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GUIDELINE

Saudi Heart Association Guidelines on Best Practices in the Management of Chronic Coronary Syndromes

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Abstract

Background: **The prevalence of both chronic coronary syndrome (CCS) and its risk factors is alarming in Saudi Arabia and only a minority of patients achieve optimal medical management. Context-specific CCS guidelines outlining best clinical practices are therefore needed to address local gaps and challenges.**

Consensus panel: **A panel of experts representing the Saudi Heart Association (SHA) reviewed existing evidence and formulated guidance relevant to local clinical practice considering the characteristics of the Saudi population, the Saudi healthcare system, its resources and medical expertise. They were reviewed by external experts to ensure scientific and medical accuracy.**

Consensus findings: **Recommendations are provided on the clinical assessment and management of CCS, along with supporting evidence. Risk reduction through non-pharmacological therapy (lifestyle modifications) remains at the core of CCS management. Great emphasis should be placed on the use of available pharmacological options (anti-anginal therapy and event prevention) only as appropriate and necessary. Lifestyle counseling and pharmacological strategy must be optimized before considering revascularization, unless otherwise indicated. Revascularization strategies should be carefully considered by the Heart Team to ensure the appropriate choice is made in accordance to current guidelines and patient preference.**

Conclusion: **Conscientious, multidisciplinary, and personalized clinical management is necessary to navigate the complex landscape of CCS in Saudi Arabia considering its population and resource differences. The reconciliation of international evidence and local characteristics is critical for the improvement of healthcare outcomes among CCS patients in Saudi Arabia.**

Keywords: Chronic coronary syndrome, Saudi Arabia, Guidelines

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1. Introduction

Coronary artery disease (CAD) is a dynamic and progressive pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries, potentially associated with vasospastic disease or thrombus in situ. The epicardial disease can be obstructive or non-obstructive and the vasospastic disease can be focal or diffuse. CAD can be both stable and unstable in its clinical presentation; its management is different between acute coronary syndromes (ACS) and the chronic pattern of the disease, chronic coronary syndromes (CCS) (formerly referred to as stable CAD) [1].

The overall prevalence of CAD of 5.5% was reported in Saudi Arabia between 1995 and 2000 [2]. Almost half of all cardiovascular disease-related deaths in the world in 2019 was attributed to CAD [3]. Some of the highest rates of age-standardized cardiovascular disease (CVD)-related disability-adjusted life-years are found in the North Africa and Middle East region [3]. In Saudi Arabia, the age-standardized CVD-related deaths has increased from 20 to 30% between 2010 and 2019 [4,5]. Moreover, cardiovascular diseases is the primary cause of death as well as years lived with disability and age-standardized disability-adjusted life-years [4,5]. CAD is very common in the Middle East, with 55% of heart failure (HF) in Middle Eastern Arab countries attributed to CAD [4]. A recent study from Saudi Arabia (HEARTS-chronic) showed that CAD can be identified as the underlying cause of 38% of HF cases [6].

The CLARIFY (ProspeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease) study investigated the long-term outcomes of CCS in 45 countries, including the Middle East (and Saudi Arabia). Patients from the Middle East had the highest body mass index (BMI), highest prevalence of diabetes, as well as the highest overall use of secondary prevention therapy [7]. Patients in this region are also distinctly younger, as age of onset of cardiovascular events (acute myocardial infarction) is at least 10 years lower in the Middle East compared to other regions [8–10]. A study modeling the burden of cardiovascular disease in the Saudi population projected that the prevalence of CVD will increase to 479,500 Nationals by 2035, incurring close to $10 billion in direct and indirect costs [11].

Considering the incidence of CCS and its risk factors in Saudi Arabia, the Saudi Heart Association (SHA) developed an official position statement on the management of these conditions in respect of available resources and expertise. Local CCS guidelines are needed to outline best clinical practices and improve access to healthcare services for all Saudi patients.

Abbreviation list

ACC	American college of cardiology
ACE	Angiotensin-converting enzyme
ACS	Acute Coronary syndromes
AHA	American heart association
ARB	Angiotensin receptor blockers
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass grafting
CAC	Coronary artery calcification
CAD	Coronary artery disease
CBC	Complete blood count
CCB	Calcium channel blockers
CCS	Chronic coronary syndrome
CCTA	Coronary computed tomography angiography
CMR	Cardiac magnetic resonance
COVID-19	Coronavirus disease 2019
CT	Computed tomography
CVD	Cardiovascular disease
DAPT	Dual antiplatelet therapy
DOAC	Direct oral anticoagulant
ECG	Electrocardiogram
ECHO	Echocardiography
ESC	European society of cardiology
FFR	Fractional flow reserve
HbA1c	Hemoglobin A1c
HF	Heart failure
ICA	Invasive coronary angiography
INOCA	Ischemia and No Obstructive CAD
LAD	Left Anterior Descending
LDL-C	Low-density lipoprotein cholesterol
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
MPI	Myocardial perfusion imaging
NICE	National Institute for Health and Clinical Excellence
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
RASi	Renin angiotensin system inhibitor
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDS	Summed Difference Score
SHA	Saudi heart association
SPECT	Single-photon emission CT

2. Methods

A series of meetings were held by a panel of experts to review existing evidence, international guidelines and formulate guidance relevant to local clinical practice considering the individual characteristics of the Saudi population, the Saudi healthcare system, its available resources and medical expertise. Data were reviewed by specialized subcommittees, who then proposed relevant recommendations. The overall guidelines were then reviewed by the steering committee as well as a secondary external expert panel to ensure accuracy, scientific integrity and relevance to the context of Saudi Arabia.

The guidelines followed the format of the Saudi Heart Association Guidelines and recommendations (Table 1).

3. Results - consensus statements

3.1. Clinical assessment

3.1.1. Risk assessment

Predictive models have been proposed to assess the pre-test probability of obstructive CAD and have been used in clinical practice since the introduction of the first model by Diamond and Forrester in 1979 [12]. These models attempt to predict the clinical likelihood of CAD based on age, sex and the nature of symptoms and undergo constant scrutiny and updates to improve their performance. In fact, CAD overestimation remains a notable issue in clinical pre-test probability assessment, even after the update of older models. Both the original Diamond-Forrester model and its 2011 update were found to overestimate the prevalence of obstructive CAD [13]. The predictive model proposed in the 2013 European Society of Cardiology (ESC) guidelines on the management of stable CAD [14] was also found to lead to the overestimation of the prevalence of obstructive disease by almost two-thirds [15–19]. This led to its update considering the contribution of pre-test probability overestimation to low diagnostic yield in invasive and non-invasive testing [19]. The newer ESC model proposed in 2019 integrated patients whose main symptom upon presentation is dyspnea and has since been validated and found to provide a more reasonable classification of the likelihood of obstructive CAD in patients compared to the previous 2013 model, as well as other models (National Institute for Health and Clinical Excellence (NICE) 2016 model and the CAD Consortium basic score) [20–23]. Using pre-test probability assessment, diagnostic imaging can be safely avoided or delayed in patients with pre-test probability<15% in the absence of compelling reasons [15,16], which will in turn reduce unnecessary use of resources and unnecessary testing in patients with stable chest pain/suspected CAD. Despite this, a minority of centers around the world follow guideline recommendations to include pre-test probability in the clinical assessment of patients with suspected CAD [24].

In addition to sex, age and the nature of symptoms, it might be useful to also consider CVD risk factors (i.e. possible heredity of CVD, dyslipidemia, diabetes, hypertension, and lifestyle factors such as smoking) when looking to identify patients with obstructive CAD [1,14,25–27]. However, the use of CVD risk factors to improve pre-test probability assessment still requires optimization. Coronary calcium score was another factor shown to improve clinical pre-test probability calculation through several models [28,29], further highlighting the need for continuous improvement of available prediction scores to reduce CAD overestimation.

The ESC models were developed mainly using patients from low CVD risk regions [1]. This could further limit their predictive ability in high-risk regions such as Saudi Arabia, where modifiable cardiovascular risk factors (e.g. dyslipidemia, hypertension, obesity, diabetes, smoking) are highly prevalent and are most often synchronous (more than three cardiovascular risk factors in almost half of the population) and the onset of cardiovascular disease is one to two decades younger in age [30]. Based on risk factors, it is estimated that a significant portion of the Saudi population will develop severe coronary events (myocardial infarction or

Table 1. Saudi Heart Association classes of recommendations.

Color	Class	Definition
(green)	Recommended	The usefulness and efficacy of a particular treatment/procedure/action is supported by available evidence.
(yellow)	Should be considered	The usefulness and efficacy of a particular treatment/procedure/action is established by favorable expert opinion on conflicting evidence.
(orange)	May be considered	The usefulness and efficacy of a particular treatment/procedure/action is not well established by evidence and expert opinion.
(red)	Not recommended	A particular treatment/procedure/action is not useful nor effective and is potentially harmful based on available evidence and/or general agreement.

coronary death) [31] or CVD [32] in the next 10 years. A gender-based approach might be appropriate in Saudi Arabia, where women seem to more often present with high risk CVD risk factors [33] and suffer from more adverse outcomes after surgery for CAD [34]. Adequate clinical assessment including medical history, patient characteristics and diagnostic imaging (when needed) coupled with comprehensive therapy and rehabilitation should improve the timely detection and management of CAD without overburdening healthcare systems with unnecessary medical services.

