO_2 , 57–63% HRmax, Borg 9–11), Moderate (40–59% VO_2 , 64–76% HRmax, 12–13 Borg), High (60–89% VO_2 , 77–95% HRmax, 14–17 Borg). “Talk test” may be used. Time: 20–30 min → progress to 45–60 min. Type: Aerobic (walking, cycling, swimming, rowing, ergometry), interval or continuous; Resistance (30–70% 1-RM upper body, 40–80% 1-RM lower body, 10–15 reps/set); flexibility, balance, inspiratory muscle training; NMES as alternative for advanced disease. Supervision: Strongly recommended in initial phases, especially for high-risk patients, with HR, BP, and rhythm monitoring.
Nutritional Counseling	Assess caloric intake, fat/sodium content, and eating habits; adjust energy intake during intensive exercise; educate patients/families on diet goals, food content, and strategies for healthy nutrition.
Weight Control Management	Measure weight, height, waist circumference; analyze dietary habits and physical activity; provide behavioural and nutrition counselling with follow-up; recommend weight reduction for obese (BMI >30 or WC >102 cm men / >88 cm women, WHtR <0.5) and consider for overweight (BMI >25 or WC >94 cm men / >80 cm women) especially with risk factors (HTN, dyslipidemia, smoking, diabetes).
Risk Factors Management	Lipids: assess profile and manage with diet, medications, activity. BP: regular rest and exercise BP monitoring; lifestyle + pharmacologic interventions. Smoking: encourage quitting all tobacco/e-smoking; provide monitoring, referrals, and pharmacologic support as needed.
Psychosocial Management	Assess psychosocial risk factors (low SES, poor support, stress, PTSD, hostility, isolation, cognitive impairment, depression, anxiety, sexual dysfunction). Use screening tools (HeartQoL for CHD, KCCQ for HF, HADS for anxiety/depression). Interventions: multimodal behavioural programs (education, exercise, psychotherapy), psychiatric/psychology referral when needed, family involvement, self-help strategies, social support, and vocational reintegration post-event.
Evaluation & Audit	Structured program evaluation and follow-up to monitor patient progress and ensure goals are achieved.

This table summarizes the multidisciplinary elements of comprehensive cardiac rehabilitation programs, emphasizing individualized, holistic care.

1-RM = one repetition maximum; BP = blood pressure; BMI = body mass index; CHD = coronary heart disease; CR = cardiac rehabilitation; CVD = cardiovascular disease; ECG = electrocardiogram; FITT = frequency, intensity, time, and type; HbA1C = glycated hemoglobin; HDL-C = high-density lipoprotein cholesterol; HF = heart failure; HR = heart rate; HeartQoL = HRQoL = health-related quality of life; KCCQ = Kansas City Cardiomyopathy Questionnaire; LDL-C = low-density lipoprotein cholesterol; MET = metabolic equivalent task; NMES = neuromuscular electrical stimulation; PSRF = psychosocial risk factors; SBP = systolic blood pressure; WHtR = waist-to-height ratio.

Table 17 - Recommended solutions to improve CR implementation, participation and adherence in Saudi Arabia.

Recommendation	Class	Level
To Improve Referral		
To assist HCPs in deciding whether to refer patients for CR programs or not, a national guiding standardized referral checklist for all HCPs is recommended .	I	B
Increasing the number of private and governmental hospitals with comprehensive CR centers across Saudi Arabia, especially in dispersed geographic areas, including rural areas, is recommended .	I	B
Increasing the number of experienced and well-trained HCPs in Saudi Arabia is recommended .	I	B
Electronic or automatic referrals, referral and liaison visits, structured follow-up by HCPs, and early program initiation after discharge are recommended to improve CR referral and uptake.	I	B
To Improve Participation & Adherence		
Patients who are eligible for CR are recommended to be automatically referred to the CR center at the time of hospital discharge.	I	B
Peer/patient navigation [in which a navigator (usually a trained layperson) provides education about CR to a patient in a one-to-one setting] is recommended .	I	B

This table outlines system-level and patient-centered strategies to strengthen CR referral pathways and improve patient engagement and adherence in Saudi Arabia. CR = cardiac rehabilitation; HCPs = healthcare professionals.

Table 18 - Screening and risk markers recommendations for CVD prevention.

Recommendation	Class	Level
Screening for hsCRP (≥ 2.0 mg/L) should be considered in adults aged 40 to 75 years without DM and at intermediate ASCVD risk [196, 237, 421, 422] *.	IIa	A
Lp(a) measurement may be considered once in a lifetime in Saudi adults to aid in the risk assessment of ASCVD [244] *.	IIb	C
Lipid assessment, using the basic lipid panel on a non-fasting blood sample and including TC, LDL-C, HDL-C, and TG, is recommended to estimate and refine ASCVD risk by SCORE system for adults aged 18 to 65 years [250–254] *.	I	C
Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
If available, Apo-B may be considered as an alternative to LDL-C as the primary measurement for screening, diagnosis, and management [196, 255] *.	IIb	C
Apo-B analysis should be considered over LDL-C or non-HDL-C for risk assessment in patients with high TG levels, DM, obesity, metabolic syndrome, or very low LDL-C [196, 255] *.	IIa	C
CAC scoring should be considered , when available, to refine ASCVD risk calculation and aid in decision-making for adults aged 18 to 65 years [256–258] *.	IIa	C
BMI, waist circumference, and waist-to-hip ratio are recommended to be systematically considered to predict ASCVD risk.	I	A
Comprehensive CVD risk assessments are recommended in individuals with unfavorable body anthropometric measurements (high BMI, high waist-to-hip ratio) [5] *.	I	B
ABI is not recommended for estimation or reclassification of ASCVD risk for adults aged 18 to 65 years with high risk for PAD.	III	C
Validated electronic (oscillometric) devices are recommended to measure BP and in the diagnosis of HTN in Saudi patients aged 18 to 65 years.	I	A

This table summarizes recommended screening tools and biomarkers for cardiovascular risk stratification, with emphasis on laboratory, imaging, and anthropometric assessments relevant to the Saudi population. hsCRP = high-sensitivity C-reactive protein; DM = diabetes mellitus; ASCVD = atherosclerotic cardiovascular disease; Lp(a) = lipoprotein(a), TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; SCORE = systemic coronary risk estimation; non-HDL-C = non-high-density lipoprotein cholesterol; Apo-B = apolipoprotein B; CAC = coronary artery calcium; BMI = body mass index; CVD = cardiovascular disease, ABI = ankle-brachial index; PAD = peripheral artery disease, BP = blood pressure; HTN = hypertension.

*Statements with new evidence following the 2021 ESC guideline.

Lipoprotein(a) as a causal biomarker in cardiovascular risk stratification. Lipoprotein(a) [Lp(a)], comprising an LDL-C-like particle covalently bound to apolipoprotein(a), is implicated in atherosclerosis (particularly aortic artery) and thrombosis [239]. Epidemiologic and genetic studies involving large cohorts demonstrate a continuous association between Lp(a) levels and CVD outcomes (including ASCVD, aortic valve stenosis, cardiovascular mortality, and all-cause mortality) across various ethnic groups. Elevated Lp(a) remains a risk factor even at very low levels of LDL-C levels [240]. An Lp(a) concentration above the 80th percentile of the general population (50 mg/dL) at baseline and during statin treatment is a significant genetic risk factor for CVD, independent of LDL-C levels [241, 242]. The additional information on Lp(a) to risk scores incorporating conventional lipid measures (total cholesterol [TC] and HDL-C) led to modest CVD prediction among individuals without known CVD [243]. Although data from Saudi Arabia are limited, Habib et al. found that Lp(a) levels significantly correlated with coronary vessel and Gensini scores [244]. Compared to their healthy peers, Saudi patients with CAD had significantly higher levels of Lp(a). This runs in line with recent large studies demonstrating a positive correlation between circulating Lp(a) levels, CHD lesion count, and Gensini scores in T2DM patients [245, 246]. Incorporating

Lp(a) measurement into risk assessments for Saudi adults, particularly those at moderate to high risk of ASCVD, is recommended due to its genetic predisposition, ability to enhance risk stratification, and enable early intervention.

Although the elevated Lp(a) has no approved treatment yet, ongoing trials, such as the HORIZON study (NCT04023552), carry a therapeutic promise for improved cardiovascular outcomes with elevated Lp(a) levels. The high expectations are mainly attributed to the substantial improvement that occurred in previous phase I–II trials with therapies that can suppress apo(a) synthesis at the RNA level, such as antisense oligonucleotides (ASO) and small-interfering RNA (siRNA) [247, 248].

Lipid panel testing and apolipoprotein B in cardiovascular risk management. LDL-C and other apolipoprotein B-containing lipoproteins play a causal role in ASCVD. The 2022 Saudi guidelines for the management of dyslipidemia recommend measuring TC, TG, HDL-C, LDL-C, and non-HDL-C (calculated as TC minus HDL-C) as the primary lipid panel to assess ASCVD risk and guide therapy [196, 249].

Observational studies show that elevated LDL-C, TG, and TC levels increase the risk of IHD, ACS, and CVD-related mortality [250, 251]. Several studies have

Table 19 - CAC Staging to Guide Therapy Intensity [423].

CAC Score	Recommended Management
CAC = 0	Defer therapy unless other risk enhancers are present
CAC 1–99	Consider a moderate-intensity statin
CAC ≥100 or ≥75th percentile	Initiate statin (≥50% LDL-C reduction)
CAC ≥300	Treat as very high risk; target LDL-C <55 mg/dL, consider non-statin add-ons

Abbreviations: CAC = coronary artery calcium; LDL-C = low-density lipoprotein cholesterol.

highlighted the significance of lipid-related risk factors in cardiovascular health within the Saudi population. Ashmaig et al. identified high TG, low HDL-C, elevated [Lp(a)], and small, dense LDL-C as critical contributors to CHD risk [252]. Similarly, Al Sifri et al. observed that suboptimal LDL-C control was associated with an increased prevalence of stable CHD and ACS in Saudi patients [253].