3.1.2. History and physical examination

All patients with documented CAD should be managed as CCS to reduce ACS, MI, stroke and death, although many patients presenting with symptoms suggesting CCS do not have documented CAD. Symptom type and duration in relation to clinical presentation should be obtained as part of establishing patient history in addition to associated traits. A focused cardiovascular assessment is advisable to rule out a possible ACS or other causes of chest pain that could be severe or life-threatening and to identify complications. History and physical examination findings should be considered collectively as to properly guide further diagnostic testing and management plan. Chest pain should be assessed in the context of age and gender as accompanying symptoms are more frequent among females [35,36] and acute coronary syndrome is likely to occur among older patients [37–39]; Furthermore, it is also important to consider alternative diagnoses (Fig. 1). It is crucial to differentiate stable versus unstable angina (i.e. rest chest pain for long duration, new-onset chest pain or equivalent, crescendo angina). Further testing is necessary to diagnose CCS [40] and its need remains dependent on pre-test probability, as outlined in sections 3.1.3 and 3.1.4. For more information on the definition and characteristics, duration and intensity of symptoms, please refer to the CAD modules available in the SHA Virtual Academy (https://sha-academy.com/).

3.1.3. Initial diagnostic evaluation

Basic diagnostic evaluation in patients with suspected CCS includes laboratory testing, a resting electrocardiogram (ECG), resting echocardiography, and a chest X-ray in specific patient groups.

3.1.3.1. Biochemical testing. Laboratory tests are requested to detect potential causes of ischemia, as well as to diagnose cardiovascular risk factors and other associated conditions. In addition to a complete blood count (CBC) including hemoglobin, renal function, fasting plasma glucose and glycated hemoglobin (HbA1c) should be determined to rule out anemia, chronic kidney disease and diabetes, respectively. Moreover, a lipid profile (including total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C),

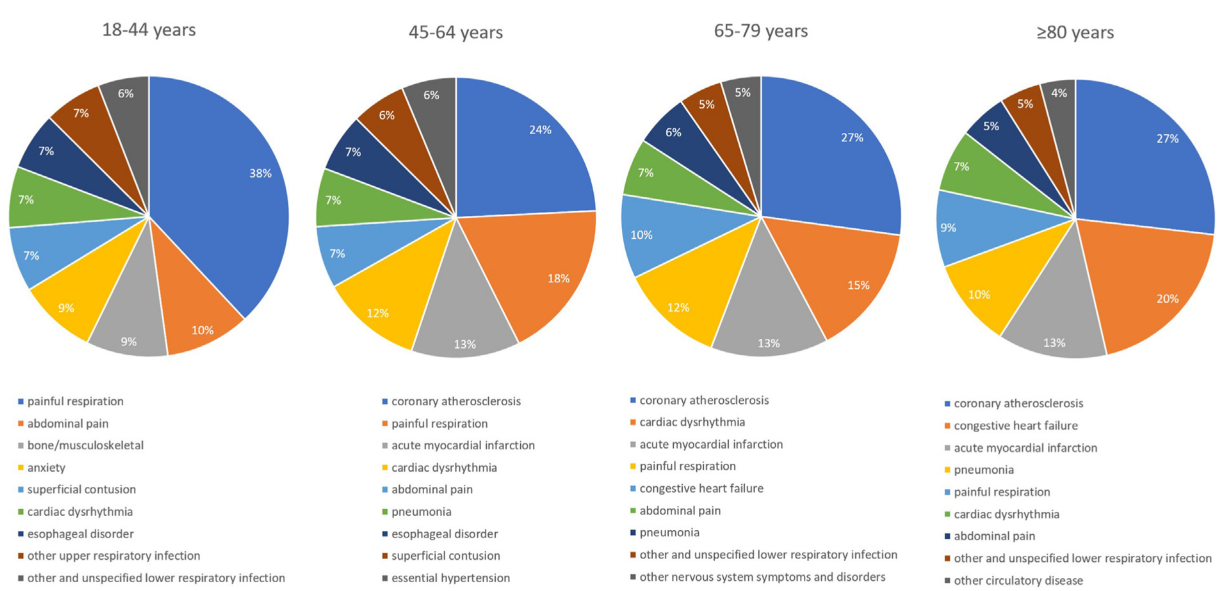

Fig. 1. Top 9 causes of chest pain in the emergency department based on age (weighted percentage; excluding nonspecific chest pain). Created using data from Hsia, RY, et al. [37].

Table 2. Recommendations for initial basic diagnostic testing for patients with suspected CCS.

No	***Recommendation***
1	Complete blood count (CBC), creatinine, estimation of glomerular filtration rate and lipid profile are recommended in all patients with suspected CAD.
2	Screening for diabetes is recommended in all patients with suspected or established CAD (including HBA1c, fasting plasma glucose). In the event that findings are inconclusive (HBA1c, fasting plasma glucose), glucose tolerance test is recommended.
3	Thyroid function test is recommended in case of suspicion of thyroid dysfunction

CAD = coronary artery disease; CBC = Complete Blood Count; HbA1c = glycated hemoglobin.

Table 3. Recommendations for electrocardiogram use in the initial evaluation of patients with suspected coronary artery disease.

No	***Recommendation***
1	***A resting 12 leads ECG*** is recommended in all patients with chest pain or equivalent.

ECG = electrocardiogram.

Table 4. Recommendations for echocardiogram for patients with suspected coronary artery disease.

No	***Recommendation***
1	A resting **transthoracic echocardiogram** is recommended for all patients to: (1) eliminate other causes of chest pain (2) Detect regional wall motion abnormalities suggestive of CAD (3) Assess LVEF for risk stratification (4) Assess diastolic function

CAD = coronary artery disease; LVEF = left ventricular ejection fraction.

Table 5. Recommendation for chest X-ray for patients with suspected coronary artery disease.

No	***Recommendation***
1	Chest X-ray may be considered to assess signs of HF, rule out pulmonary diseases, other non-cardiac causes for chest pain.

HF: heart failure

Table 6. Diagnostic accuracy of noninvasive modalities for detection of CAD.

Modality	Sensitivity	Specificity
CT Angiography	91	93
Stress Echocardiography	79	87
MPI-SPECT	86	74
MPI-PET	89	90
Stress MR perfusion	91	81
Stress MR wall motion	83	86
MR coronary angiography	73	86
Exercise electrocardiogram	68	77

CT: computed tomography; MPI: myocardial perfusion imaging; MR: magnetic resonance; PET: positron emission tomography; SPECT: single photon emission computed tomography

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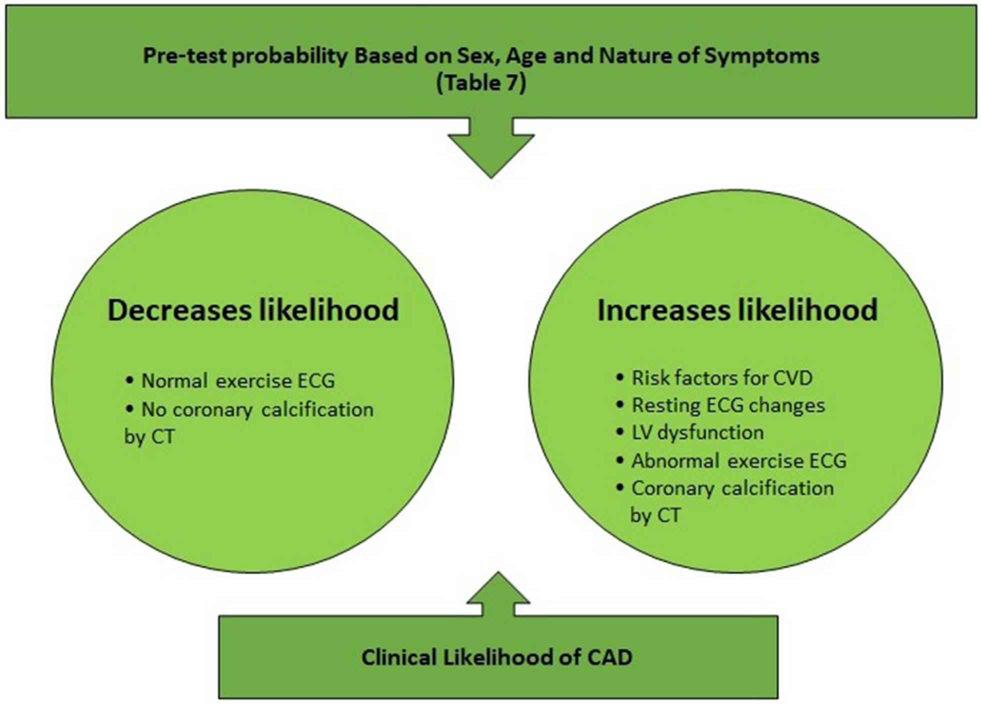

Fig. 2. ***Factors of the clinical likelihood of obstructive coronary artery disease.*** *CAD: coronary artery disease; CT: computed tomography; CVD: cardiovascular disease; ECG: electrocardiogram; LV: left ventricle.*

Table 7. Pretest probability of coronary artery disease by age, gender and symptoms.

Age (Years)	Sex	Typical/Definite Angina	Atypical/Probable Chest Pain	Non-anginal Chest Pain	Asymptomatic
30-39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Very low	Very low	Very low
40-49	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Low	Very low	Very low
50-59	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Very low	Very low
60-69	Men	High	Intermediate	Intermediate	Low
	Women	High	Intermediate	Intermediate	Low

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Table 8. High-risk features of noninvasive modalities.

Modality	High risk features
Exercise Treadmill Testing	Duke score < -11 (ST-segment depression, exercise time and symptoms) Time to onset of ST-segment depression ST-segment elevation Time to resolution of ST-segment depression Exercise induced ventricular arrhythmias
Cardiac CT	Left main stenosis ≥ 50% 3 vessel disease 2 vessel disease including proximal LAD
MPI	Large reversible perfusion defect Multiple perfusion defects SDS ≥13 Post-stress transient ischemic dilation Post-stress right ventricle uptake Post-stress lung uptake Abnormal post-stress LVEF
Stress ECHO	Post-stress new regional wall abnormalities Post-stress global LV impairment Diastolic dysfunction Post-stress LV cavity dilatation Mitral regurgitation
CMR	SDS ≥7 Presence of late gadolinium enhancement Reversible perfusion defects

CMR: cardiac magnetic resonance; CT: computed tomography; ECHO: echocardiography; LAD: Left Anterior Descending; LV: left ventricle; LVEF: left ventricular ejection fraction; MPI: myocardial perfusion imaging; SDS: Summed Difference Score

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lipoprotein a (Lp(a)) and triglycerides) would reflect risk profiles and the need for treatment (Table 2).

In case of clinical suspicion of acute coronary syndrome, refer to relevant guidelines.

3.1.3.2. 12-lead electrocardiogram. Resting 12 lead ECG allows the detection of ST-segment and T wave changes as well as indirect signs of CAD such as signs of prior myocardial infarction (MI) (pathological Q waves), conduction abnormalities or arrhythmias and is recommended for all patients with chest pain or equivalent symptoms (Table 3).

3.1.3.3. Echocardiogram. Transthoracic echocardiography commonly provides key insights into cardiac function and anatomy. Reduction in left ventricle (LV) systolic function, diastolic dysfunction, regional wall motion abnormalities may indicate ischemic myocardial damage [1]. Echocardiography plays an important role in the diagnosis of coexisting diseases of the heart, such as valvular heart diseases [41] (Table 4).

3.1.3.4. Chest X-ray. Chest X-ray could be helpful in evaluating patients with suspected HF or pulmonary problems, and to exclude other possible reasons of chest pain (Table 5).

3.1.4. Non-invasive diagnostic testing

3.1.4.1. General considerations. A wide diagnostic armamentarium is available for disease diagnosis, including treadmill stress tests, stress echocardiography (ECHO), myocardial perfusion imaging (MPI) through both single photon emission computed tomography (SPECT) and positron emission tomography (PET), coronary computed tomography angiography (CCTA), and cardiac magnetic resonance imaging (CMR).

However, making the optimal choice of diagnostic test can be challenging. Table 6 shows the diagnostic accuracy of different noninvasive approaches for the detection of CAD. Understanding the patient pre-test probability of CAD and the risk, advantages and shortcomings of each modality will prove useful for test selection (Fig. 2). In addition to this, site expertise, availability, and cost will affect the choice of test [42].

Noninvasive tests assess two essential features that are mandatory for the patient care:

What are the patient's diagnosis and prognosis?

Pre-test probability assessment is crucial when considering the need for testing, test selection/appropriateness, and test result interpretation. The clinician can estimate the patient's pre-test probability for CAD based upon age, gender and quality of symptoms [43] (Table 7). The detection of patients with obstructive CAD was also shown to be improved by clinical models taking into consideration risk factors for CCS [1,14,25–27], resting ECG changes, or coronary calcification calcium obtained by computed tomography (CT) [28,29] (Fig. 2).

3.1.4.2. Functional versus anatomical imaging for CAD. Cardiac imaging modalities fall into two, sometimes overlapping, comprehensive groups. Insights obtained from modalities such as CCTA and CMR angiography primarily reflect anatomical information for the evaluation of coronary stenosis. On the other hand, functional imaging modalities such as stress ECHO, SPECT, PET, and CMR, help in the diagnosis of ischemia. The choice between

Table 9. Recommendations on exercise electrocardiogram in the initial diagnostic management of patients with suspected coronary artery disease.

No	Recommendation
1	Exercise ECG is recommended for the assessment of exercise tolerance, symptoms, arrhythmias, BP response, and event risk in selected patients (When diagnostic or therapeutic strategy will be affected)
2	Exercise ECG may be considered as an alternative test to rule-in and rule-out ischemia in case non-invasive imaging is inaccessible
3	Exercise ECG may be considered in patients receiving therapy to assess symptom control and ischemia.
4	Exercise ECG is not recommended for the intent of diagnosis in patients with >_0.1 mV ST-segment depression on resting ECG or in patients receiving treatment with digitalis.

BP: blood pressure; ECG: electrocardiogram diagnostic methods, be it predominately anatomical or functional, should be based on the clinical question.

Available evidence shows a very low annual rate of cardiac events in patients who were found to be at low-risk of CAD through noninvasive tests (<1%) [44]. Based on this, medical treatment can be safely administered and further investigation is not necessary except in the case of uncontrolled or emerging/changed symptoms. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial [45] and the Initial Invasive or Conservative Strategy for Stable Coronary Disease (ISCHEMIA) trial [46], the largest randomized trials of patients with CCS, support this approach seeing as the use of revascularization in addition to optimal medical therapy was not found to lead to improved outcomes compared with initial optimal medical therapy alone.

3.1.4.3. Cardiac testing based on pretest probability of CAD

3.1.4.3.1. Low pretest probability of CAD. The need for noninvasive imaging in case of low pre-test probability of CAD remains indeterminate. The American Heart Association/American College of Cardiology (AHA/ACC) guidelines for exercise testing provides low level (IIb) recommendation in this patient group [43]. When pre-test probability of CAD is low, exercise treadmill testing could be beneficial by facilitating patient access to other diagnostic modalities. However, it should be noted that this approach have a relatively modest sensitivity and specificity for CAD detection (68% and 77%, respectively) with false-negative and false-positive test results [47]. It is important to note that exercise treadmill testing alone is not diagnostic and does not rule out underlying CAD. Further testing (coronary calcium score, CT) is warranted to completely exclude the diagnosis of CAD. Conversely, exercise treadmill testing still has prognostic value when used in the right patient population (low pre-test probability as opposed to intermediate or high pre-test probability). The Duke treadmill score can be used for the detection of patients who are at high risk of a future cardiac event [48]. Table 8 shows other indicators of poor prognosis in severe CAD by exercise treadmill testing [49–51] (see Table 9).

3.1.4.3.2. Intermediate pretest probability of CAD. Patients with intermediate pre-test probability of CAD are expected to benefit the most from diagnostic and prognostic testing. In this population, confirming or disprove the presence of CAD is essential.

3.1.4.3.3. High pretest probability of CAD. In the case of high pre-test probability of CAD or already-documented CAD, SPECT, PET, stress ECHO or CMR may be used for risk stratification and prognosis. This would yield appropriate information for therapy guidance and establishing the necessity of invasive angiography and revascularization.

3.1.4.4. Anatomic testing

3.1.4.4.1. Coronary computed tomography angiography (CCTA). Coronary artery calcification (CAC) detected by non-contrast enhanced CT is indicative of atherosclerosis [52–54]. The superior prognostic value of CAC compared to traditional risk factors was evident in several studies [55–57]. One meta-analysis including 3924 symptomatic patients with a 3.5-year follow-up showed that patients with CAC>0 had a yearly cardiac event rate of 2.6%, with a notable lower rate (0.5%) observed among those with 0 CAC [56].

The accuracy of CCTA in the detection of atherosclerotic plaque is the main influence on its clinical applications of CCTA. Several studies have assessed the accuracy of CCTA for detection of coronary artery stenosis compared to invasive coronary angiography (ICA) [58]; the sensitivity reportedly varies between 86% and 100% and the specificity between 91% and 98%. Given CCTA's high negative predictive value, this modality may be best used to exclude CAD and to limit ICA use for the diagnosis of CAD [59,60]. This was confirmed by the DISCHARGE trial, which demonstrated comparable risk of major adverse cardiovascular events in patients with stable chest pain and intermediate pre-test probability of CAD when initially diagnosed with CT or ICA. It should be noted that evidence from other clinical trials (i.e. the PROMISE, CONFIRM, and SCOT-Heart trials) show that CCTA is associated with increased cost, overestimates the prevalence of disease and is associated with a 50% increase in subsequent coronary angiography and revascularization with no differences in mortality as compared with functional testing [18,61–65]. Moreover, the use of CT for initial diagnosis was associated with fewer complications due to a major procedure [66]. Calculation of fractional flow reserve with CT (FFR-CT) reflects estimated lesion-specific ischemia [67]. A meta-analysis of available evidence supports the role of FFR-CT in excluding the need for further testing in patients with CCS and intermediate risk [68]. This approach seems to be relatively safe, being associated with a lower incidence of intermediate-term adverse events [68]. It is therefore important to address gaps in local practice and ensure the availability and accessibility of FFR-CT in healthcare institutions.

In the current American College of Cardiology Foundation appropriateness criteria guidelines for cardiac CT and MR, CCTA is considered to be suitable for the evaluation of intermediate risk patients with uninterpretable ECG or inability to exercise [69].

In addition to diagnostic accuracy, CCTA also reflects the possibility of coronary events and death (Table 8) [70].

3.1.4.4.1.1 Coronary CT angiography: limitations and challenges The diagnostic accuracy of CCTA is greatly dependent on image quality. It is therefore necessary to ensure image quality is optimal through adequate patient preparation and CCTA protocol. Cardiac motion artifacts arise in patients with elevated heart rates, and heart rate variability [71,72].