Expanding on these findings, Alshehri demonstrated a significant relationship between the extent and severity of CAD and lipid abnormalities, with TC and low HDL-C correlating with the number of affected vessels, while high LDL-C and low HDL-C were linked to disease severity [254]. Building on these insights, Alabduljabbar et al. recently developed a CVD risk prediction model tailored to the Saudi population, incorporating HDL-C as a key risk factor [251]. Moreover, Almahmoud et al. reported that low HDL-C levels (<1.1 mmol/L) were strongly associated with a heightened risk of all-cause mortality and IHD, while elevated TC levels were linked to an increased risk of HF in individuals aged 60 years and older [250]. Apolipoprotein-B- directly measures atherogenic particles, offering a refined ASCVD risk estimate [196, 255].

Coronary artery calcium scoring in cardiovascular risk prediction and management. Coronary artery calcium (CAC) scoring predicts cardiac events and enhances CVD risk stratification. Studies in Saudi Arabia demonstrate significant associations between CAC scores and coronary events, LDL-C, hypertension, dyslipidemia, and CAD [256–258]. When added to conventional risk factors, CAC scoring can reclassify individuals around risk thresholds but may incorrectly elevate risk categorization for some. Its cost-effectiveness, availability, and proper clinician education should be considered before widespread implementation [5, 237]. CAC staging may also guide therapeutic decision-making and intensity, as outlined in Table 19.

Body mass index and waist measurements in cardiovascular risk prediction. BMI, waist circumference, and waist-to-hip ratio are associated with CVD risk [259]. BMI > 25 necessitates evaluation for additional CVD risks such as hypertension, dyslipidemia, insulin resistance, and T2DM. However, these measures do not

significantly enhance CVD risk prediction through reclassification models [5, 260, 261].

Ankle-brachial index in cardiovascular risk assessment. The ankle-brachial index (ABI) is a strong, independent predictor of cardiovascular morbidity and mortality [262]. The 2021 ESC CVD prevention guidelines consider ABI as a risk modifier in CVD risk assessment [5]. Also, ACC/AHA 2019 guidelines on the primary prevention of ASCVD consider an ABI < 0.9 as a risk enhancer in ASCVD prediction and guide primary prevention strategies [263]. In Saudi patients, ABI is significantly correlated with CAD prognosis [264].

Blood pressure measurement and cardiovascular risk assessment. Precise BP measurement is critical for assessing cardiovascular risk. Studies show a higher hazard of MACE in individuals with elevated systolic BP>125 mmHg (HR 1.1, 95% CI, 1.06–1.14) [265]. Accurate BP measurement requires at least 14 minutes, including rest and conversation, but this duration is rarely achieved in routine clinical settings, potentially leading to BP overestimation in healthy individuals [266].

Chapter 5. Management strategies of individual risk factors.

Hypertension. Initial treatment of hypertension with combination therapy, even if low-dose, is superior to monotherapy in terms of BP reduction and time required to achieve the desired BP target without increasing the risk of AEs [267]. Hence, initial combination therapy should be considered the standard of care for hypertension [5]. When available, this combination should be administered as a fixed-dose, single-pill regimen to improve treatment adherence [267, 268]. However, patients with baseline BP close to the recommended target, as well as very old or frail patients, can be treated with monotherapy [5, 267].

Although all major classes of BP medications are beneficial in reducing cardiovascular events, the recommended treatment algorithm begins with a dual combination of renin-angiotensin system (RAS) blocker and calcium channel blocker (CCB) or diuretic. If further BP lowering is necessary, a triple combination of RAS blocker and diuretic (step 2) is introduced. If the

Table 20 - BP Management Recommendations for CVD Prevention.

Recommendation	Class	Level
A two-drug combination is recommended as initial therapy for all people with HTN except frail elderly patients and younger people with low-risk, grade 1 HTN [424–426] *.	I	A
The recommended preferred combination should include a RAS blocker plus a CCB or a diuretic [427] *.	I	A
If BP control is still not achieved (i.e., resistant hypertension) [#] , then spironolactone is recommended if tolerated. If not tolerated, another aldosterone antagonist or vasodilating beta-blocker (BB) are recommended [428] *.	I	A
RAS blockers (ACEIs or ARBs) are the recommended initial therapy for patients with HTN and diabetes, especially in the presence of microalbuminuria or proteinuric chronic kidney disease (urinary protein level > 150 mg in 24 hours or albumin to creatinine ratio > 30 mg/mmol).	I	A

These recommendations emphasize combination therapy as the cornerstone of hypertension management, with adjustments for resistant hypertension and specific comorbid conditions such as diabetes and chronic kidney disease. HTN = hypertension; RAS = renin-angiotensin system; CCB = calcium channel blocker; BP = blood pressure; ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; BB = beta-blocker. [#]Notes: Resistant hypertension is defined as uncontrolled blood pressure despite the use of three or more antihypertensive agents. Statements marked with * reflect new evidence following the 2021 ESC guideline.

target BP is still not reached, spironolactone or a vasodilating beta-blocker is added (step 3) [269].

Patients with resistant hypertension, defined as uncontrolled BP despite the use of three or more antihypertensive agents, should be referred to a specialist, particularly in patients with suspected secondary hypertension due to conditions such as primary hyperaldosteronism, renal artery stenosis, or pheochromocytoma [270]. Those patients benefit from the addition of spironolactone, as its mineralocorticoid receptor blockade helps overcome salt retention and treatment resistance [271]. In cases where spironolactone is not tolerated, alternatives like amiloride or other aldosterone antagonists should be considered [271–273].

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are significantly effective in reducing albuminuria and preventing the progression of diabetic retinopathy and nephropathy [274]. They also provide significant cardioprotective effects, reducing all-cause mortality, cardiovascular mortality, and major cardiovascular events in patients with both hypertension and diabetes [7].

RAS blockers are the most effective class of pharmacological antihypertensive agents for patients with ESRD [275], with their reno-protective effects being most prominent in those with albuminuria or proteinuria [276]. If additional BP lowering is needed, an ACE inhibitor or ARB should be combined with other antihypertensive medications, such as CCBs (Table 20) [277].

Dyslipidemia. Statins, inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase enzyme, reduce LDL-C by approximately 30% with moderate-intensity statins and up to 50% with high-intensity statins [5]. By lowering LDL-C and triglycerides, statins reduce the morbidity and mortality associated with ASCVD and decrease the need for coronary interventions, making them the drug of choice for patients at increased AS-

CVD risk [255]. Initiating statin therapy during the childhood period in patients with FH has been shown to reduce the risk of CVD in adulthood, as demonstrated by a 20-year follow-up study [278].

Ezetimibe, which reduces plasma LDL-C levels by 15 - 20% [279], is often used in combination with statins to provide additional LDL-C lowering and improve cardiovascular outcomes, including cardiovascular mortality, non-fatal MI, unstable angina requiring hospitalization, coronary revascularization, and non-fatal stroke following ACS [280]. It is recommended to add ezetimibe when the LDL-C target is not achieved with statins alone or to use it as an alternative if statins are not tolerated or contraindicated [5].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, such as alirocumab and evolocumab, lower LDL-C by up to 60% and lipoproteins by 20-50% [281], independently of the background therapy. These agents are beneficial in reducing cardiovascular events in patients at high or very high risk of CVD, including those with DM [282, 283]. Ongoing research, such as the VESALIUS-CV study, is exploring the effects of evolocumab in lower-risk patients without a history of MI or stroke [284]. Efficient, pragmatic, and immediate LDL-C lowering is critical for very high-risk patients, with the main goal being LDL-C reduction rather than focusing solely on the drug class used [285].

Bempedoic acid, an adenosine triphosphate–citrate lyase (ACL) inhibitor, can also be used to reduce LDL-C. The CLEAR Outcomes randomised trial reported the superiority of bempedoic acid over placebo in patients who were unable to receive statins. After a follow-up of 3.4 years, the trial concluded lower LDL-C and better cardiovascular outcomes with bempedoic acid [286].

Inclisiran, a siRNA therapy targeting PCSK9 synthesis, achieves sustained LDL-C reduction with

Table 21 - Lipid management recommendations for CVD prevention.

Recommendation	Class	Level
A statin therapy is recommended to be prescribed up to the highest tolerated dose to reach the specific LDL-C target for each specific risk group.	I	A
If the LDL-C goal is still not achieved with the maximum tolerated dose of statins, a combination with ezetimibe therapy is recommended [429, 430] *.	I	A
Patients with FH and at very high risk* of CVD are recommended to be treated with a high-intensity statin in combination with ezetimibe. If the target LDL-C level is not achieved, then adding PCSK9 monoclonal antibodies is recommended.	I	C
In the primary prevention for very high-risk patients [#] , without familial hypercholesterolemia (FH), not achieving the LDL-C goal on the highest tolerated dose of statin plus ezetimibe, then combination with a PCSK9 inhibitor may be considered .	IIb	C
Statin monotherapy or in combination with ezetimibe is recommended in patients with non-dialysis dependent CKD stages 3 to 5.	I	A
In patients with dialysis-dependent CKD without ASCVD, initiating statin therapy is not recommended .	III	A

LDL-C = low-density lipoprotein cholesterol; FH = familial hypercholesterolemia; CVD = cardiovascular disease; PCSK9 = proprotein convertase subtilisin/kexin type 9; CKD = chronic kidney disease; ASCVD = atherosclerotic cardiovascular disease.

***Very High-risk group:** Individuals with DM and established ASCVD and/or severe target organ damage (TOD) include those with an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m² regardless of albuminuria, those with an eGFR of 45-59 mL/min/1.73 m² with microalbuminuria (albumin-to-creatinine ratio [ACR] of 30-300 mg/g), patients with proteinuria (ACR >300 mg/g), and those with microvascular disease characterized by the presence of microalbuminuria, retinopathy, and neuropathy [5].

*Statements with new evidence following the 2021 ESC guideline.

twice-yearly dosing [287]. However, the efficacy data await confirmation from ongoing trials, such as ORION-4 (NCT03705234).