The limitations of CCTA are several and include exposure to ionizing radiation, the need for a slow heart rate, arrhythmia, severe renal impairment, extensive coronary artery calcifications, and potential allergy to contrast. Recent technological advancement in scanners have addressed some of these limitations, reducing the need for a slow heart rate and allowing imaging of patients with slow atrial fibrillation. Remarkable efforts have also made use of available technologies and approaches to limit CCTA's radiation dose [73,74].

3.1.4.4.2. MR angiography. Noninvasive visualization of the coronary artery with no exposure to ionizing radiation is possible with coronary MR angiography [75]. This modality is not without its limitations, which include extended image duration,

Table 10. Recommendation for initial diagnostic imaging tests in the assessment of symptomatic patients with suspected CAD.

No	Recommendation
1	***non-invasive functional imaging for myocardial ischemia or CCTA*** is recommended as the initial test to diagnose CAD in symptomatic patients with suspected CAD.
2	It is recommended that the choice of initial non-invasive diagnostic test be founded on the PTP of CAD and other patient characteristics with implications on test performance (contraindications), local expertise, cost and test accessibility.
3	***functional imaging for myocardial ischemia or invasive anatomical and functional invasive imaging is recommended*** for confirmation of the diagnosis of CAD in cases where diagnosis could not be established based on CCTA, or CCTA reflected CAD of uncertain functional significance.
4	Invasive coronary angiography is recommended as an initial diagnostic test for CAD in the following cases: - high PTP, - severe symptoms uncontrolled by pharmacologic therapy or - typical angina at a low level of exercise, - high event risk* based on clinical evaluation.
5	It is necessary that invasive functional assessment be accessible and it should be used to assess stenoses before revascularization when clinical significance of lesion is in doubt.
6	CCTA should be considered as an alternative to invasive angiography if inconclusive or non-diagnostic results were obtained from another non-invasive test
7	CCTA is not recommended in case obtaining good image quality is doubtful (e.g. extensive coronary calcification, irregular heart rate, significant obesity, inability to cooperate with breath-hold commands).
8	Coronary calcium detection by CT is not an alternative to CCTA and is not recommended to diagnose obstructive CAD.

*: survived sudden cardiac death or potentially life-threatening ventricular arrhythmias and those patients develop symptoms and signs of heart failure

CAD: coronary artery disease; CT: computed tomography; CCTA: coronary computed tomography angiography; PTP: pre-test probability

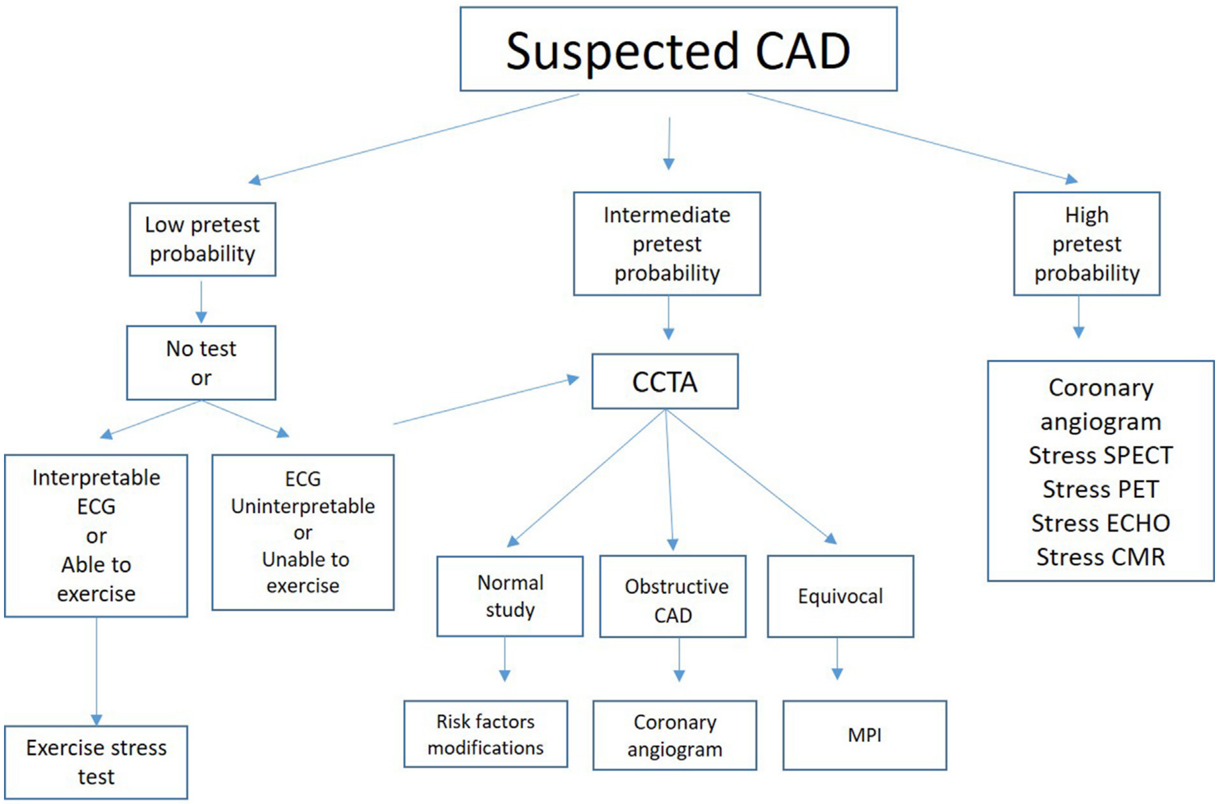

Fig. 3. Diagnostic algorithm for investigating suspected coronary artery disease. CAD: coronary artery disease; CCTA: coronary computed tomography angiography; ECG: electrocardiogram; ECHO: stress echocardiography; MPI: myocardial perfusion imaging.

lower spatial resolution, and reliance/variability related to the operator. Moreover, MR angiography has lower sensitivity and specificity compared to CCTA, with an as of yet ambiguous clinical utility [76,77].

3.1.4.5. Functional testing

3.1.4.5.1. MPI: SPECT and PET. MPI with SPECT is a widely accessible test that makes use of stressors, most commonly exercise. Other stressors may be needed depending on each case; vasodilator stress is indicated in patients with left bundle branch block (LBBB), patients unable to exercise, and patients unable to reach target heart rate [78]. Patients with severe asthma or other conditions susceptible to bronchospasm exacerbations are generally administrated dobutamine due to the contraindication of some vasodilators, such as adenosine and dipyridamole. SPECT MPI was shown to have an overall diagnostic sensitivity and specificity of 86% and 74%, respectively, by an extensive meta-analysis [79]. MPI can be used to guide coronary intervention seeing as SPECT perfusion abnormalities are closely correlated with coronary artery perfusion territories [80].

Available evidence suggests that PET might have superior accuracy to SPECT MPI [81], with a mean sensitivity and specificity of 89% (83%–100%) and 90% (73%–100%), respectively, in the diagnosis of CAD [82–85]. The prognostic value of SPECT and PET in patients with suspected or documented CAD is supported by various studies as both modalities allow the identification of patients at high risk of future cardiac events, as outlined in Table 8. These patients can then be selected for invasive investigations and coronary intervention [86–88].

3.1.4.5.1.1 SPECT and PET: limitations and challenges Radiation exposure and contraindications to the type of stress test (exercise as a stressor or pharmacologic stressors) are main limitations of SPECT and PET.

3.1.4.5.2. Stress echocardiography. Stress echocardiography is an established technique for the evaluation of CAD's functional significance and for risk