CKD patients with dyslipidemia, including those on dialysis or renal transplantation, are at high risk for cardiovascular morbidity and mortality due to atherosclerosis [288]. These patients, especially those in stages 3-5 of CKD, should be treated with high-intensity statins if they have dyslipidemia and established ASCVD [196]. Statin therapy, either alone or in combination with ezetimibe, has been shown to improve ASCVD outcomes in CKD patients [289]. A meta-analysis found that statin-based therapy reduced the risk of a first major vascular event by 21% per mmol/L reduction in LDL-C in CKD patients [290]. In addition, statins in non-dialysis-dependent CKD patients lead to a marked reduction in all-cause mortality, cardiovascular mortality, cardiovascular events, and stroke [289].

On the other hand, statin therapy is not recommended for patients on dialysis (hemodialysis or peritoneal dialysis) unless they are already on statin therapy or statin/ezetimibe at the time of dialysis [5, 288]. This recommendation is based on findings from major statin-based trials, including SHARP (Study of Heart and Renal Protection), 4D (Die Deutsche Diabetes Dialyse Studie), and AURORA trials (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events), which showed no benefit from statins in the dialysis patient population (Table 21) [290].

Diabetes. The paradigm for ASCVD prevention in individuals with T2DM should align with that for in-

dividuals without T2DM, emphasizing control of both BP and LDL-C levels [5]. Metformin has long been recommended as the first-line treatment for hyperglycemia in T2DM patients and remains the mainstay of therapy for the majority of patients diagnosed with T2DM [5, 291].

Sodium-glucose co-transporter-2 (SGLT2) inhibitors have been shown to reduce ASCVD, HF, and renal risks irrespective of baseline HbA1c or whether patients are on metformin [5]. The CREDENCE trial demonstrated that canagliflozin significantly lowered the risk of renal failure and cardiovascular events in T2DM patients with renal disease compared to placebo. After a median follow-up of 2.62 years, the primary outcome – a composite of ESRD – was 30% lower in the canagliflozin group [292]. Similarly, the DAPA-CKD trial found that dapagliflozin significantly reduced the risk of a composite outcome of a sustained reduction in eGFR by at least 50%, ESRD, or death from renal or cardiovascular causes, regardless of the presence of T2DM [293]. A meta-analysis also confirmed that SGLT2 inhibitors offer robust benefits, including a reduction in hospitalization for HF and progression of renal disease in T2DM patients, irrespective of existing ASCVD or a history of HF [294].

In a large meta-analysis involving 56,000 patients with T2DM, GLP-1receptor agonists (GLP-1RAs) were associated with a 12% reduction in MACE, 12% reduction in cardiovascular mortality, 16% reduction in stroke, 9% reduction in MI, 12% reduction in all-cause mortality, and 9% reduction in hospital admissions for HF [295]. GLP-1RAs also demonstrated beneficial

Table 22 - T2DM Management Recommendations for CVD Prevention.

Recommendation	Class	Level
In individuals with T2DM and ASCVD, using a GLP-1RA or SGLT2i with established outcome benefits is recommended to decrease CV and/or cardiorenal outcomes [431–434] *.	I	A
In patients with T2DM and TOD, using an SGLT2i or GLP-1RA with established outcome benefits may be considered to decrease CV risk and mortality [432, 435–437] *.	IIb	A
In patients with T2DM but without established ASCVD, HF, or CKD, the use of an SGLT2 inhibitor or GLP-1RA should be considered [431, 434, 438] *.	IIa	A
In individuals with T2DM and ASCVD, using a GLP-1RA or SGLT2i with established outcome benefits is recommended to decrease CV and/or cardiorenal outcomes [431–434] *.	I	A
In patients with T2DM and CKD, the use of an SGLT2 inhibitor is recommended to improve ASCVD and/or cardiorenal outcomes.	I	A
In patients with T2DM and HFrEF, the use of an SGLT2 inhibitor with proven outcome benefits is recommended to lessen HF hospitalizations and CV death [434, 436, 439–441] *.	I	A

T2DM = type 2 diabetes mellitus; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; HF = heart failure; GLP-1RA = glucagon-like peptide-1 receptor agonist; SGLT2i = sodium-glucose cotransporter 2 inhibitor; CV = cardiovascular; TOD = target organ damage; HFrEF = heart failure with reduced ejection fraction.

*Statements with new evidence following the 2021 ESC guideline.

Table 23 - Antithrombotic Recommendations for CVD Prevention.

Recommendation	Class	Level
Low-dose aspirin (100 mg/day) is recommended for secondary prevention of CVD.	I	A
Low-dose aspirin may be considered for primary prevention of CVD in patients with DM at high or very high CVD risk in the absence of clear contraindications [442, 443] *.	IIb	A
Antiplatelet therapy is not recommended in individuals with low/moderate CV risk due to the increased risk of major bleeding [444] *.	III	A

CVD = cardiovascular disease; DM = diabetes mellitus; CV = cardiovascular.

*Statements with new evidence following the 2021 ESC guideline.

effects on kidney outcomes, reducing a composite kidney outcome by 17%, primarily through a reduction in urinary albumin excretion [295].

For patients with diabetes at high risk of CVD, SGLT2 inhibitors or GLP-1RAs should be initiated irrespective of their current background therapy, and the initiation of these agents should not be delayed due to metformin treatment [5, 296]. Additionally, dapagliflozin (an SGLT2 inhibitor) has shown favorable outcomes in patients with both HF with reduced ejection fraction (HFrEF) and HFpEF (Table 22). A meta-analysis by Ali et al. demonstrated that dapagliflozin reduced the incidence of a composite outcome of HF hospitalization or urgent HF visits, offering significant benefits for these patients [297].

Antithrombotic therapy. Although aspirin has been shown to reduce the risk of non-fatal MI and ischemic stroke, it should not be routinely prescribed for primary prevention in patients without established ASCVD due to its associated risk of major bleeding, intracranial bleeding, and major gastrointestinal bleeding [298]. In healthy elderly individuals (≥ 70 years of age), primary prevention with low-dose aspirin was found to significantly increase the risk of major hemorrhage without significantly lowering CVD risk compared to placebo [299].

In patients with high or very high CVD risk who are not at increased risk of bleeding, the benefits of aspirin might outweigh the bleeding risks [300]. A recent meta-analysis showed that in patients with DM and no established CVD, aspirin led to a significant reduction in the risk of MACE [301], which supports its consideration in high or very-high-risk individuals [5]. Ultimately, the use of low-dose aspirin should be individualized, carefully considering each patient's baseline CVD and bleeding risks (Table 23) [5, 301].

Chapter 6. Risk management of disease-specific cardiovascular disease. This section will discuss CVD management in specific CV-related diseases from a clinical perspective. These conditions include CAD, HF, cerebrovascular disease, peripheral arterial disease, and AF [302].

Coronary artery disease. Managing CAD or CHD aims to reduce mortality and hospitalization and improve QoL by decreasing cardiac workload and improving coronary blood flow. CAD is classified into chronic coronary syndrome (CCS) and ACS, which include ST-elevation myocardial infarction (STEMI), non-STEMI, and unstable angina [303].

Historically, aspirin was used for primary prevention of CVD, but as of 2021, updated guidelines (USPSTF,

ACC, ESC) recommend careful evaluation of aspirin use based on its benefit-risk profile [304].

Aspirin remains a cornerstone in dual antiplatelet therapy (DAPT) for ACS patients [305, 306], with a 6-month DAPT course for CCS patients post-percutaneous coronary intervention (PCI) [307]. DAPT duration may be adjusted based on clinical judgment [308].

For CCS patients undergoing elective PCI, a standard six-month course of DAPT (aspirin combined with, preferably, clopidogrel) is recommended [309]. In some cases, especially if bleeding risks are high, the duration may be shortened to 1-3 months [309]. For secondary prevention beyond 12 months, especially in those with moderate-to-high ischemic risk and no bleeding risk, additional antithrombotic therapy (such as a P2Y₁₂ inhibitor or low-dose rivaroxaban [2.5 mg bid]) may be added [309, 310]. Clopidogrel is the first-choice P2Y₁₂ inhibitor for CCS patients undergoing PCI, though prasugrel and ticagrelor may be considered when there are anatomical or procedural complexities [309, 310]. A large retrospective cohort study showed no significant difference in the incidence of MI events or death between patients on prasugrel or ticagrelor versus clopidogrel (ticagrelor/prasugrel vs clopidogrel: 2.7% vs 3.1%, adjusted hazard ratio (adjHR) = 0.86, 95% CI: 0.62-1.17, $p=0.33$) [310].

For CCS patients with comorbidities like hypertension, HF with low left ventricular ejection fraction (LVEF <40%), diabetes (DM), or CKD, the initiation of **angiotensin-converting enzyme (ACE) inhibitors** or **angiotensin receptor blockers (ARBs)** (if ACE inhibitors are not tolerated) is recommended [309]. Previous trials have shown that ACE inhibitors or ARBs reduce the risk of MI, stroke, and mortality while improving outcomes in patients with HF (LV dysfunction), a history of vascular disease, or DM [311]. A large retrospective study conducted in Korea, which included 12,134 patients, compared the effects of ACE inhibitors and ARBs on cardiovascular outcomes in a real-world clinical setting. This study found a 52% reduction in HF incidence among patients treated with ARBs (HR [95% CI] = 0.48 [0.39-0.60], $p<0.001$) but a 62% increase in cerebrovascular events (HR [95% CI] = 1.62 [1.26-2.07], $p<0.001$) [312]. No significant differences were observed between the two ACE inhibitors and ARBs in terms of IHD or MACE ($p > 0.5$).

The role of **beta-blockers (BBs)** in patients with chronic HFrEF or systolic dysfunction has been well established [313]. However, beta-blocker therapy is not without risks and should be assessed individually. Clinicians should be aware of the common side effects of BB use, which include fatigue, depression, bradycardia,

heart block, bronchospasm, peripheral vasoconstriction, postural hypotension, impotence, and the masking of hypoglycemia symptoms (Table 24) [309].