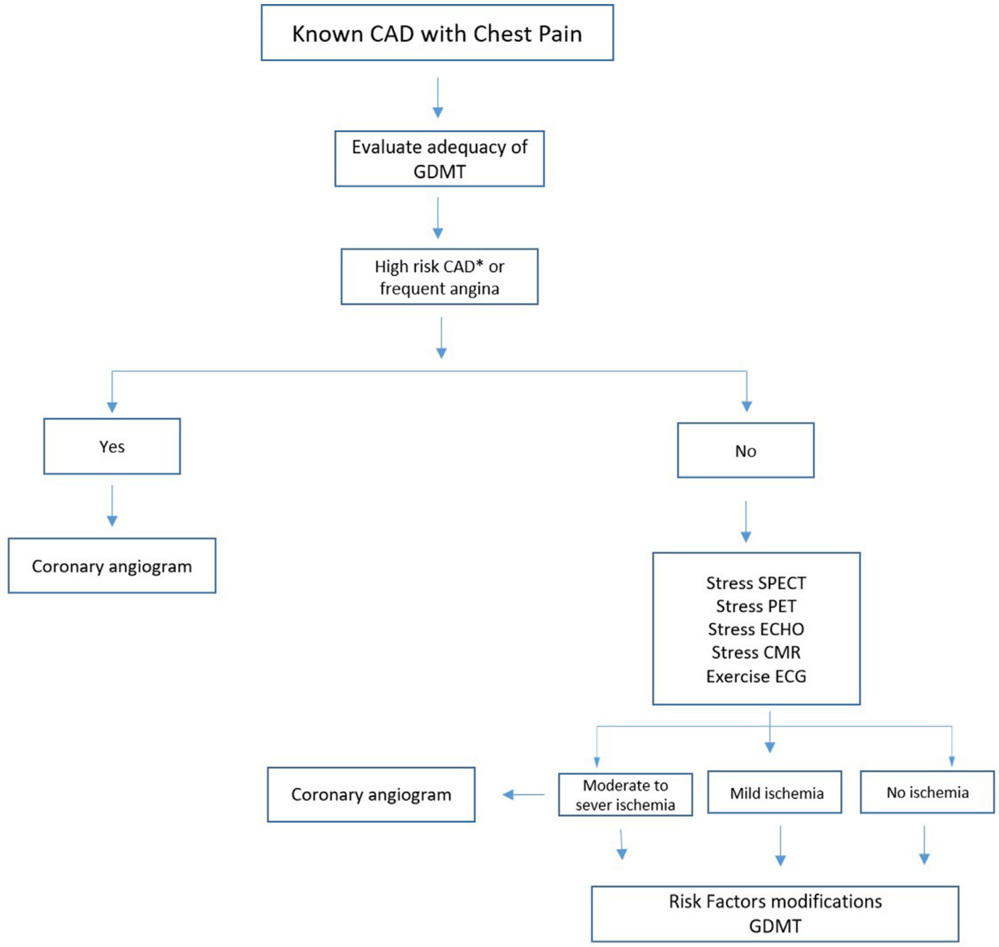

*Fig. 4. Diagnostic algorithm for patients with known CAD and chest pain. * high risk features or previous revascularization. CAD: coronary artery disease; CMR: cardiac magnetic resonance; ECG: electrocardiogram; ECHO: echocardiography; GDMT: guideline-directed medical therapy; PET: positron emission tomography; SPECT: single-photon emission CT.*

Table 11. Recommendations for patient with INOCA.

No	***Recommendation***
1	Invasive coronary function testing should be considered for better diagnosis of INOCA and risk stratification in patients with persistent stable chest pain and nonobstructive CAD with mild or worse myocardial ischemia (as observed on imaging)
2	Stress PET MPI with myocardial blood flow reserve should be considered for the diagnosis of microvascular dysfunction and the improvement of risk stratification in patients with persistent stable chest pain and nonobstructive CAD.
3	Stress CMR with the addition of MBFR measurement should be considered for better diagnosis of coronary myocardial dysfunction and MACE risk estimation in patients with persistent stable chest pain and nonobstructive CAD.
4	Stress echocardiography with the addition of coronary flow velocity reserve measurement may be considered for better diagnosis of coronary myocardial dysfunction and for MACE risk estimation in patients with persistent stable chest pain and nonobstructive CAD.

CAD: coronary artery disease; CMR: cardiac magnetic resonance; MACE: major adverse cardiovascular events; MPI: myocardial perfusion imaging; PET: positron emission tomography stratification [89]. Exercise and pharmacologic stress echocardiography are commonly available, less costly, and well tolerated.

Stress ECHO is suitable for symptomatic disease with an intermediate pre-test probability of CAD [90]. The diagnostic goal to detect myocardial ischemia is deteriorating or emerging wall motion abnormality. Stress ECHO can be used for the detection of criteria relevant for the diagnosis and prognosis of severe CAD (Table 8) [91,92].

3.1.4.5.2.1 Stress echocardiography: limitations and challenges The diagnostic accuracy of stress ECHO is significantly affected by local expertise, similarly to routine ECHO. Additionally, study quality is constrained by patient-related variables such as body build; however, the implementation of contrast agents may improve image quality and diagnostic accuracy [93].

3.1.4.5.3. CMR. CMR can be conducted based on several protocols, such as first-pass gadolinium myocardial enhancement with vasodilator and dobutamine stress test [94]. Additional insights on wall motion abnormalities, systolic function, and areas of fibrosis will be obtained. CMR stress perfusion imaging was reported to have high sensitivity and specificity (90% and 94%, respectively) with a high event-free survival rate for a negative study (Table 8) [95]. Challenges include a time-consuming workflow and limited expertise for this test. Moreover, CMR may be contraindicated by the presence of implanted devices or by severe renal failure (contraindication of the administration of gadolinium contrast).

3.1.5. Invasive testing

ICA should not be conducted routinely and is indicated in case of inconclusive non-invasive testing in patients with suspected CAD. Early ICA with no previous non-invasive testing could be reasonable in several cases, such as high pre-test probability of CAD, persistent symptoms despite medical therapy or with typical angina at a low level of exercise, and a possible high risk of cardiac event (defined as having survived sudden cardiac death or potentially life-threatening ventricular arrhythmias and those patients develop symptoms and signs of heart failure) based on initial clinical evaluation [1]. Considering the aforementioned limitations of visual stenoses assessment, invasive functional assessment should integrate fractional flow reserve (FFR)/Instantaneous wave-free ratio with ICA [96]. That being said, the performance of ICA still carries a small risk of complications and should remain dependent on patient preference related to invasive procedures and revascularization, the expected efficacy of revascularization, as well as choice of percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG).

Table 10 offers overall recommendations for initial diagnostic imaging tests in the assessment of symptomatic patients with suspected CAD. Diagnostic algorithms for patients with suspected CAD or known CAD with chest pain are shown in Figs. 3 and 4, respectively.

3.1.6. Patients with suspected ischemia and No obstructive CAD (INOCA)

Angina with nonobstructive CAD is defined as "effort-induced angina with positive stress test/MPI for myocardial ischemia and "normal" or "near normal" coronary arteries on angiography" [97]. It is not uncommon in our practice to find marked discrepancy between patient's symptoms, ischemia on non-invasive testing with non-obstructive

Table 12. Non-pharmacological therapy recommendations.

No	Recommendation
1	Referral to smoking cessation clinic is recommended.
2	It is recommended to advise patients to follow the Mediterranean diet and high intake of fruits and legumes.
3	Sustained physical activity is recommended.
4	It is recommended to advise patients to maintain healthy weight, defined as body mass index of 18.5 to 24.9 kg/m^2, and waist circumference less than 102 cm (40 inches) in men and less than 88 cm (35 inches) in women
5	Psychosocial assessment to direct psychological interventions is recommended.
6	Annual Influenza vaccination may be considered, especially in elderly patients

epicardial vessels [98]. This should suggest the possibility of non-obstructive cause of ischemia, most likely as a result of change in intra-microvasculature flow [99]. Coronary microvascular dysfunction is most like to occur in female patients, hypertensives, diabetics and patients with other insulin-resistant states [100]. Invasive coronary reactivity testing can be used for the evaluation of vasospasm as well as nonendothelial–dependent and endothelium-dependent microvascular reactivity (Table 11). Calcium Channel Blockade is considered a second-line antianginal therapy in CCS patients but considered the first line therapy in variant angina as the beta blocker is contraindicated.

3.2. Non-pharmacological therapy

Controlling risk factors is an essential component of CCS management in addition to reducing symptoms and improving prognosis. This can be achieved through lifestyle modification supplemented with appropriate medical therapy for optimal disease management. Non-pharmacological interventions carry notable weight in the treatment of CCS and the improvement of patient survival [101]. The benefit of lifestyle modification in the prevention of future cardiovascular events is shown in several studies, notwithstanding the use of secondary prevention therapy and interventions [102–105]. A multidisciplinary approach should be targeted to educate and empower patients to implement appropriate lifestyle and behavior modifications, as well as better adhere to their medication.

As previously mentioned, modifiable cardiovascular risk factors are very common in the Saudi population and include hypertension, dyslipidemia, obesity, abdominal obesity [2,106–109]. Low compliance to recommended dietary and physical activity patterns is frequent [110], and the prevalence of smoking continues to rise [111]. The PURE-Saudi study revealed the alarming prevalence of CVD risk factors in the adult Saudi population; of 2047 participants, approximately 70% had low physical activity, half were obese, 34% followed an unhealthy diet, 32% had dyslipidemia, 30% were hypertensive, and 25% were diabetic. Current smoking, sadness/depression, anxiety and stress were also relatively prevalent in the Saudi population [32,107]. Gender-based approaches might be needed in Saudi Arabia seeing as women might have a higher predisposition to exhibit high risk for CVD compared to similarly aged men [33,108].

Unfortunately knowledge and awareness of CVD and CCS risk factors remains relatively limited in the Saudi population [112,113], highlighting the need for population-wide as well as individualized awareness and educational interventions to promote a healthy lifestyle.

Little evidence is available on the efficacy of lifestyle interventions for the modification of CVD risk. A local study investigated the efficacy of a three-month lifestyle intervention in women aged 30 and

Table 13. Recommendations on the use of anti-anginal agents.

No	***Recommendation***
1	Beta-blockers are indicated to control heart rate and symptoms.
2	CCB is the second-line antianginal therapy in patients with contraindications to Beta-blockers, such as variant angina
3	Non-dihydropyridine-CCB is alternative therapy to Beta-blockers for heart rate control if there is no LV dysfunction
4	Combination of a beta-blocker with a dihydropyridine-CCB should be considered if angina symptoms are uncontrolled
5	Long-acting nitrates can be considered when initial therapy with a beta-blocker and/or a CCB is contraindicated, is not well tolerated, or not sufficient to control angina symptoms. Consider a nitrate-free or nitrate-low interval of ~10-14 h to avoid tolerance
6	Short-acting nitrates are recommended for immediate alleviation of angina.

CCB: Calcium channel blocker;

above with moderate to high risk of CVD and found that providing personalized health education, exercise training and diet counselling was associated with an improvement in the 10-year cardiovascular Framingham risk score [114]. In a similarly-aged sample of military personnel in Saudi Arabia, the National Guard Health Promotion Program for Chronic Diseases and Comorbid Conditions led to improvement in modifiable risk factors such as body mass index, waist circumference, blood sugar levels, and fruits and vegetables consumption [115].