Heart failure with reduced ejection fraction. Pharmacological treatment is the mainstay of treatment of patients with HFrEF and should be initiated while considering other treatment options such as device therapy or non-pharmacological options. Adopting a healthy lifestyle, including consistent PA, keeping an average weight (i.e., BMI), BP level, and blood glucose levels, eating a healthy diet, decreasing alcohol intake, and avoiding smoking, is associated with a reduced risk of HF development (Table 25) [314]. The detailed guideline-directed medical treatment and advanced therapies in managing HFrEF are beyond this guideline's scope, and readers are referred to the 2023 Saudi Guidelines for HF Management [315]. The Saudi HF guideline divides HF prevention into primary (at HF onset) and secondary (risk of morbidity and mortality in established HF) prevention [315].

Cerebrovascular disease. Cerebrovascular disease management varies by pathology, focusing on restoring cerebral perfusion in ischemic cases and controlling bleeding in hemorrhagic cases [316]. Ischemic events, including strokes and transient ischemic attacks (TIAs), are primarily caused by large artery atherosclerosis, cardiac embolism, or small vessel disease [317]. Acute ischemic stroke management involves thrombolysis with tissue plasminogen activator (tPA) within 4.5 hours of symptom onset or mechanical thrombectomy for large vessel occlusions within 6-24 hours [318]. Secondary prevention emphasizes antithrombotic therapy, with direct oral anticoagulants (DOACs) preferred over vitamin K antagonists for cardioembolic strokes due to lower intracranial hemorrhage risks [319]. For non-cardioembolic strokes, antiplatelet agents like clopidogrel or aspirin are recommended, with clopidogrel showing superior outcomes [320, 321]. Short-term dual antiplatelet therapy (DAPT) benefits high-risk cases but carries bleeding risks with extended use [322, 323]. Carotid revascularization via endarterectomy or stenting reduces recurrence risk, though each has procedure-specific risks [324].

Hypertension and dyslipidemia management are essential for secondary prevention. Current guidelines recommend BP control (e.g., SBP <140/90 mmHg) and high-intensity statins for patients with ischemic stroke or TIA with LDL-C ≥ 100 mg/dL [7, 325]. Hemorrhagic strokes, often caused by hypertensive or cerebral amyloid angiopathy, necessitate intensive SBP lowering (<140 mmHg) to reduce hematoma expansion and prevent recurrence [7, 326]. Silent cerebrovascular lesions, though asymptomatic, increase the risk of

Table 24 - CAD Management Recommendations for CVD Prevention.

Recommendation	Class	Level
In patients with a previous MI or revascularization, aspirin 75 - 100 mg daily is recommended .	I	A
In patients without a history of MI or revascularization, aspirin 75 - 100 mg daily may be considered , but with definitive evidence of CAD on imaging.	IIb	C
In ACS, DAPT with a P2Y12 inhibitor in addition to aspirin is recommended for 12 months unless there are contraindications such as a high risk of bleeding [445, 446] *.	I	A
De-escalation to ticagrelor monotherapy after a period of DAPT in patients with CAD may be considered [22,23]*.	IIb	B
In patients with CCS, clopidogrel 75 mg daily and aspirin 75-100 mg are recommended for six months following coronary stenting, regardless of stent type. When there is a risk of life-threatening bleeding, a shorter duration (1 - 3 months) is indicated [447, 448] *.	I	A
Adding a second antithrombotic drug (a P2Y12 inhibitor or low-dose rivaroxaban) to aspirin for long-term secondary prevention should be considered in patients with a high risk of ischaemic events and without high bleeding risk [449–451] *.	IIa	A
In patients with a moderate risk of ischemic events and without a high risk of bleeding, adding a second antithrombotic drug to aspirin for long-term secondary prevention may be considered .	IIb	A
In patients with other medical conditions (e.g., HF, hypertension, or DM), ACE inhibitors (or ARBs) are recommended .	I	A
In patients with LV dysfunction or systolic HF, beta-blockers are recommended .	I	A

ACE = angiotensin-converting enzyme; ACS = acute coronary syndromes; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CCS = chronic coronary syndromes; DAPT = dual antiplatelet therapy; DM = diabetes mellitus; HF = heart failure; LV = left ventricular; MI = myocardial infarction.

*Statements with new evidence following the 2021 ESC guideline.

Table 25 - HF Recommendations for CVD Prevention.

Recommendation	Class	Level
Screening patients with HF for both CV and non-CV comorbidities is recommended . Comorbidities should be treated if present, provided safe and effective interventions exist to alleviate symptoms and improve prognosis [452, 453] ^a .	I	A

CV = cardiovascular; HF = heart failure.

^aApplies to all patients with HF, regardless of LVEF.

*Statements with new evidence following the 2021 ESC guideline.

stroke and cognitive decline, requiring aggressive vascular risk factor control [327, 328]. In cryptogenic stroke with patent foramen ovale (PFO), percutaneous closure with antiplatelet therapy is preferred for high-risk cases, while individualized antithrombotic therapy is advised for those ineligible for closure [329]. These tailored management strategies highlight the importance of personalized approaches based on clinical profiles and risk factors (Table 26).

Peripheral arterial disease. Peripheral arterial disease (PAD) is ranked the third leading cause of cardiovascular diseases after CAD and cerebrovascular disease [330]. While its prevalence is significant globally, affecting millions in Europe [331], only 12% of a Saudi cohort were diagnosed [332], with 93% asymptomatic. PAD is a critical predictor of cardiovascular mortality and AEs [333].

The management of PAD emphasizes lifestyle modifications such as smoking cessation and maintaining a healthy diet. Smoking accelerates vascular damage through endothelial dysfunction, platelet activation, and coagulation dysregulation, driven by harmful substances like nicotine and acrolein [334, 335]. Smoking cessation not only reduces complications but also improves PAD symptoms, including walking performance

in lower extremity artery disease (LEAD) [336]. Additionally, adhering to a healthy diet has been shown to lower PAD risk, as evidenced by findings from the PREDIMED trial [337, 338].

Supervised exercise training/therapy (SET) significantly improves symptoms of LEAD, such as walking performance [339]. High-intensity home-based exercise therapy has demonstrated greater walking distance improvements than low-intensity interventions [340].

DM is a key risk factor for PAD, contributing to arteriosclerosis, endothelial damage, and an increased likelihood of non-traumatic lower limb amputations [341]. A study of diabetic patients with infra-popliteal lesions treated with balloon angioplasty found that elevated FBG at the time of the procedure was strongly associated with higher rates of major adverse limb events (MALE) and major amputations above the ankle [342].

The use of Rivaroxaban 2.5 mg or 5 mg twice a day in patients with recent ACS reduced the rates of MALE, MACE, and cardiovascular mortality compared to placebo [341]. Findings from the COMPASS trial further demonstrated that a combination of rivaroxaban (2.5 mg or 5 mg twice a day) with aspirin (100 mg daily) improves outcomes by reducing the risk of ASCVD events and MALE (Table 27) [343].

Table 26 - Cerebrovascular Diseases Management Recommendations for CVD Prevention.

Recommendation	Class	Level
Lifestyle modifications, with appropriate pharmacological management, are recommended in patients with a cerebrovascular event.	I	A
In patients with ischemic stroke or TIA, secondary prevention with antithrombotic is recommended ; the choice of antithrombotic depends mainly on the mechanism of the event. Also, antiplatelets are recommended for patients with non-cardioembolic ischemic stroke or TIA, and anticoagulants are recommended in patients with cardioembolic ischemic stroke or TIA [454, 455] *.	I	A
Secondary prevention of patients with non-cardioembolic ischemic stroke or TIA with aspirin only, dipyridamole and aspirin, or clopidogrel alone is recommended .	I	A
After an acute event of minor ischemic stroke or TIA, DAPT with aspirin and clopidogrel or with aspirin and ticagrelor for three weeks should be considered .	IIa	A
In patients with stroke or TIA who have a BP of $\geq 140/90$ mmHg, initiating the appropriate BP-lowering drug is recommended [456] *.	I	A
In patients between the ages of 18 and 60 with a prior PFO-associated stroke, PFO closure combined with antiplatelet therapy is recommended .	I	A

BP = blood pressure; DAPT = dual antiplatelet therapy; TIA = transient ischemic attack.

^cMinor ischemic stroke is defined as a score on the National Institutes of Health Stroke Scale $<_3$ or ≤ 5 , depending on the trial.

*Statements with new evidence following the 2021 ESC guideline.

Table 27 - PAD Management Recommendations for CVD Prevention.

Recommendation	Class	Level
Smoking cessation is recommended in all patients with PAD [457].	I	A
Physical activity and a healthy diet are recommended for all patients with LEAD [458–461] *.	I	A
In patients with intermittent claudication, supervised exercise training is recommended [462, 463] *.	I	A
If supervised exercise training is not feasible or not available, then non-supervised exercise training is recommended instead [462] *.	I	A
Antiplatelet therapy is recommended in patients with symptomatic LEAD. ^c	I	C
In patients with LEAD and HTN, controlling BP at $<140/90$ mmHg is recommended .	I	A
In patients with LEAD and diabetes, strict glycemic control is recommended .	I	A
ACE inhibitors or ARBs should be considered as first-line therapy in patients with PAD and HTN. ^d	IIa	B
In patients with DM and chronic symptomatic LEAD without high bleeding risk, a combination of low-dose rivaroxaban (2.5 mg b.i.d.) and aspirin (100 mg o.d.) may be considered .	IIb	B

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; b.i.d. = bis in die (twice a day); BP = blood pressure; CCB = calcium channel blocker; DM = diabetes mellitus; HTN = hypertension; LEAD = lower extremity artery disease; o.d. = omni die (once a day); PAD = peripheral artery disease.

^cEvidence is not available for all sites. When evidence is available, recommendations specific to the vascular site are presented in corresponding sections.

^dCCBs should be proposed in black individuals.

*Statements with new evidence following the 2021 ESC guideline.

Atrial fibrillation. The multidisciplinary “AF-CARE” approach for the management of AF (“C” = Comorbidity and risk factor management; “A” = Avoid stroke and thromboembolism; “R” = Reduce symptoms through rate and rhythm control; “E” = Evaluation and regular assessment) represents an integrated management plan for AF and its associated risk factors [344]. The AF-CARE approach integrates the best available medical care, patient preferences, and multidisciplinary cooperation of specialists involved in managing AF patients.

Data from previous studies showed that women with AF experience worse outcomes (i.e., higher incidence of morbidity and mortality) than men [84, 345, 346]. Notably, female patients with AF are older, have more prevalent hypertension and HFpEF, and have less preva-

lent CAD [347]. However, these different outcomes were not explained whether they are related to delayed diagnosis and seeking medical care or factors related to gender differences.

The prevention of stroke and systemic embolism (SSE) is a primary goal in managing AF patients. Risk stratification using the CHA₂DS₂-VASc score is recommended to guide OAC therapy [348]. In both patients with and without established CVD, OAC is indicated for men with a CHA₂DS₂-VASc score ≥ 2 and for women with a score ≥ 3 , with DOACs preferred over vitamin K antagonists except in cases with moderate-to-severe mitral stenosis or mechanical heart valves [86, 349]. Optimal anticoagulation significantly reduces the risk of stroke, systemic embolism, and all-cause mortality.

BBs remain the first-line therapy for rate control in patients with/without CVD, especially in AF patients with hypertension, HFrEF, or myocardial ischemia [86]. Rate control aims to improve symptoms and prevent the development of cardiomyopathy. In patients with persistent symptoms despite rate control or in those with younger age or paroxysmal AF, rhythm control strategies including antiarrhythmic drugs and/or catheter ablation may be considered [350–352].

AF has multiple associated comorbidities that increase recurrence and disease progression. Variable comorbidities have been reported among AF patients in the literature, including HF, hypertension, DM, obesity, hypercholesterolemia, COPD, inherited cardiomyopathies, OSA, CKD, frailty, and mental health disorders [349]. Management of the concomitant conditions improves rhythm control and reduces the frequency of persistent AF symptoms [353]. Therefore, pharmacological strategies for AF should be individualized based on patient comorbidities, bleeding risk, renal function, and patient preferences.

Weight loss in obese patients is proven to protect them from recurrent AF and decrease the frequency of symptoms [354, 355]. The CARDIO-FIT Study reported that arrhythmia-free survival was significantly higher in patients with high cardiorespiratory fitness than in adequate or low cardiorespiratory fitness groups [355]. Previous studies showed that moderate PA has beneficial effects on disease outcomes. These effects include improving the volume of oxygen (Vo₂) peak, symptom frequency, function of the left cardiac chamber, and patient QoL [356, 357]. However, AF incidence seems to be increased in elite athletes practising endurance sports [358]. The prolonged intensive cardiovascular strain may explain this during training.

Hypertension is a major risk factor for AF; therefore, BP control in all hypertensive AF patients is a crucial step. In a recent meta-analysis of 22 trials, the investigators found that a five mmHg reduction of the SBP over a median of 4.5 years decreases the risk of MACE in patients with AF [359].

Heavy alcohol consumption (>20 drinks/week for men and >13 drinks/week for women or ≥200 g/week) is associated with an increased risk of MACE. Multiple studies showed that heavy alcohol use increases the risk of future thromboembolism, ischaemic stroke, TIA, hospitalization, and death [360]. Also, data from meta-analyses that studied the relationship between alcohol intake and the risk of AF development showed a dose-response relationship between alcohol consumption and the risk of AF [361].

Previous studies showed that AF patients with OSA who were untreated by continuous positive airway

pressure (CPAP) therapy had a poor response to AF treatment (Table 28) [362].

Chapter 7. Practical points: Access to care and policy interventions at the population level.

Barriers to cardiovascular care access in Saudi Arabia. Saudi Arabia is the largest country in the Greater Gulf region and one of the largest in the Middle East region, with a population exceeding 32 million, according to the 2022 General Authority for Statistics census [363]. The nation is dedicated to providing quality healthcare services to both Saudi nationals and residents, yet this effort imposes a substantial financial burden on the country's national income and healthcare sector.

Given Saudi Arabia's vast geographic size, there are significant disparities in healthcare access between rural and urban areas. Geographical location plays a pivotal role in the distribution and utilization of healthcare resources. A study by Moafa et al. found that rural areas in the Riyadh Region had six times more ambulance crews available than urban areas. Additionally, the number of missions per 1000 inhabitants was nearly double in urban areas compared to rural ones, and the median response time for urgent trauma was 15.2 minutes in urban areas versus 20.2 minutes in rural areas. These findings underscore the gaps in healthcare access across the country [364].

Healthcare expenditures in Saudi Arabia are primarily driven by the government budget, which is allocated to institutions such as the MOH, the Saudi Health Council (SHC), the Health Holding Company (HHC), and other affiliated organizations, including military healthcare and university hospitals [365]. Additionally, the government provides free healthcare services to pilgrims during the Umrah and Hajj seasons, placing a considerable strain on the healthcare system [366]. This financial burden contributes to the unsustainability of the current healthcare structure, prompting the ongoing health transformation initiative aimed at providing high-quality, value-based care with reduced economic strain on the nation [367].

Cardiac rehabilitation programs, which are proven to be cost-effective and essential for patients recovering from cardiac events [368], remain underutilized in Saudi Arabia due to several challenges. These include the high costs of CR programs, the need for specialized HCPs, the absence of local clinical practice guidelines, and a lack of widespread patient adoption following hospital discharge [232, 369]. Moreover, factors such as patient education levels and gender-specific barriers also affect access to cardiovascular care. A Saudi cross-sectional study found that HF patients, particularly

Table 28 - AF Recommendations for CVD Prevention.

Recommendation	Class	Level
Identification and management of risk factors and concomitant diseases in patients with AF are recommended to be an integral part of treatment [464, 465] *.	I	A
Modification of unhealthy lifestyles and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity [466, 467] *.	I	A
Attention to good BP control is recommended in AF patients with HTN to reduce AF recurrences and the risk of stroke and bleeding [468, 469] *.	I	A
In obese patients with AF, weight loss, in addition to management of other risk factors, should be considered to reduce AF incidence, AF progression, AF recurrences, and symptoms [470] *.	IIa	B
Advice and management to avoid alcohol excess should be considered for AF prevention and in AF patients considered for oral anticoagulant therapy [471, 472] *.	IIa	A
Mild-to-moderate physical activity should be considered to decrease the risk of AF development or recurrence [473–475] *.	IIa	A
Optimal management of OSA may be considered to reduce AF incidence, AF progression, AF recurrences, and frequency of symptoms [476] *.	IIb	A

AF = atrial fibrillation; BP = blood pressure; HTN = hypertension; OSA = obstructive sleep apnea.

*Statements with new evidence following the 2021 ESC guideline.

those with lower education levels and female participants, reported poorer HRQoL [370].

Healthcare system capacity and resource allocation.

The Saudi health transformation program, a cornerstone of Saudi Vision 2030, is an ambitious healthcare reform initiative that focuses on innovation, financial sustainability, and disease prevention while improving healthcare accessibility [371]. The program is built on eight key pillars:

1. **Healthcare Model Transformation:** A shift towards a preventive care model.
2. **Access to Healthcare Services:** Expanding and improving healthcare accessibility.
3. **Value-based Healthcare:** Emphasizing cost-effective, patient-centered care.
4. **Digital Health and Innovation:** Leveraging technologies like electronic health records (EHRs), telemedicine, and AI.
5. **Private Sector Participation:** Expanding the role of private entities in healthcare delivery.
6. **Workforce Development:** Training a skilled, motivated healthcare workforce.
7. **Public Health Initiatives:** Targeting lifestyle-related diseases, infectious diseases, and mental health.
8. **Health Financing Reform:** Ensuring the financial sustainability of the healthcare system.

Accessibility, affordability, and quality of primary healthcare services are fundamental to the success of any healthcare system. Primary healthcare serves as the first point of contact for most patients and is crucial for preventive care, screening, and early disease detection. In Saudi Arabia, the previous healthcare system—dominated by the MOH hospitals and PHC—focused more on hospital care rather than primary care [372]. However, with the ongoing health transforma-

tion and the privatization of healthcare delivery under the HHC and health clusters, the emphasis has shifted toward preventive services and screening [373, 374]. The new model aims to deliver more efficient care closer to patients' homes and strengthen the role of primary healthcare [373]. Additionally, population health management strategies use data-driven approaches to identify and target high-risk populations [375].

The Saudi healthcare workforce has experienced significant growth and transformation. In 2018, the country had 494 hospitals, 75,225 beds, and 104,775 physicians, compared to 497 hospitals, 77,224 beds, and 99,617 physicians in 2021 [376, 377]. However, there is a persistent disparity in the distribution of healthcare resources between urban and rural areas, leading to challenges in healthcare access for rural populations [372].

Cardiovascular assessment is a routine part of the physical examination in primary healthcare settings. Studies suggest that when care involves collaboration between cardiac specialists and PCPs, patient adherence to treatment guidelines for HF improves, resulting in better clinical outcomes [378]. Primary healthcare settings are well-positioned to offer initial cardiovascular care, such as screening and early detection of common CVDs, as well as managing risk factors like hypertension, diabetes, and hypercholesterolemia. A team-based approach, which includes advanced practice providers in preventive cardiology clinics, has been shown to reduce cardiovascular risk through effective risk stratification and preventive measures [379]. Similarly, a Chinese study highlighted the positive impact of cardiovascular risk reduction strategies in primary healthcare, including increased use of preventive medications, reduced smoking rates, and improved BP control [380].

Despite the availability of advanced diagnostic and therapeutic tools in some hospitals, poor resource allocation and a shortage of qualified medical staff

have limited their effective use [2]. The affordability of these advanced diagnostic tools also affects patients' access to necessary care. Furthermore, adherence to international clinical guidelines among PCP in Saudi Arabia has been reported as suboptimal, which impedes the effective implementation and monitoring of these guidelines [381, 382]. Integrated healthcare management, including risk stratification, is essential to help providers prioritize interventions and allocate resources appropriately [383, 384].