International evidence in support of each lifestyle intervention will be detailed in the following subsections. Non-pharmacological therapy recommendations are shown in Table 12.

3.2.1. *Smoking cessation*

Smoking is clearly associated to a greater risk of cardiovascular diseases, including CCS. An earlier health survey of 17,350 participants from Saudi Arabia showed a clear association between smoking and development of CCS [116]. As shown in the COURAGE trial, greater risk factor control can improve survival in patients with CCS, with smoking cessation/no smoking being one of the strongest predictors of improved 1-year survival [101]. The decrease in patient mortality was also reported in other studies in patients with CCS [117]. Smoking cessation can also help achieve BP control in younger patients with premature CCS and thereby decrease the clinical burden of the disease [118].

Table 14. Recommendations for event prevention.

No	Recommendation
1	Aspirin 75-100 mg daily is recommended in patients with documented CAD.
2	Clopidogrel 75 mg daily is recommended as an alternative to aspirin in patients with aspirin intolerance or allergy.
3	Ticagrelor 60mg could be used in combination with aspirin in patients post MI.
4	DOAC is recommended in preference to a Vitamin K antagonist in eligible patients with atrial fibrillation.
5	The DOAC rivaroxaban 2.5mg twice daily may be considered in patients with CCS and polyvascular disease
6	Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or oral anticoagulant monotherapy with high risk of bleeding.
7	Statins are recommended in all patients with CCS.
8	Combination of statin with ezetimibe is recommended if treatment goal is not achieved with statins.
9	Combination of statin with a PCSK9 inhibitor (±ezetimibe) is recommended in high-risk population who do not achieve LDL-C treatment goals
10	ACE inhibitors (or ARBs) are recommended if a patient has LV systolic dysfunction, hypertension, diabetes, or chronic kidney disease.
11	Beta-blockers are recommended in patients with LV dysfunction, HF and ongoing symptoms.
12	Hormone replacement therapy is not recommended.
13	Administration of a proton pump inhibitor is generally not recommended in the absence of gastrointestinal indications

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CAD: coronary artery disease; CCS: chronic coronary syndrome; DAPT: dual antiplatelet therapy; DOAC: direct oral anticoagulant; HF: heart failure; LDL-C: low-density lipid cholesterol; LV: left ventricle; MI: myocardial infarction; PCSK9: Proprotein convertase subtilisin/kexin type 9;

A Cochrane meta-analysis showed that the use of one of the forms of nicotine replacement therapy (gum, transdermal patch, nasal spray, inhalator and sublingual tablets/lozenges) can lead to up to 60% higher rates of quitting [119]. The intensity of additional support provided while using nicotine replacement therapy can influence the efficacy of this approach [119]. Nicotine replacement is an effective strategy for smoking cessation and should be considered in combination with behavioral modification. Switching from conventional cigarettes to modified-risk tobacco products has been shown to potentially reduce adverse health effects [120] as well as CVD risk associated with continued smoking [121]. Individuals who quit conventional cigarettes and use noncombustible nicotine or tobacco products are at a higher CVD risk compared to those who abstain from all tobacco products [121]. One study actually suggests that e-cigarettes ensure a higher rate of sustained 1-year smoking abstinence compared to nicotine replacement therapy [122]. However, the evidence supporting the superiority of e-cigarettes to placebo or nicotine replacement therapy remains limited or of low quality [123–125].

Promoting smoking cessation is therefore important in CCS management and can be achieved through counselling, behavioral interventions, as well as pharmacological therapy (including nicotine replacement).

3.2.2. Healthy diet

Following healthy eating patterns can lead to clinically meaningful reduction in mortality and cardiovascular events [126]. The progression of CCS and other CVDs is influenced by unhealthy diets and available evidence supports the ability of modifying dietary intake of fruits and vegetables to prevent CVD as well as other non-communicable diseases such as cancer [127]. In general, a Mediterranean dietary pattern seems to carry a clinically relevant benefit for the prevention of CVD [128–130]. Appropriate diets are those that are high in fruits, vegetables, legumes, fiber, monounsaturated fats, nuts, and fish. In the last decade, there was a paradigm shift on the concept of diet and cardiovascular risk related to the balance between carbohydrate and fat, where the earlier is more harmful than the latter. The PREDIMED trial showed that fat are not harmful in the usual ranges consumed by most people and that monounsaturated fatty acid is actually protective while polyunsaturated fatty acid appear neutral [129].

3.2.3. Physical activity

Regular physical activity is an independent predictor of improved survival [101] and lower cardiovascular mortality in patients with CCS [131]. Extensive data confirmed that both adopting or preserving a physically active lifestyle leads to significant reductions (up to 50%) of all-cause and cardiovascular disease mortality in patients with CCS compared to physical inactivity [132]. Sustained physical activity was also suggested to lead to more substantial reductions in mortality than weight loss in coronary heart disease [133]. Vigorous physical activity up to 2 times weekly shows an association with better cardiac outcomes (all-cause death, CV death and stroke) in patients with CCS compared to low-level or no physical activity [134]. High-intensity interval exercise was suggested to be safe and possibly superior to moderate-intensity continuous training in patients with CCS, particularly for the improvement of cardiorespiratory fitness in cardiac rehabilitation [135] and aerobic capacity [136,137]. Though for more sustainable physical activities, a 30–40 min a day of brisk walking for at least four days a week would have greater impact compared to interrupted physical activities.

3.2.4. Healthy weight

Overweight and obesity significantly increase the risk of cardiovascular morbidity and mortality, in addition to the risk of developing CVD at an earlier age [138]. The implication of obesity might be superior to that of overweight on mortality in patients with CCS [139]. Regardless, intentional weight loss was shown to reduce clinical events in patients with CCS [140]. Weight loss is an effective way to improve cardiovascular risk profile in CCS patients with positive implications on body composition, BP and lipids [141]. Weight loss might be more effective than exercise in the improvement of atherogenic lipid profile of CCS patients what are sedentary and overweight [142].

3.2.5. Psychosocial factors

Patients with CCS, particularly women, were described to be more vulnerable to psychological distress, such as anxiety, stress and depression [143]. Psychological stress in CCS patients might have implications on disease evolution and should therefore be assessed to improve individualization of comprehensive rehabilitation programs [144]. A Cochrane systematic review and meta-analysis showed that psychological intervention in coronary

Table 15. Recommendations for revascularization.

No	Recommendation
1	It is recommended that a procedure consent form be obtained prior to revascularization with adequate information about the amplitude, benefits, risks, therapeutic consequences.
2	It is recommended that the Heart Team formulate institutional protocols to ensure optimal and suitable revascularization strategy is used in compliance with relevant guidelines.
Revascularization as an Approach to Improve Survival Compared with Medical Therapy	
3	Revascularization is recommended to improve survival in patients with CCS and concomitant: • significant left main stenosis. • multivessel CAD appropriate for CABG with severe left ventricular systolic dysfunction (left ventricular ejection fraction <35%). • proximal LAD stenosis >50% with documented ischemia or a hemodynamically relevant lesion defined by FFR ≤0.80 or iwFR ≤0.89 or >90% stenosis by visual estimation. • large areas of ischemia detected by functional testing (>10% of LV).
4	Revascularization by CABG may be considered to improve survival in patients with CCS and concomitant mild to moderate left ventricular dysfunction (LVEF 35% - 50%) and multivessel CAD.
5	Revascularization may be considered to improve survival in patients with CCS and multivessel CAD appropriate for either CABG or PCI, by lowering the risk of cardiovascular events such as spontaneous MI, unplanned urgent revascularizations, or cardiac death.
6	coronary revascularization should NOT be performed with the primary or sole intent to improve survival in patients with single- or double-vessel disease not involving the proximal LAD not anatomically or functionally significant.
Revascularization as an Approach to Improve Symptoms	
7	Revascularization is recommended to improve symptoms in patients with significant coronary artery stenosis amenable to revascularization with the presence of limiting angina or angina equivalent on optimal medical therapy
PCI vs CABG	
	Assessment of CAD complexity
8	It is recommended to calculate the SYNTAX score (http://syntaxscore.org/) to assess the anatomical complexity of CAD.

heart disease can lead to a significant improvement in psychological symptoms as well as a reduction in cardiac mortality [145]. Perceived social support carries a significant positive effect on depression and fatigue in CCS patients [146].

3.2.6. Influenza vaccination and other viral illnesses

Evidence supports the potential benefit of influenza vaccination in reducing cardiovascular mortality as well as cardiovascular events in patients with CVD [147,148] and after a MI [149]. Influenza vaccination may therefore be considered for patients, especially those at higher risk (such as the elderly). Vaccination against other viral diseases such as COVID-19 may also be beneficial based on recent evidence, particularly that many patients infected and admitted with COVID-19 have CCS or ischemic equivalents such diabetes or other CVD [150]. Emerging data suggests that the risk of one-year incidental cardiovascular events is higher non vaccinated COVID-19 survivors [151], and that the risk of AMI or stroke can also be reduced through COVID-19 vaccination [152].

GUIDELINE

Table 15. (Continued).