Policy interventions for cardiovascular disease prevention and care. In recent years, Saudi Arabia has taken significant steps to enhance CVD prevention and strengthen the healthcare system as part of broader socio-economic development goals outlined in **Saudi Vision 2030** [385]. Key Programs and Initiatives are:

National Transformation Program (2016): Launched as part of Saudi Vision 2030, this program includes the Health Sector Transformation initiative aimed at improving healthcare services and outcomes.

Health in All Policies (HiAP) Framework (2017): A ministerial committee was established to integrate health considerations into all regulatory and legislative processes. The objectives include reducing CVD risk factors across various sectors (e.g., urban planning, transport, food regulation, and smoking cessation policies) [386]. HiAP reflects principles of transparency, collaboration, and accountability to improve national health equity [387].

Regulatory Interventions in Nutrition enforced reforms in the food industry, including a salt reduction in processed foods, menu labeling, awareness campaigns, and product reformulation. The goal is to reduce the population's salt intake by 30% by 2025 [388].

The Saudi Public Health Authority (PHA) also plays a pivotal role in planning and overseeing health policy interventions. They collaborated with the World Bank Group to develop a strategic master plan for mitigating the health and economic impacts of non-communicable diseases, including CVD, thus helping increase life expectancy across the country [389].

Saudi Screening Programs to promote early detection and prevention, including Premarital and Newborn Screening Program, Colorectal Cancer Early Detection Program, and Breast Cancer Screening Program [385, 390, 391]: As per the Health Sector Transformation Program 2023 achievement report, more than five million have been screened for early obesity, more than one million for early DM, more than 200,000 for breast cancer, and more than 100,000 for colorectal cancer [392].

Family Medicine Initiative: Implementing a "PCP for each family" in the Saudi primary healthcare system [393]. This is another national healthcare program that

was established to enhance the effectiveness of screening initiatives and ensure continuity and access to healthcare services for all citizens and families in Saudi Arabia.

Development of Health Registries: To enhance patient care and research, Saudi Arabia has established robust health registries. **SPACE registry** – A Saudi Project for Assessment of Coronary Events – was launched in 2009 to track the prevalence of risk factors and treatment strategies for ACS patients, offering critical insights into cardiac care [394].

Environmental Initiatives: Recognizing the impact of air pollution on public health, Saudi Arabia has prioritized sustainable environmental policies under **the Saudi Green Initiative (SGI) (2021)**, which aims to reduce carbon emissions, promote afforestation, restore degraded land, and protect natural ecosystems. Includes comprehensive programs focused on environmental protection, renewable energy transition, and long-term sustainability [395]. Additional measures have been taken, including expanding air emission standards to cover more activities, strengthening environmental codes and enforcement, promoting electric vehicles, and enhancing vehicle emission inspections [396]. These efforts align with Saudi Arabia's commitment to fostering a healthier population and creating a resilient, low-carbon future.

Health promotion and community-based interventions. Enhancing public health and promoting awareness of the Saudi population about health, environmental, and social issues are key objectives of Saudi Vision 2030. The MOH has launched several national public health campaigns focused on diet, healthy lifestyle and exercise, and smoking cessation [397]. These include ongoing initiatives targeting overweight and obesity, aimed at promoting better dietary habits and encouraging PA among Saudi nationals. Additionally, anti-smoking campaigns are part of a broader governmental strategy to increase awareness of the health risks associated with tobacco use and to ensure the availability of affordable smoking cessation services [398]. Campaigns against drug addiction also highlight the severe health consequences of substance abuse, seeking to reshape public attitudes and foster healthier behaviors across the nation.

As part of the community participation initiative, the health endowment fund introduced the "Shefa" platform to provide healthcare services, medicines, and medical devices to individuals in urgent need who lack access to health facilities. According to the 2023 Health Sector Transformation Program achievement report, over 7,000 cases have been treated through the Shefa platform, with contributions exceeding 200 million SAR [392].

To promote healthier lifestyles, the MOH has implemented new national strategies, including the "Vital Community" initiative. This initiative encourages participation in physical activities, supports sports groups and federations, and promotes women's involvement in community sports [386]. The Saudi Sports for All Federation has played a significant role in these efforts through activities such as the Riyadh Marathon, educational and recreational clubs for youth, the National Cricket Championship, and targeted awareness campaigns like "Move Your World." [399]. These initiatives are designed to create an environment where healthy choices are easier, more accessible, and widely adopted. By fostering public engagement and reshaping societal norms, these programs contribute to improved public health outcomes and align with the goals of Saudi Vision 2030.

Improving health equity and inclusion. As Braveman and Gruskin define, "equity in health is the absence of systematic disparities in health (or in the major social determinants of health) between groups with different levels of underlying social advantage/disadvantage—that is, wealth, power, or prestige" [400]. In Saudi Arabia, promoting health equity for CVD prevention involves adopting targeted strategies for underserved and vulnerable groups, such as the elderly, low-income individuals, non-Saudi residents, and people with disabilities. The Saudi MOH has implemented initiatives to enhance access to affordable healthcare services for these populations [373]. Community clinics, for example, provide disease screening and preventive care, making primary healthcare more accessible, particularly for those in rural and remote areas. Social support programs offer financial aid to low-income individuals, while disability-related resources ensure inclusive care for people with diverse disabilities. Together, these initiatives aim to deliver quality healthcare for all segments of society.

Aligned with Saudi Vision 2030, reducing health disparities related to CVD is a national priority. Targeted interventions address factors such as hypertension and DM in communities with high-risk profiles. Mobile health units and clinics deliver essential CVD care to underserved regions, while public health campaigns are developed in multiple languages and accessible formats. These efforts aim to raise health awareness and encourage preventive measures, bridging gaps in CVD outcomes across diverse demographics [397].

Further initiatives, including establishing rural medical colleges, expanding mobile health units, and advancements in telemedicine, reflect a commitment to improving health equity and inclusion. These strategies align with the objectives of Saudi Vision 2030, fostering nationwide equitable access to healthcare [373, 401].

Telemedicine and digital health solutions in cardiovascular care. Telemedicine plays a pivotal role in facilitating access to cardiovascular care in Saudi Arabia, especially for patients in remote and underserved regions. In 2011, the Saudi MOH launched the "National E-Health Strategy", guided by the WHO framework, to modernize healthcare services and implement innovative digital solutions. As part of this strategy, the adoption of telehealth services was prioritized within the enhanced national framework [402]. One of the strategy's key objectives was to develop a robust information technology (IT) infrastructure to support digital transformation, focusing on connectivity, technical support, and interoperable systems [403]. Additionally, the strategy emphasized e-health education, adoption, and providing training programs for HCPs to promote effective utilization [404].

Telemedicine practices such as virtual consultations (teleconsultations) and remote monitoring reduce the need for long-distance travel and physical attendance, enabling patients to access timely medical care and support from specialists nationwide [405]. To this end, the Saudi MOH established the "Seha Virtual Hospital", the largest virtual hospital in the region [406]. This platform connects over 170 hospitals across the country, offering more than 30 specialized healthcare services, including cardiology. By ensuring continuity of care for cardiovascular patients, who often require regular monitoring and quick interventions, this approach improves access to specialized services, particularly for underserved and remote populations [407].

Digital tools like EHRs and mobile health (mHealth) applications, such as the "Sehati" app, are increasingly utilized to support patients through their care journey. These tools enable continuous monitoring, facilitate regular follow-ups, promote lifestyle interventions, and improve treatment outcomes [407–409]. Features include tracking key health metrics (e.g., BP, heart rate, and diabetes control), accessing health records, and easy communication with HCPs [410, 411]. Providers, in turn, can remotely monitor patient progress, clinical outcomes, and adherence to treatment plans. Emerging digital tools also deliver personalized recommendations for PA, dietary habits, and medication reminders, encouraging patients to adopt healthier lifestyles critical for improved cardiovascular health.

Since implementing the "National E-Health Strategy" and the broader goals of Saudi Vision 2030, the Saudi healthcare system has undergone significant advancements aligned with digital transformation. The COVID-19 pandemic further accelerated the adoption and utilization of digital tools, particularly mHealth applications worldwide [410–412].

Another important application of telemedicine in the CV field is telerehabilitation, which offers remote delivery of CR services virtually via digital platforms. Given the limited availability of in-person CR centers in Saudi Arabia, particularly in rural and underpopulated/underserved regions, telerehabilitation presents a promising solution to address geographic and logistical barriers, such as long travel distances and a lack of transportation [413]. Through virtual consultations, remote monitoring, and guided home-based exercise programs, CR experts/physiotherapists can provide CR services and supervise cardiac patients in their homes. International evidence supports the safety, feasibility, and cost-effectiveness of telerehabilitation, with comparable outcomes to center-based programs in improving exercise capacity, adherence, and QoL in different patients [413–416]. Initiating pilot projects or national Saudi CR frameworks that integrate telerehabilitation could significantly improve CR outcomes and continuity in Saudi Arabia.

While these advancements present exciting opportunities, they also bring challenges. Key barriers include the need for robust data security measures, limitations in IT infrastructure, gaps in digital literacy among patients and providers, and challenges in integrating digital technologies into the existing healthcare framework. However, with continued investment and governmental support, these digital health solutions have the potential to transform cardiovascular care across Saudi Arabia, improving accessibility, efficiency, and patient outcomes while reducing healthcare costs.

Chapter 8. Gaps in evidence.

Screening [382].

1. CVD Screening Practices:

- Lack of standardized national guidelines for CVD screening in asymptomatic individuals.
- Limited availability of advanced screening tools, such as coronary artery calcium (CAC) scoring, for risk stratification.
- Insufficient integration of non-traditional risk factors (e.g., genetic predisposition, inflammation markers) into screening protocols.
- Inadequate data on the effectiveness of opportunistic versus systematic screening approaches.

2. Population-Specific Gaps:

- Gaps exist in tailored screening strategies for high-risk groups, including individuals with metabolic syndrome, older adults, and women with pregnancy-related complications.
- The effectiveness of digital health technologies in improving screening uptake remains underexplored.

Risk modifiers.

1. Environmental and Socioeconomic Factors:

- Limited research quantifies the association between air pollution (e.g., PM2.5, PM10) and cardiovascular outcomes in Saudi Arabia.
- No longitudinal studies assess the cumulative effects of environmental exposures or industrial pollution on CVD risk.
- The impact of socioeconomic disparities (income, education, rural-urban differences) on CVD prevalence and outcomes remains poorly understood.

2. Smoking and Emerging Trends:

- Data on the cardiovascular effects of emerging smoking trends, such as e-cigarettes, and the impact of passive smoking on CVD outcomes are scarce.

3. Psychosocial and Lifestyle Factors:

- Limited studies explore the effects of stress, depression, and anxiety on CVD risk.
- Population-based studies on the prevalence of sleep disorders (e.g., insomnia, sleep apnea) and their contribution to CVD risk are lacking.

4. Genetic and Age-Related Risk Modifiers:

- Gaps exist in understanding population-specific genetic variants and their role in CVD risk.
- The interplay between geriatric syndromes (e.g., frailty, cognitive decline) and CVD risk in older adults is poorly studied.
- Evidence on screening and managing CVD risk in individuals aged >85 years with significant frailty is insufficient.

Clinical conditions.

1. Chronic Conditions and Comorbidities:

- **Chronic Kidney Disease (CKD):** There is a lack of biomarkers, apart from albuminuria, to effectively classify cardiovascular risk. CAC scoring for better risk stratification warrants investigation.
- **Atrial Fibrillation (AF):** Improved stroke risk prediction tools for low-risk AF patients and the relationship between AF and CVD morbidity need exploration.
- **Heart Failure (HF):** Research is needed to determine if ischemic HFrEF patients require different LDL-C targets than non-HF populations.
- **Cancer and COPD:** Limited evidence exists on preventive therapies for cardiovascular events in cancer patients and shared mechanisms between CVD and COPD.

2. Inflammatory and Infectious Conditions:

- The integration of chronic inflammatory conditions and infections (e.g., periodontitis, influenza) into cardiovascular risk assessment needs further study.

3. Special Populations:

- **Women:** Limited research addresses cardiovascular risks associated with female-specific conditions (e.g., gestational diabetes, preeclampsia).
- **Other Conditions:** The roles of migraine, sleep disorders, mental disorders, NAFLD, and erectile dysfunction in increasing CVD risk require further evidence.

Management of risk factors [382].

1. Hypertension:

- Demographic and behavioral factors influence wide variability in treatment rates (27.9% – 78.9%).
- Medication adherence and BP control rates are low, with insufficient evidence addressing barriers such as healthcare delivery, cultural behaviors, and treatment regimens.

2. Dyslipidemia:

- Lipid control rates are suboptimal due to inadequate follow-up, low adherence to lipid-lowering therapies, and reliance on non-pharmacological interventions.
- Evidence on the utilization and barriers to novel therapies (e.g., PCSK9 inhibitors) in Saudi Arabia is scarce.

3. Diabetes Mellitus:

- Risk scores for predicting MACE and HF in T2DM patients need refinement.
- The additive benefits of combining SGLT2 inhibitors with GLP-1RAs require further exploration.

4. Lifestyle Interventions:

- Evidence is limited on effective strategies for promoting PA, healthy diets, and sustained weight management.
- Research on eHealth tools and scalable interventions for lifestyle changes is needed.

5. Mental Healthcare and Smoking Cessation:

- Effective CVD prevention strategies for high-risk individuals with mental disorders and long-term outcomes of smoking cessation interventions require investigation.

6. Cardiac Rehabilitation (CR):

- Gaps exist in the effectiveness of CR programs for specific groups (e.g., women, the elderly, and multi-comorbid patients).
- Alternative delivery models such as telerehabilitation and mHealth technologies represent a promising and practical solution, but need further evaluation.

7. Environmental and Climate Exposures:

- Evidence on mitigation strategies for environmental and climate-related cardiovascular risks is lacking.

8. Specific CVD Conditions:

- **Coronary Artery Disease:** The safety of aspirin in asymptomatic patients with subclinical atherosclerosis and optimal antithrombotic therapies needs to be studied.
- **Heart Failure:** Lack of effective interventions for HFpEF and gender-specific dosing for HFrEF persists.
- **Cerebrovascular Disease:** Evidence is insufficient on optimal BP targets, LDL-C goals, and silent cerebrovascular disease treatment.
- **Lower Extremity Artery Disease (LEAD):** The potency and type of antithrombotic therapy for symptomatic and asymptomatic LEAD patients are unclear.
- **Multimorbidity:** The effects of cardiovascular and non-cardiovascular comorbidities on outcomes require further understanding.

Conclusion and Recommendations to address these gaps, future efforts should.

- Standardize and expand CVD screening and risk stratification initiatives.
- Conduct longitudinal and population-specific studies to explore environmental, genetic, and psychosocial factors.
- Integrate advanced diagnostic tools, biomarkers, and lifestyle interventions into clinical practice.
- Develop country-specific treatment strategies tailored to unique population characteristics, leveraging technology for scalable healthcare delivery.

Chapter 9. Key messages. In summary, the NHC/SHA 2025 Guidelines for Cardiovascular Diseases Prevention and Risk Assessment represent a comprehensive, evidence-based approach to tackling ASCVD in Saudi Arabia. These guidelines incorporate updated treatment strategies, a personalized approach to care, and a focus on cultural relevance and specific risk factors. They provide healthcare professionals with the tools necessary to reduce the burden of CVDs and improve both individual and population-level health outcomes (Table 29).

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Table 29 - Key recommendations for CVD prevention.

Recommendation	Class	Level
I. Optimizing CVD Prevention		
A healthy diet, focusing on replacing saturated with unsaturated fats, reducing salt intake, restricting processed meat and sugar, and increasing fiber, fruits, and vegetables is recommended to lower the risk of CVD.	I	B
All forms of tobacco smoking are recommended to be stopped to improve the CVD risk profile.	I	A
Aerobic physical activity of moderate intensity for at least 150 to 300 minutes a week or vigorous intensity for at least 75 to 150 minutes a week – or an equivalent combination – is recommended for all adults to reduce all-cause mortality, CV mortality and morbidity.	I	A
Adults who are not able to perform the minimal moderate-intensity PA (150 minutes per week) are recommended to stay as active as their health condition allows.	I	B
Besides aerobic PA, resistance training is recommended at least twice per week to reduce all-cause mortality.	I	B
Weight reduction is recommended for all overweight and obese individuals to reduce their CVD risk factors and improve their CVD risk profile.	I	A
A target HbA1c of $\leq 6.5\%$ (48 mmol/L) is recommended for the majority of non-pregnant adults with either T1DM or T2DM, if it can be achieved safely, to reduce CVD risk and microvascular complications of DM.	I	B
A SBP target of 120-130 mmHg is recommended in patients aged 18 to 65 years with stage 2 hypertension (BP $>140/90$ mmHg) and heart failure (HFrEF or HFpEF).	I	A
A SBP target of 130-140 mmHg is recommended in patients aged 18 to 65 years with hypertension and CKD.	I	A
A treatment SBP target of 120-130 mmHg and DBP target of 70-80 mmHg is recommended in patients aged 18 to 65 years with hypertension and CAD.	I	A
A treatment SBP target of 130-140 mmHg is recommended for older patients (≥ 65 years) with hypertension and CAD.	I	A
In secondary prevention of patients at very high risk, an LDL-C reduction of $\geq 50\%$ from baseline and an LDL-C goal of < 1.4 mmol/L (< 55 mg/dL) are recommended .	I	A
In primary prevention of individuals at very high risk and no familial hypercholesterolemia (FH), an LDL-C reduction of $\geq 50\%$ from baseline and an LDL-C goal of < 1.4 mmol/L (< 55 mg/dL) are recommended .	I	C
In patients at high risk, an LDL-C reduction of $\geq 50\%$ from baseline and an LDL-C goal of < 1.8 mmol/L (< 70 mg/dL) are recommended .	I	A
In individuals at moderate risk, an LDL-C goal of < 2.6 mmol/L (< 100 mg/dL) is recommended .	I	A
In individuals at low risk, an LDL-C goal of < 3.0 mmol/L (< 116 mg/dL) should be considered .	IIa	A
Intensified psychosocial attention and support are recommended for patients with mental disorders to improve their adherence to CVD prevention or risk improvement measures (such as lifestyle changes and drug treatments).	I	C
When addressing alcohol consumption, it is recommended to prioritize overall health and well-being. Individuals with comorbidities or a history of alcohol use disorder are strongly advised to abstain from alcohol to avoid potential harm.	I	A
Comprehensive EBCR managing all recognized CV risk factors should be considered for all eligible patients immediately following a cardiac event or surgery.	I	A
Comprehensive EBCR programs lasting at least one year or a high CR dose (≥ 36 sessions) should be considered for HF patients.	IIa	A
To assist HCPs in deciding whether to refer patients for CR programs or not, a national guiding standardized referral checklist for all HCPs is recommended .	I	B
Increasing the number of private and governmental hospitals with comprehensive CR centers across Saudi Arabia, especially in dispersed geographic areas, including rural areas, is recommended .	I	B
Increasing the number of experienced and well-trained HCPs in Saudi Arabia is recommended .	I	B
Electronic or automatic referrals, referral and liaison visits, structured follow-up by HCPs, and early program initiation after discharge is recommended to improve CR referral and uptake.	I	B
It is recommended that all patients eligible for CR be automatically referred to the CR center at the time of hospital discharge.	I	B
Peer/patient navigation [in which a navigator (usually a trained layperson) provides education about CR to a patient in a one-to-one setting] is recommended .	I	B
II. Screening for CVD Risk		
Screening for hsCRP (≥ 2.0 mg/L) should be considered in adults aged 40 to 75 years without DM and at intermediate ASCVD risk [196, 237, 421, 422].	IIa	A
Lp(a) measurement may be considered once in a lifetime in Saudi adults to aid in the risk assessment of ASCVD [244].	IIb	C
Lipid assessment, using the basic lipid panel on a non-fasting blood sample, including TC, LDL-C, HDL-C, and TG, is recommended to estimate and refine ASCVD risk by SCORE system for adults aged 18 to 65 years [250–254].	I	C
Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
If available, Apo-B may be considered as an alternative to LDL-C as the primary measurement for screening, diagnosis, and management [196, 255]	IIb	C
Apo-B analysis should be considered over LDL-C or non-HDL-C for risk assessment in patients with high TG levels, DM, obesity, metabolic syndrome, or very low LDL-C [196, 255]	IIa	C
CAC scoring should be considered to refine ASCVD risk calculation and aid in decision-making for adults aged 18 to 65 years according to the availability of CAC scanning [256–258]	IIa	C
BMI, waist circumference, and waist-to-hip ratio are recommended to be systematically considered to predict ASCVD risk.	I	A
Comprehensive CVD risk assessment are recommended in individuals with unfavorable body anthropometric measurements (high BMI, high waist-to-hip ratio) [5]	I	B

(Continued)

Table 29 - Continued.