9	It is recommended to consider complete revascularization when choosing between CABG and PCI.
	Revascularization in patients with CCS and suitable coronary anatomy for both procedures with acceptable predicted surgical mortality (based on STS Score (https://riskcalc.sts.org/stswebriskcalc/calculate) and heart team consensus).
10	Both PCI and CABG are recommended as the preferred revascularization choice in patients with: • left main CAD and low SYNTAX score (low (≤16), and intermediate (16-22). • one or two vessel disease with proximal LAD. • three-vessel CAD without diabetes and low SYNTAX score.
11	CABG is recommended over PCI as the preferred revascularization strategy in patients with: • left main CAD and high SYNTAX score. • three-vessel CAD without diabetes and intermediate or high SYNTAX score. • three-vessel CAD or two-vessel CAD with proximal LAD involvement with diabetes.
12	PCI is recommended over CABG as the preferred revascularization choice in patients with one or two vessel disease without proximal LAD.
13	It is recommended that all clinical, anatomical and technical aspects be considered before choosing the mode of revascularization.
	Revascularization in Left Ventricular Dysfunction (EF <35%)
14	CABG is recommended as the first revascularization strategy choice in patients with multivessel disease, viable myocardium and acceptable surgical risk.
15	PCI should be recommended as an alternative for CABG in patients with multivessel disease and LV dysfunction in high surgical risk patients.

CABG: Coronary artery bypass grafting; CAD: coronary artery disease; CCS: chronic coronary syndrome; EF: ejection fraction; FFR: fractional flow reserve; iwFR: Instantaneous wave-free ratio; LAD: Left Anterior Descending; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: Percutaneous coronary intervention

3.3. Pharmacological therapy

The goal of pharmacological therapy is to control symptoms, improve quality of life and the prevention of cardiovascular events [153–156].

3.3.1. Anti-anginal therapy

Recommendations for anti-anginal therapy are shown in Table 13. First choice of treatment is generally beta-adrenergic blockers. If beta-blockers are contraindicated or cannot be tolerated, then the use of calcium channel blockers (CCBs) may be considered [154,157,158].

Meta-analyses of available evidence suggest second-line or add-on options (to beta-blocker or a CCB) to include long-acting nitrates, ranolazine, trimetazidine, and in some cases, ivabradine [158].

When angina relief is needed but initial therapy with a beta-blocker or non-dihydropyridine CCB is contraindicated, cannot provide sufficient symptom control, or is poorly tolerated, clinicians can consider the use of a long-acting nitrate (e.g. nitroglycerin, isosorbide dinitrate, and isosorbide mononitrate) [159]. Prolonged exposure to nitrates provokes tolerance with loss of efficacy, which could be addressed by abstaining from nitrate exposure or using a low dose of nitrates for an interval of 10–14 h [160]. Short-acting sublingual and spray nitroglycerin formulations can both provide instant alleviation of effort angina, with spray nitroglycerin having a faster onset of action [161]. Furthermore, the short acting nitrate can be used as a prophylaxis in patients who are well aware of their pain pattern and triggers, the short-acting nitrates can be used prior to the physical (or even psychological) stressor that will occur, e.g sexual activity or uphill walking.

The benefit of ranolazine monotherapy for CCS remains uncertain when all evidence is taken collectively, but its use as add-on therapy carries significant benefit in the reduction of angina episodes [162]. While ranolazine might reduce the number of anginal episodes in CCS, it is also linked to a higher number of adverse effects with no improvement in mortality of risk of acute MI [163]. That being said, another meta-analysis shows that the use of ranolazine with a beta blocker or CCB was beneficial across all examined outcomes [158]. Ranolazine might also lead to significant benefit when added to standard anti-ischemic therapy in patients after percutaneous coronary revascularization [164]. Regardless, ranolazine is not registered in SFDA.

Trimetazidine has less consistently reported benefit in the treatment of CCS [158]. An early meta-analysis of 13 RCTs demonstrated the efficacy of trimetazidine in patients with CCS compared to conventional antianginal agents, with a significant improvement on angina attack frequency, weekly nitroglycerin use and other functional outcomes [165]. More recent evidence from the retrospective analysis of an open-label observational study investigating the safety and efficacy of trimetazidine (the ATPCI trial) reported similar outcomes, showing that once daily prolonged-release 80 mg trimetazidine led to significant reductions in the frequency and severity of angina as well as weekly short-acting nitroglycerin use independently of revascularization status [166]. That being said, the initial analysis of the ATPCI trial failed to show that the use of twice-daily 35 mg trimetazidine over several years after successful PCI affects the recurrence of angina or clinical outcomes [167].

Ivabradine reduces the frequency of hospitalization in CCS but does not seem to have a collective effect on cardiovascular mortality nor the frequency of CCS episodes [168]. In addition to its unreliable effect on mortality, the use of ivabradine in patients with CCS should be limited to HF patients and those with uncontrolled heart rate despite beta blockers therapy [169,170].

3.3.2. *Event prevention*

Recommendations for event prevention are detailed in Table 14. Supporting evidence is provided in the following sections.

3.3.2.1. Antiplatelet therapy. Low-dose aspirin as single antiplatelet therapy (SAPT) strategy is a pillar of event prevention in CCS patients while dual antiplatelet therapy (DAPT) with aspirin and an oral P2Y12 inhibitor and should be used only as a secondary prevention. Evidence suggests that patients with untimely discontinuation of a P2Y12 inhibitor are more likely to suffer from stent thrombosis [171]. For optimal benefit and safety, DAPT should be given for 6 months after PCI [171]. However, a shorter course of DAPT (3 months) may be considered in patients who are at a high risk of bleeding but at a very low risk of stent thrombosis [171].

The THEMIS trial demonstrated that ticagrelor in combination with aspirin can reduce the risk of ischemic cardiovascular events in patients with CCS and diabetes without a history of MI or stroke, albeit with more occurrence of major bleeding compared to aspirin alone [172]. The PEGASUS-TIMI 54 trial also showed a significant reduction of the risk of MI, stroke or cardiovascular death with ticagrelor 60 mg and 90 mg along with a higher risk of breeding, but in patients with a previous history of MI [173]. In general, available evidence support a favorable risk/benefit ratio with ticagrelor 60 mg in patients with prior MI [174].

The addition of direct oral anticoagulant (DOAC) rivaroxaban 2.5 mg to antiplatelet therapy in CCS was shown to lead to significantly less MACE and ischemic stroke, with a relatively low risk of major bleeding [175,176].

3.3.2.2. Lipid-lowering therapy. The management of dyslipidemia is necessary in patients with CCS who are at high risk of cardiovascular events and should include both a lifestyle and pharmacological component consistently with available lipid guidelines. In regards to medical therapy, statins must be considered to lower LDL-C levels and have been shown to be effective especially in high-dose regimens, alone or in combination with ezetimibe [177]. The reduction of LDL-C levels with intensive therapy after acute coronary events carries a significant positive effect on long-term cardiovascular outcomes [178]. Intensive statin therapy was suggested to confer a higher degree of reduction in the risk of stroke in patients with CCS compared to standard statin therapy [179]. The addition of other drugs such as ezetimibe is justified in case target lipid levels could not be achieved with statins alone. To note that a meta-analysis showed that ezetimibe can ensure more reduction in LDL-C in patients with high CVD already on statins compared to doubling the dose of statin therapy [180]. PCSK9 monoclonal antibodies can also be beneficial in patients who cannot receive other lipid lowering drugs or could not achieve target LDL levels [181], albeit at a high cost often limiting their accessibility.

Pre-treatment with high-dose statin has been consistently shown to be beneficial in reducing the risk of complications and major adverse cardiac events after percutaneous coronary intervention (PCI) [182,183].

Current Saudi Guidelines for Dyslipidemia Management recommend a treatment goal for LDL cholesterol of <1.4 mmol/L (<55 mg/dL) for very-high-risk patients and of <1 mmol/L in extremely high-risk group with recurrent cardiac events [184].

3.3.2.3. Renin-angiotensin-Aldosterone blocker therapy. In patients with CCS without HF, renin angiotensin system inhibitors (RASi) were found to be beneficial in reducing cardiovascular events and mortality only when compared to placebo, with this benefit lost when RASi are compared to active controls [185]. While the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) might be questioned in CCS patients without HF [186], RASi have also been reported to reduce the occurrence of HF and cardiovascular events in individuals with high CVD risk and atrial fibrillation [187]. The use of RASi might be better limited to CCS patients with other indications for this therapy, such as concomitant hypertension, LV dysfunction, diabetes or chronic kidney disease.

3.3.2.4. Other therapies

3.3.2.4.1. Proton pump inhibitors. Proton pump inhibitors that inhibit CYP2C19, particularly omeprazole and esomeprazole, have been suggested to dampen the pharmacodynamic response to clopidogrel. It is therefore not recommended to administer omeprazole or esomeprazole with clopidogrel in the absence of gastrointestinal indications [188].

3.3.2.4.2. Hormone replacement therapy. Available RCTs have failed to show a prognostic benefit with hormone replacement therapy provides, which was shown to lead to an increased CVD risk in women aged >60 years [189]. Hormone replacement therapy should not be used.