Recommendation	Class	Level
ABI is not recommended for estimation or reclassification of ASCVD risk for adults aged 18 to 65 years with high risk for PAD.	III	C
Validated electronic (oscillometric) devices are recommended to measure BP and in the diagnosis of HTN in Saudi patients aged 18 to 65 years	I	A
III. Management of Individual Risk Factors		
A two-drug combination in the form of a single-pill treatment is recommended as initial therapy for all people with HTN except frail elderly patients and younger people with low-risk, grade 1 HTN [424–426].	I	A
The recommended preferred combination should include a RAS blocker plus a CCB or a diuretic [427].	I	A
If BP control is still not achieved (i.e., resistant hypertension), then spironolactone is recommended if tolerated. If not tolerated, another aldosterone antagonist or vasodilating beta-blocker (BB) are recommended [428].	I	A
RAS blockers (ACEIs or ARBs) are the recommended initial therapy for patients with HTN and diabetes, especially in the presence of microalbuminuria or proteinuric chronic kidney disease (urinary protein level > 150 mg in 24 hours or albumin to creatinine ratio > 30 mg/mmol).	I	A
A statin therapy is recommended to be prescribed up to the highest tolerated dose to reach the specific LDL-C target for each specific risk group.	I	A
If the LDL-C goal is still not achieved with the maximum tolerated dose of statins, a combination with ezetimibe therapy is recommended [429, 430].	I	A
Patients with FH and at very high risk* of CVD are recommended to be treated with a high-intensity statin in combination with ezetimibe. If the target LDL-C level is not achieved, then adding PCSK9 monoclonal antibodies is recommended.	I	C
In the primary prevention for very high-risk patients*, without familial hypercholesterolemia (FH), not achieving the LDL-C goal on the highest tolerated dose of statin plus ezetimibe, then combination with a PCSK9 inhibitor may be considered .	IIb	C
Statin monotherapy or in combination with ezetimibe is recommended in patients with non-dialysis dependent CKD stages 3 to 5.	I	A
In patients with dialysis-dependent CKD without ASCVD, initiating statin therapy is not recommended .	III	A
A statin therapy is recommended to be prescribed up to the highest tolerated dose to reach the specific LDL-C target for each specific risk group.	I	A
In individuals with T2DM and ASCVD, using a GLP-1RA or SGLT2i with established outcome benefits is recommended to decrease CV and/or cardiorenal outcomes [431–434].	I	A
In patients with T2DM and TOD, using an SGLT2i or GLP-1RA with established outcome benefits may be considered to decrease CV risk and mortality [432, 435–437].	IIb	A
In patients with T2DM but without established ASCVD, HF, or CKD, the use of an SGLT2 inhibitor or GLP-1RA should be considered [431, 434, 438].	IIa	A
In individuals with T2DM and ASCVD, using a GLP-1RA or SGLT2i with established outcome benefits is recommended to decrease CV and/or cardiorenal outcomes [431–434].	I	A
In patients with T2DM and CKD, the use of an SGLT2 inhibitor is recommended to improve ASCVD and/or cardiorenal outcomes.	I	A
In patients with T2DM and HFrEF, the use of an SGLT2 inhibitor with proven outcome benefits is recommended to lessen HF hospitalizations and CV death [434, 436, 439–441].	I	A
Low-dose aspirin (100 mg/day) is recommended for secondary prevention of CVD.	I	A
Low-dose aspirin may be considered for primary prevention of CVD in patients with DM at high or very high CVD risk, in the absence of clear contraindications [442, 443].	IIb	A
Antiplatelet therapy is not recommended in individuals with low/moderate CV risk due to the increased risk of major bleeding [444].	III	A
IV. Management of Disease-Specific Risk Factors		
In patients with a previous MI or revascularization, aspirin 75 - 100 mg daily is recommended .	I	A
In patients without a history of MI or revascularization, aspirin 75 - 100 mg daily may be considered , but with definitive evidence of CAD on imaging.	IIb	C
In ACS, DAPT with a P2Y12 inhibitor in addition to aspirin is recommended for 12 months, unless there are contraindications such as a high risk of bleeding [445, 446].	I	A
De-escalation to ticagrelor monotherapy after a period of DAPT in patients with CAD may be considered [22,23].	IIb	B
In patients with CCS, clopidogrel 75 mg daily and aspirin 75-100 mg are recommended for six months following coronary stenting, regardless of stent type, unless a shorter duration (1 - 3 months) is indicated due to risk or occurrence of life-threatening bleeding [447, 448].	I	A
Adding a second antithrombotic drug (a P2Y12 inhibitor or low-dose rivaroxaban) to aspirin for long-term secondary prevention should be considered in patients with a high risk of ischaemic events and without high bleeding risk [449–451].	IIa	A
In patients with a moderate risk of ischemic events and without a high risk of bleeding, adding a second antithrombotic drug to aspirin for long-term secondary prevention may be considered .	IIb	A
In patients with other medical conditions (e.g., HF, hypertension, or DM), ACE inhibitors (or ARBs) are recommended .	I	A
In patients with LV dysfunction or systolic HF, beta-blockers are recommended .	I	A
Screening patients with HF for both CV and non-CV comorbidities is recommended . Comorbidities should be treated if present, provided safe and effective interventions exist to alleviate symptoms and improve prognosis [452, 453].	I	A
Lifestyle modifications, with appropriate pharmacological management, are recommended in patients with a cerebrovascular event.	I	A

(Continued)

Table 29 - Continued.

Recommendation	Class	Level
In patients with ischemic stroke or TIA, secondary prevention with antithrombotic is recommended ; the choice of antithrombotic depends mainly on the mechanism of the event. Also, antiplatelets are recommended for patients with non-cardioembolic ischemic stroke or TIA, and anticoagulants are recommended in patients with cardioembolic ischemic stroke or TIA [454, 455].	I	A
Secondary prevention of patients with non-cardioembolic ischemic stroke or TIA with aspirin only, dipyridamole and aspirin, or clopidogrel alone is recommended .	I	A
After an acute event of minor ischemic stroke or TIA, DAPT with aspirin and clopidogrel or with aspirin and ticagrelor for three weeks should be considered .	IIa	A
In patients with stroke or TIA who have a BP of $\geq 140/90$ mmHg, initiating the appropriate BP-lowering drug is recommended [456].	I	A
In patients between the ages of 18 and 60 with a prior PFO-associated stroke, PFO closure combined with antiplatelet therapy is recommended .	I	A
Smoking cessation is recommended in all patients with PAD [457].	I	A
Physical activity and a healthy diet are recommended for all patients with LEAD [458–461].	I	A
In patients with intermittent claudication, supervised exercise training is recommended [462, 463].	I	A
If supervised exercise training is not feasible or not available, then non-supervised exercise training is recommended instead [462].	I	A
Antiplatelet therapy is recommended in patients with symptomatic LEAD. ^c	I	C
In patients with LEAD and HTN, controlling BP at $<140/90$ mmHg is recommended .	I	A
In patients with LEAD and diabetes, strict glycemic control is recommended .	I	A
ACE inhibitors or ARBs should be considered as first-line therapy in patients with PAD and HTN. ^d	IIa	B
In patients with DM and chronic symptomatic LEAD without high bleeding risk, a combination of low-dose rivaroxaban (2.5 mg b.i.d.) and aspirin (100 mg o.d.) may be considered .	IIb	B
Identification and management of risk factors and concomitant diseases in patients with AF are recommended to be an integral part of treatment [464, 465].	I	A
Modification of unhealthy lifestyles and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity [466, 467].	I	A
Attention to good BP control is recommended in AF patients with HTN to reduce AF recurrences and the risk of stroke and bleeding [468, 469].	I	A
In obese patients with AF, weight loss, in addition to management of other risk factors, should be considered to reduce AF incidence, AF progression, AF recurrences, and symptoms [470].	IIa	B
Advice and management to avoid alcohol excess should be considered for AF prevention and in AF patients considered for oral anticoagulant therapy [471, 472].	IIa	A
Mild-to-moderate physical activity should be considered to decrease the risk of AF development or recurrence [473–475].	IIa	A
Optimal management of OSA may be considered to reduce AF incidence, AF progression, AF recurrences, and frequency of symptoms [476].	IIb	A

This table presents evidence-based recommendations for optimizing cardiovascular disease (CVD) prevention. It covers lifestyle measures (healthy diet, smoking cessation, physical activity, weight reduction), psychosocial support, alcohol moderation, and structured cardiac rehabilitation. It also summarizes treatment targets for blood pressure, diabetes, and lipid control across risk categories, as well as strategies for improving referral and access to rehabilitation services. Recommendations are classified by **Class of Recommendation (COR)** and **Level of Evidence (LOE)**.

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