3.4. Revascularization

Contemporary international chronic coronary syndrome guidelines consider myocardial revascularization as a second line therapy to optimal medical therapy to improve symptoms in case the patient remained symptomatic. However, a single center study in Qassim Saudi Arabia showed optimal medical therapy is achieved in only 10% of the study cohort. Therefore, it is important to improve clinical management of CCS and adequately fulfil first line therapy before considering myocardial revascularization in local populations [190]. Although there is a mortality benefit of revascularization in selected cases, such as left main disease, severe LV dysfunction, proximal left anterior descending (LAD) artery disease and diabetics [191], available evidence shows no improvement of survival in the general CCS population with myocardial revascularization; in the ISCHEMIA trial, initial myocardial revascularization by Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Graft (CABG) surgery showed no mortality benefit compared to initial optimal medical therapy in patients with CCS and moderate or severe ischemia [46]. Several current meta-analyses demonstrate that the survival advantage observed in chronic coronary syndrome patients with medical therapy cannot be improved with the addition of revascularization [192–194]. When exploring the implication of the number of diseased vessels and the degree of ischemia based on data from the COURAGE trial, the association between the number of diseased vessels (but not ischemia) and mortality after PCI was evident in univariate analysis but did not persist after accounting for baseline variables [195]. Very limited evidence is available from Saudi Arabia. One study showed that long-term risk of cardiac-related deaths after surgical revascularization (CABG) in CCS is not influenced by pre-operative significant myocardial ischemia and ventricular dysfunction [196].

Conversely, while the degree of ischemia was not associated with any changes in risk, some benefit (6.3% decrease) was observed with invasive therapy in the patient group with the highest CAD severity on the level of cardiovascular death or MI in the long-term outcomes of the ISCHEMIA trial [197]. It is very important to recognize that not all available data are in concordance, and several patient categories (namely those with multivessel disease with impaired LV function, advanced kidney disease, prior revascularization, left main disease, advanced age and complex heart disease) were excluded from the trials based on which the conclusions about the lack of survival advantage with revascularization were made. A deep dive into available data reveals clear exceptions to the lack of survival benefit with myocardial revascularization. In direct opposition to the ISCHEMIA trial and other studies, the degree of ischemia was suggested in a meta-analysis to affect the benefit that can be expected from myocardial revascularization; while patients with no ischemia might not expect myocardial revascularization to reduce the incidence of MACE or death compared to medical therapy, those with objective evidence of moderate to severe ischemia will benefit in terms of

MACE incidence reduction [198]. More importantly, survival benefits can be expected in addition to a lower incidence of MACE with revascularization in patients who have severe ischemia [198]. Evidence therefore suggest to a survival advantage in patients undergoing early revascularization with greater extent of ischemia, as evidenced on PET MPI [199].

A sub-analysis of the EXCEL (XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial showed that CABG and PCI with everolimus-eluting stents are comparable in terms of a composite measure of death, MI, or stroke among patients with left main CAD, irrespective of baseline anatomic complexity and the extent of CAD [200]. However, PCI was associated with significantly more frequent major adverse cardiac event or ischemia-driven revascularization compared to CABG, especially with increasing SYNTHAX scores [200]. In the G-LM (Gulf Left Main) registry for unprotected left main coronary artery disease in 2138 underwent PCI or CABG, showed comparable outcomes between those treated with PCI and CABG (rates of freedom from revascularization, MACCE, or total mortality) after a follow-up of 15 months. Similarly, comparable survival was observed after PCI and CABG in patients with single-vessel, proximal LAD disease, but CABG provided more effective angina relief and less need for repeat revascularizations [201]. In the SYNTHAX trial, it was also evident that CABG is preferable to PCI for revascularization as it leads to less death (all causes), stroke, MI, or repeat revascularization in patients with 3 vessel disease or left main disease [202], especially those with concomitant diabetes [203]. In the same vein, the FREEDOM trial showed PCI to be inferior to CABG in patients with advanced CAD (multivessel) and diabetes; CABG led to a less all-cause mortality and non-fatal MI compared to PCI, albeit with higher rates of stroke [204]. The superiority of CABG in diabetic patients was also reported in a pooled analysis from major trials (e.g. COURAGE [Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation], BARI 2D [Bypass Angioplasty Revascularization Investigation 2 Diabetes], and FREEDOM [Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multi-vessel Disease]) [205]. This study also noted a non-significant but positive trend towards improved rates of all-cause death, MI, or stroke with CABG in patients with concomitant diabetes and chronic kidney disease [205].

In conclusion, conservative medical therapy is preferable for the first-line treatment of CCS in the absence of a compelling indication. Revascularization should be considered in certain clinical scenarios, as detailed in Table 15. The choice of revascularization should be personalized and subject to patient preference as well as multi-disciplinary heart team discussions regardless of the presence or absence of a compelling indication. Clinical characteristics, disease complexity and technical feasibility should also inform the choice of revascularization.

3.5. Impact of the COVID-19 pandemic

The coronavirus disease 2019 (COVID-19) pandemic and the ensuing lockdowns impacted not only patient's adherence to lifestyle and therapies but also access to care. In a French study involving 195 patients with mean age of 65.5 years, 3% of patients discontinued their medications while 85% remained adherent to the recommended daily intake of prescribed aspirin. However, adherence to recommended lifestyle was lower, with close to half of patients reporting more than 25% reduction in physical activity, and around a quarter of patients reporting body weight gain of more than 2 Kgs. This was reported in addition to an increase in tobacco consumption among smokers [206]. Moreover, the mortality of patients with COVID-19 is higher among those with comorbidities such as CVD, hypertension, diabetes, congestive HF, chronic kidney disease and cancer compared to those without [207]. Worse clinical outcomes and death after COVID-19 were also reported and could be predicted among patients with pre-existing inflammatory conditions (related to conditions such as chronic coronary diseases, type 2 diabetes mellitus or obesity). A notable example is the possibility of COVID-19 disease and its inherent cytokine storm triggering or predisposing patients for the rupture of a silent atheromatous plaque. This would lead to sudden clinical deterioration as a result of the arising ACS [208]. It is clear that by impeding the delivery of patient care, the COVID-19 pandemic led to a notable decrease in patient safety and treatment efficacy. To note that cardiac CT was utilized more frequently in North America during the COVID-19 pandemic due to some advantages in certain cases, namely: (1) the need to distinguish between myocardial injury and MI; (2) presentation with acute chest pain; (3) cases of disease with concomitant stable chest pain; (4)

suspected intracardiac thrombus; (5) concomitant valvular heart disease [209]. Moreover, PCI rates decreased during the pandemic as significantly fewer patients underwent elective PCI in England as reported by the British Cardiovascular Intervention Society [210].

3.6. Cardiac rehabilitation

Exercise-based cardiac rehabilitation was shown to be beneficial to patients with chronic heart disease. This approach leads to lower rates of MI, possibly fewer deaths from all causes, substantially less all-cause hospitalization and associated healthcare costs, as well as better quality of life for up to 12 months. Long-term benefits have been suggested to include a protective effect against cardiovascular mortality and MI [211]. One study showed that a phase 2 cardiac rehabilitation program in patients with CCS can lead to an improvement in CVD risk factors in both obese and non-obese patients. To note that obese patients show a greater decrease in BMI, BP, and LDL-C levels [212]. Participation of patients with CCS in an exercise-based cardiac rehabilitation program was also associated with significantly less frequent angina and improved exercise capacity [213]. A retrospective cohort study that was conducted online on real-world dataset of CCS patients showed a lower risk of all-cause mortality, rehospitalization and cardiovascular morbidity 1.5 years after diagnosis among patients who underwent exercise-based cardiac rehabilitation compared to those who were referred to PCI. Moreover, the benefit of exercise-based cardiac rehabilitation persisted in several regards (all-cause mortality, rehospitalization, acute MI or stroke) with or without the addition of PCI [214]. A home-based cardiac rehabilitation program with remote monitoring for frail patients with the help of home physiotherapist and a care giver is feasible for patients with logistical problems attending center -based cardiac rehabilitation programs. The program should cover exercise training, risk factors management (dietary education, smoking cessation) medication management and psychological support. The safety and efficacy of this requires further evaluation [215,216]. Reducing and preventing cardiovascular events through a phase 3 cardiac rehabilitation carries an established benefit even in elderly patients with CCS [217]. Finally, outcomes of cardiac rehabilitation in low to moderate risk CAD patients are comparable between programs delivered via telehealth and center-based supervised program. This offers the opportunity to address cardiac rehabilitation access issues that might be faced by some patients through the use of telehealth intervention as an alternative for center-based cardiac rehabilitation [218].

4. Conclusions

Over two million patients suffer from CCS in Saudi Arabia. Only a minority of patients achieve optimal medical therapy. These guidelines which are evidence based when implemented will improve the care of patients with CCS and will lead to more appropriate use of available resources. It can be not be overemphasized that a cornerstone of successful management is control of CCS risk factors. Adequate control of risk factors with optimal achievements of targets for weight, HbA1c, LDL, BP as well as smoking cessation in addition to being involved in either a formal cardiac rehabilitation program or being engaged in regular physical exercise is likely to prevent the onset of acute coronary events in patients with CCS. When symptoms persist the appropriate and timely use of revascularization either by PCI or CABG is likely to relieve symptoms and improve outcomes.

Author contributions

Conception and design of Study: OA, WAH. Literature review: OA, SAS, HA, MA, FQ, MA, YT, AT, WA, FA, RD, WM, WA, KA. Acquisition of data: OA. Drafting of manuscript: OA, SAS, HA, MA, FQ, MA, YT, AT, WA, FA, RD, WM, WA, KA. Revising and editing the manuscript critically for important intellectual contents: OA, SAS, HA, MA, FQ, MA, YT, AT, WA, FA, RD, WM, WA, KA. Data preparation and presentation: OA, SAS, HA, MA, FQ, MA, YT, AT, WA, FA, RD, WM, WA, KA. Supervision of the research: OA. Research coordination and management: OA. Funding for the research: OA.

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Conflict of interest

None declared.

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